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First synthesis of the antifungal and antibacterial agent cladobotryal

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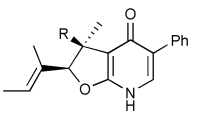
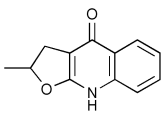
The antifungal and antibacterial agent cladobotryal (1) was synthesized by a convergent route from lactone 5 and aldehyde 12, a key step in the elaboration of the pyridinone ring being conversion of a *t*-BuOC(O) group on nitrogen into an *i*-$Pr_3SiOC(O)$ group.

Cladobotryal (**1**),[1,2] which is a metabolite of the fungus *Caldobotrium varium* Nees:Fries (CBS 331.95), has potentially useful biological properties; it inhibits the growth of a number of plant pathogens belonging to Oomyceta[1] and it also shows moderate activity against some drug-resistant bacteria[2] such as methicillin-resistant *Staphylococcus aureus*. A number of related dihydrofuro[2,3-*b*]pyridinones (*e.g.* **2**) have also been isolated recently[2] from the same organism (*C. varium*, CL 12284), but the parent heterocyclic system is a rare structural type and examination of the Beilstein database shows no other dihydrofuro[2,3-*b*]pyridinones besides the natural products recently reported,[1,2] and compounds that are benzo-fused (*e.g.* **3**[3]). Several compounds, such as **4**,[2] with the isomeric, and better-known,[4] dihydrofuro[3,2-*c*]pyridinone structure have also been isolated from *C. varium* (CL 12284).



1 R = CHO
2 R = CH_2OH



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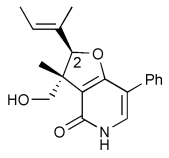

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Synthetic routes to the heterocyclic system represented by **1** have not previously been reported, and we now describe the total synthesis of racemic **1** as well as its naturally-occurring congener **2**.

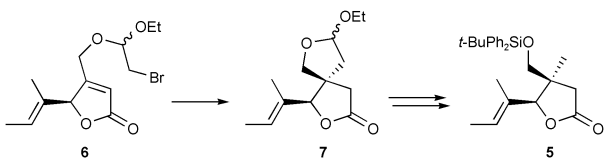
Our route is convergent and is based on two subunits—a γ-lactone, destined to provide the dihydrofuran segment of the natural product, and an aldehyde carrying both the phenyl substituent and a suitably protected nitrogen β to the carbonyl group. In the event, several such aldehydes had to be tried in order to identify a satisfactory one.

In exploratory work,[5] we had prepared the C(2) epimer of **4**, using the substituted lactone **5** (see Scheme 1), and the same lactone served for the present synthesis. As described earlier,[5] it was made by radical cyclization of **6**, and the product **7** was elaborated into **5**. Our radical cyclization is stereoselective, the radical approaching the double bond from the face opposite to the adjacent substituent.

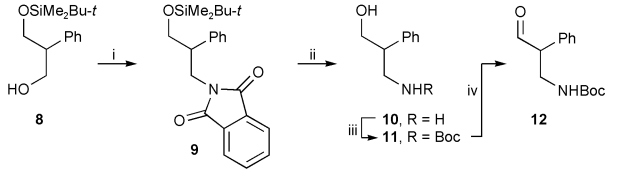
The known[6] aldehyde **12** (Scheme 2) served as the other subunit, which we made by the sequence **10** → **11** → **12**, along lines given[6] in the literature, but we found it convenient to prepare amino alcohol **10** by a different route from those previously reported.[6,7] The readily available alcohol **8**[8] was converted (91%) into phthalimide **9** under Mitsunobu conditions. Treatment with $N_2H_4{\cdot}H_2O$ in EtOH and then with 5% hydrochloric acid produced amino alcohol **10**[6,7] (93%), which was easily converted into **11**[6] (96%) by reaction with Boc_2O. Dess–Martin oxidation (93%) then afforded the required aldehyde **12**.

Deprotonation of lactone **5** (3 equiv. LDA, THF) and addition of a mixture of aldehyde **12** and HMPA (1.5 equiv.) in THF gave the expected condensation product **13** (Scheme 3) as a mixture of isomers in 71% yield [100% after correction for recovered starting lactone (29%)]. DIBAL-H reduction generated the corresponding lactols (**13** → **14**, *ca.* 100%), and these could be cyclized in the required manner (**14** → **15**) by the action of pyridinium *p*-toluenesulfonate. The product was isolated as two fractions, the chromatographically faster-moving fraction (**15f**) being obtained in 54% yield, and the slower-moving fraction (**15s**) in 27% yield. Each fraction was a single isomer of undetermined stereochemistry. Oxidation to the corresponding ketones was achieved with the Dess–Martin reagent (96% for **15f**; 85% for **15s**). Each ketone was a single isomer differing in stereochemistry at C(5).

At this stage, introduction of the first of the required double bonds was readily achieved (both **16f** and **16s** → **17**) by phenylselenation [$(Me_3Si)_2NK$, THF, PhSeCl] and selenoxide elimination (H_2O_2, pyridine, CH_2Cl_2). However, the product **17** resisted further desaturation. Phenylselenation of **17** at C(3a) proved impossible [LDA or $(Me_3Si)_2NK$, followed by PhSeCl], probably because severe steric crowding blocks access to C(3a), and dehydrogenation under a variety of conditions[9] was also unsuccessful. Furthermore, attempts to remove the Boc group using CF_3CO_2H or bromocatecholborane caused decomposition. We were forced, therefore, to explore several modified versions of the above route. During these studies, we attempted to protect the hydroxyl of **13** as its triisopropylsilyl ether (*i*-$Pr_3SiOSO_2CF_3$, 2,6-lutidine), but found instead that the Boc group was converted into a COOSiPr-*i*$_3$ group before the hydroxyl itself was silylated. The related conversion of *N*-Boc into *N*-$COOSiMe_2Bu$-*t* has in fact been observed before, with *t*-$BuMe_2SiOSO_2CF_3$,[10] and our own experimental observation prompted us to treat **16f** and **16s** with *i*-$Pr_3SiOSO_2CF_3$. In the event this was the key reaction that removed the earlier barriers preventing introduction of the C(3a)–C(7a) double bond. Both **16f** and **16s** were converted quantitatively into the silyl carbamates **19f** and **19s**, respectively, and both carbamates could be desaturated at C(5)–C(6) by phenylselenation and selenoxide elimination, under the conditions we had used to



Scheme 1



Scheme 2 (i) Phthalimide, DEAD, Ph_3P, THF, 91%; (ii) $N_2H_4{\cdot}H_2O$, EtOH, then HCl, 93%; (iii) Boc_2O, $NaHCO_3$, 4 : 1 acetone–water, 96%; (iv) Dess–Martin periodinane, CH_2Cl_2, 93%.

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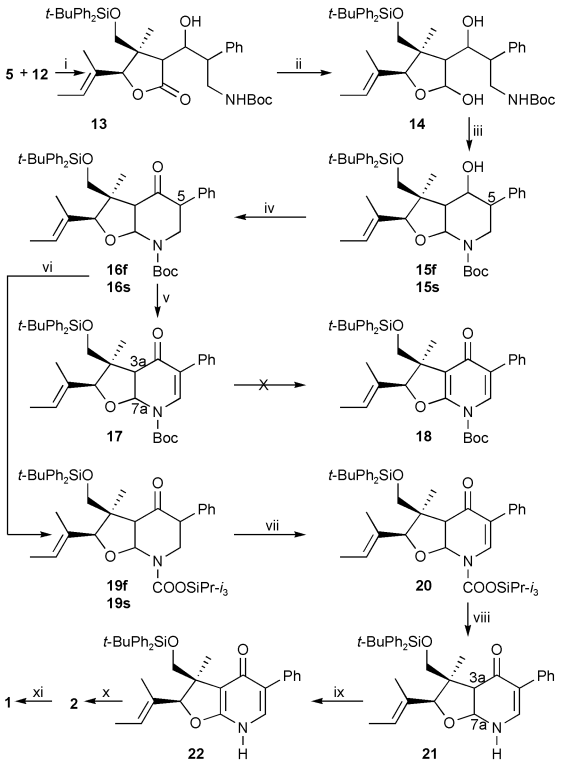
make **17**. The crude products (**20**) from each series (**19f** or **19s**) were identical, and the nitrogen protecting group could be then be removed under non-acidic conditions (Bu_4NF, THF) to afford **21** (53% overall from **19f**, 49% overall from **19s**). Compound **21**, which was stable to silica gel flash chromatography, now provided an opportunity to generate an imine that would be expected to tautomerize spontaneously to **22**. Several methods are available for converting an amine into an imine,[11] but the classical procedure[11b] of *N*-chlorination (*t*-BuOCl)[12] and base treatment (DBU) proved satisfactory (71%), and took the route as far as the pyridinone **22**. From this point, cladobotryal (**1**) was easily reached *via* the natural product **2** by desilylation (Bu_4NF, THF, 97%) and Dess–Martin oxidation (**2** → **1**, 97%). The ^1H and ^{13}C NMR spectra of our racemic materials matched those reported for the natural products.



Scheme 3 (i) 3 equiv. LDA, THF, −78 °C, then room temp.; then add **12** in THF–HMPA at −78 °C, 71%, recovery of **5** = 29%; (ii) DIBAL-H, CH_2Cl_2, −78 °C, *ca.* 100% ; (iii) TsOH·pyridine, THF, 45 °C, 54% of **15f**, 27% of **15s**; (iv) Dess–Martin periodinane, CH_2Cl_2, 96% for **15f**, 85% for **15s**; (v) (a) $(Me_3Si)_2NK$, THF, 0 °C, then PhSeCl, −78 °C, (b) H_2O_2, pyridine, CH_2Cl_2, 74% overall for **16f**, 24% (not optimized) for **16s**; (vi) *i*-$Pr_3SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, reflux, 100% for both **16f** and **16s**; (vii) (a) $(Me_3Si)_2NK$, THF, −78 °C, PhSeCl, −78 °C, (b) H_2O_2, pyridine, CH_2Cl_2; (viii) Bu_4NF, THF, 0 °C, 53% overall for **16f**, 49% for **16s**; (ix) (a) *t*-BuOCl, CH_2Cl_2, −78 °C, (b) DBU, PhMe, 71%; (x) Bu_4NF, THF, 97%; (xi) Dess–Martin, CH_2Cl_2, 97%.

All new compounds except for **14** and **20**, which were used crude, were fully characterized by spectroscopic methods, including high resolution mass spectrometry.

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Notes and references

1 J. Breinholt, H. C. Jensen, A. Kjær, C. E. Olsen, B. R. Rassing, C. N. Rosendahl and I. Søtofte, *Acta Chem. Scand.*, 1998, **52**, 631–634.

2 S. Sakemi, J. Bordner, D. L. DeCosta, K. A. Dekker, H. Hirai, T. Inagaki, Y.-J. Kim, N. Kojima, J. C. Sims, Y. Sugie, A. Sugiura, J. A. Sutcliffe, K. Tachikawa, S. J. Truesdell, J. W. Wong, N. Yoshikawa and Y. Kojima, *J. Antibiot.*, 2002, **55**, 6–18.

3 (*a*) T. Kappe, P. F. Fritz and E. Ziegler, *Chem. Ber.*, 1973, **106**, 1927–1942; (*b*) see also S. Goodwin, J. N. Shoolery and L. F. Johnson, *J. Am. Chem. Soc.*, 1959, **81**, 3065–3069; (*c*) S. Goodwin, A. F. Smith, A. A. Velasquez and E. C. Horning, *J. Am. Chem. Soc.*, 1959, **81**, 6209–6213.

4 *E.g.* 3,5-Dihydro-2*H*-furo[3,2-*c*]pyridin-4-one (the parent system): B. A. J. Clark, M. S. El-Bakoush and J. Parrick, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1531–1536.

5 D. L. J. Clive and X. Huang, *Tetrahedron*, 2002, **58**, 10243–10250.

6 S. Campestrini, F. Di Furia and G. Modena, *J. Org. Chem.*, 1990, **55**, 3658–3660.

7 (*a*) E. Testa, L. Fontanella, G. F. Cristiani and L. Mariani, *Liebigs Ann.*, 1961, **639**, 166–180; (*b*) H. V. Secor and E. B. Sanders, *J. Org. Chem.*, 1978, **43**, 2539–2541; (*c*) W. J. Gensler and S. K. Dheer, *J. Org. Chem.*, 1981, **46**, 4051–4057.

8 (*a*) Y. Yuasa, N. Fujimaki, T. Yokomatsu, J. Ando and S. Shibuya, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3577–3584; (*b*) G. Guanti, E. Narisano, T. Podgorski, S. Thea and A. Williams, *Tetrahedron*, 1990, **46**, 7081–7090.

9 DDQ, PhH, reflux; Pd/C, xylene, reflux or PhOPh at 220 °C; MnO_2, xylene, reflux; DDQ, CF_3CO_2H, PhMe, 80 °C; $(NH_4)_2Ce(NO_3)_6$, water–acetone or MeCN; $(NH_4)_2Ce(NO_3)_6$, 2,6-pyridinedicarboxylic acid *N*-oxide, water–MeCN; Ph_3CPF_6, CH_2Cl_2; DDQ, $Me_3SiOSO_2CF_3$, PhH; $[PhSe(O)]_2O$, PhMe, reflux.

10 (*a*) M. Sakaitani and Y. Ohfune, *J. Org. Chem.*, 1990, **55**, 870–876; (*b*) P. A. Grieco and A. Perez-Medrano, *Tetrahedron Lett.*, 1988, **29**, 4225–4228; (*c*) F. Busqué, P. de March, M. Figueredo, J. Font, T. Gallagher and S. Milán, *Tetrahedron: Asymmetry*, 2002, **13**, 437–445; (*d*) *Cf.* A. D. Brosius, L. E. Overman and L. Schwink, *J. Am. Chem. Soc.*, 1999, **121**, 700–709.

11 (*a*) *Cf.* S. Dayagi and Y. Degani, in *The Chemistry of the Carbon–Nitrogen Double Bond*, ed. S. Patai, Interscience, New York, 1970, pp. 117–120; (*b*) W. E. Bachmann, M. P. Cava and A. S. Dreiding, *J. Am. Chem. Soc.*, 1954, **76**, 5554–5555; (*c*) M. P. Cava and B. R. Vogt, *Tetrahedron Lett.*, 1964, 2813–2816; (*d*) J. J. Cornejo, K. D. Larson and G. D. Mendenhall, *J. Org. Chem.*, 1985, **50**, 5382–5383 and references therein (*e*) Reviews: R. V. Hoffman, R. A. Bartsch and B. R. Cho, *Acc. Chem. Res.*, 1989, **22**, 211–217; (*f*) S. Pawlenko, in *Methoden der Organischen Chemie (Houben-Weyl)*, Georg Thieme Verlag, Stuttgart, 1990, vol. E14b, pp. 226–233.

12 (*a*) M. J. Mintz and C. Walling, *Org. Synth., Coll. Vol. V*, 1973, 184–187; (*b*) **Hazard warning**: *Org. Synth., Coll. Vol. V*, 1973, pp. 183–184.