Stereoselective synthesis of calonectrin

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Abstract
Several macrocyclic lactones of the trichothecene class of compounds exhibit significant anticancer activity. A common structural subunit in each of these lactones is the sesquiterpene verrucarol(1). Anguidin (2), a more highly oxygenated analogue, also shows inhibitory activity against several cancers., Calonectrin (3), considered to be the biogenetic precursor to verru-aron, has recently been isolated.

Disciplines
Chemistry | Organic Chemistry | Other Chemistry | Polymer Chemistry

Comments
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regiosomer as determined by analysis of the $^{13}$C NMR spectrum. The acetate of 6 is more basic than formaldehyde and complexes to EtAlCl$_2$. This complex reacts with CH$_2$O-EtAlCl$_2$ at the terminal double bond to give the ene adduct 7, presumably as a 4:1 trans-cis mixture, which loses ethane to give 8. This then complexes to CH$_2$O to give 9, which undergoes a quasi-intramolecular Lewis acid catalyzed Diels–Alder reaction to give 10. Aqueous workup gives 11. Deactivation of 6 by complexation of Lewis acid to the acetate necessitates the use of EtAlCl$_2$, which is a stronger Lewis acid than Me$_2$AlCl with a less nucleophilic alkyl group.

The structure of 11 is assigned based on spectroscopic evidence and its conversion to 15. The cis stereochemistry, which is expected for the Diels–Alder adduct from a trans,trans diene, can be assigned from the coupling constants of the vinylic protons. H$_9$ is weakly coupled to the vicinal pseudoaxial proton H$_7$ (7 Hz) and to the allylic pseudoequatorial proton H$_4$ (1 Hz). Conversely, H$_6$ is strongly coupled to the vicinal pseudoequatorial proton H$_5$ (5 Hz) and to the allylic pseudoaxial proton H$_4$ (2 Hz). If the substituents were trans, H$_9$ and H$_6$ would both be pseudoaxial and the coupling constants of the two vinyl hydrogen would be similar.

The regiochemistry of 11 is established by NMR decoupling experiments on the aldehyde 12. Irradiation of the allylic proton $\alpha$ to the oxygen at $\delta$ 4.5 collapses the signal from the methylene group $\alpha$ to the aldehyde at $\delta$ 2.51 to a broad singlet. The regioselectivity of the reaction depends critically on the solvent. Reaction in methylene chloride gives a 3:1 mixture of 11 and the undesired regiosomer which gives a single diol after hydrolysis.

Oxidation of 11 (pyridinium CrO$_3$Cl, NaOAc) gives the aldehyde 12 in 87% yield. Addition of crude 12 to excess methymagnesium chloride gives the diol 13. Selective silylation of the primary alcohol (t-BuPh$_2$SiCl; NE$_3$, Me$_2$NC$_2$H$_2$N) followed by oxidation of the secondary alcohol (pyridinium CrO$_3$Cl) gives the methyl ketone 14 in 60% yield from 12. Cis hydroxylation from the less hindered side (cat. Os$_3$O$_n$, N-methylmorpholine $N$-oxide) followed by protection of the diol as the cyclohexene ketal (C$_6$H$_{12}$O, TsOH, CuSO$_4$) gives 15 in 82% yield (13% from 1,5-hexadiene). This material is identical with an authentic sample, kindly provided by Professor Kozikowski, by spectral and chromatographic comparison. Since 15 has been converted to pseudomonic acids A and C by Kozikowski, Schmiesing, and Sorgi, this constitutes a formal total synthesis of these antibiotics.

The synthesis of 11 in three steps from 1,5-hexadiene demonstrates the utility of alkylaluminum halide catalyzed reactions of aldehydes and quasi-intramolecular Diels–Alder reactions in organic synthesis.

**Acknowledgment.** We thank the National Institutes of Health and the Mobil Foundation for financial support and David J. Rodini for conducting preliminary experiments.

**Registry No.** (E)-1, 80558-54-9; 4, 592-42-7; (E)-5, 80502-28-9; (Z)-5, 80502-29-0; 6, 80502-30-3; 7, 80502-31-4; 8, 80502-32-5; (E)-11, 8053-23-6; (E)-12, 80514-57-4; (E)-13, 8053-34-7; (E)-14, 80502-35-8; (E)-15, 80558-55-0; (E)-pseudomonic acid C, 80558-56-1.

**Stereoselective Synthesis of Calonectrin**

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Several macrocyclic lactones of the trichothecene class of compounds exhibit significant anticancer activity. A common structural subunit in each of these lactones is the sesquiterpene verrucarol (1). Anguidin (2), a more highly oxygenated analogue, also shows inhibitory activity against several cancers. Calonectrin (3), considered to be the biogenetic precursor to verrucarol, has recently been isolated. Several synthetic approaches to this interesting class of molecules have been reported. Among these are two total syntheses

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(10) All new compounds gave satisfactory spectral and analytical data.

(11) The conformation shown for II minimizes 1,3-diaxial interactions. In cyclohexenes, the vicinal coupling constant of the vinylic proton is larger for a pseudoequatorial proton which has a dihedral angle closer to the optimal 0°. The allylic coupling constant is larger for the pseudoequatorial proton which has a dihedral angle closer to the optimal 90°. See: Abraham, R. J.; Gottschalk, H.; Paulsen, H.; Thomas, W. A. J. Chem. Soc. 1965, 6268.


of trichodermin (15-deoxyverrucarol) by Raphael and Still and the chemical conversion of angelin to verrucarol by Fraser-Reid. Schlessinger has recently reported the total synthesis of 1. Synthetic strategies for the tricyclic trichothecene system by Still and Rouhs have focused on the opening of a functionalized [2,2,2] bicyclic system. We wish to report the stereoselective synthesis of calonectrin by an alternate strategy which produces the tricyclic system. Initially, we envisioned a sequence involving tetracyclic diacetal of iodotrimethylsilane was vital to avoid undesired side reactions. The cyclization of crude afforded several products in addition to keto lactone verrucarin J. Ketol, prepared previously in 10% overall yield, was acylated with bromoacetyl bromide at 0 °C. The resulting bromo keto ester was transformed into enol silyl ether syntheses of calonectrin by an alternate strategy which produces 4b via the intramolecular alkylation of enol silyl ether (Scheme I). Ketol 5, prepared previously in 10% overall yield, was acylated with bromoacetyl bromide at 0 °C. The resulting bromo keto ester was transformed into enol silyl ether 6 by using 0.95 equivalents of iodotrimethylsilane and hexamethyldisilizane in methylene chloride at -25 °C. The isomeric enol silyl ether was also formed in approximately 5% yield. The use of a slight deficiency of iodotrimethylsilane was vital to avoid undesired side reactions. The cyclization of crude 6 to keto lactone 7 could be effected with tetrahydroammonium fluoride in tetrahydrofuran. Direct cyclization of the bromo keto ester afforded several products in addition to 4a. Although the hindered ketone in 7 proved to be resistant to ketalization, selective reduction of the lactone to a lactol could be achieved by using 1 equiv of disbutyldimethylaluminum hydride (DIBAL) at -78 °C. Unfortunately, the product, identified as tetracyclic diacetal 10 on the basis of 13C NMR absorption at 81.1 and 99.4 and also infrared and high-resolution mass spectroscopy data, could not be induced to cyclize to 4a (CH3ONa, 0 °C).

Scheme I

**Reagents:** (a) CH3OH, p-TolNO2, py, 0 °C; (b) Me3SiCl, Me2SO, CH3OH; (c) Ph2P=CH2, Me2SO, CH3OH; (d) PCC, CH2Cl2; (e) Bu4NF, THF; (f) NBS, CH2CN, 0 °C; (g) LiAlH4, Et2O; (h) Me3SO, CICO3O, Et2N; (i) NaOCH3, CH2OH I.

**Scheme II**

**Reagents:** (a) CH3=CHOEt, PPTS; (b) Ph2P=CH2, Me2SO, 70 °C; (c) PPTS, CH3OH; (d) FCC, CH2Cl2; (e) Bu4NF, THF; (f) NBS, CH2CN; (g) NaBH4, CH2OH; (h) CF3CO2H, Na2CO3, 0 °C; (i) Zn-Ag; (j) Ac2O, DMAP, CH2Cl2.

**References**


(7) Schlesinger, R. H.; private communication.


(9) The formation of the tricyclic ring system via intramolecular aldol condensation has also been explored by Raphael and Fujimoto.


(12) An alternate structure for 10 that is consistent with our data is shown below. We thank a referee for the suggestion.
according to the procedure defined by Welch,\textsuperscript{17} deprotection,\textsuperscript{16} and PCC oxidation provided ketone 11. Desilylation with tetra-n-butylammonium fluoride\textsuperscript{14} and bromo ether formation\textsuperscript{14} were necessary to effect epoxidation of the exocyclic methylene group. Sodium borohydride reduction of the ketone was highly stereoselective since the exo face of the bicyclic [3,2,1] subunit is much more accessible. Epoxidation was accomplished with buffered trifluoroperacetic acid at 0°C.\textsuperscript{20} Regeneration of the trisubstituted olefin was effected with zinc-silver couple.\textsuperscript{21} Other reagents such as zinc dust (DMF or THF or CH\textsubscript{2}OH) or magnesium (ether, THF) were ineffective. Th acetylation with acetyl anhydride and (4-dimethylamino)pyridine in CH\textsubscript{2}Cl\textsubscript{2} provided calonectrin. Synthetic calonectrin was identical (\textsuperscript{1}H, \textsuperscript{13}C NMR, IR, MS, TLC) with an authentic sample.

The synthetic route described above is efficient and highly stereoselective. We intend to synthesize anguidin and verculcarol using olefinic ketone 11.

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Registry No. 3, 38818-51-8; 4b-(a-OH), 80484-01-1; 4b-(\&OH), 80484-02-2; 5, 80513-95-7; 6, 80484-04-4; 6a, 80484-05-5; 7, 80484-06-6; 8, 80484-07-7; (3a,9A,1116)-10-bromo-9,15-epoxy-12-methylribohycetocane-3-ol, 80484-08-8.


Total Synthesis of Racemic Verculcarol

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The molecular array, verculcarol (1),\textsuperscript{1} is the sesquiterpene linchin of a large family of macrocyclic di- and tri lactones which possess novel and synthetically challenging structures together with significant antitumor activity.\textsuperscript{2} As part of a larger program directed toward the synthesis of representatives of these macrocyclic systems,\textsuperscript{3} the construction of verculcarol became desirable.\textsuperscript{4} Herein, we describe a biomimetic formulation of racemic 1 by a route which will ultimately allow its preparation in the required optical form.

We chose as the starting material for construction of 1 the readily available ketonic substance 2. This material contains two elements required by the structure 1, namely, the oxygen residue on C\textsubscript{4} and the angular C\textsubscript{14} methyl group.\textsuperscript{5} Thus, our initial task was the transformation of this substance into the keto acid 3. Degradation of the six-membered ring of 2 was commenced by kinetic deprotonation of the enone with lithium dibromopropylamide in THF solution followed by trapping of the enolate with trimethylsilyl chloride. The resulting enol ether was subjected to oxidation with m-chloroperbenzoic acid in hexane/tert-butyl alcohol at 0°C yield the \(\alpha\)-trimethylsilyloxy enone 4.\textsuperscript{6} Ozonolysis of 4 in methanol at -78°C followed by oxidation of the intermediate \(\alpha\)-hydroxy acid with sodium metaperiodate/chromium trioxide in acetic acid at 22°C afforded the keto acid 3 (mp 126-127°C) in 53% yield from 2.\textsuperscript{7}

Two reductive reactions were then encountered during the elaboration of 3 into the \(\alpha\)-methylene lactone 5, a key synthetic intermediate in our route to 1. The first of these difficulties was the conversion of 3 into the exocyclic olefin 6—a reaction which was successful only if the ylide derived from methyltriphenylphosphonium bromide was generated with sodium tert-amylate in toluene and the reaction carried out at 110°C for 12 h. under these conditions, 6 was readily obtained from 3.\textsuperscript{8} Oxidation of 6 with selenium dioxide and tert-butyl hydroperoxide in methylene chloride at 22°C afforded a mixture of allylic alcohols in which the \(\alpha\)-oriented isomer 7 predominated in a ratio of 5:1.\textsuperscript{9} Treatment of this mixture with p-toluenesulfonic acid in methylene chloride at 22°C for 24 h gave the lactone 8 in 55% yield from 3.\textsuperscript{10} Surprisingly, methylation of 8 to obtain the lactone 5 proved to be the second difficulty encountered in the reaction scheme. A novel and unexpected solution to this problem was discovered, however, during the course of reacting the enolate derived from 8 with methyltriphenylphosphonium chloride at 150°C in a flow system. The reactant and reagent were combined at -78°C and then brought to 22°C followed by stirring for 14 h; this afforded the \(\alpha\)-methylene lactone 5 and not the expected hydroxymethyl lactone.\textsuperscript{11} Compound 5 was obtained in 62% yield from 8.

We next faced the problem of spiroannulating the lactone 5 to obtain 9—a compound which we felt could be readily converted into the target natural product. The Diels–Alder reaction was the obvious choice for this annihilation process, and after careful consideration of molecular models of 5, we were able to convince ourselves that a [4 + 2] cycloaddition between 1-methoxy-3-(trimethylsilyl)-1,3-butanediene and the methylene lactone would result in addition of the diene from the \(\beta\) surface of the lactone to ultimately afford the unsaturated ketone 9.\textsuperscript{12} Indeed, our view of this reaction course was borne out upon thermal combination of 5 and the above cited butadiene derivative at 140°C in toluene solvent containing a small amount of methylene blue as a stabilizer. After 48 h of heating followed by removal of the volatiles under vacuum and treatment of the residue with Amberlite IR-120 in methylene chloride for 30 min at 22°C, we obtained 9 as the sole unsaturated ketone product in 76% yield from 5.\textsuperscript{13}

We had several divergent plans for conversion of 9 into verculcarol. Interestingly, two of these routes were successful, and

(18) Hase, T. A.; McCoy, K. Synth. Commun. 1980, 10, 63. Satisfactory spectral and physical data were obtained for all new compounds.
(21) The \(\beta\)-allylic alcohol could also be converted into the lactone 5 using a procedure described by: Mischeb, O. Synthesis 1981, 1.