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Synthesis of Cladobotryal, CJ16,169, and CJ16,170

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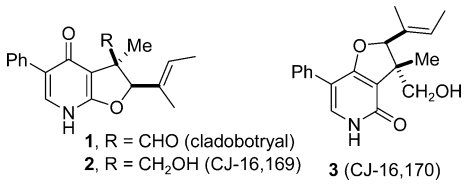
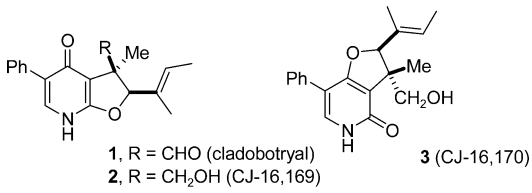
ABSTRACT



Condensation of hydroxypyridone 7 with ethyl pyruvate and *p*-chlorothiophenol, reduction, and cyclization afforded 77% of lactone 6. Protection of the pyridone, acylation of the enolate with tigloyl chloride, and deprotection provided keto lactone 22. Reduction and dehydrative cyclization completed short and efficient syntheses of 2 and 3.

The antifungal furopyridone cladobotryal (**1**) was first isolated from the mycoparasitic fungus *Cladobotrium varium* Nees:Fries (CBS 331.95).[1] More recently, cladobotryal (**1**) was isolated with seven related furopyridones from *Cladobotrium varium* CL12284 and was shown to possess moderate activity against various Gram-positive bacteria, including some drug resistant strains.[2] The seven congeners include the analogous primary alcohol CJ16,169 (**2**) and CJ16,170 (**3**), which differs from **2** in both the relative stereochemistry of the two side chains and the formation of the dihydrofuran with the 4- rather than 2-pyridone oxygen.

Clive and Hang recently reported stereospecific, but lengthy, syntheses of *epi*-CJ16,170 (**26**)[3] and cladobotryal (**1**)[4] by routes in which the pyridone ring was constructed at the end of the synthesis. Our retrosynthetic analysis suggested that alcohols **2** and **3** should be available by dehydration of diol **4**, which should be available by reduction of lactone **5** (see Scheme 1). Lactone **5** should be obtainable from an aldol reaction of **6** with tiglaldehyde. Finally, we thought that lactone **6** should be accessible from 5-phenyl-4-hydroxy-2-pyridone (**7**). Although it was not clear how this last transformation would be accomplished, this approach was attractive because **7** can be prepared in two steps in 74% overall yield by condensation of phenylacetonitrile and malonyl chloride.[5]



We have previously used pyridone **7** to construct leporins A and B.[5,6] Knoevenagel condensation of **7** with dienal **8** afforded quinone methide **9**, which underwent an intramolecular inverse electron demand Diels−Alder reaction to give 35% of tricycle **10** (see Scheme 2). Oxidation and methylation afforded leporins B (**11**) and A (**12**). We have used

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

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

(3) Clive, D. L. J.; Huang, X. *Tetrahedron* **2002**, *58*, 10243−10250.

(4) (a) Clive, D. L. J.; Huang, X. *Chem. Commun.* **2003**, 2062−2063. (b) Clive, D. L. J.; Huang, X. *J. Org. Chem.* **2004**, *69*, 1872−1880.

(5) Snider, B. B.; Lu, Q. *J. Org. Chem.* **1996**, *61*, 2839−2844.

(6) Synthesis of leporin B was completed in 1996,[5] although the compound was not isolated as a natural product and named until 2003: Zhang, C.; Jin, L.; Mondie, B.; Mitchell, S. S.; Castelhano, A. L.; Cai, W.; Bergenhem, N. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1433−1435.

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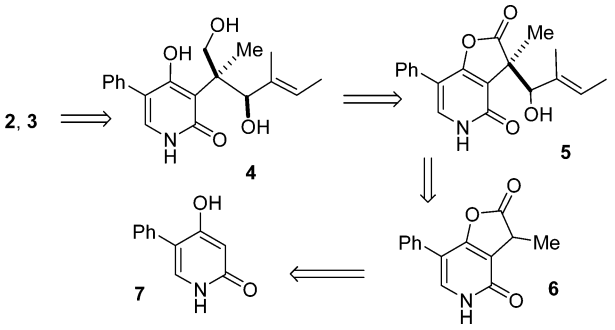
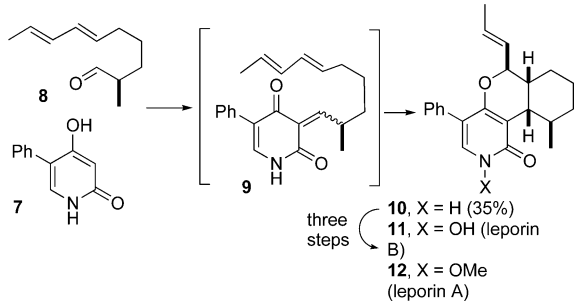
Scheme 1. Retrosynthetic Analysis of Cladobotryal



similar strategies for the synthesis of pyridone alkaloids pyridoxatin and fusaricide.[7] Although **7** is a suitable starting material for both the leporins and **1**−**3**, the presence of the quaternary center in **1**−**3** required the use of the very different strategy shown in Scheme 1.

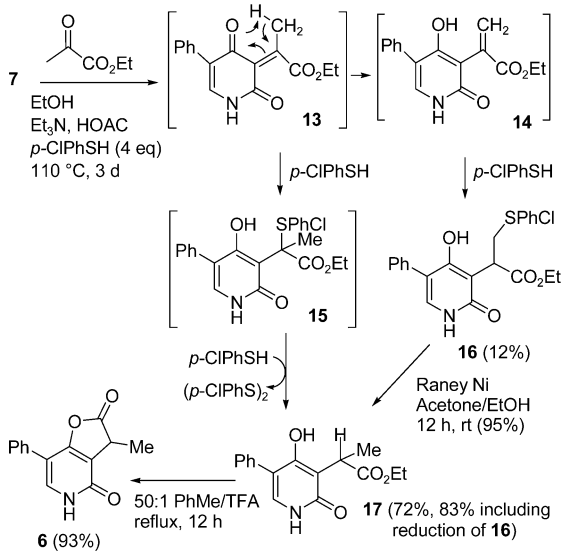
Our experience with Knoevenagel condensations of **7** suggested that the three carbons needed for lactone **6** could be introduced by reaction of **7** with ethyl pyruvate, which should give quinone methide **13**, which should undergo a 1,5-hydride shift to give acrylate **14**. Neither **13** nor **14** will be stable to the Knoevenagel condensation conditions and must be trapped by the addition of a nucleophile, such as a thiol, which is known to trap quinone methides formed from condensations with aldehydes.[8]

Scheme 2. Synthesis of Leporin A and B



Condensation of **7** with ethyl pyruvate (4 equiv) and *p*-ClPhSH in EtOH containing Et_3N and HOAc in a sealed tube in a 110 °C oil bath for 3 days afforded 72% of propionate **17** and 12% of 3-arylthiopropionate **16** (see Scheme 3). The latter is formed by conjugate addition of *p*-ClPhSH to acrylate **14**. Propionate **17** is probably formed by addition of *p*-ClPhSH to quinone methide **13** to give 2-arylthiopropionate **15**, which was not observed as a reaction product. Presumably, reduction of **15** with excess *p*-chlorothiophenol led to major product **17**, and $(p\text{-ClPhS})_2$, which was isolated

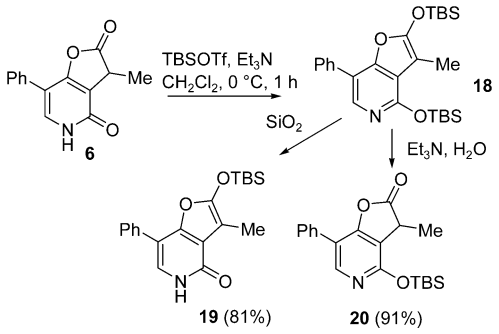
Scheme 3. Synthesis of Lactone **6**



from the reaction. Reduction of **16** with Raney Ni[8] in acetone/EtOH for 12 h at 25 °C provided 95% of **17**, which was thus obtained in 83% overall yield from pyridone **7**.[9,10] Lactonization to give **6** was achieved in 93% by heating **17** in 50:1 toluene/TFA at reflux for 12 h.[11]

Protection of the pyridone nitrogen of **6** was required before the formation of the lactone enolate and addition of the five-carbon side chain. Reaction of **6** with excess TBSOTf and Et_3N in CH_2Cl_2 afforded the unstable bis(silyloxy) furopyridine **18** (see Scheme 4). Chromatography

Scheme 4. Protection of Lactone **6**



on silica gel cleaved the pyridine silyloxy group to give 81% of furan **19**. Stirring crude **18** with aqueous Et_3N cleaved the furan silyloxy group to provide 91% of the desired protected lactone **20**.

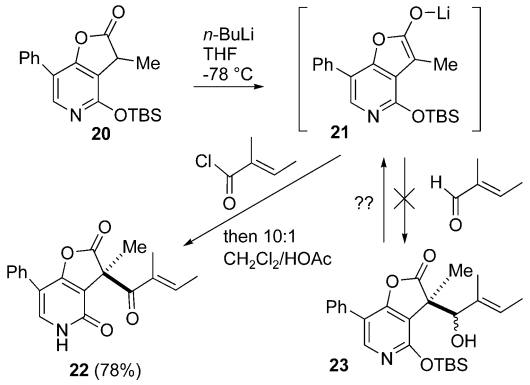
(7) (a) Snider, B. B.; Lu, Q. *J. Org. Chem.* **1994**, *59*, 8065−8070. (b) Snider, B. B.; Smith, R. B. *Synth. Commun.* **2001**, *31*, 111−123.

(8) (a) Moreno-Manas, M.; Pleixats, R. *Synthesis* **1984**, 430−431. (b) Fuchs, K.; Paquette, L. *J. Org. Chem.* **1994**, *59*, 528−532. (c) Tabakovic, I.; Tabakovic, K.; Gaon, I. *Org. Prep. Proced. Int.* **1997**, *29*, 223−226.

(9) Condensation of **7** and ethyl pyruvate can also be carried out using formic acid as a reductive trapping agent.[10] Heating pyridone **7** and ethyl pyruvate (2 equiv) in $(Et_3N)_2(HCO_2H)_5$ in a sealed tube at 140−150 °C for 5 h gave 40% of the propionic acid, which was esterified to give **17** in 93% yield with H_2SO_4 in EtOH at 60 °C.

(10) (a) Sekiya, M.; Yanihara, C. *Chem. Pharm. Bull.* **1967**, *17*, 747−751. (b) Tóth, G.; Molnár, S.; Tamás, T.; Borbély, I. *Org. Prep. Proced. Int.* **1999**, *31*, 222−225.

Scheme 5. Acylation to Form **22**



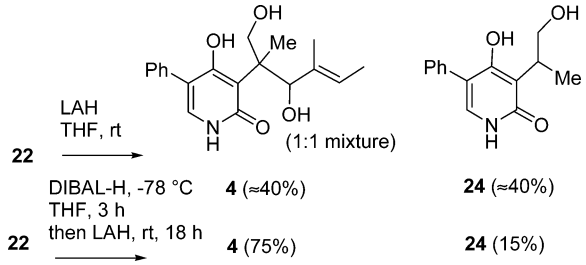
Treatment of lactone **20** with *n*-BuLi in THF at −78 °C followed by addition of tiglaldehyde failed to give **23** (see Scheme 5). The formation of enolate **21** under these conditions was established by trapping in high yield with MeI or D_2O. We hypothesized that the aldol reaction to give **23** might be thermodynamically unfavorable. Furan enolate **21** is aromatic, the conjugation of tiglaldehyde is lost on the aldol reaction, and adduct **23** is sterically congested. We therefore investigated the irreversible Claisen condensation of tigloyl chloride with enolate **21**, which proceeded in high yield. Deprotection of the crude product by stirring in 10:1 CH_2Cl_2/HOAc cleaved the silyl ether to give keto lactone **22** in 78% yield from **20**.

We now turned to the reduction of keto lactone **22** to form diol **4**. Reduction of **22** with $NaBH_4$ and $CeCl_3$ in MeOH gave the methyl ester corresponding to **17**. Presumably, reduction of the ketone provided secondary alcohol **5**, which underwent a retro aldol reaction to give lactone **6**, which opened to give the methyl ester. This supports our analysis that aldol adduct **23** is thermodynamically disfavored. Concomitant reduction of both the lactone and ketone should prevent the retro aldol reaction. Reduction of **22** with LAH in THF afforded 80% of a 1:1 mixture of the desired diol **4** and alcohol **24**, which was formed by reduction of the retro aldol product, lactone **6** (see Scheme 6). We then investigated the use of DIBAL-H, which reduces lactones rapidly to lactols, which might further reduce the extent of retro aldol reaction. We were pleased to find that treatment of **22** with DIBAL-H for 3 h at −78 °C, followed by addition of LAH and stirring for 18 h at 25 °C to complete the reduction, yielded 75% of **4** as an unstable 1:1 mixture of diasteromers and only 15% of the undesired alcohol **24**.

Diol **4** cyclized partially on flash chromatography to give a complex mixture of **2**, **3**, **25**, **26**, and other products. Therefore, we cyclized the crude mixture by stirring in 4:1 CH_2Cl_2/TFA for 3 h at 25 °C to provide 15% of CJ16,169 (**2**), 19% of CJ16,170 (**3**), 34% of *epi*-CJ16,169 (**25**), and 7% of *epi*-CJ16,170 (**26**) (see Scheme 7). The spectral data of **2**,[2,4] **3**,[2,4] and **26**[3] are identical to those previously reported.

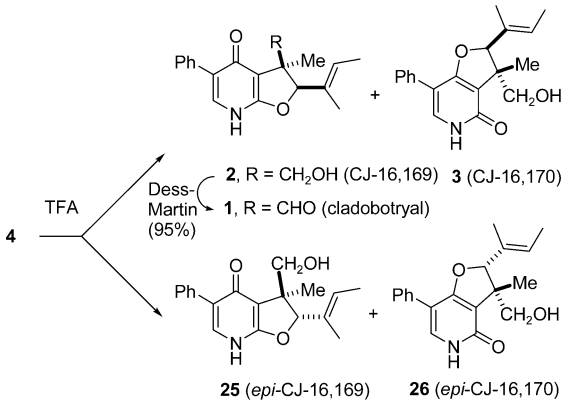
(11) (a) Faber, K.; Stückler, H.; Kappe, T. *J. Heterocycl. Chem.* **1984**, *21*, 1177−1181. (b) Schley, D.; Radspieler, A.; Christoph, G.; Liebscher, J. *Eur. J. Org. Chem.* **2002**, 369−374.

Scheme 6. Reduction to Give Diol **4**



Although, the overall yield of the four products from **22** is 75%, the selectivity for **2** is not good. We thought that the biosynthesis of **2** and **3** might involve a similar cyclization in water. We were pleased to observe that cyclization of crude **4** in 4:1 H_2O/TFA for 12 h at 25 °C provided 24% of **2**, 13% of **3**, 30% of **25**, and 8% of **26**. The yield of **2** increased from 15% in CH_2Cl_2/TFA to 24% in H_2O/TFA. Oxidation of **2** with Dess−Martin periodinane as previously described[4] gave cladobotryal (**1**) in 95% yield.[12,13]

Scheme 7. Cyclization of **4**

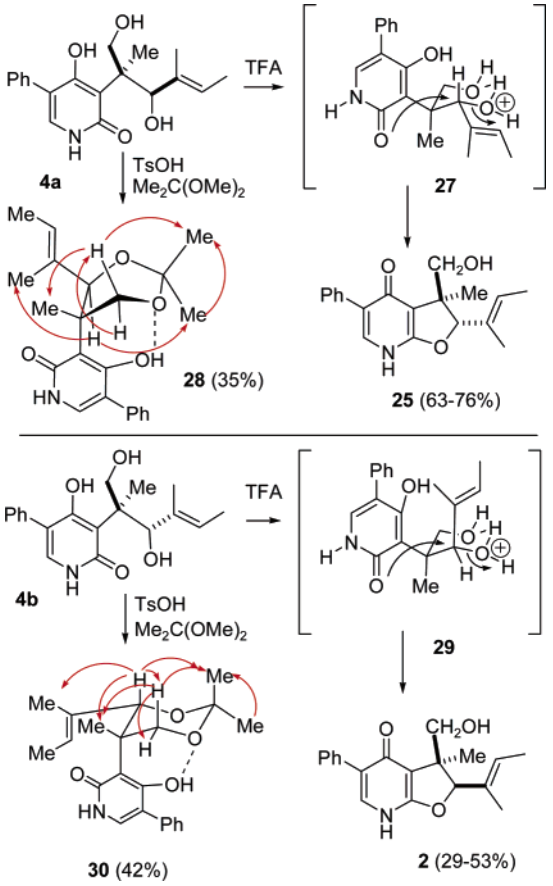


To understand the details of the cyclization, we needed to separate the diastereomers of **4**, establish their stereochemistry, and cyclize the individual isomers. Flash chromatography of crude **4** afforded 20% of 70% pure **4a** and 22% of 80% pure **4b**. Recrystallization ($CHCl_3$) gave pure **4a** in 12% yield from **22**, while reverse-phase chromatography gave pure **4b** in 16% yield from **22**. Reaction of **4a** with TsOH and 2,2-dimethoxypropane for 24 h afforded 35% of **28**, whose structure was established by the NOEs shown in Scheme 8.[14] A similar reaction of **4b** provided 42% of **30**, whose structure was established by the NOEs shown in Scheme 8.[14] The low yields of **4a**, **4b**, **28**, and **30** result from partial cyclization during chromatography and acetal formation.

(12) As previously observed,[2,4] the NMR spectra of **1**, **2**, and **25** are broadened, presumably due to slow prototropic tautomerism on the NMR time scale. There is less broadening in CD_3OD.[13]

(13) Elguero, J.; Katritzky, A. R.; Denisko, O. V. *Adv. Heterocycl. Chem.* **2000**, *76*, 1−84.

Scheme 8. Characterization and Cyclization of **4a** and **4b**



The ratio of products formed in the cyclizations of **4**, **4a**, and **4b** in CH_2Cl_2/TFA at 0 and 25 °C and H_2O/TFA at 25 °C are shown in Table 1. All four products are stable when resubjected to the cyclization conditions, indicating that the product ratios are kinetically controlled. Cyclization of **4a** preferentially formed **25** (63−76%) with inversion, possibly by an S_N2-like displacement through protonated intermediate **27**. CJ16,170 (**3**) was formed in 13−22% yield by displacement with inversion from the other pyridone oxygen. Cyclization of **4b** was less selective but did give 53% of CJ16,169 (**2**) in water by displacement with inversion. The S_N2-like reaction through protonated intermediate **29** is less favorable because of steric repulsion between the axial alkenyl side chain and the pyridone. Cyclization therefore proceeded by an S_N1 reaction with an allylic cation intermediate.

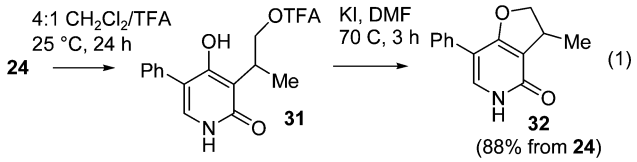
(14) For similar analyses, see: (a) Crump, R. A. N. C.; Fleming, L.; Hill, J. H. M.; Parker, D.; Reddy, N. L.; Waterson, D. *J. Chem. Soc., Perkin Trans. 1* **1992**, *24*, 3277−3294. (b) Ziegler, F. E.; Zheng, Z.-L. *J. Org. Chem.* **1990**, *55*, 1416−1418.

Table 1. Cyclization Product Ratios from **4**, **4a**, and **4b**

diol	temp	solvent[a]	% **2**	% **3**	% **25**	% **26**
4[b]	25 °C	CH_2Cl_2	20	25	46	9
4[b]	25 °C	H_2O	32	17	40	11
4a[c]	25 °C	CH_2Cl_2	10	22	63	5
4b[c]	25 °C	CH_2Cl_2	32	17	35	16
4a[c]	0 °C	CH_2Cl_2	5	21	71	3
4b[c]	0 °C	CH_2Cl_2	29	18	39	14
4a[c]	25 °C	H_2O	7	13	76	4
4b[c]	25 °C	H_2O	53	12	16	19

[a] Mixture (4:1) of indicated solvent and TFA. [b] Mixture (1:1) of crude **4** was used. 75% Overall isolated yield of **2**, **3**, **25**, and **26** from **22**. [c] Ratio of products determined by ^1H NMR in CD_3OD containing residual TFA.

Treatment of primary alcohol **24** in 4:1 CH_2Cl_2/TFA for 24 h at 25 °C provided only trifluoroacetate ester **31**, indicating that the protonated primary alcohol does not cyclize by an S_N2 displacement under these conditions. Heating **31** with KI in DMF for 3 h at 70 °C afforded **32** in 88% yield from **24** (eq 1). Presumably, the primary iodide formed from the trifluoroacetate and underwent an S_N2 cyclization.



In conclusion, we have completed short, efficient syntheses of cladobotryal (**1**) and CJ16,169 (**2**) and the first synthesis of CJ16,170 (**3**). Condensation of pyridone **7** with ethyl pyruvate and *p*-chlorothiophenol, reduction, and cyclization afforded 77% of lactone **6**. Protection of the pyridone, acylation of the enolate with tigloyl chloride, and deprotection provided keto lactone **22**. Reduction and dehydrative cyclization completed the syntheses.

Acknowledgment. We thank the National Institutes of Health (GM-50151) for financial support.

Supporting Information Available: Full experimental details and copies of ^1H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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