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Studies of novel cyclitols. A synthesis of 3′*O*,4′*O*-dimethylfuniculosin†

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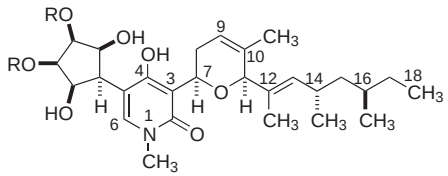
Abstract

A synthesis of funiculosin dimethyl ether (**2**) is described. Methodologies for an asymmetric conjugate addition to establish the 1,3-*anti* dimethyl array, stereocontrolled formation of the *Z*,*E*-bis-allylic C-11 alcohol, and interception of a reactive pyridinone methide are examined. © 2000 Published by Elsevier Science Ltd.

Funiculosin (**1**) is isolated as a unique metabolite from the fermentation broth of *Penicillium funiculosium* (Thom Iam 7013).[1] Significant biological activity is exhibited as a potent, broad-spectrum antifungal with activities comparable to griseofulvin. Most notably, funiculosin shows consistently excellent results against *Trichophyton asteroide*, *T. mentagrophytes* and *T. yubrum*. The natural product also demonstrates in vitro activity against Herpes simplex virus (Strain HF) and Newcastle disease virus with modest antitumor effects. The structural characterization of **1** was disclosed in 1978 upon hydrogenation to yield 9,10,12,13-tetrahydrofuniculosin, which provided for unambiguous assignment via a single-crystal X-ray diffraction study.[1b] The structure displays an unusual all *syn*-cyclopentanetetrol as a rare example of a substituted cyclitol that is directly C-linked to the 5-position of the heterocyclic nucleus.[2] In fact, the presence of the 3,5-disubstituted-4-hydroxy-2-pyridinone in naturally occurring secondary metabolites is also unusual. Recent representatives of this family, including pyridomacrolidin,[3a] oxysporidinone,[3b] apiosporamide,[3c] fischerin,[3d] and sambutoxin,[3e] possess a range of biological properties.



1 (Funiculosin) R = H
2 (3′*O*,4′*O*-Dimethylfuniculosin) R = CH_3

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† Dedicated as a tribute to Professor Harry H. Wasserman in recognition of his statesmanship, his leadership, and his unwavering passion in support of excellence in our science.

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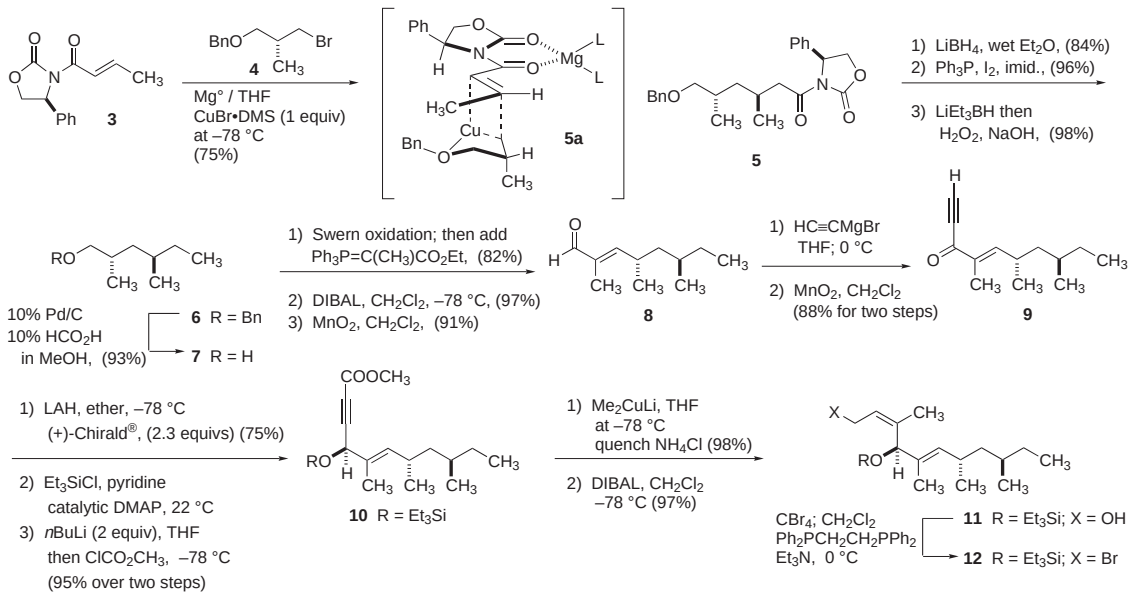
Our earlier efforts toward tenellin and ilicicolin H provided the first examples of total syntheses within this class of natural products.[4] Additional advances in these laboratories, as well as others, have underscored interest in the fundamental chemistry of these heterocyclic systems.[5] Herein we have described the first synthesis pathway leading to the enantiocontrolled construction of the intact funiculosin nucleus with the stereoselective preparation of funiculosin dimethyl ether **2**.

Our synthesis strategy recognized the *meso* plane of symmetry in the all-*syn*-cyclopentanetetrol portion of **1**, greatly simplifying issues of stereochemistry for a convergent pathway. In fact, we have studied intramolecular enolate condensations using stable carboxamidimidazolides as a general preparation of functionalized 4-hydroxy-2-pyridinones incorporating the cyclitol fragment.[5a] Pattenden has also described a route to the all-*syn*-cyclopentanetetrol.[6] However, we were unable to utilize intermediates containing the intact pyridone to further synthesis efforts toward **1**. Therefore, we have explored formation of the heterocyclic system as a late-stage event after stereocontrolled assembly of the intact carbon backbone. These efforts began with the asymmetric conjugate addition utilizing the Hruby 4-phenyloxazolidinone auxiliary[7] as shown in Scheme 1.



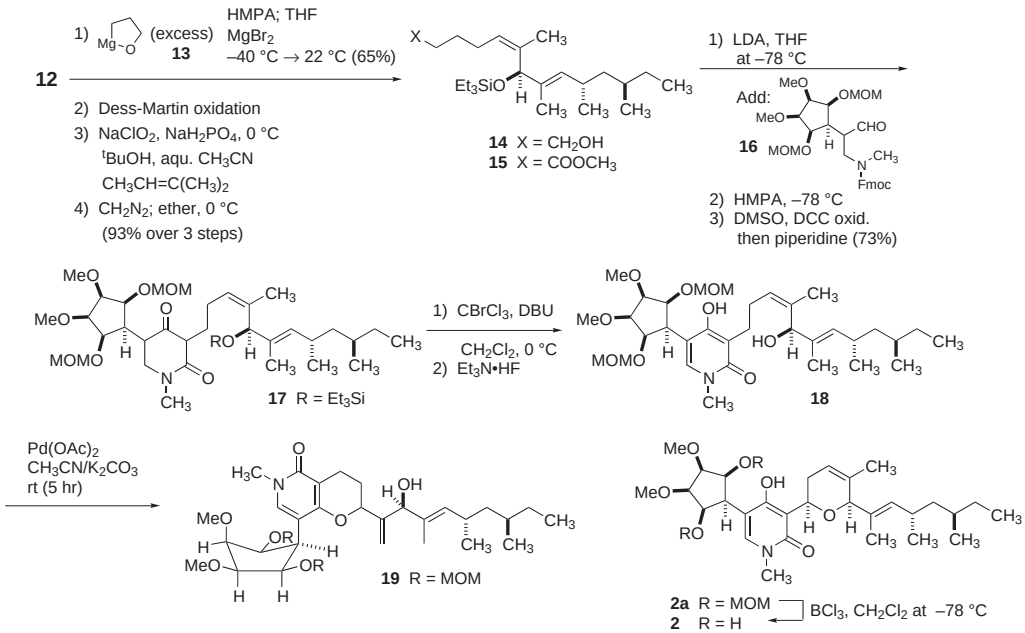
Scheme 1.

Addition of the Yamamoto organocopper reagent derived from bromide **4**[8] provided the 1,3-*anti*-dimethyl array in **5** with complete diastereofacial selectivity. Chelation in the *S*-*syn*-conformer as depicted in **5a** facilitated a process of double stereodifferentiation, and benzyl ether **6** was obtained in 79% overall yield following reductive removal of the chiral auxiliary.[9] Subsequent conversion to the enal **8** proceeded in straightforward fashion.

Selective construction of the C_9–C_{10} *Z*-trisubstituted alkene offered the additional challenge for the introduction of the desired (*S*)-stereochemistry of the bis-allylic C_{11}-alcohol. This was resolved by production of the acetylenic α,β-unsaturated enone **9**, and successful deployment of the Mosher asymmetric reduction,[10] resulting in remarkably high facial selectivity for this

modified hydride reagent.[13] Thus, the addition of an ethereal solution of 2.3 equivalents of (2*S*,3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol((+)-Chirald®)[10c] to a suspension of $LiAlH_4$ (1 equiv.) in ether at 0°C resulted in a thick precipitate which was cooled to −78°C. Slow addition of an ether solution of ketone **9** over 1.5 h and continued stirring for 4.5 h provided an 88% yield of acetylenic alcohols (85:15 dr).[11] This stereoselective reduction of acyclic, cross-conjugated alkynones is notable in light of reported results for steric recognition of unsaturated aromatic, acetylenic, or vinylic substitution versus larger sp^3 aliphatic substitution. In our case, the modified aluminum hydride is capable of steric discrimination between the smaller alkyne unit and the adjacent, conjugated alkenyl residue.[12] Silyl ether formation led to the separation of diastereomers by silica gel chromatography, and *C*-acylation gave the acetylenic ester **10**. Finally, the *syn*-addition of dimethylcuprate at low temperature was followed by DIBAL reduction to yield the doubly unsaturated *Z*,*E*-allylic alcohol **11**.

In order to explore our carbonyl condensation strategy for formation of the pyridone ring, a three-carbon extension of the acyclic chain was required. Conversion to the allylic bromide **12** (Scheme 1) permitted nucleophilic displacement with Grignard reagent **13** (Scheme 2) prepared from 3-chloro-1-propanol via initial deprotonation with ethylmagnesium chloride (1 equiv.) yielding **14** (65%).[13] Oxidation and transformation to the desired methyl ester **15** was uneventful. Production of the lithium enolate of **15** and low temperature aldol condensation with aldehyde **16**[14] was immediately followed by Moffat oxidation of the crude product mixture and removal of Fmoc protection to produce the 5,6-dihydropyridinone **17** in 73% yield.[15] Mild oxidation with $BrCCl_3$ and DBU[16] and desilylation gave the penultimate intermediate **18**. Our plans for the formation of the 2,6-*cis*-dihydropyranyl system of **2** required the generation of a highly reactive pyridone methide to effect spontaneous intramolecular conjugate addition of the bis-allylic (C_{11}) hydroxyl group.[17] In the event, our application of Saguesa oxidation conditions[18] afforded a 48% yield of two novel products, which were separated by flash silica gel chromatography (2:1



Scheme 2.

ratio). Upon deprotection at −78°C, funiculosin dimethyl ether (**2**) was isolated as the product of palladium-induced allylic oxidation. The major component of the cyclization reaction was the unique C-linked glycoside **19**, rationalized as the product of competing π-palladium complexation, initiating a formal 6-*exo*-trig etherification followed by palladium hydride elimination.[19] The structural assignment of funiculosin dimethyl ether (**2**) was confirmed by direct spectral comparisons of carbon and proton NMR data obtained from a sample of the natural product **1**.[20] Further efforts will be reported in due course.

Acknowledgements

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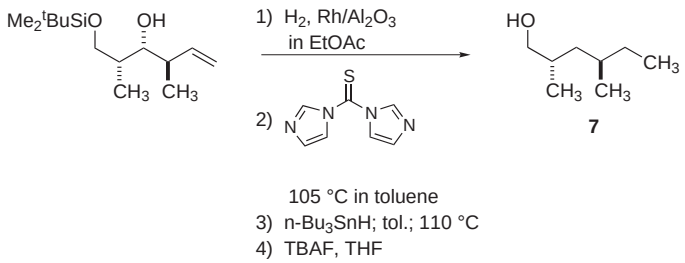
8. Bromide **4** and its corresponding Grignard reagent were prepared from (2*R*)-methyl-3-hydroxy-2-methylpropionate (Aldrich) via reaction with benzyl 2,2,2-trichloroacetimidate, $LiAlH_4$ reduction, tosylation and exchange with LiBr in DMF at 50°C (J. Earley, Ph.D. Thesis, Indiana University 1996).
9. Confirmation of our 1,3-stereochemistry was established by an independent synthesis using asymmetric allylation methodology to produce a homochiral allylic alcohol. (Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. *J. Org. Chem*. **1987**, *52*, 316.) Conversion to alcohol **7** was accomplished in four steps (65% overall yield).



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11. The diastereomer ratio was determined by ^{1}H NMR integration of chemical shifts of bis-allylic methine hydrogens and Mosher ester analysis (see Ref. 10b). Conversion to **2** attests to the *S*-assignment.
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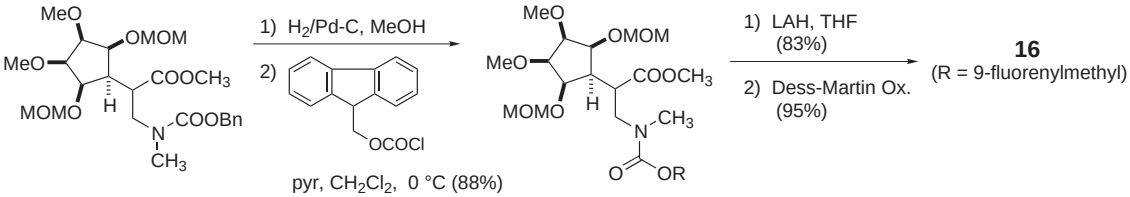
14. Aldehyde **16** was prepared by an extension of previous studies (Ref. 5a) as summarized below.



15. Crude products of intermediate steps stemming from the aldol reaction contain *N*-protected and cyclized materials from partial loss of the Fmoc unit. Lactam **17** is a mixture of diastereomers, existing as keto tautomers, whereas ^{1}H NMR evidence describes **18** as completely enolic at C-4.
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19. The C-9 stereochemistry of **19** cannot be unambiguously assigned from ^{1}H NMR data.
20. We thank Dr. P. Bollinger (Sandoz AG, Basel) for a generous sample of funiculosin to assist our studies.