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A Formal Total Synthesis of (-)-Isoavenaciolide

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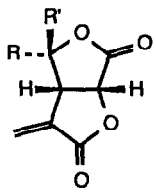
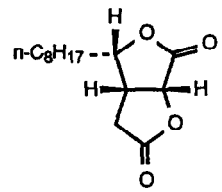
Abstract: Starting from D-ribose, a formal total synthesis of the antifungal mold metabolite (–)-isoavenaciolide is described.

The antifungal mold metabolites avenaciolide (1)[2], isoavenaciolide (2)[3], and ethisolide (3)[4] have attracted much attention due to their biological activity as well as their unique bis-butyrolactone skeleton. A number of syntheses of avenaciolide have appeared however much less work has been directed towards isoavenaciolide or ethisolide. Herein we report a very efficient synthesis (18% overall yield) of bislactone 4 (a known precursor of (-)-isoavenaciolide[2d]) utilizing D-ribose as our starting material.



1 R=H, R'=n-C_8H_{17}
2 R=n-C_8H_{17}, R'=H
3 R=n-C_4H_9, R'=H



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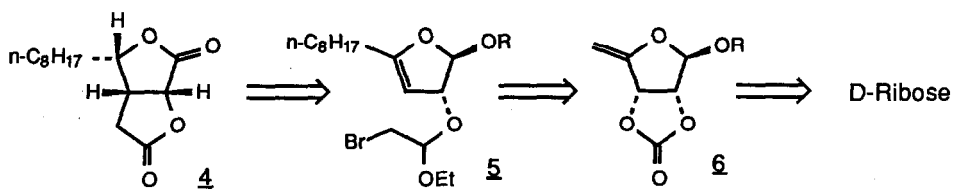
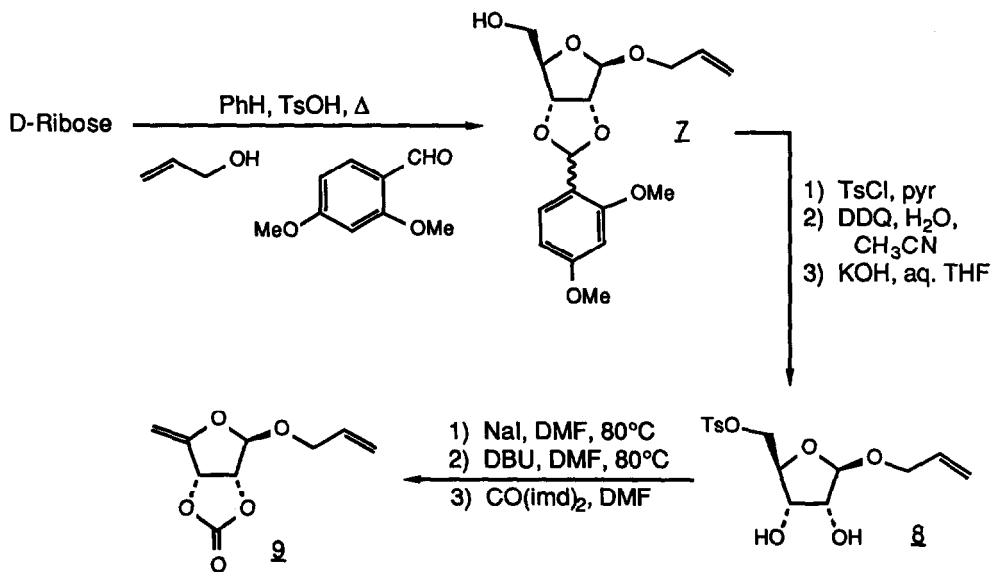
Retrosynthetically, the target molecule 4 was envisioned to be available from 5 via a Bu_3SnH mediated radical cyclization and subsequent oxidation of the acetals. Enol ether 5 was to be constructed by an S_N2' opening of vinyl carbonate 6 which was envisioned to arise from D-ribose.



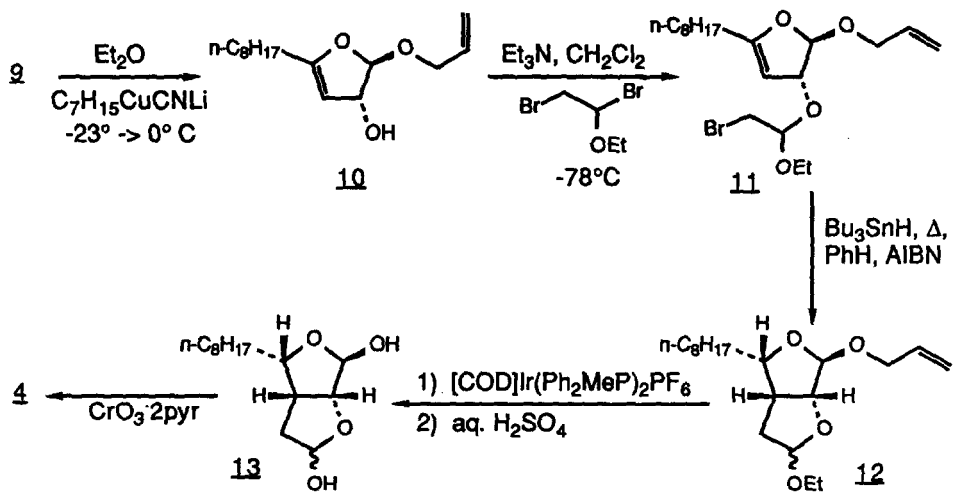
The synthesis of the requisite vinyl carbonate is shown in Scheme 1. Treatment of D-ribose with allyl alcohol[5] and 2,4-dimethoxybenzaldehyde with azeotropic removal of water afforded furanoside 7 (81%)[6] as a 4:1 mixture of diastereomers at the benzylic position. Tosylation of the primary alcohol followed by oxidation (DDQ, H_2O, CH_3CN) of the dimethoxybenzylidene acetal[7] and hydrolysis (aq. KOH, MeOH) of the resulting dimethoxybenzoates (a 1:1 regioisomeric mixture) produced diol 8 in 69% yield. Sequential treatment of a DMF solution of 8 with NaI, DBU then carbonyl diimidazole yielded vinyl carbonate 9 (65% from 8, 36% overall from ribose).

Scheme 1



Conversion of carbonate 9 to bislactone 4 (Scheme 2) was initiated by treatment of 9 with (n-C_7H_{15})CuCNLi[8] producing the desired S_N2' product (10) in 85% yield. Conversion to bromoacetal 11 followed by free radical cyclization (Bu_3SnH, AIBN, PhH) of the crude product gave the bisacetal 12 (as a 1:1 mixture at the new acetal center, 76% from 10)[9]. The octyl side chain was exclusively endo as one would predict from approach of the bulky Bu_3SnH from the least sterically hindered face of the molecule. At this point 12 was treated with a catalytic amount of H_2 activated $[COD]Ir(Ph_2MeP)_2PF_6$ to isomerize the allyl unit to the easily removable vinyl ether[10]. After isomerization was complete addition of aqueous H_2SO_4 to the reaction mixture produced the bishemiacetal 13 as a mixture of diastereomers. Collins oxidation of 13 affords the crystalline bislactone 4 (78% from 12). Bislactone 4 showed virtually identical melting point (110.5-111° C, lit.[2d] 110.5-111.5° C) and rotation ($[a]^{20}_D$ = -7.35° (c=1.0, CHCl3), lit.[2d] $[a]^{20}_D$ = -7.52°) as those reported previously for this compound.

Scheme 2



References and Notes

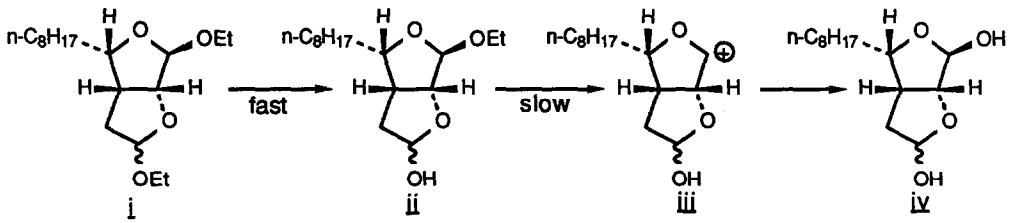
1. Current address: Pfizer Central Research, Process Research and Development, Eastern Point Road, Groton, CT, 06340.

2. Isolation: a) Brookes, D.; Turner, W. B. *J. Chem Soc.* **1963**, 5385. Synthesis: b) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *Tetrahedron Lett.* **1986**, *27*, 3345, c) Suzuki, K.; Miyazawa, M.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1986**, *27*, 6237, d) Anderson, R. C.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 4781, e) Gould, T. J.; Kallmerten, J. *J. Org. Chem.* **1985**, *50*, 1128, f) Schreiber, S. L.; Hoyveyda, A. H. *J. Am. Chem. Soc.* **1984**, *106*, 7200, g) Kido, F.; Tooyama, Y.; Noda, Y.; Yoshikoshi, A. *Chem. Lett.* **1983**, *881*, h) Murai, A.; Takahashi, K.; Taketsuru, H.; Masamune, T. *J. Chem. Soc. Chem. Comm.* **1981**, 221, i) Takei, H.; Fukuda, Y.; Taguchi, T.; Kawara, T.; Mitzutani, H.; Mukuta, T. *Chem. Lett.* **1980**, 1311, j) Sakai, T.; Horikawa, H.; Takeda, A. *J. Org. Chem.* **1980**, *45*, 2039, k) Herrman, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem.Soc.* **1979**, *101*, 1544, l) Ohrui, H.; Emoto, S. *Tetrahedron Lett.* **1975**, 3657, m) Parker, W. L.; Johnson, F.; *J. Org. Chem.* **1973**, *38*, 2489.

3. Isolation: a) Aldridge, D. C.; Turner, W. B. *J. Chem. Soc. C* **1971**, 2431. Synthesis: b) ref. 2b-2d, c) Damon, R. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1975**, 4551, d) Yamada, K.; Kato, M.; Iyoda, M.; Hirata, Y. *J. Chem. Soc. Chem. Commun.* **1973**, 499.

4. Isolation: See ref 3a. Synthesis: a) Burke, S. D.; Pacofsky, G. J. *Tetrahedron Lett.* **1986**, *27*, 445.

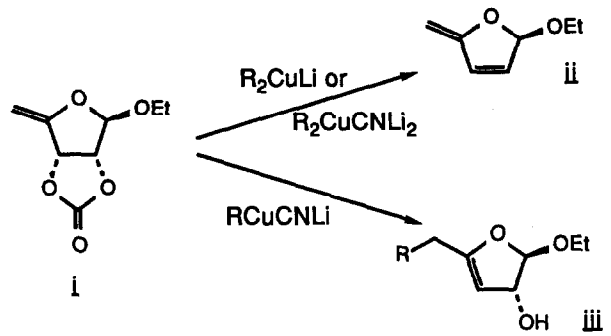
5. In the early stages of our work on this synthesis we found that it was extremely difficult to hydrolyze bisacetal i to iv, presumably cation iii is destabilized by the inductive effect of the α-oxygen. An allyl protecting group for the acetal was then chosen since removal of the allyl group can be accomplished without proceeding through iii. For a similar effect in the MCPBA/BF_3 oxidation of i see reference 2f.



6. For the analogous acetonide see Levene, P.; Stiller, E. *J. Biol. Chem.* **1933**, *102*, 187.

7. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.

8. Interestingly, different cuprate reagents produce different results. Treatment of vinyl carbonate i with dialkyl cuprates produced diene ii (requires two equivalents of cuprate for complete conversion). Dialkylcyanocuprates also produced ii but monoalkylcyanocuprates yielded the S_N2' product iii.



9. Stork, G; Mook, R.; Biller, S.; Rychnovsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3741.

10. Baudry, D.; Ephritikhine, M.; Felkin, H. *J. Chem. Soc.* **1978**, 694.

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