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TOTAL SYNTHESIS OF (±)-ALLOSAMIZOLINE FROM A SYMMETRIC TRISUBSTITUTED CYCLOPENTENE

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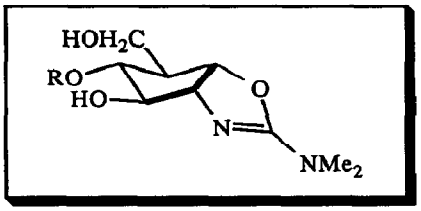
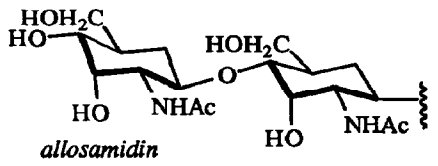
Abstract: A convergent synthesis of the aminocyclitol allosamizoline **1**, which is found in a class of pseudotrisaccharide chitinase inhibitors known as the allosamidins, is reported.

Chitin (the β-1,4-linked polymer of N-acetylglucosamine) is one of nature's most abundant polysaccharides.[1] Besides being the main component of insect cuticle, chitin is also a constituent of fungal cell wall, yielding approximately 3 x 10^4 metric tons of the polysaccharide annually.[2] As the principal structural macromolecule in crustacean shells, chitin is also a major waste product of the seafood processing industry, with an estimated 1.2 x 10^5 metric tons being produced worldwide annually.[2] Not surprisingly, interest in research on chitinases, which can degrade chitin to soluble mono- and oligosaccharides, has grown enormously over the past five years.[3] Chitinase inhibitors are also of potential import as insecticides or fungicides.[4]



1 R= H *allosamizoline*

2 R= 

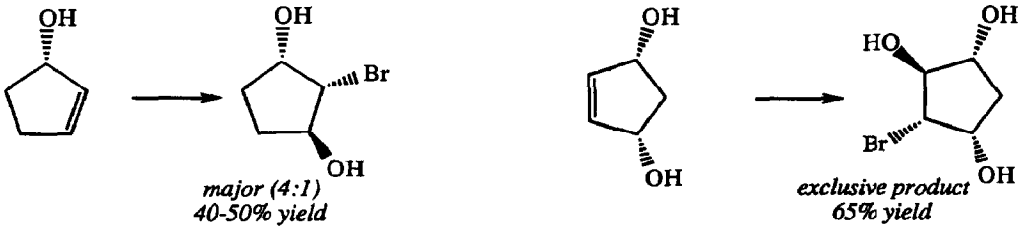
allosamidin

The aminocyclitol allosamizoline **1** is a common hydrolysis product of the allosamidins, a class of pseudotrisaccharide chitinase inhibitors whose first representative was characterized as **2**.[5] Here we report a short stereoselective synthesis of allosamizoline from cyclopentadiene by an alkylation/cycloaddition route recently developed in our laboratory.[6] Three groups have achieved total syntheses of allosamidins,[7-9] and several routes to **1** have been developed from carbohydrate precursors.[10-14]

Retrosynthetic analysis of allosamizoline focused on construction of the (dimethylamino)oxazoline late in the overall plan, and this tactic revealed an inherent symmetry which we hoped to exploit. Aminotriol **8** (Scheme), the precursor of thiooxazolidinone **9**, might be prepared by azidolysis of *meso*-epoxydiol **6**, which in turn seemed accessible by an appropriate functionalization of the *meso*-trisubstituted cyclopentene **4**.

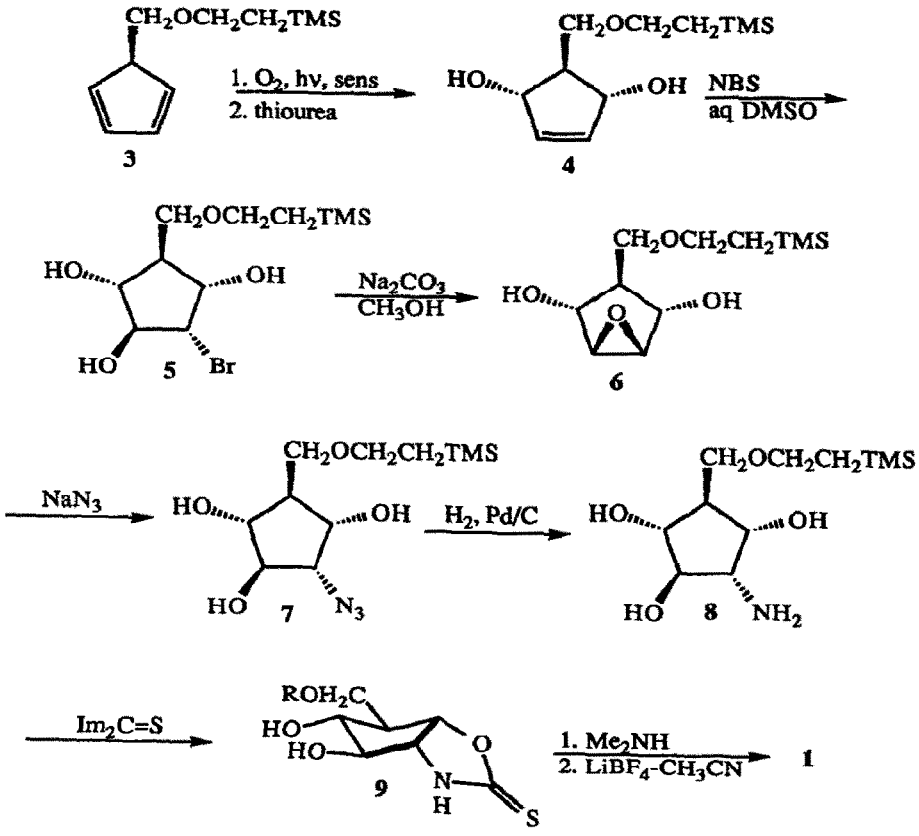
A suspension of thallous cyclopentadienide (Aldrich, freshly sublimed) in CH_2Cl_2 was reacted with β-trimethylsilylethoxymethyl chloride (SEM-Cl) to afford monosubstituted cyclopentadiene **3**, which without purification was immediately subjected to singlet oxygen generated using methylene blue as sensitizer. Reduction *in situ* of the transient endoperoxide afforded *meso*-cyclopentenediol **4** in 35% overall yield.[15]

As expected, peracid epoxidation of **4** gave exclusively the undesired *syn*-epoxydiol. Even using *bis*-trimethylsilyl-**4**[16] we were unable to obtain better than a 2:1 facial selectivity for the *anti*-epoxydiol **6**. Additions of HOBr and HOCl to 3-methoxy and 3-alkylcyclohexenes have been reported to proceed via *syn*-halonium ions.[17-19] In fact, reaction of diol **4** at room temperature with NBS in wet DMSO furnished a single bromohydrin **5** (60% yield) whose structure was confirmed by cyclization (Na_2CO_3-CH_3OH) exclusively to **6**. Addition of HOCl to **4** likewise gave **6** via the corresponding chlorohydrin. Hypohalous acid additions to 2-cyclopenten-1-ol and cyclopentene-*cis*-1,4-diol also occurred with good *syn*-stereoselectivity.



Epoxydiol **6** underwent smooth ring opening with NaN_3 (5 equiv, 8:1 $CH_3OCH_2CH_2OH$:H_2O) to afford racemic azidotriol **7** (66%) which was then quantitatively reduced to the corresponding aminotriol **8**. Cyclization with thiocarbonyldiimidazole produced thiooxazolidinone **9** in 81% yield. From **9**, a one-step construction of the (dimethylamino)oxazoline ring was achieved by heating with $(CH_3)_2NH$-CH_3OH in a sealed tube. After deprotection of the SEM group ($LiBF_4$), racemic allosamizoline **1** was obtained (85% yield for 2 steps) whose NMR and other spectral data were identical with those of an authentic sample.[20] By adaptation to several analogs, this convergent route to **1** should prove useful in exploring structure-activity relationships in the allosamidins.

SCHEME



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REFERENCES AND NOTES

1. Pariser, E. R. *Chitin Sourcebook: A Guide to the Research Literature* **1989,** Wiley, New York.
2. Knorr, D. *Food Technology* **1991,** *45,* 114.
3. Flach, J.; Pilet, P.-E.; Jollés, P. *Experientia* **1992,** *48,* 701.
4. Cabib, E.; Sburlati, A.; Bowers, B.; Silverman, S. J. *J. Cell. Biol.* **1989,** *108,* 1665.
5. (a) Sakuda, S.; Isogai, A.; Matsumoto, S.; Suzuki, A.; Koseki, K.; Kodama, H.; Suzuki, A. *Agric. Biol. Chem.* **1987,** *51,* 3251; (b) Sakuda, S.; Isogai, A.; Makita, T.; Matsumoto, S.; Suzuki, A.; Koseki, K.; Kodama, H.; Yamada, Y.. *Agric. Biol. Chem.* **1988,** *52,* 1615.
6. King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1994,** *116,* 562.
7. Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991,** *113,* 5863.
8. (a) Maloisel, J.-L.; Vasella, A,; Trost, B. M.; van Vranken, D. L. *J. Chem. Soc. Chem. Commun.* **1991,** 1099; (b) idem, *Helv. Chim. Acta* **1992,** *75,* 1515.
9. Takahashi, S.; Terayama, H.; Kuzuhara, H. *Tetrahedron Lett.* **1992,** *33,* 7565.
10. Trost, B. M.; van Vranken, D. L. *J. Am. Chem. Soc.* **1990,** *112,* 1261.
11. Takahashi, S.; Terayama, H.; Kuzuhara, H. *Tetrahedron Lett.* **1991,** *32,* 5123.
12. Nakata, M.; Akazawa, S.; Kitamura, S.; Tatsuta, K. *Tetrahedron Lett.* **1991,** *32,* 5363.
13. (a) Simpkins, N. S.; Stokes, S; Whittle, A. J. *Tetrahedron Lett.* **1992,** *33,* 793; (b) idem, *J. Chem. Soc. Perkin Trans. I* **1992,** 2471.
14. Kitahara, T.; Suzuki, N.; Koseki, K.; Mori, K. *Biosci. Biotech. Biochem.* **1993,** *57,* 1906.
15. Satisfactory ^{1}H, ^{13}C-NMR, IR and mass spectrometric data were obtained for all new compounds.
16. (a) Chavdarian, C. G.; Heathcock, C. H. *Syn. Commun.* **1976,** *6,* 277; (b) Schlessinger, R. H.; Lopes, A. *J. Org. Chem.* **1991,** *46,* 5252.
17. Bannard, R. A. B.; Casselman, A. A.; Hawkins, L. R. *Can J. Chem.* **1965,** *43,* 2398.
18. Langstaff, E. J.; Hamanaka, E.; Neville, G. A.; Moir, R. Y. *Can J. Chem.* **1967,** *45,* 1907.
19. Bellucci, G.; Berti, G.; Ingrosso, G.; Mastrorilli, E. *Tetrahedron Lett.* **1973,** 3911.

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