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Spongistatin Synthetic Studies. An Efficient, Second-Generation Construction of an Advanced ABCD Intermediate

Amos B. Smith, III,* Victoria A. Doughty, Chris Sfouggatakis, Clay S. Bennett, Jyunichi Koyanagi, and Makoto Takeuchi

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

smithab@sas.upenn.edu

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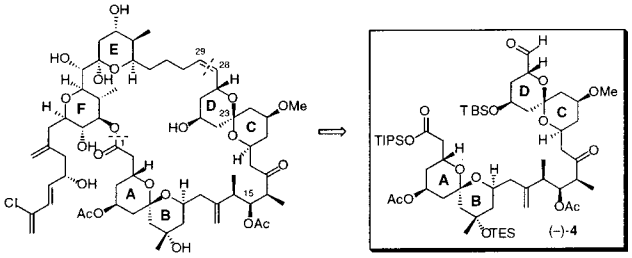
ABSTRACT



Spongistatin 1 (**1**)

A short, efficient, and stereocontrolled synthesis of (−)-4, an advanced ABCD subunit of the spongistatins, has been achieved. Central to the synthetic strategy is the multicomponent linchpin union of silyl dithianes with epoxides to access both the AB and CD fragments. Fragment coupling was then achieved via an efficient stereoselective aldol reaction. The linear sequence required 22 steps and proceeded in 4.0% overall yield.

The spongistatins (aka altohyrtins) comprise a family of unique, architecturally complex bisspiroketal macrolides, which display extraordinary cytotoxicity.[1] Since their independent isolation by three research groups,[2−4] the spongistatins have been the focus of considerable attention in both the chemical and biological communities, based on their intriguing structures and potent antitumor activities.[5] The relative and absolute stereochemistries, first deduced by Kitagawa,[4] were confirmed via the total syntheses of spongistatin 1 (**1**) by Kishi[6] and spongistatin 2 (**2**) by Evans (Figure 1).[7] More recently, we[8] and Paterson[9] have also

(1) (a) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302. (b) Pettit, G. R. *Pure Appl. Chem.* **1994**, *66*, 2271. (c) Bai, R.; Taylor, G. F.; Cichacz, Z. A.; Herald, C. L.; Kepler, J. A.; Pettit, G. R.; Hamel, E. *Biochemistry* **1995**, *34*, 9714.

(2) (a) Pettit, G. R.; Tan, R.; Gao, F.; Williams, M. D.; Doubek, D. L.; Boyd, M. R.; Schmidt, J. M.; Chapuis, J.-C.; Hamel, E.; Bai, R.; Hooper, J. N. A.; Tackett, L. P. *J. Org. Chem.* **1993**, *58*, 2538. (b) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1166. (c) Pettit, G. R.; Herald, C. L.; Cichacz, Z. A.; Gao, F.; Schmidt, J. M.; Boyd, M. R.; Christie, N. D.; Boettner, F. E. *J. Chem. Soc., Chem. Commun*. **1993**, 1805. (d) Pettit, G. R.; Herald, C. L.; Cichacz, Z. A.; Gao, F.; Boyd, M. R.; Christie, N. D.; Schmidt, J. M. *Nat. Prod. Lett.* **1993**, *3*, 239. (e) Pettit, G. R.; Cichacz, Z. A.; Herald, C. L.; Gao, F.; Boyd, M. R.; Schmidt, J. M.; Hamel, E.; Bai, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1605.

(3) Fusetani, N.; Shinoda, K.; Matsunaga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977.

(4) (a) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazoe, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett.* **1993**, *34*, 2795. (b) Kobayashi, M.; Aoki, S.; Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 1243. (c) Kobayashi, M.; Aoki, S.; Sakai, H.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1993**, *41*, 989. (d) Kobayashi, M.; Aoki, S.; Gato, Kitagawa, K. I. *Chem. Pharm. Bull.* **1996**, *44*, 2142.

(5) See ref 8a and also ref 9 for a list to date of synthetic studies towards the spongistatins.

(6) (a) Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi,Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 187. (b) Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J.; Kishi, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 192.

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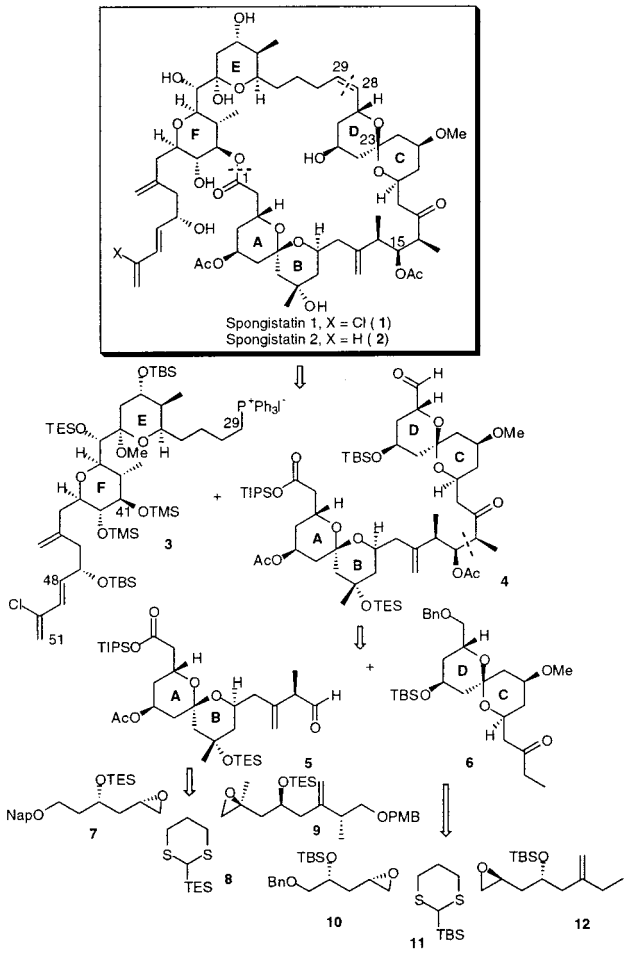


Figure 1.

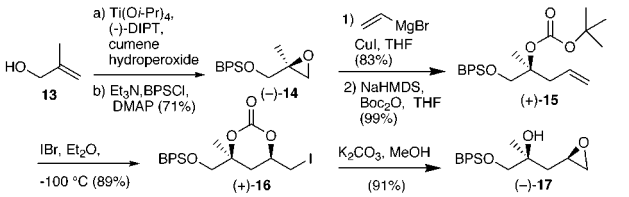
achieved successful total syntheses of **1** and **2**. Structurally, the spongistatins possess a striking array of features, including a 42-membered macrolactone incorporating two spiroketals, a hemiacetal, and a pyran, which is subtended by a highly unsaturated side chain.

Recognizing the power of the *anti*-aldol reaction to unite the AB and CD fragments, as exploited to great advantage by Evans,[7] Paterson,[9] and Heathcock,[10] we reasoned that with our multicomponent linchpin[11] and iodocarbonate cyclization[12] tactics, an efficient synthesis of an ABCD fragment could be achieved as outlined in Figure 1. In this Letter we describe a second-generation approach to subunit **4**, which sets the stage for efficient syntheses of both spongistatins 1 and 2, as well as numerous analogues for further biological study.

Construction of the AB spiroketal fragment **5** called for linchpin union of epoxides **7** and **9**, the former prepared in nearly identical fashion as our first-generation synthesis except for selection of the 2-naphthylmethyl protecting group, recently introduced by Spencer, Gaunt, and Yu.[13,14]

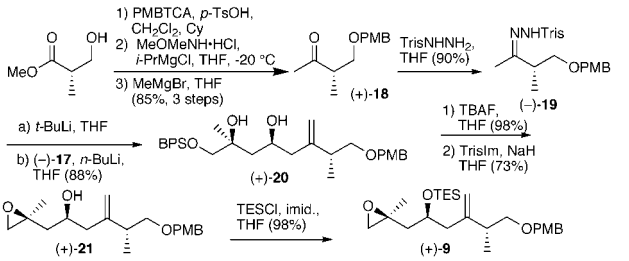
Epoxide (+)-**9** in turn was prepared in 7 steps via coupling epoxide (−)-**17** (Scheme 1) with hydrazone (−)-**19** (Scheme 2), exploiting a Shapiro coupling tactic. To this end, Sharpless epoxidation of commercially available **13**, followed by in situ silyl protection furnished known epoxide (−)-**14**.[15,16] Treatment with vinyl cuprate, formation of the mixed BOC carbonate, and execution of our iodocarbonate cyclization protocol[12] then led to (+)-**16** as a readily separable mixture (7:1) of diastereomers favoring the desired *syn* isomer. Basic methanolysis provided epoxide (−)-**17**.

Scheme 1



Ketone (+)-**18** was next prepared via protection of Roche's ester (PMBTCA, *p*-TsOH) (Scheme 2), followed by formation of the Weinreb amide, employing the Merck protocol[17]

Scheme 2



(7) (a) Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2738. (b) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2741. (c) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2744. (d) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671.

(8) (a) Smith, A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 191; (b) Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase N.; Nakayama K. *Angew. Chem., Int. Ed.* **2001**, *40*, 196.

(9) Paterson, I.; Chen D. Y.-K.; Coster, M. J.; Aceña, J. L.; Bach, J.; Gibson, K. R.; Keown, L. E.; Oballa, R. M.; Trieselmann, T.; Wallace, D. J.; Norcross, R. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4055.

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(11) Smith, A. B., III; Boldi, A. M. *J. Am. Chem. Soc*. **1997**, *119*, 6925.

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(13) Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem*. **1998**, *63*, 4172.

(14) See Supporting Information.

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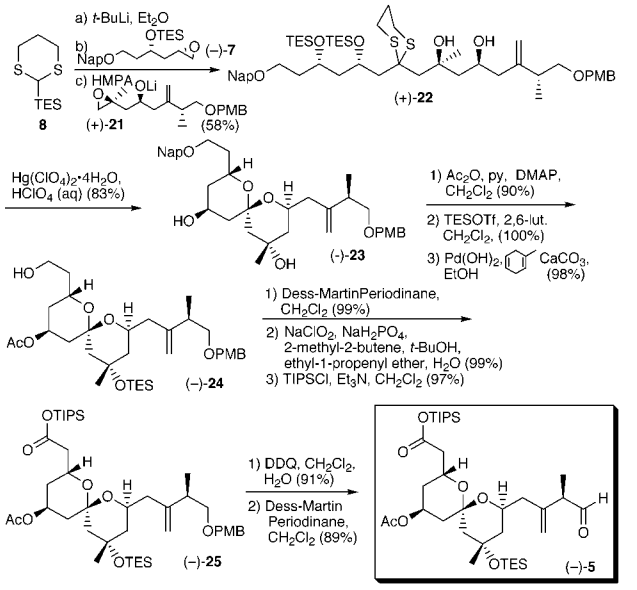
(16) Behnke, D.; Hennig, L.; Findeisen, M.; Welzel, P.; Müller, D.; Thormann, M.; Hofmann, H.-J. *Tetrahedron* **2000**, *56*, 1081.

(17) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

(*i*-PrMgCl, MeOMeNH·HCl), which both avoids the use of pyrophoric trimethylaluminum and is readily amenable to scale-up. Addition of methyl-magnesium bromide furnished ketone (+)-**18**. Formation of the trisyl hydrazone (−)-**19** (trisyl hydrazide, THF, 90%),[18−20] followed by deprotonation with 2 equiv of *t*-BuLi, and introduction of the lithium anion derived from epoxide (−)-**17** resulted in diol (+)-**20** (88% yield). Importantly, this reaction can be carried out on a multiple-gram scale. Completion of the synthesis of (+)-**9** entailed removal of the silyl ether (TBAF, 98%), formation of epoxide (+)-**21** (trisylimidazole, NaH, THF, 73%),[21] and silyl protection (TESCl, imid., 98%).

Studies on the linchpin union of (−)-**7** and (+)-**9** began by employing (+)-**9** as the first epoxide (Scheme 3). Lithiated

Scheme 3

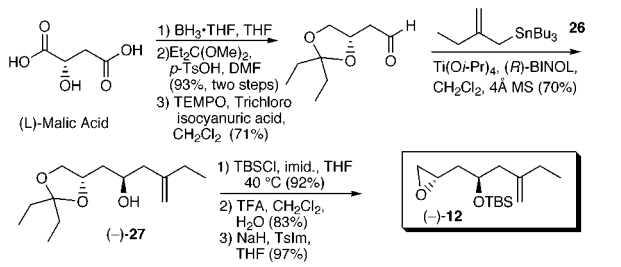


2-TES-1,3-dithiane, however, did not react with the epoxide; only elimination products and recovered epoxide (+)-**9** were observed. To circumvent this problem, the order of epoxide coupling was reversed, with the lithium anion of epoxide (+)-**21** serving as the second component. This tactic provided the desired coupled product (+)-**22** in 58% yield. Importantly, the sequence removed the need for silyl protection, thereby shortening the longest linear sequence by one step.

To our delight, in situ spiroketalization occurred upon removal of both the dithiane and silyl ethers in (+)-**22** with $Hg(ClO_4)_2 \cdot 4H_2O$ to furnish spiroketal (−)-**23** as the sole product in 83% yield (Scheme 3). Careful NOESY NMR experiments revealed that spiroketal (−)-**23** indeed possessed the thermodynamically most stable bisaxial configuration. Selective acetylation of the secondary hydroxyl followed by TES protection of the tertiary hydroxyl and removal of the naphthylmethyl group (catalytic transfer hydrogenolysis) then led to (−)-**24**. Of considerable note, the naphthylmethyl group was removed in the presence of a PMB ether, an exomethylene, a TES ether, an acetate, and the spiroketal. Two-step oxidation, followed in turn by TIPS protection of the derived acid to afford (−)-**25**, removal of the PMB group (DDQ, 91%), and Dess−Martin periodinane oxidation completed construction of aldehyde (−)-**5**, which because of the unstable nature was used directly in the Evans aldol (vide infra).

Linchpin assembly of the CD spiroketal fragment **6** employed epoxide (+)-**10** as in our first-generation synthesis,[8,22] beginning with (*R*)-glycidol.[23] Construction of the second epoxide (−)-**12** began with inexpensive (L)-malic acid (Scheme 4). Highlights of this sequence included oxidation

Scheme 4



employing TEMPO/trichloroisocyanuric acid, a method recently reported by Giacomelli et al.,[24,25] excellent 1,3-*anti* selectivity (>10:1)[26] in the Keck alkylation protocol[27] with known allyl stannane **26**[28] [Ti(O*i*-Pr)$_4$/BINOL] to afford (−)-**27**, and a one-pot Kishi epoxide construction.[29]

Pleasingly, the multicomponent union of (−)-**10** and (−)-**12** again proceeded in good yield to furnish (+)-**28** (Scheme 5).[30] Methylation of the hydroxyl was followed in turn by

(18) Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157.

(19) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem*. **1978**, *43*, 147.

(20) Initial studies employing the tosyl hydrazone did not lead to the desired deprotonation.

(21) The use of tosyl imidazole, a more commonly employed reagent for this type of transformation, led to competitive sulfonation of the secondary hydroxyl after epoxide formation, as well as recovered starting material.

(22) Smith, A. B., III; Zhuang, L.; Brook, C. S.; Lin, Q.; Moser, W. H.; Trout, R. E. L.; Boldi, A. M. *Tetrahedron Lett.* **1997**, *38*, 8671.

(23) Large-scale preparation of this valuable intermediate was carried out using Jacobsen's kinetic resolution methodology; see: Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *68*, 6776.

(24) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041−3043.

(25) Hanessian, S.; Ugolini, A.; Dubé, D.; Glamyan, A. *Can. J. Chem.* **1984**, *62*, 2146.

(26) Treatment with both chelating and nonchelating Lewis acids only afforded a 2.6−2.2:1 ratio of *anti/syn* diastereomers.

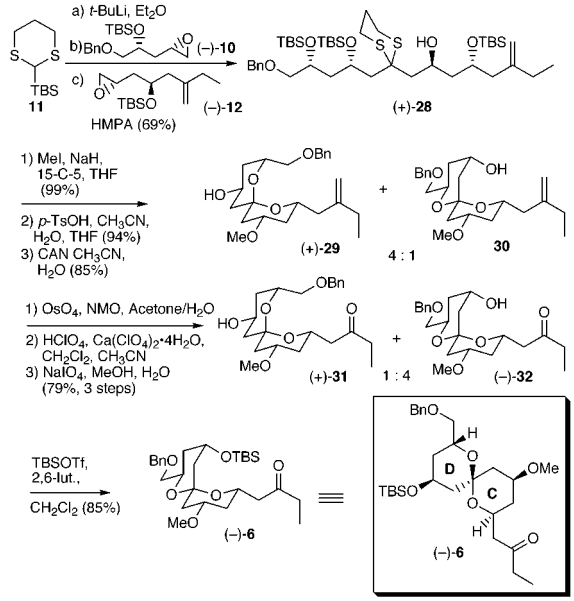
(27) (a) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem*. **1993**, *58*, 6543. (b) Keck, G. E.; Tarbet, K. H.; Gerachi, L. S. *J. Am. Chem. Soc*. **1993**, *115*, 8467. (c) Molinski, T. F.; Searle, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 9422.

(28) Keck, G. E.; Wager, C. A.; Wager, T. T.; Savin, K. A.; Covel, J. A.; McLaws, M. D.; Krishnamurthy, D.; Cee, V. *Angew. Chem., Int. Ed.* **2001**, *40*, 231.

(29) A 20:1 mixture of diastereomers was obtained. This minor diastereomer resulted from competitive tosylation at the secondary hydroxyl followed by displacement of the tosylate.

(30) The reaction proved sensitive to oxygen on small scale. Use of oxyclear argon improved the reproducibility of the reaction.

Scheme 5

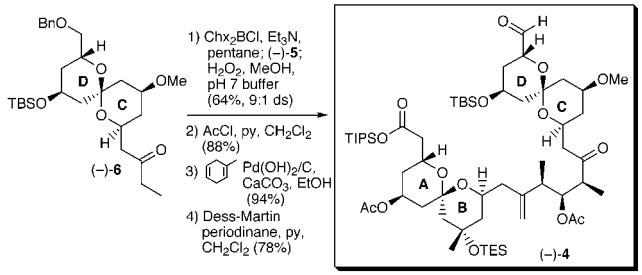


removal of the silyl groups (*p*-TsOH) and hydrolysis of the dithiane moiety (CAN), the latter providing a mixture of spiroketals (+)-**29** and **30** (4:1), favoring undesired axial-axial spiroketal (+)-**29**.

We reasoned that the introduction of additional hydroxyl functionality would permit use of the calcium perchlorate/perchloric acid equilibration protocol discovered in our first generation synthesis.[8a,22] Toward this end, dihydroxylation of the olefin (OsO_4, NMO), followed by treatment of the mixture with calcium perchlorate/perchloric acid, and then 1,2-diol cleavage via $NaIO_4$ afforded a separable mixture of (+)-**31** and (−)-**32** (1:4), now favoring the desired axial-equatorial spiroketal (−)-**32**; silyl protection (TBSOTf) completed the synthesis of the CD spiroketal ketone (−)-**6**. Stereochemical assignments for both spiroketals (+)-**31** and (−)-**32** were again confirmed by detailed NOESY NMR analysis.[14]

Aldol union[7d,10,31] of the AB and CD fragments was next achieved, as anticipated by the earlier precedent of Evans, both in good yield (64%) and with high *anti*-selectivity (9:1) (Scheme 6). Acetylation of the derived alcohol, followed by removal of the benzyl group and oxidation, completed

Scheme 6



construction of the fully elaborated ABCD aldehyde (−)-**4**. The synthesis of (−)-**4** was achieved with a longest linear sequence of 22 steps (4.0% overall yield) and with average yield per step of 87%. Four well precedented steps[8b] (Wittig coupling, selective silyl deprotection, macrolactonization, and global deprotection) should lead to the spongistatins. Importantly, the linear sequence for our second generation synthesis is 15 steps shorter than our previous synthesis of the C(23) epimeric ABCD aldehyde[8a] and is highly competitive with other published approaches to the ABCD subunit.[6a,7d,31,32]

To confirm the structure, and in particular the stereochemistry of (−)-**4** initially based on extensive NOESY analysis, we completed a two-step chemical correlation with an advanced Paterson intermediate,[9,14,33] which further constitutes a formal total synthesis of spongistatin 1 (**1**).

In conclusion, we have achieved a short, efficient, and stereocontrolled synthesis of the ABCD fragment (−)-**4** of the spongistatins, highlighted by application of both our iodocarbonate cyclization and muliticomponent linchpin coupling of silyl dithianes. AB and CD fragment union was then achieved via a stereoselective aldol reaction.

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Supporting Information Available: Spectroscopic and analytical data and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(33) We thank Professor I. Paterson for providing spectroscopic data for the correlation compound.