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SYNTHETIC STUDIES OF TRICHOTHECENES, AN ENANTIOSELECTIVE SYNTHESIS OF A C-RING PRECURSOR OF ANGUIDINE

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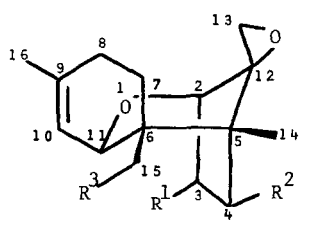
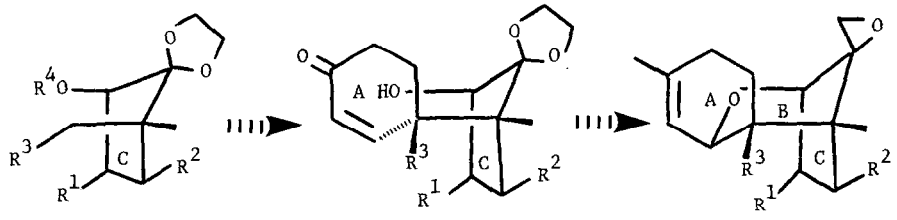
Summary: An enantioselective synthesis of a cyclopentanoid C-ring precursor 19 of anguidine 3, a representative trichothecene with antitumor activity, from 2-allyl-2-methylcyclopentane-1,3-dione is described.

The naturally occurring trichothecenes exhibit varied biological activities depending on the respective functional groups present on the tricyclic backbone.[1] Synthetic studies of this group of natural products have been actively pursued,[2] and the total synthesis of racemic trichodermol 1,[3,4] verrucarol 2[5], and calonectrin 4[6] have been completed. Several of the previous studies support a general scheme for assembling the trichothecene skeleton involving the addition of an A-ring unit to a C-ring unit followed by an intramolecular cyclization providing the B-ring, as outlined in Scheme I. Since several trichothecenes, especially anguidine 3, exhibit antitumor activity,[1] we deemed it important to develop an enantioselective synthetic approach, according to Scheme I, which could provide chiral intermediates for structure-activity analysis as the target molecule is progressively assembled. In this communication, we wish to describe an enantioselective synthesis of a C-ring precursor of anguidine 3 (outlined in Scheme II).[7]

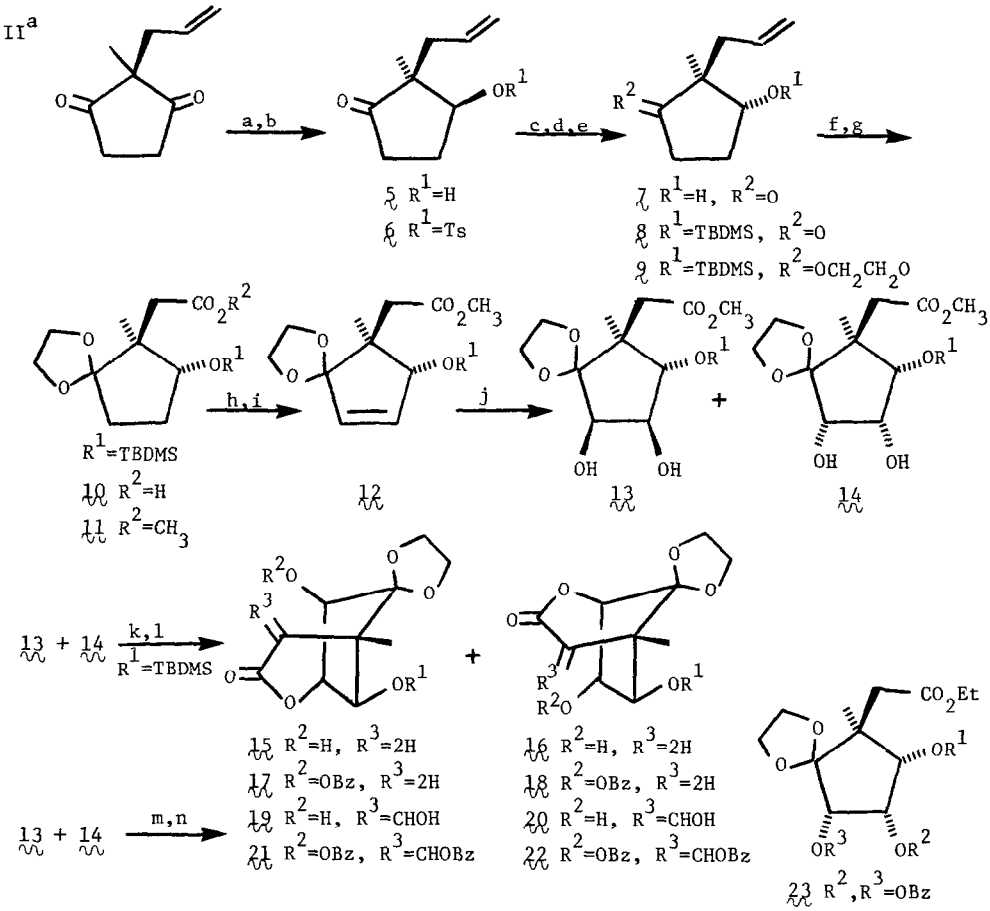


	R^1	R^2	R^3
trichodermol 1	H	OH	H
verrucarol 2	H	OH	OH
anguidine 3	OH	OAc	OAc
calonectrin 4	OAc	H	OAc

SCHEME I



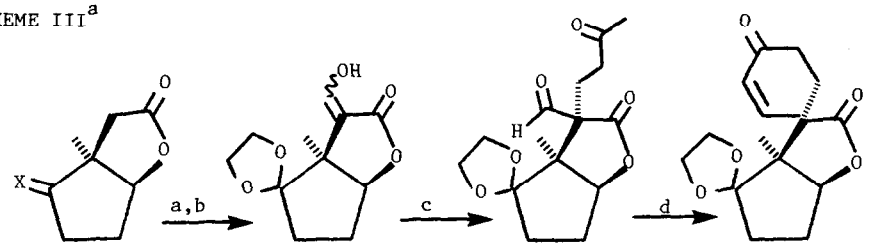
SCHEME II[a]



[a](a) dry active Bakers' yeast, pH 7 phosphate buffer, D-glucose, 25°C, 24h, 70%. (b) 1.2 equiv p-toluenesulphonyl chloride, pyridine (1.0M), 25°C, 64h, 85%. (c) 6, 0.1M in dimethylformamide, 15 equiv KNO_2, 85°C, 36h, 70%. (d) 7, 0.5M in dimethylformamide, 3 equiv imidazole, 0.1 equiv 4-dimethylaminopyridine, 1.2 equiv t-butyldimethylsilyl chloride, 60°C, 16h, 90%. (e) 8, 0.3M in ethylene glycol, 0.1 equiv p-toluenesulphonic acid, 2.0 equiv triethyl orthoformate, 20°C, 24h, 90%. (f) 9, 0.02M in 1:2 tert-butanol, H_2O, 3 equiv K_2CO_3, 4.0 equiv $NaIO_4$, 0.01 equiv $KMnO_4$, 25°C, 16h, 75%. (g) 10, 0.5M in ether, add 1.5 equiv diazomethane (0.5M in ether), 95%. (h) 11, 0.3M in tetrahydrofuran, 1.3 equiv phenyltrimethylammonium tribromide, 25°C, 1h, 95%. (i) preceding material, 6 equiv 1,8-diazabicyclo[5.4.0]undec-7-ene, 90°C, 6h, 85%. (j) 12, 0.2M in 1:1 acetone, H_2O, 1.1 equiv 4-methylmorpholine-4-oxide monohydrate, 0.1 equiv OsO_4, 25°C, 16h, 95%. (k) 13 and 14, 0.5M in methanol, 1 equiv 1N KOH, 25°C, 16h. (l) preceding material at 0°C, 10 equiv acetic anhydride, 5 min, 15 (60%) and 16 (15%). (m) 13 and 14, 0.1M in ether, 5 equiv NaH, 20 equiv ethyl formate, 25°C, 16h. (n) 19 and 20, 0.5M in ether, 3 equiv pyridine, 2.5 equiv benzoyl chloride, 25°C, 24h, 21, (60%), 22 (15%) and 23 (15%).

We discovered that actively fermenting Bakers' yeast (Saccharomyces cerevisiae) would reduce one of the two enantiotopic homomorphic carbonyl groups of 2-allyl-2-methyl-1,3-cyclopentanedione, providing the chiral starting material [2S,3S]-ketol 5.[8] Examination of the C-ring of anguidine reveals that the ketol 5 has the correct absolute configuration at the quaternary carbon C5. However, the configuration of the hydroxy group in 5 is opposite to that required at C4. This situation was corrected by treatment of the corresponding tosylate 6 with potassium nitrite[8] to give the [2S,3S]-ketol 7. Protection of the hydroxy group and the ketone function was followed by oxidative cleavage of the olefin[9] to provide the carboxylic acid 10 which was converted to the corresponding methyl ester 11.[10] Bromination of 11 with phenyltrimethylammonium tribromide[11] followed by treatment with DBU gave the olefin 12. Osmium tetroxide catalyzed oxidation[12] gave a 5:1 mixture of two isomeric cis-vicinal diols. Separation of the diols was possible by silica gel chromatography (10% ether in dichloromethane). It was hoped that the bulky silyl ether group in 12 would sterically screen the appropriate face of the olefin and provide stereoselective formation of diol 13. Saponification of the major diol product and subsequent treatment of the corresponding carboxylate salt with excess acetic anhydride gave a 3:1 mixture of bicyclic lactones 15 and 16 in 75% yield. The corresponding benzoates 17 and 18 could be separated by silica gel chromatography (30% ether in hexane) and the identity of the major diol was established as 13. The carboxylic acid derived from 14 cannot undergo intramolecular lactonization due to the geometrical constraints of the molecule and is easily separated from the lactones 15 and 16 by an aqueous workup. A more efficient route to a chiral C-ring precursor involved direct treatment of the diol mixture 13 and 14 with 5 equiv of NaH in the presence of excess ethyl formate providing the bicyclic hydroxymethylenelactone 19 as the major product. Treatment of the crude reaction product with excess benzoyl chloride in pyridine and separation of the products by silica gel chromatography (dichloromethane) gave the dibenzoates 21 (60%), 22 (15%), and 23 (15%). A feasible strategy for stereoselective addition of the A-ring unit could involve a Robinson annelation on a suitable derivative of 19. A preferred exo-addition of methylvinylketone to 19 is expected on the basis of the geometry and steric effects in this bicyclo[3.2.1] system.[13] The site of this spiroannelation, α to the lactone in 19 is sterically congested and for this reason we carried out a model study (outlined in Scheme III) on the readily available lactone 24[8] which has similar steric requirements. After a routine protection of the ketone group, the hydroxymethylenelactone 26 was prepared and condensed with methyl vinyl ketone to give the desired adduct 27.[14] The intramolecular aldol condensation was accomplished using the method of Plieninger[15] to provide the enone 28. Preparation of C-ring derivatives with an epoxide group for structure-activity screening and further studies to complete the synthesis of anguidine 3 are in progress.

SCHEME III[a]



24 X=O

25 X=OCH_2CH_2O

26 27 28

[a](a) 24, 0.03M in ethylene glycol, 0.1 equiv p-toluenesulphonic acid, 2 equiv triethyl orthoformate, 25°C, 24h, 90%. (b) 25, 0.5M in tetrahydrofuran, 5 equiv NaH, 20 equiv ethyl formate, 25°C, 5h, 95%. (c) 26, 0.5M in 1:1 toluene, tert-butanol, 2 equiv methyl vinyl ketone, 0.1 equiv t-$C_4H_9O^-$ K^+, 0°C, 1h, 25°C, 12h, (65%). (d) 27, 0.01M in benzene, 0.1 equiv piperidine acetate, reflux with removal of H_2O, 60%.

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