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Microwave-assisted gold(I) catalyzed pyran ring opening in brevifloralactone: synthesis of the hawtriwaic acid core

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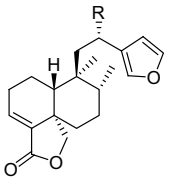
ABSTRACT

An efficient microwave-assisted Au(I) catalyzed cleavage of the pyran ring of brevifloralactone is described. We report one of the first combination reactions of gold and microwave irradiation. In base to this reaction, nine new *ent*-clerodane diterpene derivatives have been obtained by partial synthesis from brevifloralactone, a naturally occurring clerodane-type diterpene isolated in large quantities from the aerial part of Salvia breviflora. The clerodane diterpenes have very interesting biological activities and the semisynthetic approach described here represents an alternative to obtain them from other major diterpenes isolated from natural sources. The structures of these compounds were stablished from their physical and spectroscopic data.

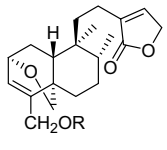
The clerodane natural products are diterpenes that exhibit a wide-ranging structural diversity.[1] Of particular interest are hawtriwaic acid derivatives (**1a–b**, Fig. 1), some of which exhibit anti-proliferative activity against SW1573 lung cell line[2] and an immunomodulatory action.[3] Tanabalin **1c** exhibits potent insect antifeedant activity against pink bollworm, Pectinophora gossypiella, a severe cotton pest.[4] These remarkable bioactivities made these compounds to be attractive synthetic targets. Interestingly, brevifloralactone **2a**, a naturally occurring clerodane-type diterpene isolated in large quantities from the aerial part of Salvia breviflora,[5] contains the central core of the hawtriwaic natural product family. It is obvious that a pyran ring opening process in this molecule would afford a compound closely related to **1a–c** which might serve as starting material for the synthesis of other analogs or other minor biologically active natural clerodane diterpenes. As a part of our interest in bioactive natural products,[6] herein we describe a practical methodology for such a pyran ring opening process using **2a** as the starting material.

Strongly acidic conditions[7] or activated substrates[8] are typically required to achieve cleavage of cyclic ethers. Other methodologies rely on hydrogenation employing high pressure and temperature, or strong acids, conditions which are of limited scope.[9] Dissolving metal reduction has also been employed with some degree of success,[10] and reductive cleavage conditions utilizing trialkylsilanes have also been described. Recently, an efficient method for the nucleophilic ring opening of aryl pyranosides promoted by $Sc(OTf)_3$ was described by Panek and co-workers.[11] We recognized that the $\Delta^{3,4}$ double bond present in brevifloralactone **2a** should facilitate opening of the pyran ring. Thus, we hypothesized that a π-selective Lewis acid might be useful in accomplishing this goal. In this context, gold complexes have increasingly been used as π-selective catalysts in a variety of organic transformations.[12]

Thus, heating a methanolic solution of **2a** containing a catalytic amount of [bis (trifluoromethanesulfonyl) imidate] (triphenylphosphine) gold(I)[13] at 50 °C for four days gave the methyl acetal **3a** in 70% yield (Table 1, entry 1). We were pleased to observe that not only the expected pyran ring opening process occurred, but also an apparent oxidation of the allylic alcohol and migration of the double bond took place. Because of the excessively long reaction time, we elected to examine the process under microwave radiation conditions. Microwave irradiation of a methanol solution of **2a** produced **3a** in 94% yield within 30 min (Table 1, entry 2). In addition, when ethanol was used as the solvent, the ethyl acetal **3b** was formed in nearly quantitative yield,[14] while in THF a product identified as the hemiacetal **3c** was obtained in 75% yield (Table 1, entries 3 and 4). In contrast, when the reaction was carried out in toluene, decomposition of the starting material occurred



1a R=H Hawtriwaic acid lactone
1b R=OH 12α-Hydroxyhautriwaic acid-19-lactone
1c R=OAc Tanabalin



2a R=H Brevifloralactone
2b R=TBS
2c R=Ac

Figure 1. Structure of clerodane diterpenoids.

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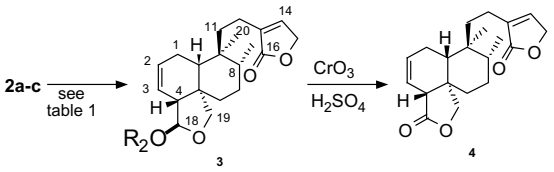
Table 1
Optimization of the Au(I) catalyzed pyran ring cleavage of brevifloralactone



Entry	Conditions[a]	R_1	R_2	Yield (%)
(1)	Au(I)/MeOH/50 °C/4days	H (**2a**)	Me (**3a**)	70
(2)	Au(I)/MeOH/MW/56 °C/0.5 h	H (**2a**)	Me (**3a**)	94
(3)	Au(I)/EtOH/MW/73 °C/0.5 h	H (**2a**)	Et (**3b**)	98
(4)	Au(I)/THF/MW/60 °C/0.5 h	H (**2a**)	H (**3c**)	75
(5)	Au(I)/Toluene/MW/100 °C/0.5 h	H (**2a**)	—	—
(6)	$AuCl_3$/EtOH/MW/73 °C/0.25 h	H (**2a**)	Et (**3b**)	72
(7)	Au(I)/EtOH/MW/73 °C/0.5 h	TBS (**2b**)	—	—
(8)	Au(I)/EtOH/MW/73 °C/0.5 h	Ac (**2c**)	—	—
(9)	TfOH/MeOH/50 °C/12 h	H (**2a**)	Me (**3a**)	51
(10)	$GaCl_3$/THF/60 °C/12 h	H (**2a**)	H (**3c**)	19
(11)	$Sc(OTf)_3$/THF/60 °C/12 h	H (**2a**)	H (**3c**)	49

[a] Reactions were conducted with 0.1–0.2 mmol of substrate and 1–2 mol % of [Au] in 1 mL of solvent, while being irradiated with microwaves in an open vessel system (Discover, CEM). The temperature was maintained by power modulation from 255 to 300 W. Reactions were conducted with simultaneous cooling of the flask with pressurized air.

and no identifiable product could be isolated. (Table 1, entry 5). The use of $AuCl_3$ in ethanol also resulted in the formation of ethyl acetal **3b**, but in somewhat lower yield (Table 1, entry 6). Significantly, microwave irradiation of ethanol solutions of the *tert*-butyldimethylsilyl ether **2b** or the acetate **2c** resulted in recovery of the starting materials (Table 1, entries 7 and 8). The presence of the hydroxyl group is thus essential for the success of the reaction. Protic acids such as trifluoromethanesulfonic acid were also found to effect the above transformation, although considerably less efficient (Table 1, entry 9).[15] Other Lewis acids surveyed included $PtCl_2$, $InCl_3$, CuBr, and $AgSbF_5$. In all cases, the unaltered starting material was recovered. $GaCl_3$ and $Sc(OTf)_3$ provided hemiacetalic material, albeit with low yields (Table 1, entries 10 and 11).

The structure of **3b** was determined by spectroscopic data.[16] Comparison of the ^{1}H NMR spectrum of **3b** with that of **2a** showed that the signals corresponding to the protons of the east side of the molecule were very similar in both systems. In addition, the spectrum showed the expected signals for an ethoxy group and a new absorption at 2.45 ppm (1H, d, J = 2.7 Hz) which was assigned to H-4. Two low field signals at 5.49 and 5.81 ppm were ascribed to the olefinic hydrogens. Signals for hemiacetal proton H-18 and the H-19 protons were found at 4.66 (1H, s) and 3.81 (2H, m) ppm, respectively. The ^{13}C NMR spectrum showed signals for 22 carbon atoms, including absorptions at δ 174.3 (s, C-16 lactone carbonyl group), δ 62.9 (t), 70.1 (t), 71.6 (t) (assignable to three CH_2 carbon bearing an oxygen), δ 126.0 (d), 128.0 (d), 134.9 (s), 143.4 (d) (four olefinic carbons), and δ 107.2 (C-18 hemiacetal carbon).

All the above data, together with the COSY, HSQC, and HMBC experiments, are in accordance with the structure of 18-ethoxy-18,19-epoxy-*ent*-clerodan-2, 13(14)-dien-16-15-olide for **3b**.

The treatment of **3b** with Jones reagent yields the expected dilactone **4** in 79% yield, the structure of which was confirmed through single-crystal X-ray analysis (Fig. 2), which also confirms the structure of lactol **3b**.

Although further studies are necessary to elucidate the mechanism of the process, the experimental observations and literature precedents lead us to propose the sequence depicted in Scheme 1. The first step would involve coordination of Au(I) to the alkene assisted by the hydroxyl group to form complex A. Migration of the double bond would generate the organoaurate B. Opening of the pyran ring would afford the conjugated enol C and regenerate

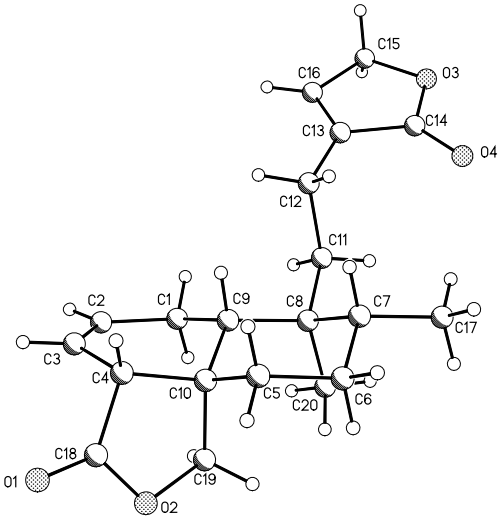
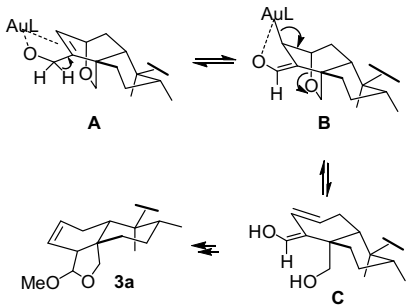


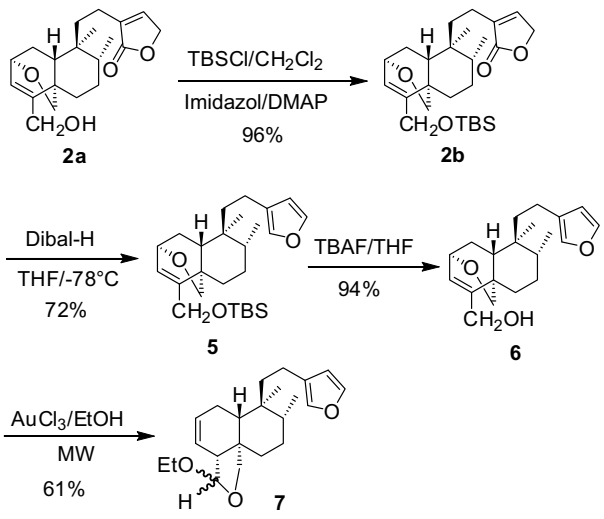
Figure 2. ORTEP plot of 4.



Scheme 1. Proposed Mechanism.

the Au(I) salt. The final product then results from cyclization of the newly generated hydroxyl moiety at C-19 with the C-18 aldehyde group. A similar transformation has rarely been observed in Pd-catalyzed reactions.[17]

In order to have structural diversity and to extend the scope of the reaction, we decided to reduce the lactone to the corresponding furan ring in the lateral chain of brevifloralactone **2a**. Thus,



Scheme 2. Synthesis of compound **7**.

protection of **2a** (Scheme 2) was carried out using *tert*-butyldimethylsilyl chloride to give the C-18 protected derivative **2b** in 96% yield, which was reduced with Dibal-H at −78 °C to yield the compound **5** containing the furan ring present in the hawtriwaic acid natural product family. Interestingly, after removal of the silyl ether with tetrabutylammoniumfluoride, the reaction of the resultant primary alcohol **6** with a catalytic amount of [bis(trifluoromethanesulfonyl) imidate] (triphenylphosphine) gold(I) at 73 °C for 30 min under microwave irradiation failed and the unaltered starting material was recovered. Satisfyingly, when $AuCl_3$ was used, the lactol **7** was obtained in good yield.[18] The failure of the reaction when gold(I) catalyst was used might be the consequence of the formation of some gold-furyl species, as reported before by Kharasch,[19] Fuchita,[20] and Hashmi et al.[21] It seems that $AuCl_3$ selectively reacts with the allylic alcohol under these conditions. However, we currently have no definite explanation for this behavior.

In conclusion, an efficient gold catalyzed method for pyran ring opening of brevifloralactone **2a** is presented. The use of microwave irradiation allowed completion of the reaction in a much shorter time and in significantly better yields than observed under conventional thermal conditions. It should be noted that when the lactone was changed for a furan ring in the lateral chain, the pyran ring opening is catalyzed by $AuCl_3$ but not by [bis (trifluoromethanesulfonyl) imidate] (triphenylphosphine) gold(I). Moreover, we have obtained several new clerodane-type diterpenes by partial synthesis from brevifloralactone. Current efforts are now directed toward the total synthesis of natural clerodane diterpenes.

Acknowledgments

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14. 52.8 mg of brevifloralactone **2a** (0.159 mmol) and 4.2 mg (1.7 mol %) of [Bis(trifluoromethanesulfonyl)imidate] (triphenylphosphine) gold (I) were dissolved in 1 mL of EtOH. The reaction mixture was subjected to microwaveirradiation at 73 °C (power from 255 to 300 W, with external cooling) for 30 min. Then the solvent was eliminated in vacuo, and the crude was chromatographed over silica gel using *n*-hexane/dichloromethane/acetone (3:1:1) as eluent to give **3b** (56.3 mg, 98.3%).
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16. 18-Ethoxy-18,19-epoxy-ent-clerodan-2(3),13(14)-dien-16,15-olide **3b**: ^{1}H NMR δ 0.61 (3H, s, Me-20), 0.83 (3H, d, J = 6.6 Hz, Me-17), 1.20 (3H, t, J = 7.2 Hz, O-CH_2CH_3), 2.42 (2H, t, J = 3.3 Hz, H-6), 2.46 (1H, d, J = 2.7 Hz, H-4), 3.40 (1H, dq, J^1 = 2.7 Hz, J^2 = 7.2 Hz, O-CH_2CH_3), 3.70 (1H, dq, J^1 = 2.7 Hz, J^2 = 7.2 Hz, O-CH_2CH_3), 3.81 (2H, m, H-19), 4.66 (1H, s, H-18), 4.76 (2H, q , J = 1.8 Hz, H-15), 5.48, (1H, dd, J^1 = 1.5 Hz, J^2 = 8.9 Hz, H-3), 5.81 (1H, m, H-2), 7.08 (1H, t, J = 1.5 Hz, H-14); ^{13}C NMR δ 15.3 (q, CH_3–CH_2O), 15.6 (q, C-17), 16.7 (q, C-20), 18.8 (d, C-8), 21.7 (t, C-12), 27.9 (t, C-1), 34.5 (t, C-7), 36.7 (t, C-11), 38.5 (t, C-6), 38.8 (s, C-9), 41.5 (d, C-10), 43.5 (s, C-5), 56.7 (d, C-4), 62.9 (t, OCH_2CH_3), 70.1 (t, C-15), 71.6 (t, C-19), 107.2 (d, C-18), 126.0 (d, C-3), 128.0 (d, C-2), 134.9 (s, C-13), 143.4 (d, C-14), 174.3 (s, C-16); IR (film) ν_{max} 2928, 1753, 1446, 1067, 950, 751 cm^{-1}; EI-MS m/z 361 [M+1]$^+$ (7), 315 (10), 286 (10), 219 (21), 175 (100), 147 (20), 112 (31), 91 (30); HR-FAB+-MS m/z 361.2369 (calcd for $C_{22}H_{33}O_4$, 361.2379).
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18. 18-Ethoxy-18,19:15,16-diepoxy-ent-clerodan-2(3),13(16),14-trieno **7**: ^{1}H NMR δ 0.60 (3H, s, Me-20), 0.83 (3H, d, J = 6.6 Hz, Me-17), 1.21 (3H, t, J = 7.0 Hz, CH_3–CH_2-O), 2.46 (1H, d, J = 2.6 Hz, H-4), 3.40 (1H, dq, J^1 = 2.6, J^2 = 7.0 Hz, O-CH_2CH_3), 3.72 (1H, dq, J^1 = 2.6, J^2 = 7.0 Hz, O-CH_2CH_3), 3.84 (2H, m, H-19), 4.67 (1H, s, H-18), 5.50 (1H, dt, J^1 = 2.4 Hz, J^2 = 15 Hz, H-3), 5.83 (1H, m, H-2), 6.25 (1H, q, J = 0.8, H-14), 7.20 (1H, m, H-16), 7.34 (1H, t, J = 1.7 Hz, H-15); ^{13}C NMR δ 15.4 (q, CH_3–CH_2O), 15.7 (q, C-17), 16.8 (q, C-20), 17.8 (d, C-8), 21.8 (t, C-12), 27.9 (t, C-1), 36.7 (t, C-7), 37.2 (t, C-11), 38.6 (t, C-6), 38.8 (s, C-9), 41.5 (d, C-10), 43.5 (s, C-5), 56.7 (d, C-4), 62.8 (q, OCH_2CH_3), 71.7 (t, C-19), 107.2 (d, C-18), 110.9 (d, C-14), 125.4 (s, C-13), 126.0 (d, C-3), 128.2 (d, C-2), 138.4 (s, C-16), 142.7 (d, C-15); IR (film) ν_{max} 2918, 1731, 1448, 1060, 873, 778 cm^{-1}; EI-MS m/z 345 [M+1]$^+$ (7), 299 (41), 270 (100), 203 (88), (10), 219 (21), 175 (71), 91 (73); HR-FAB+-MS m/z 345.2369 (calcd for $C_{22}H_{33}O_4$, 345.2382).
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