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Communications

Synthetic Studies on Thaxtomins A and B, Phytotoxins Associated with *Streptomyces scabies*, the Causal Organism of Potato Common Scab

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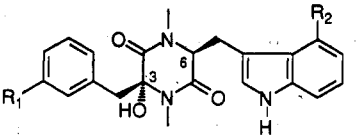
Summary: The preliminary results of a study on the stereocontrolled racemic synthesis of thaxtomins A and B are disclosed. The synthesis features a new C–C bond-forming reaction: dilithium tetrachlorocuprate was shown to be an efficient catalyst for cross-coupling reactions of lithiated 1,4-dialkyl-2,5-piperazinedione anions with gramine methosulfate and alkyl halides.

A new series of toxins named thaxtomins has been recently isolated from *Streptomyces scabies* and related fungi.[1] The two main representatives of this class of fungal metabolites are thaxtomins A and B assigned, respectively, as **1a** and **1b** on the basis of spectroscopic evidence.[2] King et al. have reported that ng quantities of these phytotoxins produced extracellularly by pathogenic strains induce the development of scablike lesions on aseptically cultured potato tubers.[3] As part of a program directed toward synthesizing and studying 2,5-piperazinediones possessing pesticidal properties, **1a** and **1b** were chosen as potentially interesting targets. Although numerous synthetic studies toward structural analogs such as fumitremorgins, saframycins, or bicyclomycins have appeared,[4] the multistep pathways that have been developed to install the indol-3-yl group preclude convenient access to reasonable quantities for further elaboration or study. Herein we report a straightforward racemic synthesis to this new class of compounds which involves a new bimolecular C–C bond-forming reaction.



1 (3R, 6S)

a Thaxtomin A (R_1= OH, R_2= NO_2)
b Thaxtomin B (R_1= H, R_2= NO_2)
c (R_1= OH, R_2= H)

Synthetic analysis of the structure **1c** chosen as a model indicates a possible first route represented in Scheme I. Aldol condensation of the readily available 1,4-diacetyl-2,5-piperazinedione (**2**)[5] and 3-(benzyloxy)benzaldehyde gave arylidenepiperazinedione **3** in 76% yield as the sole product (NEt_3/DMF).[6] After deacetylation of **3** with hydrazine (DMF, 23 °C, 83%),[7] the *Z* isomer **4** was

(1) (a) Lawrence, C. H.; Clark, M. C.; King, R. R. *Phytopathology* **1990**, *80*, 606. (b) King, R. R.; Lawrence, C. H.; Calhoun, L. A. *J. Agric. Food Chem.* **1992**, *40*, 834.

(2) King, R. R.; Lawrence, C. H.; Clark, M. C.; Calhoun, L. A. *J. Chem. Soc., Chem. Commun.* **1989**, 849. In this article, the absolute stereochemistry was established by the synthesis of cyclo(L-4-(nitrotryptophyl)-L-phenylalanyl) and cyclo(D-4-(nitrotryptophyl)-L-phenylalanyl). Only the former compound exhibited thaxtomin-like activity.

(3) Common scab of potato caused by the bacterium *Streptomyces scabies* is considered as a disease of major economic importance in many potato-producing areas in the world.

(4) (a) Nakatsuka, S.; Miyazaki, H.; Teranishi, K.; Goto, T. *Tetrahedron Lett.* **1986**, *27*(21), 2391. (b) Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 3712. (c) Williams, R. M.; Maruyama, L. K. *J. Org. Chem.* **1987**, *53*, 4044.

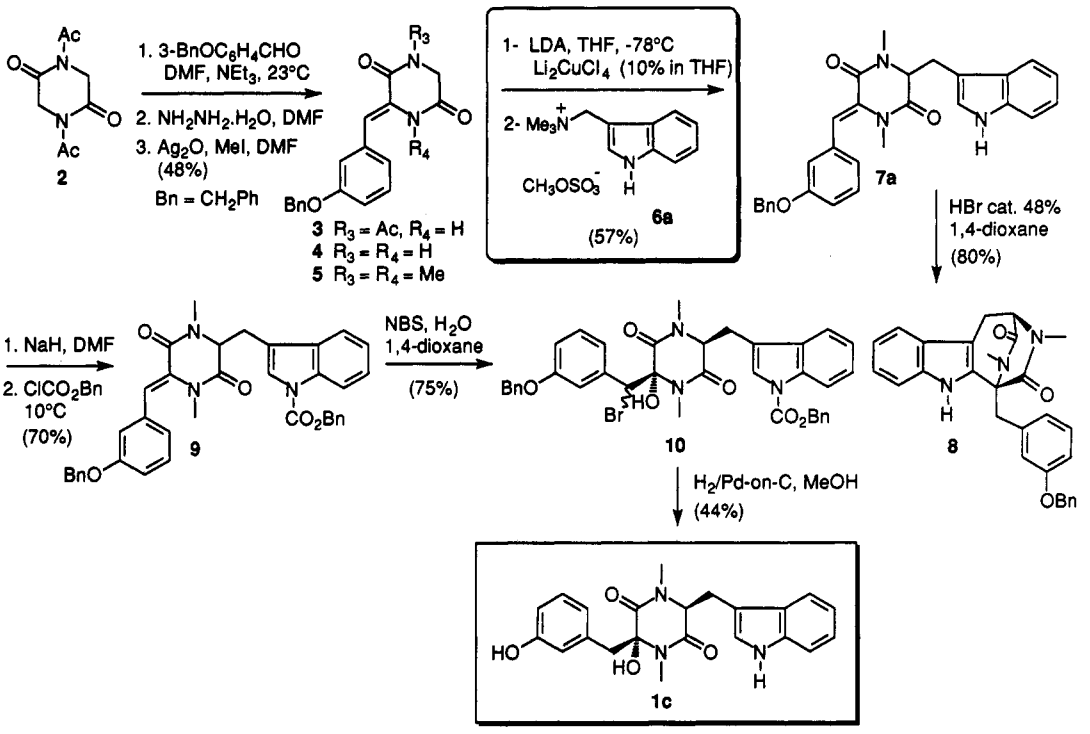
(5) Marcuccio, S. M.; Elix, J. A. *Aust. J. Chem.* **1984**, *37*(8), 1791.

(6) Gallina, C.; Liberatori, A. *Tetrahedron Lett.* **1973**, 1135.

(7) Yonezawa, Y.; Hayakawa, M. *Heterocycles* **1980**, *14*(11), 1767.

0022-3263/93/1958-3473$04.00/0

Scheme I



dialkylated with methyl iodide in the presence of silver oxide in DMF to afford **5** in 75% yield.[8]

Direct introduction of the indole nucleus onto **5** proved more difficult. Although the methodology devised by Kametani and later developed by Williams for the synthesis of brevianamides A and E could be utilized,[9,10] we were interested in a more direct and more efficient route. Our initial efforts to bring about the direct functionalization of **5** to the derivative **7a** were uniformly unsuccessful under a variety of conditions: e.g., treatment of **5** with LDA in THF at −78 °C in the presence of HMPT followed by quenching with gramine methosulfate (**6a**)[11] gave only traces of the desired substrate corresponding to **7a**.

We were quite surprised to discover that simply replacing HMPT by dilithium tetrachlorocuprate[12] as catalyst in the reaction above produced **7a** in a yield which was satisfactory (LDA, THF, −78 °C; Li_2CuCl_4 10% in THF; gramine methosulfate (**6a**), −78 to 23 °C; 57%).[13,14]

With the successful achievement of target **7a**, efforts were then directed at functionalizing the hydroxy group in the bridgehead position of the piperazinedione ring. It was found that after treatment with *N*-bromosuccinimide and water at ambient temperature,[15] the structure **8** resulting from the Pictet–Spengler cyclization of **7a** was formed.[16] Furthermore, this cyclization was found to be catalyzed by hydrobromic acid. Thus, **8** was obtained as a single product in 80% yield by heating **7a** in 1,4-dioxane for 3 h with a catalytic amount of HBr.

Protection of amino group of the indole nucleus as the corresponding benzyl carbamate was accomplished by treatment of **7a** with benzyl chloroformate in DMF in the presence of sodium hydride to afford the derivative **9** (70%).[17] Finally, compound **9** was converted via a mixture of two diastereoisomers **10** (NBS, H_2O, 1,4-dioxane, 23 °C

Table I. Li_2CuCl_4-Catalyzed Alkylation of the Lithiated 2,5-Piperazinedione Anion 5 with Alkyl Halides

entry	alkyl halide	product[a-c] (%)	mp (°C)
1	MeI	**7b** (50)	oil
2	iPrI	**7c** (33)	oil
3	$PhCH_2Br$	**7d** (68)	146–148
4	$3\text{-}NO_2C_6H_4CH_2Br$	**7e** (39)	59–62
5	$Br(CH_2)_2CO_2Et$	**7f** (27)	96–98

[a] In a typical experimental procedure, a solution of **5** (15 mmol) in THF was added to a solution of LDA (30 mmol) in THF at −78 °C. The mixture was stirred for 30 min under a N_2 atmosphere. After consecutive addition of a solution of Li_2CuCl_4 (1.5 mmol) in THF (5 mL) and the alkyl halide (17.8 mmol) at −78 °C, the mixture was stirred for 40 additional min, heated gradually to ambient temperature, and concentrated and the crude residue purified by flash chromatography to yield pure compounds **7b–f**. [b] Isolated yields based on starting material **5**. [c] Attempted reactions of **5** with nBuLi in the absence of Li_2CuCl_4 were not successful. When HMPT instead of Li_2CuCl_4 was employed, only traces of **7b** (<5%) were formed.

(8) Colombo, L.; Gennari, C.; Scolastico, C.; Guanti, G.; Narcisano, E. *J. Chem. Soc., Chem. Commun.* **1979**, 591.

(9) (a) Kametani, T.; Kanaya, N.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 3974. (b) Somei, M.; Karazawa, Y.; Kaneko, C. *Heterocycles* **1981**, *16*, 941.

(10) (a) Williams, R. M.; Glinka, T.; Kwast, E. *J. Am. Chem. Soc.* **1988**, *110*, 5927. (b) Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 808.

(11) (a) Hester, J. B. *J. Org. Chem.* **1964**, *29*, 1158. (b) Endo, Y.; Shudo, K.; Itai, A.; Hasegawa, M.; Sakai, S. *Tetrahedron* **1986**, *42*(21), 5905.

(12) The catalytic effect of copper derivatives for coupling Grignard reagents with alkyl halides has been well established: (a) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303. (b) Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82–83. (c) Friedman, L.; Shani, A. *J. Am. Chem. Soc.* **1974**, *96*(22), 7101.

(13) The catalytically active species appear to be a copper(I) derivative: CuI was as effective as Li_2CuCl_4 in this reaction.

(14) Joucla reported that imine anions of α-amino esters undergo copper-catalyzed substitution reactions with α,ω-dihaloalkanes. See: Joucla, M.; El Goumzili, M. *Tetrahedron Lett.* **1986**, *27*(15), 1681.

(15) (a) Shin, C.; Sato, Y.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1909. (b) Shin, C.; Sato, Y.; Ohmatsu, H.; Yoshimura, J. *Ibid.* **1981**, *54*, 1137.

(16) An analogous example has already been reported: Plate, R.; Nivard, R. J. F.; Ottenheijm, H. C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2473.

(17) Dirlam, J. P.; Clark, D. A.; Hecker, S. J. *J. Org. Chem.* **1986**, *51*(25), 4920.

(1:1), 75%)[18] into the target 2,5-piperazinedione **1c** as a sole stereoisomer, after simultaneous removal of the two protective groups and the bromine atom by catalytic hydrogenation with H_2/Pd on charcoal (Et_3N, MeOH, 44%).

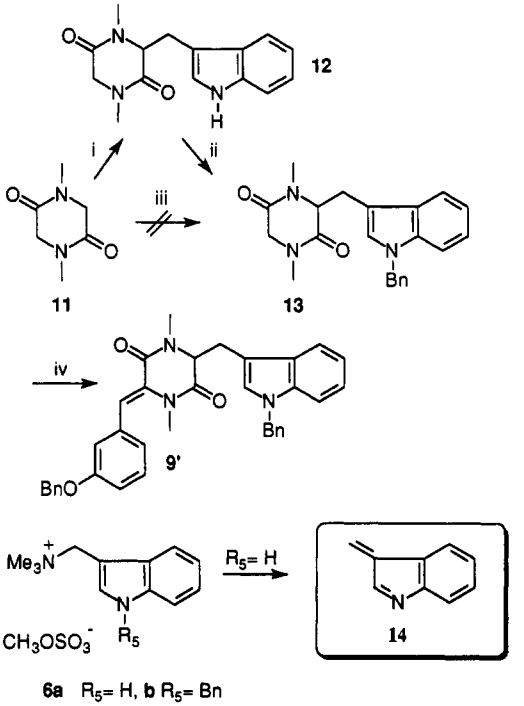
To help the establishment of the scope of this new carbon homologation, several commonly available precursors were coupled with the lithiated anion of **5** to give rise, in moderate to good yields, to the corresponding branched piperazinediones **7b–f** that hitherto have been relatively inaccessible (Table I).

A more direct and more efficient route to **1c** was then realized as outlined in Scheme II. It was found that our new methodology could be utilized with the parent 1,4-dimethyl-2,5-piperazinedione: treatment of **11** with 1 equiv of LDA at −78 °C in the presence of Li_2CuCl_4 followed by addition of 1 equiv of gramine methosulfate **6a** afforded the expected product **12** in 45% yield; when 2 equiv of LDA were used, **12** was obtained in 80% yield. However, 1-benzylgramine methosulfate (**6b**)[19] did not react in the same reaction conditions.

These results indicate that gramine methosulfate (**6a**) could react with lithiated piperazinedione anions via the 1-azadiene intermediate **14** in a stepwise elimination–addition mechanism.[20] Finally, after protection of amino group of the indole nucleus of **12**[21] with benzyl bromide (NaH, DMF, 0 °C, 78%), condensation of **13** with 3-(benzyloxy)benzaldehyde proceeded smoothly (*t*BuOK, DMF, 23 °C) to give exclusively the key intermediate arylidenepiperazinedione **9′** in 90% yield.[22]

Studies are in progress to elucidate the fundamental chemical, structural, and biological properties of these cyclic dipeptides. It is anticipated that the new carbon homologation strategy employed herein will lead to more efficient syntheses of other piperazinediones related to and including the thaxtomin series.

Scheme II[a]



[a] (i) LDA, THF, −78 °C; Li_2CuCl_4 (10% in THF); **6a**, −78 to +23 °C; mp 115 °C (80%); (ii) BnBr, NaH, DMF, 0 °C (78%); (iii) LDA, THF, −78 °C; Li_2CuCl_4 (10% in THF); **6b**, −78 to +23 °C (0%); (iv) 3-(benzyloxy)benzaldehyde, tBuOK, DMF, rt, mp 60 °C (90%).

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Supplementary Material Available: Procedures and NMR spectra (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(18) (a) The relative stereochemistry of the diastereoisomers **10** was assigned by analogy with prior published reports involving similar structural types. See: Shin, C.; Yonesawa, Y.; Sato, Y.; Nakano, T. *Heterocycles* **1983**, *20*(3), 405 and ref 15. (b) Isomers ratio determined by ^1H NMR analysis of the crude mixture.

(19) Somei, M.; Karazawa, Y.; Kaneko, C. *Heterocycles* **1981**, *16*(6), 941.

(20) (a) Synder, H. R.; Eliel, E. L. *J. Am. Chem. Soc.* **1948**, *70*, 1703. (b) Melhado, L. L. *J. Org. Chem.* **1981**, *46*(9), 1920.

(21) (a) Meier, J. *Bull. Soc. Chim. Fr.* **1962**, 290. (b) Leonard, N. J.; Fujii, T. *J. Am. Chem. Soc.* **1963**, *85*, 3719.

(22) (a) Gallina, C.; Liberatori, A. *Tetrahedron* **1974**, *30*, 667. (b) Fukuyama, T.; Nunes, J. *J. Am. Chem. Soc.* **1988**, *110*, 5196.