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Studies Directed Toward the Synthesis of (+)-Mycotrienin I. Asymmetric Synthesis of the C9-N21 Aromatic Synthon

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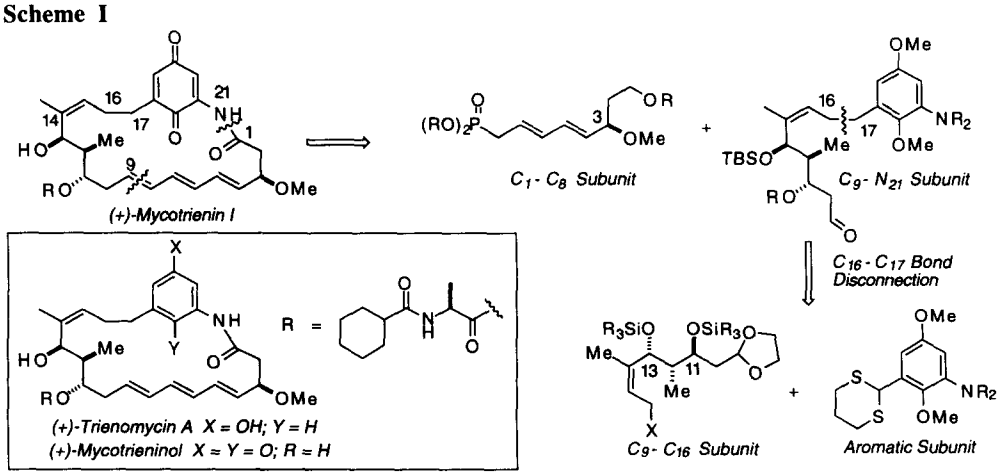
Abstract. The asymmetric synthesis of the C_9-N_{21} fragment of (+)-mycotrienin I is described employing chiral allylsilane bond construction methodology for the installation of the C_{12}-C_{13} absolute stereochemical relationships. In this convergent synthesis the construction of the C_9-C_{16} and C_{17}-N_{21} aromatic synthon subunits and their coupling through a lithio dithiane alkylation strategy are detailed.

(+)-Mycotrienin I and related ansamycin antibiotics trienomycin and mycotrieninol were isolated in 1985 from the culture broth of *Streptomyces* sp No. 83-16, and have been shown to exhibit potent antifungal and antitumor activitiy (Scheme I).[1] These molecules have also been obtained from the fermentation broth of *Streptomyces rishiriensis* T-23[2] and the mycotrienins alone from the broth of *Streptomyces collinus*. Trienomycin A and its derivatives have displayed potent antitumor activity, exhibiting strong cytotoxicity against HeLa S_3 cells *in vitro*. The mycotrienins, while bearing little structural difference from the trienomycins, are potent anti fungal agents.[3] In addition, it was found that (+)-mycotrieninol is eight times less potent than mycotrienin I, which bears a cyclohexylcarbonyl-δ-alanine unit indicating this functionalized amino acid moiety is crucial for the biological activity of these agents. In this report we have provided an efficient route to an advanced synthon which should allow access to other members of this class of natural products.

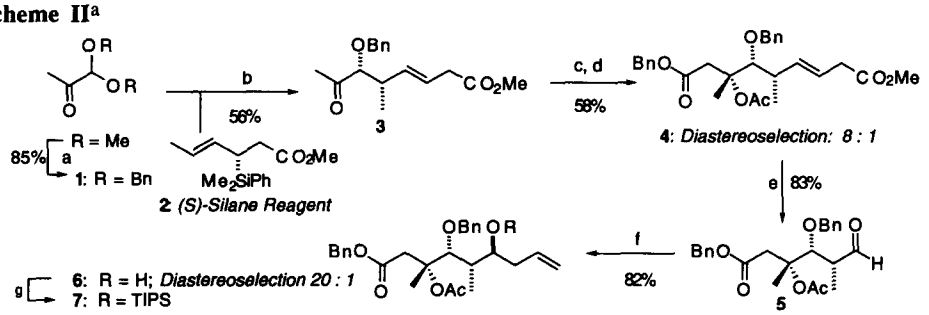
Scheme I



It was anticipated that the absolute stereochemical relationships in this subunit might be controlled through the use of chiral (*E*)-crotylsilane bond construction methodology to establish the C_{12} and C_{13}

centers.[4] From these stereogenic centers, the adjacent center at C_{11} might be constructed through chelate-controlled aldehyde addition of allyltrimethylsilane (Hosomi-Sakurai reaction).[5] The synthesis of this subunit was initiated with a TMSOTf-catalyzed addition of crotylsilane **2** to pyruvic aldehyde dibenzylacetal **1** to give the homoallylic benzylether **3** (56% yield, 96% de) (Scheme II). The facial bias exhibited in this reaction was that expected from a Lewis acid catalyzed electrophilic attack on a (*S, E*)-crotylsilane. The absolute and relative stereochemical assignments of the two new vicinal stereocenters of product **3** were based on previous results from our laboratory.[6] The methyl ketone was then treated with the lithium enolate of benzyl acetate to give a β-tertiary alcohol which was immediately converted to the corresponding acetate under DMAP-catalyzed acylation conditions (NEt_3, Ac_2O, DMAP, CH_2Cl_2, 0 °C → RT, 54% two steps) to give **4** as the major diastereomer (diastereoselection 8:1 */syn:anti*). The sense of diastereoselectivity was thought to result from a Felkin-Anh mode of addition,[7] where the strongly sigma-donating benzyloxy moiety holds the position *anti* to nucleophillic attack of the incoming enolate, generating a *syn*-hydroxy, benzyloxy relative configuration. Ozonolysis of the *trans* double bond of **4** followed by work-up with Me_2S gave the β-benzyloxy aldehyde **5** in 83% yield and was followed by a Hosomi-Sakurai reaction to furnish the C_{11}-C_{13} *anti*-1,3-diol (**6**; 82% yield; diastereoselection 20:1 *anti:syn*). The chelation-controlled allylation of chiral β-alkoxy aldyhydes has been well documented.[8, 9] Silation of the resulting secondary hydroxyl with TIPSOTf[10] and 2,6-lutidine in CH_2Cl_2 furnished the silyl ether **7**, in 99% yield, completing assembly of the four stereochemical elements of this subunit.

Scheme II[a]

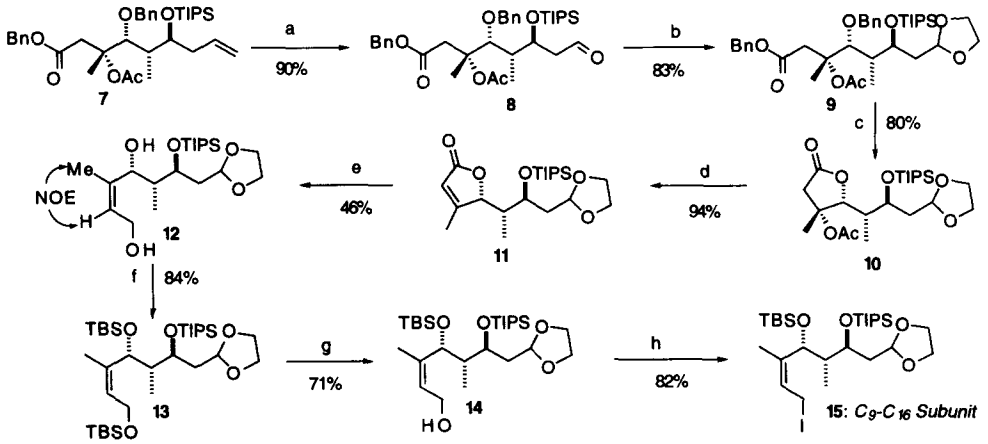


Legend.[a] (a) pyruvate dimethylacetal, benzyl alcohol, catalytic *p*-TsOH, neat, 80 °C, 10 h; (b) TMSOTf, (*E*)-Crotylsilane, CH_2Cl_2, -78 °C → -35 °C, 13 h; (c) benzyl acetate, LiN(TMS)$_2$, THF, -78 °C; (d) NEt_3, Ac_2O, DMAP,CH_2Cl_2, 58% for 2 steps; (e) O_3, methyl sulfide, MeOH, -78 °C → rt, 15 h; (f) $TiCl_4$, allyltrimethylsilane, CH_2Cl_2, -78 °C, 8 h; (g) 2,6-lutidine, TIPSOTf, CH_2Cl_2, 0 °C, 99%.

The installation of the *Z*-olefin and completion of the synthesis of the C_9-C_{16} fragment is summarized in Scheme III. The terminal olefin of **7** was oxidatively cleaved by ozone affording a β-silyoxy aldehyde which was subsequently converted to the ethylene acetal **9**. Hydrogenolysis cleaved both of the benzyl ethers and the derived hydroxy-acid cyclized spontaneously to give the γ-lactone **10**. This transformation removed the benzyl group and set up the ring closure to allow subsequent elimination to form the *Z*-olefin. The completion of this subunit was achieved by DBU catalyzed β-elimination of the acetoxy group. At this juncture, the α,β-unsaturated lactone **11** was subjected to an LAH reduction (Et_2O, TMEDA, 0 °C, 46% yield) to give diol **12** as a single olefin isomer with a *Z* configuration. NOE measurements on this compound supported the assignment of the olefin configuration as the *Z* isomer.

Complete silation of the diol was accomplished using excess TBSOTf and 2,6-lutidine to give the silylether **13** (84% yield) which was followed by the selective removal of the primary TBS ether with HF•pyridine to give the primary allylic alcohol. Finally, the primary hydroxyl of **14** was directly converted to the corresponding allylic iodide using methyltriphenoxyphosphonium iodide in DMF[11] to give **15** through the *in situ* formation of a trialkoxyphosphorane leaving group and subsequent displacement with free iodide ion.

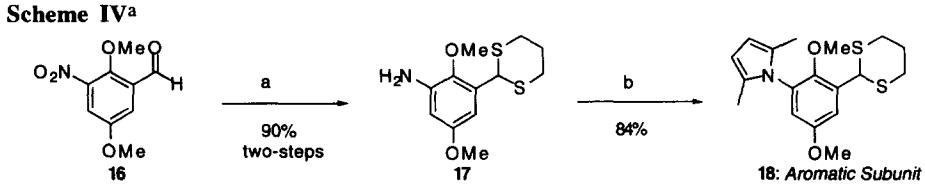
Scheme III[a]



Legend.[a] (a) O_3, methyl sulfide, MeOH, -78 °C → rt, 15 h; (b) ethylene glycol, BF_3•OEt_2, CH_2Cl_2, -78 °C → 0 °C, 15 min; (c) H_2, 10% Pd-C, EtOAc, 10 Parr, 16h; (d) DBU, THF, -78 °C → 0 °C, 0.5 h; (e) LAH, TMEDA, Et_2O, 0 °C, 5 min; (f) 2,6-lutidine, TBSOTf, CH_2Cl_2, 0 °C, 10 min; (g) HF•Pyridine (4:1), THF, rt, 3 h; (h) $H_3CP(OPh)_3I$, DMF, 0 °C → rt, 1 h.

The design of C_{17}-C_{20} subunit was centered around generation of a functionalized aromatic synthon that would alkylate the 1,3-diol fragment after establishment of the trisubstituted *Z*-olefin. To implement this strategy, the primary allylic iodide of the C_9-C_{16} synthon was installed with the intention of displacing it with a strong nucleophile, thus effecting an efficient alkylation procedure. On the basis of literature precedent,[12] a cyclic dithioacetal **18** was chosen as a precursor to a stabilized carbanion. This reagent type illustrates the well documented umpolung strategy by the generation of a formal negative charge at an otherwise electrophillic carbon.[13] The corresponding acyl group, of which this intermediate is a synthetic equivalent, is a benzaldehyde derivative which is ultimately obtained from 2,5-dimethoxy-3-nitrobenzaldehyde **16** (Scheme IV), was chosen because of its synthon equivlency to the desired amido-benzoquinone system of the ansamycin natural products.

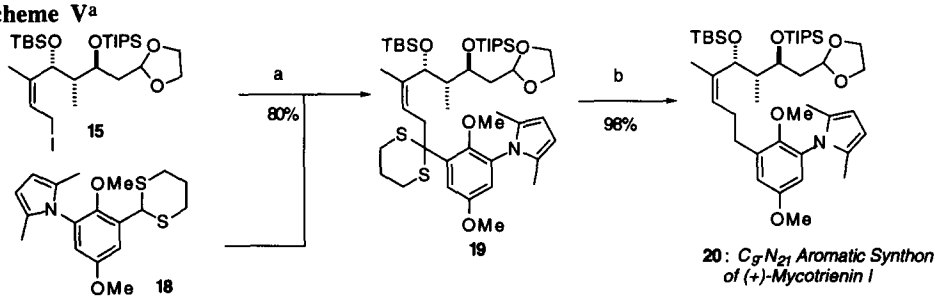
Scheme IV[a]



Legend.[a] (a) i. BF_3•OEt_2, propanedithiol, CH_2Cl_2, -30 °C, 15 min; ii. $SnCl_2$•$2H_2O$, EtOAc, 70 °C, 2h; (b) 2,5-hexadione, AcOH, toluene, reflux, 16 h.

With the 1,3-diol synthon **15** and aromatic synthon **18** in hand, the two subunits were assembled according to the alkylation procedure outlined in Scheme V. The ensuing coupling reaction consisted of low temperature deprotonation of the dithioacetal with n-BuLi followed by subsequent alkylation with the allylic iodide. The subunit coupling reaction proceeded cleanly at -78°C (1.5 h) to give the desired thioketal **19** in 80% yield. The dithioketal was then cleaved by treatment with a 50% slurry of W-7 Raney-nickel in ethanol under a hydrogen atmosphere to give rise to the desired methylene unit at C_{17} completeing the assembly of the C_9-N_{21} aromatic synthon of (+)-mycotrienin I. Noteworthy is the fact that the desulfurization proceeded cleanly and rapidly (10 minutes) with no apparent reduction of the trisubstituted olefin or involvement of the pyrrole system.

Scheme V[a]



Legend.[a] (a) n-BuLi, -78 °C, THF; (b) Raney-nickel, EtOH, rt.

In conclusion, we have described the asymmetric synthesis of the C_9-N_{21} aromatic fragment of (+)-mycotrienin I employing chiral allylsilane bond construction methodology. Studies on the total synthesis of the ansamycin benzoquinone antibiotics will be reported in due course.

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