First total synthesis of (±)-longianone

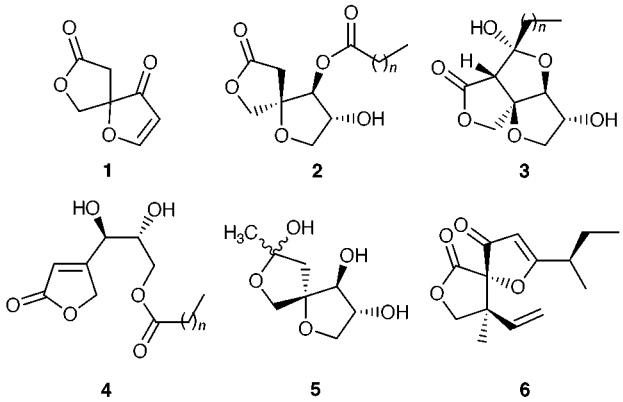
Patrick G. Steel*

Department of Chemistry, University of Durham, Science Laboratories, South Road, Durham, UK DH1 3LE. E-mail: p.g.steel@durham.ac.uk

Received (in Cambridge, UK) 9th September 1999, Accepted 1st October 1999

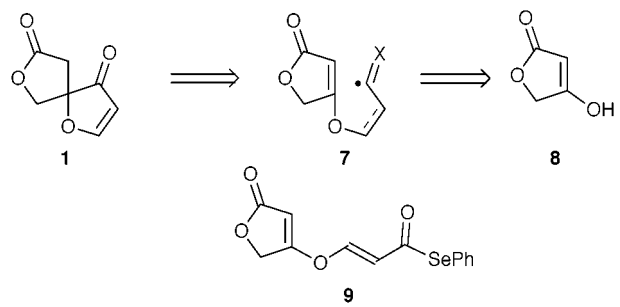
The first total synthesis of (±)-longianone, isolated from *Xyloria longiana*, is reported starting from tetronic acid.

Longianone **1**, recently isolated from the fungal strain *Xyloria longiana* found in various tropical and temperate locations



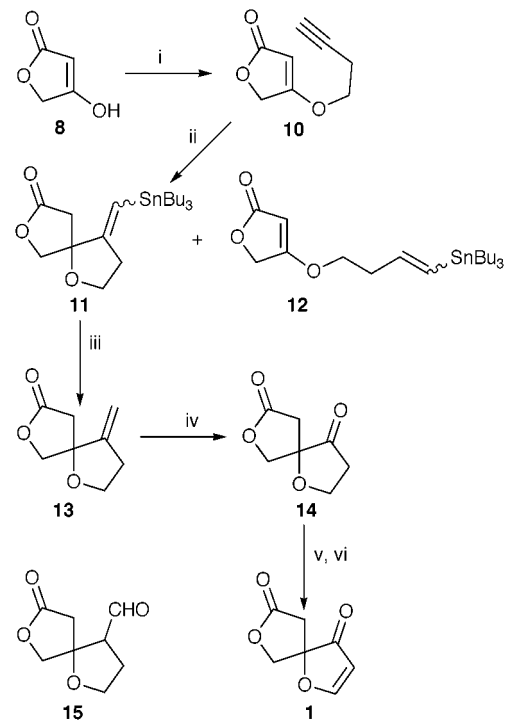
throughout the world, possesses an unusual 1,7-dioxaspiro-[4,4]non-2-ene-4,8-dione skeleton.[1] As such it is the simplest member of a family of structurally related but biosynthetically different natural products containing this spirobicyclic core.[2] These include the bacterial metabolites Secosyrins **2** and the related syringolides **3** and syributins **4** isolated from *Pseudomonas syringae*[3,4] as well as sphydrofuran **5** obtained, much earlier, from a strain of Actinomycetes. Reflecting this unusual skeleton there has been considerable interest in the synthesis of these natural products, resulting in a number of total syntheses.[5–9] A synthesis of a structurally similar natural product, hyperolactone A **6**, which possess an alternative 1,7-dioxaspiro-[4.4]non-2-enedione skeleton, has also been recently communicated.[10] Here we report a highly concise synthesis of (±)-longianone which, in addition to being the first synthesis of this natural product, has potential to provide advanced intermediates for the synthesis of these other natural products.

We envisaged a synthetic route in which the crucial spirocentre could be established by means of an intramolecular radical cyclisation of a suitably functionalised tetronate derivative (Scheme 1).[11] In the ideal situation, the use of an α,β-unsaturated acyl radical precursor **7** (X = O), as pioneered by Pattenden, would generate Longianone in a single operation.[12] Unfortunately, generation of the required acyl selenide was complicated by the instability of several of the proposed intermediates and we turned to a more stepwise route involving cyclisation of a vinyl radical species **7** (X = CHR).



Scheme 1

Condensation of but-3-ynol with tetronic acid **8** was achieved by heating under reflux in a Dean–Stark apparatus using a catalytic amount of TsOH as catalyst (Scheme 2).[13]† Slow addition of Bu_3SnH to a refluxing solution of this vinylogous ester **10** in benzene containing AIBN (10 mol%) afforded a separable 5 : 1 mixture of the desired spirocycle **11** accompanied by the vinyl stannane **12** generated by simple alkyl hydrostannylation.[14] Initial attempts to convert the vinyl stannane to the desired ketone by ozonolysis in CH_2Cl_2 were complicated by preferential formation of the rather unstable aldehyde **15**. This reaction presumably proceeds *via* oxidative cleavage of the carbon–tin bond to give the enol and subsequent tautomerisation. Related conversions of alkyl–tin bonds have been previously reported.[15] This minor difficulty could simply be circumvented by protiodestannylation after separation of the isomeric vinyl stannanes.[16] Subsequent ozonolysis of the resulting alkene **13**, with a reductive work up using dimethyl sulfide, proceeded smoothly to afford the desired bicyclic ketone **14** in good overall yield.



Scheme 2 *Reagents and conditions*: i, but-3-ynol, TsOH, PhH, 18 h, 76%; ii, Bu_3SnH, AlBN (10 mol%), PhH, reflux, 5 h, 71% (**11**:**12** = 5:1); iii, 1 M HCl, CH_2Cl_2, room temp. 1 h, 100%; iv, O_3, CH_2Cl_2, −78 °C, then DMS, −78 °C to room temp., 2 h, 79%; v, PhSeCl, THF, H_2O (cat), 5 days, 38% (+15% **14**); vi, O_3, CH_2Cl_2, −78 °C, then purge N_2 and warm to room temp. 12 h, 44%.

To complete the synthesis we sought a method for the introduction of the α,β-unsaturation which requires selective reaction at the ketone carbonyl group. Initial attempts to generate the silyl enol ether using standard combinations such as LDA/TMSCl or TMSOTf/Et_3N proved unsuccessful. Attempts to directly introduce an α-seleno group through direct reaction of the enolate with PhSeX (X = Cl, SePh) led principally to decomposition of the starting material, presumably *via* β-elimination of the β-alkoxy ketone unit. This conversion was ultimately achieved following an earlier precedent reported by Sharpless involving stirring the ketone and phenylselenenyl chloride in THF containing a trace amount of water.[17] The yellow selenoketone was obtained in moderate yield as a 1 : 1 mixture of diastereoisomers. Attempted oxidation and selenoxide elimination using aqueous oxidants failed to yield any isolable products, presumably due to Michael addition and subsequent ring opening of the lactol ring under the reaction conditions. In the course of his isolation studies Edwards has noted the propensity for the natural product to form the corresponding methanol adduct.[1] These problems could be circumvented by carrying out the oxidation, using ozone as the oxidant, in anhydrous CH_2Cl_2 at −78 °C, followed by warming to room temperature overnight to achieve the elimination. Following simple chromatography, racemic longianone **1**, identical in all respects (TLC, mp, NMR, IR and *m/z*) with an authentic sample,[2] was isolated in 44% yield. All attempts to enhance this process and avoid isolation of the selenide through the use of the corresponding benzeneseleninic anhydride afforded only a trace amount of the desired enone accompanied by significant decomposition.[18]

In conclusion, we report a concise synthesis of (±)-longianone that can also provide access to the structurally related secosyrins and syringolides. Studies in this direction and those towards an enantioselective synthesis are in progress and will be reported in due course.

We thank Professor David O'Hagan for bring this structure to our attention and for providing an authentic sample of longianone, the EPSRC Mass Spectrometry Service at Swansea for accurate mass determinations, Dr A. M. Kenwright and Mr I. H. McKeag for assistance with NMR experiments, and Dr M. Jones for mass spectra.

Notes and references

† All new compounds have satisfactory spectral and analytical data. Yields refer to pure isolated products.

1 R. L. Edwards, D. J. Maitland, C. L. Oliver, M. S. Pacey, L. Shields and A. J. S. Whalley, *J. Chem. Soc., Perkin Trans. 1*, 1999, 715.
2 Although structurally similar it appears that the biosyntheses of these natural products are different. Whereas these other natural products are suggested to be produced through the condensation of a triketide with a pentose unit, longianone is derived from 6-methylsalicyclic acid. See R. J. M. Gross, J. Fuscher and D. O'Hagan, *Chem. Commun.*, 1999, 2255.
3 S. L. Midland, N. T. Keen, J. J. Sims, M. M. Midland, M. M. Stayton, V. Burton, M. J. Smith, E. P. Mazzola, K. J. Graham and J. Clardy, *J. Org. Chem.*, 1993, **58**, 2940.
4 S. L. Midland, N. T. Keen and J. J. Sims, *J. Org. Chem.*, 1995, **60**, 1118.
5 P. Yu, Q. G. Wang, T. Mak and H. Wong, *Tetrahedron*, 1998, **54**, 1783.
6 P. Yu, Y. Yang, Z. Y. Zhang, T. Mak and H. Wong, *J. Org. Chem.*, 1997, **62**, 6359.
7 C. Mukai, S. M. Moharram, S. Azukizawa and M. Hanaoka, *J. Org. Chem.*, 1997, **62**, 8095.
8 M. Carda, E. Castillo, S. Rodriguez, E. Falomir and J. A. Marco, *Tetrahedron Lett.*, 1998, **39**, 8895.
9 H. Yoda, M. Kawauchi, K. Takabe and K. Hosoya, *Heterocycles*, 1997, **45**, 1895 and 1906 and references therein.
10 D. Ichinari, T. Ueki, K. Yoshihara and T. Kinoshita, *Chem. Commun.*, 1997, 1743.
11 Similar radical cyclisations to generate spirocyclic ethers are precedented. See for example, D. S. Middleton, N. S. Simpkins, M. J. Begley and N. K. Terrett, *Tetrahedron*, 1990, **46**, 545.
12 C. J. Hayes and G. Pattenden, *Tetrahedron Lett.*, 1996, **37**, 271.
13 H. Hoffmann, B. Schmidt and S. Wolff, *Tetrahedron*, 1989, **45**, 6113.
14 G. Stork and R. Mook, *J. Am. Chem. Soc.*, 1987, **109**, 2829.
15 R. J. Linderman and M. Jaber, *Tetrahedron Lett.*, 1994, **35**, 5993.
16 The workup of this protiodestannylation is much simplified if the the tin residues are removed by stirring the crude reaction mixture with KF: J. E. Leibner and J. Jacobus, *J. Org. Chem.*, 1979, **44**, 449.
17 K. B. Sharpless, R. F. Lauer and A. Y. Teranishi, *J. Am. Chem. Soc.*, 1973, **95**, 6137.
18 D. H. R. Barton, D. J. Lester and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2209.

Communication 9/07313B