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Synthesis of a Greek tobacco lactonic natural product and its analogues

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ABSTRACT

A total synthesis of a Greek tobacco lactonic natural product and three of its analogues has been achieved using a commercially available starting material and our furan approach to oxacyclic systems, the proven scope of which is thus broadened.

Wahlberg and co-workers isolated in 1993,[1] 13 lactones from an extract of sun-cured leaves of Greek tobacco. Nine of these lactones were new natural products, some of them are depicted in Figure 1.

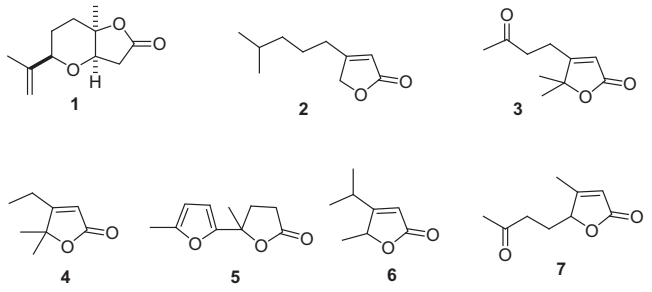


Figure 1. Structures of some of the new natural products isolated by Wahlberg and co-workers from sun-cured Greek tobacco leaves.

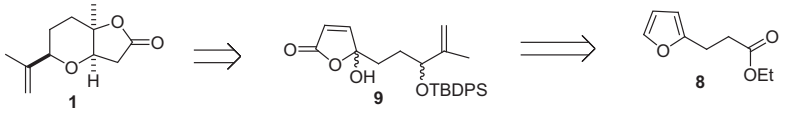
The bicyclic lactone (3a*R*,5*R*,7a*R*)-7a-methyl-5-(prop-1-en-2-yl)hexahydro-2*H*-furo[3,2-*b*]pyran-2-one (**1**) was isolated in racemic form due to the fact that its proposed biogenesis is not an enantioselective process. Clark et al.[2] published in 2007 the first total synthesis of **1**, completed its characterization and confirmed its relative stereochemistry.

As outlined in Scheme 1, we anticipated that lactone **1** could be synthesized using a methodology we developed in our laboratories and which we coined the furan approach to oxacyclic systems.[3]

Accordingly, 4-hydroxybutenolide (**9**) was prepared as shown in Scheme 2.

Commercially available ester **8** was easily transformed into aldehyde **11** in two steps (85% overall) or in one step using DIBAL-H (75% yield). Metalation of vinyl bromide **12** and addition to aldehyde **11** afforded alcohol **13** (70%) which was protected as *tert*-butyldiphenylsilylether, giving **14** in 99% yield. Furan **14** was subjected to singlet oxygen oxidation[3f] affording hydroxybutenolide **9** in 77% yield.

With hydroxybutenolide **9** in hand, our next goal was to introduce an angular methyl group, which was achieved by addition of



Scheme 1. Retrosynthetic analysis of lactone **1**.

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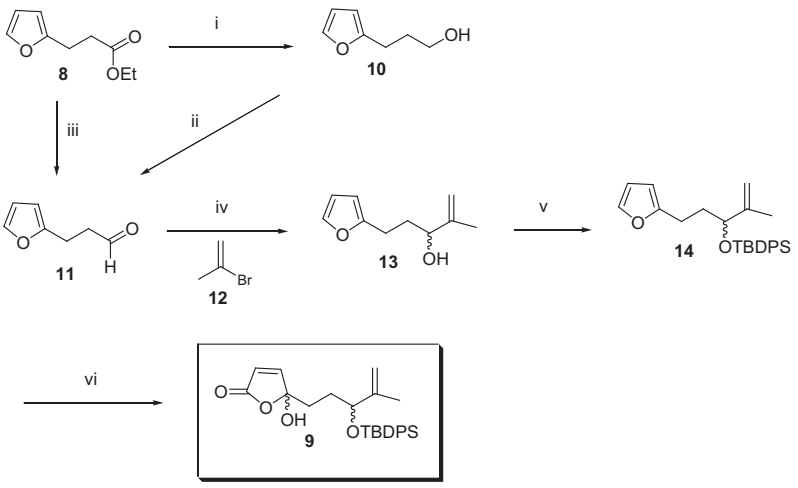
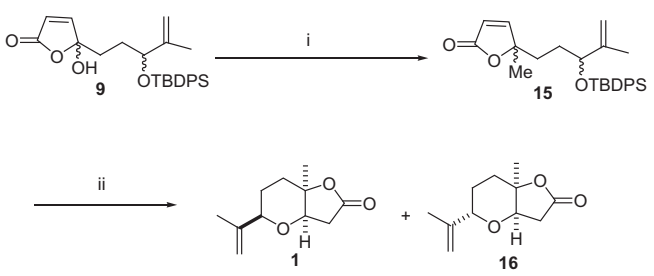


Scheme 2. Reagents and conditions: (i) $LiAlH_4$, Et_2O, rt (96%); (ii) TEMPO, BAIB, CH_2Cl_2 (89%); (iii) DIBAL-H, CH_2Cl_2, −78 °C (75%); (iv) **12**, ^tBuLi, THF, −78 °C (70%); (v) TBDPSCl, Imid, DMAP, DMF, rt (99%); (vi) O_2, MeOH, Rose Bengal, DIPEA, hν −78 °C (77%).



Scheme 3. Reagents and conditions: (i) $(i\text{-PrO})_3TiCl$, MeLi, −78 °C to rt (63%); (ii) TBAF, THF, rt [**1** (51%) and **16** (30%)].

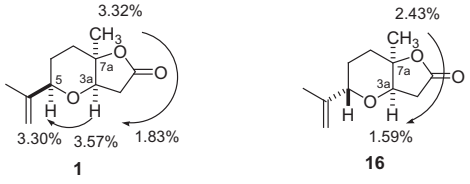


Figure 2. NOE correlations for lactones **1** and **16**.

$(i\text{-PrO})_3TiCH_3$ to **9**, following Miles's procedure.[4] In our case, however, the best yields for **15** were obtained when the organotitanium reagent was generated in situ (Scheme 3). Use of lithium or Grignard reagents afforded very poor yields of compound **15**. Reaction of γ-lactone **15** with TBAF at room temperature afforded target compound **1**[5] in 51% yield, together with 30% of diastereoisomeric lactone **16**.[6] The NMR data of lactone **1** were in close agreement with those reported by Clark et al.[2]

The relative stereochemistries of **1** and **16** were established by NOE experiments (Fig. 2).

Having synthesized lactone **1** and its diastereoisomer **16**, we decided to use our furan approach to oxacyclic systems,[3] for the synthesis of **19** and **20**, two new analogues of **1** (Scheme 4).

Accordingly, alcohol **13** was protected as *tert*-butyldimethylsilylether, giving **17** in 99% yield. Furan **17** was subjected to singlet oxygen oxidation[3i] affording methoxybutenolide **18** in 81% yield. Reaction of butenolide **18** with TBAF at room temperature afforded lactones **19**[7] and **20**[8] in 53% and 24% yields, respectively.

The relative stereochemistries of **19** and **20** were established by NOE experiments (Fig. 3).

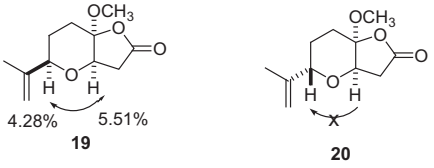
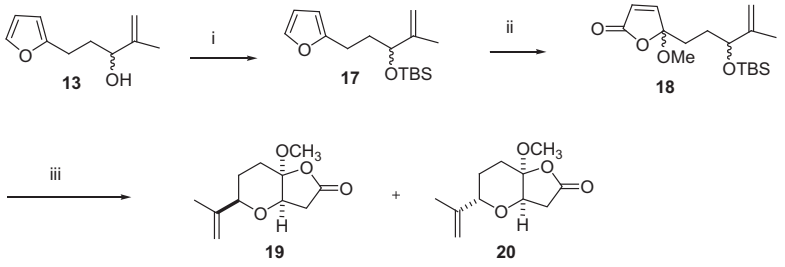


Figure 3. NOE correlations for lactones **19** and **20**.

In conclusion, using our furan approach we have synthesized bicyclic lactone (3a*R*,5*R*,7a*R*)-7a-methyl-5-(prop-1-en-2-yl)hexahydro-2*H*-furo[3,2-*b*]pyran-2-one (**1**) and its three new analogues **16**, **19,** and **20** which were fully characterized.



Scheme 4. Reagents and conditions: (i) TBSCl, imidazole, DMAP, DMF (99%); (ii) (a) O_2, hν, Rose Bengal, MeOH; (b) Ac_2O, Py, DMAP (81%); (iii) TBAF, THF, rt [**19** (53%) and **20** (24%)].

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.151.

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5. Compound **1**: colorless oil, R_f: 0.39 (50% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, δ): 4.96 (s, 1H, CH_2-1′), 4.85 (s, 1H, CH_2-1′), 4.08 (d, J = 4.3 Hz, 1H, CH-3a), 3.73 (d, J = 9.7 Hz, 1H, CH-5), 2.88 (dd, J = 17.5, 4.3 Hz, 1H, CH_2-3), 2.53 (d, J = 17.5 Hz, 1H, CH_2-3), 2.30 (m, 1H, CH_2-7), 1.72 (s, 3H, CH_3-2′), 1.65 (m, 2H, CH_2-6), 1.31 (s, 3H, CH_3-7a); ^{13}C NMR ($CDCl_3$, δ): 175.8 (CO), 144.8 (C-2′), 111.4 (CH2-1′), 81.6 (C-7a), 78.6 (CH-5), 77.5 (CH-3a), 38.2 (CH_2-3), 32.3 (CH_2-7), 25.2 (CH_3-7a), 25.1 (CH_2-6), 18.4 (CH_3-2′); MS (EI) [m/z, (%)]: 197 (100, $[M+1]^+$), 179 (12); HRMS (EI): 197.11722 calcd for $C_{11}H_{17}O_3$, found 197.11627.
6. Compound **16**: colorless oil, R_f: 0.42(50% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, δ): 4.96 (m, 2H, CH_2-1′), 4.19 (m, 1H, CH-5), 4.09 (dd, J = 5.9, 2.4 Hz, 1H, CH-3a), 2.80 (dd, J = 17.9, 5.9 Hz, 1H, CH_2-3), 2.60 (d, J = 17.9, 2.4 Hz, 1H, CH_2-3), 1.93 (m, 3H, CH_2-7, CH_2-6), 1.74 (s, 3H, CH_3-2′), 1.62 (m, 1H, CH_2-6), 1.34 (s, 3H, CH_3-7a); ^{13}C NMR ($CDCl_3$, δ): 175.1 (CO), 143.5 (C-2′), 111.4 (CH2-1′), 83.5 (C-7a), 73.7 (CH-5), 73.4 (CH-3a), 35.7 (CH_2-3), 29.4 (CH_2-7), 24.3 (CH_3-7a), 22.8 (CH_2-6), 19.5 (CH_3-2′); MS (EI) [m/z, (%)]: 197 (100, $[M+1]^+$), 179 (12); HRMS (EI): calcd for $C_{11}H_{17}O_3$: 197.11722; found 197.11744.
7. Compound **19**: colorless oil, R_f: 0.29 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, δ): 4.97 (s, 1H, CH_2-1′), 4.86 (s, 1H, CH_2-1′), 4.05 (d, J = 4.4 Hz, 1H, CH-3a), 3.79 (d, J = 10.8 Hz, 1H, CH-5), 3.37 (s, 3H, OCH_3), 2.94 (dd, J = 17.2, 4.4 Hz, 1H, CH_2-3), 2.58 (m, 1H, CH_2-7), 2.45 (d, J = 17.2 Hz, 1H, CH_2-3), 1.77 (m, 2H, CH_2-7, CH_2-6), 1.72 (s, 3H, CH_3-2′), 1.65 (m, 1H, CH_2-6); ^{13}C NMR ($CDCl_3$, δ): 176.1 (CO), 144.2 (C-2′), 111.7 (CH_2-1′), 104.4 (C-7a), 78.5 (CH-5), 76.9 (CH-3a), 49.6 (OCH_3), 37.1 (CH_2-3), 27.6 (CH_2-7), 25.9 (CH_2-6), 18.5 (CH_3-2′); MS (EI) [m/z, (%)]: 235 (100, $[M+Na]^+$), 213 (82, $[M+1]^+$), 201 (42); HRMS (EI): calcd for $C_{11}H_{17}O_4$: 213.11214; found 213.11177.
8. Compound **20**: colorless oil, R_f: 0.24 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, δ): 5.04 (s, 1H, CH_2-1′), 4.97 (s, 1H, CH_2-1′), 4.05 (m, 1H, CH-5), 3.79 (d, J = 5.1 Hz, 1H, CH-3a), 3.34 (s, 3H, OCH_3), 2.90 (dd, J = 17.5, 5.1 Hz, 1H, CH_2-3), 2.41 (d, J = 17.5 Hz, 1H, CH_2-3), 2.16 (m, 1H, CH_2-7), 2.00 (m, 1H, CH_2-7), 1.94 (m, 2H, CH_2-6), 1.75 (s, 3H, CH_3-2′); ^{13}C NMR ($CDCl_3$, δ): 175.9 (CO), 142.4 (C-2′), 112.6 (CH_2-1′), 106.4 (C-7a), 73.9 (CH-5), 71.6 (CH-3a), 49.5 (OCH_3), 36.3 (CH_2-3), 23.5 (CH_2-7), 21.9 (CH_2-6), 19.9 (CH_3-2′); MS (EI) [m/z, (%)]: 235 (77, $[M+Na]^+$), 213 (100, $[M+1]^+$); HRMS (EI): calcd for $C_{11}H_{17}O_4$: 213.11214; found 213.11194.