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Synthesis of a lactone natural product found in Greek tobacco

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Abstract—A short and stereoselective synthesis of (3*R**,4*R**,7*R**)-3,7-epoxy-4,8-dimethyl-8-nonen-4-olide, a natural product isolated from cured tobacco leaves, has been completed in six steps and 22% overall yield. A samarium(II) iodide mediated reductive cyclisation has been used to construct the functionalised tetrahydropyranol core and subsequent sequential stereoselective addition of methyllithium and lactonisation furnished the natural product.

The bicyclic lactone (3*R**,4*R**,7*R**)-3,7-epoxy-4,8-dimethyl-8-nonen-4-olide (**1**) was isolated by Wahlberg and co-workers from sun-cured leaves of Greek tobacco in 1993.[1] Several other lactone-containing metabolites were isolated from the same source, most notably α-levantenolide (**2**) and diterpenoid lactone **3**, which had been isolated from other sources previously (Fig. 1).[2]

We have recently initiated a research programme concerning the total synthesis of structurally complex marine diterpene natural products.[3] In the course of this work, we became interested in exploiting reductive coupling reactions to prepare highly functionalised tetrahydropyrans as early synthetic intermediates. In order to establish the synthetic viability of reductive coupling reactions to prepare the required intermediates, we chose to undertake a total synthesis of the simple lactonic natural product **1**.

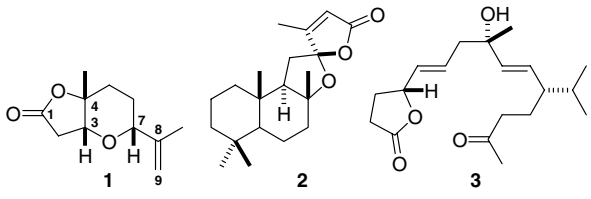
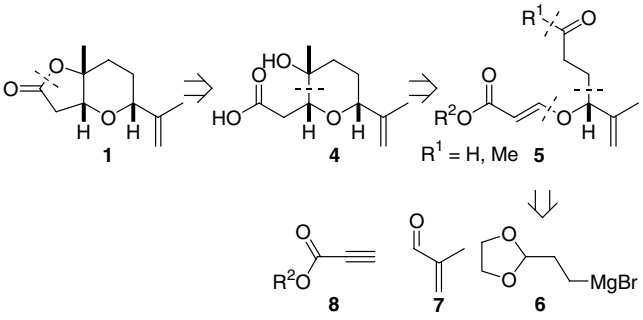


Figure 1. Lactone-containing natural products isolated from sun-cured Greek tobacco leaves.

Lactone **1** was isolated in racemic form and characterised solely on the basis of NMR data.[1] Lactone **1** is proposed to be the product of degradation of more complex terpenes, and it is believed that the oxidative degradation process is not enantioselective resulting in a racemic product.[1] To date, no synthesis of lactone **1** has been reported and herein we describe the first total synthesis of the compound and the confirmation of its relative stereochemistry.

Our retrosynthetic analysis of lactone **1** is shown in Scheme 1. Opening of the lactone reveals γ-hydroxy carboxylic acid **4**. Ring opening of the tetrahydropyranol via a retrosynthetic reductive cyclisation reaction leads to the acyclic enol ether **5** bearing an aldehyde ($R^1 = H$) or a methyl ketone ($R^1 = Me$) in the main carbon chain. Further disconnection suggests three simple materials: Grignard reagent **6**, methacrolein (**7**), and the simple propiolate ester **8**.



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

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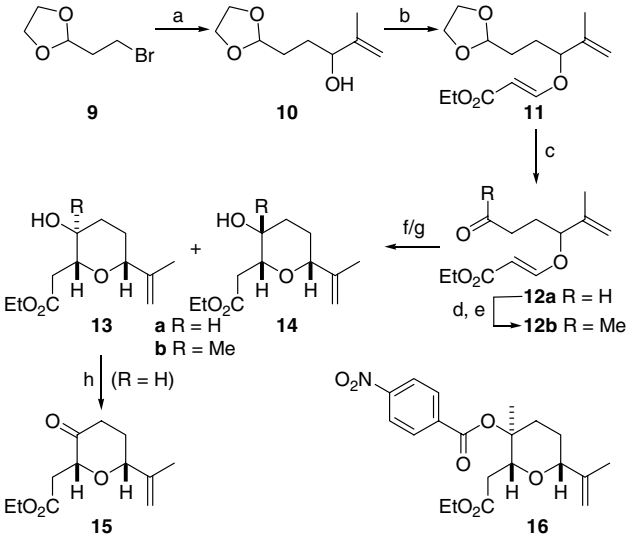
Nakata and co-workers have employed samarium(II) iodide mediated cyclisation reactions to prepare fused polycyclic ethers[4] but the synthesis of monocyclic ethers from completely acyclic precursors has been explored less frequently.[5] The reductive cyclisation precursor **12a**, required to implement the route implicit from the retrosynthetic analysis above, was synthesised in just three steps and in excellent yield (Scheme 2). Reaction of methacrolein with the Grignard reagent prepared from the commercially available bromide **9** delivered allylic alcohol **10** in excellent yield. Alkylation of the hydroxyl group with ethyl propiolate[6] produced vinylogous carbonate **11** and subsequent acetal deprotection afforded aldehyde **12a**, which was converted into methyl ketone **12b** by sequential addition of trimethylaluminium and Swern oxidation. Reductive cyclisation was accomplished by treatment of aldehyde **12a** and ketone **12b** with freshly prepared samarium(II) iodide in the presence of methanol.[5] The reductive cyclisation of aldehyde **12a** afforded tetrahydropyranol **13a**. The corresponding methyl ketone **12b** underwent cyclisation to give, in excellent yield, the tertiary alcohol **13b** possessing incorrect stereochemistry at the hydroxyl-bearing stereogenic centre.

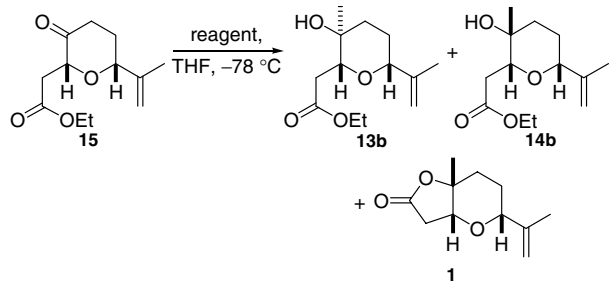
In contrast to the reactions of substrates **12a** and **12b** with samarium(II) iodide, treatment of substrate **12a** with tri-*n*-butyltin hydride following Lee's protocol[7] resulted in a complex mixture of products from which alcohol **13a** was isolated in relatively low yield.

Direct cyclisation of ketone **12b** had given alcohol **13b** possessing incorrect stereochemistry at the hydroxyl-bearing stereogenic centre and so stereoselective introduction of the methyl group after reductive cyclisation was explored. Swern oxidation of alcohol **13a** furnished dihydropyranone **15** and treatment of this ketone with a variety of organometallic reagents delivered the hydroxyesters **13b** and **14b** along with the required lactone **1** in varying amounts depending on the specific reagent employed (Scheme 3, Table 1). Treatment of ketone **15** with trimethylaluminium resulted in nearly exclusive formation of the tertiary alcohol **13b**, and the reaction with methylmagnesium iodide gave the same major product but in a decreased yield. The reaction of ketone **15** with methyllithium was complicated by competing addition to the ester functionality. However, it was apparent that the facial selectivity of the carbonyl addition reaction had been reversed in this case;[8] the major product isolated from the reaction was the required bicyclic lactone **1** corresponding to the natural product.

Stereochemical assignments were made after conversion of the tertiary alcohol **13b** into the crystalline *p*-nitrobenzoate **16**. Both ^{1}H NMR data (NOE) and single crystal X-ray crystallography confirmed that the relative stereochemistry of alcohol **13b** did not correspond to that which is found in the natural product (Fig. 2).[9]



Scheme 2. Synthesis of tetrahydropyranone **15**. Reagents and conditions: (a) Mg, THF, methacrolein, 0 °C→rt [84%]; (b) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt [88%]; (c) 5% HCl aq., THF, rt, [80%]; (d) $AlMe_3$, CH_2Cl_2, −78 °C→rt; (e) (i) $(COCl)_2$, Me_2SO, CH_2Cl_2, −78 °C, (ii) Et_3N, −78 °C→rt, [45% over two steps]; (f) SmI_2, MeOH, THF, rt, [R = H, 75% of **13a**; R = Me, 80% of **13b**]; (g) *n*-Bu_3SnH, AIBN, C_6H_6, reflux [R = H, 31% of **13a**]; (h) (i) $(COCl)_2$, Me_2SO, CH_2Cl_2, −78 °C, (ii) Et_3N, 78 °C→rt, [90%].



Scheme 3. Nucleophilic addition reactions of tetrahydropyranone **15**.

Table 1. Addition of methyl nucleophiles to tetrahydropyranone **15**

Reagent	Equivalents	Yields (%)			Σ Products (%)
		13b	**14b**	**1**	
$AlMe_3$	1	80			80
$AlMe_3$	3	65	10		75
MeMgI	1	53	11		64
MeLi	1			56	56

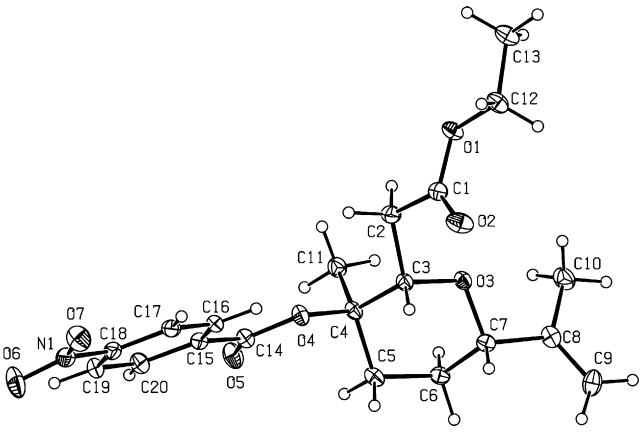


Figure 2. X-ray structure (ORTEP plot) of *p*-nitrobenzoyl ester **16** prepared from the tertiary alcohol **13b** (Scheme 2).

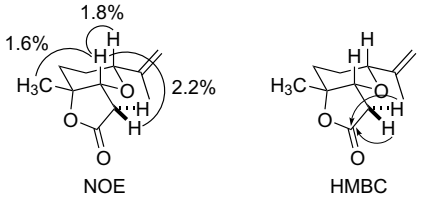


Figure 3. Confirmation of the relative stereochemistry of lactone **1** by NMR spectroscopy.

Extensive NMR investigations (HMQC, HMBC and NOE experiments) were performed on the lactone **1** and these confirmed that the connectivity and relative stereochemistry were correct (Fig. 3). The ^{1}H and ^{13}C NMR spectra for the synthetic lactone **1** were essentially identical to those reported for the isolated natural product except in one respect: the value of 174.9 ppm for the resonance in the ^{13}C NMR spectrum corresponding to the lactone carbonyl carbon differed considerably from the figure of 160.8 ppm reported by Wahlberg and coworkers.[1,10] Crucially, the lactone carbonyl signal in the ^{13}C NMR spectrum of the synthetic material was of very low intensity in comparison to the other signals in the spectrum. Only a small amount of lactone **1** was isolated from the sun-cured tobacco leaves and examination of the original ^{13}C NMR data for the compound revealed that the signal to noise ratio was such that the lactone carbonyl would not have been visible. We therefore believe that the low-intensity signal in the original ^{13}C NMR spectrum that was assigned as belonging to the lactone carbonyl group was probably an artifact, a conclusion which is supported by the fact that the chemical shift for the carbonyl resonance in the ^{13}C NMR of our compound is in very close agreement with literature data (~176 ppm) for very similar bicyclic lactones.[4,11]

In conclusion, an efficient six-step synthesis of lactone **1** has been accomplished starting from simple commercially available materials with an overall yield of 22%. A samarium(II) iodide mediated reductive cyclisation reaction has been used to construct the tetrahydropyran core. Subsequent diastereoselective addition of methyllithium to dihydropyranone **15** occurs with concomitant lactonisation to furnish the bicyclic lactone in reasonable yield. The synthesis has allowed us to correct the misassignment of the peak for the carbonyl group in the original ^{13}C NMR spectrum of the natural product.

Acknowledgements

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References and notes

1. Petterson, T.; Eklund, A.-M.; Wahlberg, I. *J. Agric. Food Chem.* **1993**, *41*, 2097–2103.
2. (a) Giles, J. A.; Schumacher, J. N. *Tetrahedron* **1961**, *14*, 246–251; (b) Wahlberg, I.; Arndt, R.; Nishida, T.; Enzell, C. R. *Acta Chem. Scand. B* **1986**, *40*, 123–134.
3. Clark, J. S.; Hayes, S. T.; Wilson, C.; Gobbi, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 437–440.
4. (a) Takahashi, S.; Kubota, A.; Nakata, T. *Org. Lett.* **2003**, *5*, 1353–1356; (b) Takahashi, S.; Ogawa, N.; Koshino, H.; Nakata, T. *Org. Lett.* **2005**, *7*, 2783–2786.
5. Matsuo, G.; Kadohama, H.; Nakata, T. *Chem. Lett.* **2002**, 148–149.
6. (a) Winterfeldt, E. *Chem. Ber.* **1964**, *97*, 1952–1958; (b) Winterfeldt, E.; Preuss, H. *Chem. Ber.* **1966**, *99*, 450–458.
7. Lee, E.; Tae, J. S.; Chong, Y. H.; Park, Y. C. *Tetrahedron Lett.* **1994**, *35*, 129–132.
8. The stereochemical outcome of the addition reaction of methyllithium to ketone **15** is difficult to rationalise, but presumably occurs as a result of non-chelation controlled addition. Reactions of methyllithium and methyl Grignard reagents with related oxo sugars are known to be highly dependent on factors such as the reaction temperature, solvent polarity and the presence of lithium or magnesium halide salts. Opposite facial selectivities during the addition of methyllithium and methylmagnesium halides have been observed in some cases. For a full discussion of these effects and a proposed rationalisation, see: Miljkovic, M.; Gligorijevic, M.; Satoh, T.; Miljkovic, D. *J. Org. Chem.* **1974**, *39*, 1379–1384.
9. Crystallographic data (excluding structure factors) for ester **16** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 631603. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, United Kingdom [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
10. Natural **1**—IR (CCl_4) 1780, 1560, 1245, 1200, 1130, 1025, 935 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (3H, s, H-11), 1.48–1.75 (3H, m, 1 × H-5, H-6), 1.73 (3H, m, H-10), 2.25–2.35 (1H, m, 1 × H-5) 2.54 (d, $J = 17.6$ Hz, H-2a), 2.89 (dd, $J = 4.3$, 17.6 Hz, H-2b), 3.73 (br d, $J = 9.3$ Hz, H-7), 4.09 (d, $J = 4.3$ Hz, H-3), 4.86 (1H, m, H-9a), 4.97 (1H, m, H-9b); ^{13}C NMR (C_6D_6) δ 18.5 (C-10), 24.9/25.2 (C-6/C-11), 32.3 (C-5), 38.0 (C-2), 77.6/78.5 (C-3/C-7), 80.2 (C-4), 111.1 (C-9), 145.2 (C-8), 160.8 (C-1); HRMS (EI): calcd for $C_{11}H_{16}O_3$ (M^+): 196.1099. Found: 196.1080.
Synthetic **1**—IR ($CHCl_3$) 2977, 2934, 2850, 1780, 1742, 1654, 909 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (3H, s, H-11), 1.56–1.77 (3H, m, 1 × H-5, H-6), 1.73 (3H, br s, H-10), 2.28–2.34 (1H, m, 1 × H-5), 2.54 (1H, dd, $J = 0.7$, 17.5 Hz, H-2a), 2.89 (1H, dd, $J = 4.3$, 17.5 Hz, H-2b), 3.71–3.75 (1H, m, H-7), 4.09 (1H, d, $J = 4.3$ Hz, H-3), 4.84–4.86 (1H, m, H-9a), 4.96–4.97 (1H, m, H-9b); ^{13}C NMR (100 MHz, C_6D_6) δ 19.1 (C-10), 25.5/25.8 (C-6/C-11), 32.9 (C-5), 38.6 (C-2), 78.2/79.1 (C-3/C-7), 80.8 (C-4), 111.7 (C-9), 145.8 (C-8), 174.9 (C-1); HRMS (EI+): calcd for $C_{11}H_{16}O_3Na$ ($[M+Na]^+$): 219.0997. Found: 219.0979.
11. (a) Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc. Perkin Trans. 1* **1989**, 507–518; (b) Evans, P. A.; Raina, S.; Ahsan, K. *Chem. Commun.* **2001**, 2504–2505.