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A Formal Synthesis of Psymberin

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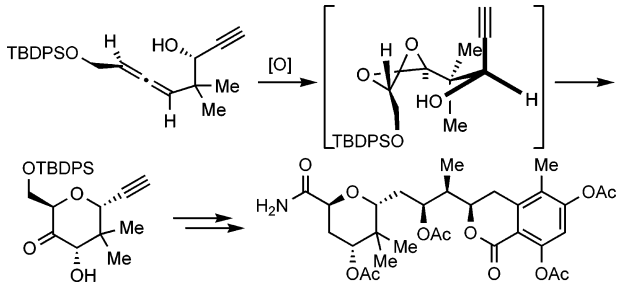
ABSTRACT



A formal synthesis of psymberin (irciniastatin A) is presented. Notable features of the synthesis include the chemo-, regio-, and stereoselective oxidation of a 1,3-disubstituted allene, a configuration-dependent spirodiepoxide opening, the efficient syntheses of functionalized trans-2,6-disubstituted pyrans, and the union of a highly functionalized aldehyde with a pentasubstituted aryl homoenolate to give a dihydroisocumarin.

Psymberin[1] (irciniastatin A[2]) (**1**) is one of 36 natural products of which pederin (**2**) is the archetype. In contrast to other members of this class, psymberin is both potent and selective, with an index of $>10^4$ against certain solid tumors. These natural products are characterized by an amide side chain, a pyran core, and a polyacetate appendage (e.g., **1**−**4**, Figure 1).[3] With the exception of psymberin, the pederamide side chain is invariant, although potential structural similarities between these side chains have been noted.[4] The pyran core is limited primarily to either a pyran (see **1** and **2**) or a trioxadecalin system (see **3** and **4**). The polyacetate chain varies considerably for the pederins.[3] Although other members have a C_{12} side chain with unsaturation (e.g., 4-*Z*-onnomide A, **3**), the dihydroisocumarin appendage in psymberin is unique.

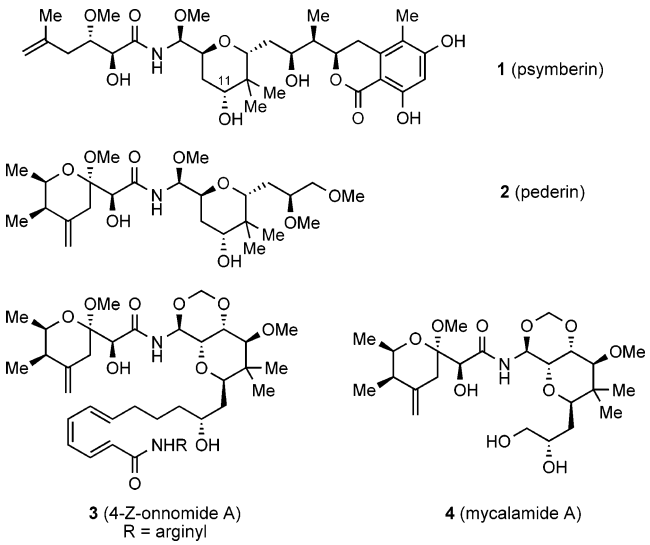


Figure 1. Members of the pederin family.

(1) Isolated from *Psammocinia* sp. in the waters of Papua, New Guinea. (a) Cichewicz, R. H.; Valeriote, F. A.; Crews, P. *Org. Lett.* **2004**, *6*, 1951. (b) A list of all the pederin natural products can be found in the Supporting Information of ref 1a.

(2) Isolated from *Ircinia* sp. near Samporna, Borneo. Pettit, G. R.; Xu, J.-P.; Chapuis, J.-C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schimdt, J. M. *J. Med. Chem.* **2004**, *47*, 1149.

(3) (a) Piel, J.; Hui, D.; Wen, G.; Butzke, D.; Platzer, M.; Fusetani, N.; Matsunaga, S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 16222. (b) Piel, J.; Butzke, D.; Fusetani, N.; Hui, D.; Platzer, M.; Wen, G.; Matsunaga, S. *J. Nat. Prod.* **2005**, *68*, 472.

(4) Segment synthesis and analysis: (a) Green, M. E.; Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2005**, *7*, 4117. (b) Kiren, S.; Williams, L. J. *Org. Lett.* **2005**, *7*, 2905.

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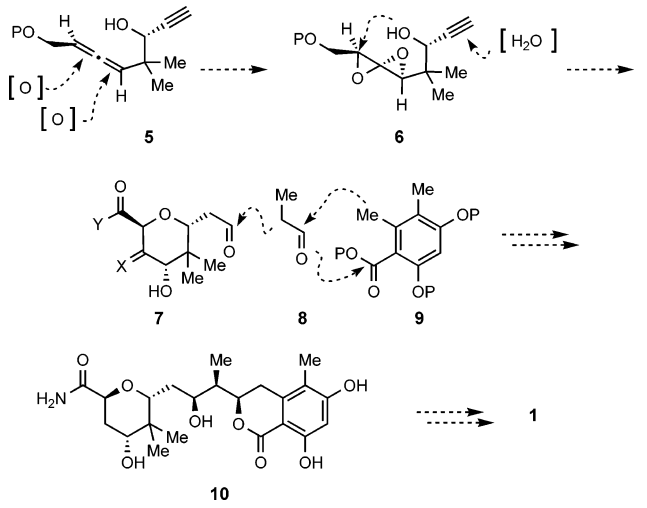
The cellular targets the pederin family acts upon have not been identified. Structure−activity correlations of the pederins have appeared,[5] and a recent preliminary report on psymberin has determined that the dihydroisocumarin moiety cannot be deleted without significantly compromising the activity.[6] The combined structural and biological data demonstrate that a high degree of both activity and selectivity is possible based on the pederin scaffold. We sought, therefore, to prepare psymberin by a route amenable to the synthesis of pederin family hybrids.

Our strategy focused on generalized intermediates **5**−**10** (Scheme 1). We reasoned that oxidation of **5** via spirodiepoxide (SDE) **6** would give a pyran of type **7** and thus enable entry to highly oxygenated (X = O) and simpler pederins (X = H_2). The biological profile of this class is sensitive to the oxidation state of the pyran ring (e.g., irciniastatin B[2] is the C11 ketone analogue of **1**). Of further interest was sequential insertion of a propionate equivalent (**8**) and dihydroisocumarin assembly using **9**.

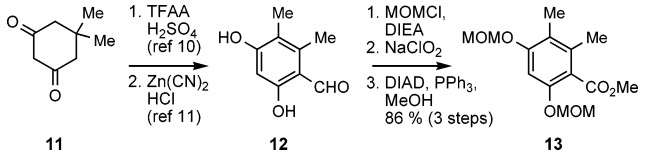
Scheme 1. Synthetic Plan



One advantage of this strategy (**5**→**7**→**10**) is the straightforward preparation of a suite of analogues and hybrids that vary in the central pyran as well as the two side chains. Indeed, as will be shown, this route enabled the preparation of several pyran derivatives that are not accessible from current psymberin syntheses or from the natural product itself.[7,8] The plan also postpones the preparation of the *N*-acyl aminal, arguably the primary synthetic challenge posed by the psymberin architecture, to the final stage of the synthesis. Although aware of the Kocienski precedent,[9] where a closely related amide was carried through a multistep sequence, we set as our initial goal preparation of an amide of type **10** (Scheme 1). Conversion of this amide, as the peracetate, to psymberin is known following a three-step sequence.[7a]

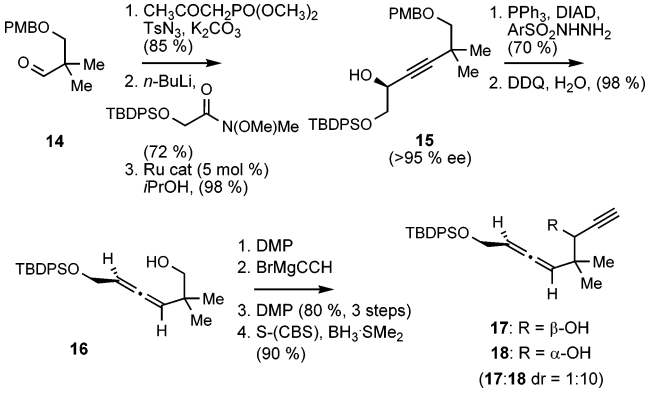
Schemes 2−7 provide a summary of our findings. We began with the preparation of **12**, directly available by the acid-induced rearrangement and concomitant aromatization of dimedone[10] followed by formylation.[11] A subsequent protection/oxidation/esterification sequence, which does not require purification of the intermediates, gave pentasubstituted arene **13** (Scheme 2). Multigram quantities of the right-hand segment of the target system were thereby prepared.

Scheme 2. Arene Side Chain Synthesis



Our focus then shifted to the preparation of allene **18** from aldehyde **14**[12] according to the sequence in Scheme 3.

Scheme 3. Allene Synthesis



Conversion of **14** to the alkyne[13] followed by addition to a glycolic acid-derived Weinreb amide,[14] and then asym-

(5) (a) Jacobs-Lorena, M.; Brega, A.; Bagloni, C. *Biochem. Biophys. Acta* **1971**, *240*, 293. (b) Jimenez, A.; Carrasco, L.; Vazquez, D. *Biochemistry* **1977**, *16*, 4727. (c) Brega, A.; Falaschi, A.; De CArli, L.; Pavan, M. *J. Cell Biol.* **1968**, *36*, 485. (d) Burres, N. S.; Clement, J. J. *J. Cancer Res.* **1989**, *49*, 2935. (e) Richter, A.; Kocienski, P.; Raubo, P.; Davies, D. E. *Anti-Cancer Drug Des.* **1997**, *12*, 217.

(6) Analogue synthesis: Jiang, X.; Williams, N.; De Brabander, J. K. *Org. Lett.* **2007**, *9*, 227−230.

(7) Total synthesis: (a) Jiang, X.; Garcia-Fortanet, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2005**, *127*, 11254. Formal synthesis: (b) Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2005**, *7*, 5175.

(8) The logic is in accord with the diverted synthesis concept. See, for example: Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329.

(9) (a) Kocienski, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, F. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2357. (b) Kocienski, P.; Jarowicki, K.; Marczak, S. *Synthesis* **1991**, 1191. For other representative synthetic studies, see: (c) Kagawa, N.; Ihara, M.; Toyota, M. *Org. Lett.* **2006**, *8*, 875. (d) Sohn, J.-H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 7290. (e) Trost, B. M.; Yang, H.; Probst, G. D. *J. Am. Chem. Soc.* **2004**, *126*, 48. (f) Roush, W. R.; Pfeifer, L. A. *Org. Lett.* **2000**, *2*, 859. (g) Takemura, T.; Nishiii, Y.; Takabashi, S.; Kobayashi, J.; Nakata, T. *Tetrahedron* **2002**, *58*, 6359.

(10) Nelson, P. H.; Nelson, J. P. *Synthesis* **1992**, 1287.

(11) Robertson, A.; Whalley, W. B. *J. Chem. Soc.* **1949**, 3033.

(12) Available in multigram quantities from the corresponding diol. Paterson, I.; Francesco, M. E.; Kuhn, T. *Org. Lett.* **2003**, *5*, 599.

(13) Roth, G. J.; Liepold, B.; Mueller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59.

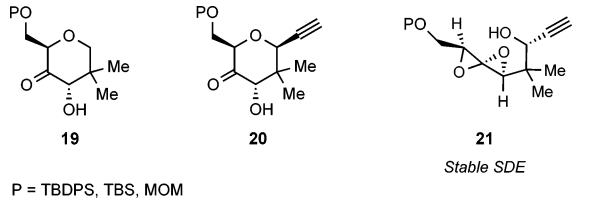
(14) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

metric reduction[15] provided **15**, a single isomer according to Mosher ester analysis. Propargyl alcohol **15** was transformed into the allene by the Myers[16] procedure, and the PMB group was then removed (→**16**). Oxidation of **16** to the aldehyde, addition of acetylide to give the propargyl alcohols (**17**/**18**, dr = 1:1), oxidation of this mixture to the corresponding ynone, and then CBS[17] reduction gave **18**.

The behavior of allene **18** upon oxidation was one of our central chemical interrogatives. We reasoned that dimethyl dioxirane (DMDO) would oxidize an allene more rapidly than an alkyne (e.g., **5**, **17**, and **18**).[18] Furthermore, the oxygen substituent (PO in **5**) should deactivate the proximal allenic double bond and thereby induce regioselective oxidation of the distal double bond,[19] which should occur from the most accessible face. The second oxidation should occur on the face opposite the sterically demanding *tert*-butyl-like appendage.[20] Certain allenic alcohols spontaneously cyclize to give pyrans upon oxidation,[21] and the corresponding SDE intermediates are not observed. Accordingly, we expected oxidation of **18**, and related allenes, to proceed rapidly and selectively.

During protecting group optimization studies,[22] oxidation of allenes of type **16** led directly to pyrans **19** and oxidation of allenes of type **17** led directly to cis-substituted pyrans **20** (Scheme 4). The cyclizations, although unoptimized, were

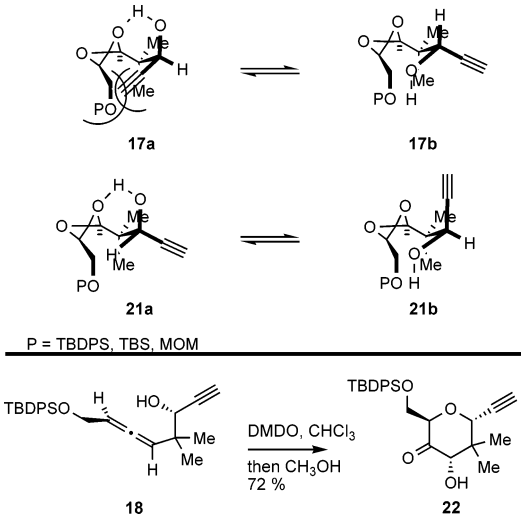
Scheme 4. Spirodiepoxide Cyclization



efficient (50−70% yield), and no SDE was observed. *Remarkably, oxidation of allenes of type **18** gave stable spirodiepoxides (e.g., **21**).*[23]

Presumably, these configuration-dependent cyclizations reflect conformational biases. Two conformers of the SDE derived from **17** (**17a** and **17b**) are shown in Scheme 5 along

Scheme 5. Spirodiepoxide Cyclization Model



with the analogous conformers of the diastereomeric SDE derived from **18** (**21a** and **21b**). Conformational preferences, perhaps reinforced by hydrogen bonding, may render **21a** stable. Moreover, the reactive conformer (**21b**) may be further destabilized by unfavorable steric interactions between the alkyne and the SDE. The combined effect could account for the observed resistance of this SDE toward cyclization. Analogous conformers of diastereomeric secondary alcohol (**17a**) would be disfavored due to severe steric interactions, whereas **17b** would be favored and lead to product. This model would also predict that cyclization of the SDE derived from **16** would be faster than the SDE derived from **18**, as observed. *Indeed, conditions expected to disrupt hydrogen bonding induced cyclization of the otherwise stable SDE derived from **18**.* Thus, after complete oxidation, addition of methanol as cosolvent to the mixture effected the slow (12 h) conversion of **18** to *trans*-pyran **22** in 72% yield.[24]

Scheme 6 presents the preparation of a suite of related pyrans en route to psymberin, which are also related to the trioxadecalin system of more complex pederins (cf. **3** and **4**). Stereoselective reduction[25] of **22** gave the *trans*-diol **23**, which was converted directly to the epoxide (**24**) under the action of sodium hydride and toluenesulfonyl chloride, provided that wet THF was used as solvent.[26] Reduction of the epoxide[27] and then treatment with MOM−Cl gave **25**. Hydroboration of **25** (→**26**), introduction of C17−C18 by asymmetric aldol addition,[28] conversion to the Weinreb amide,[29] and silylation were followed by reduction[30] to aldehyde **28**.

(15) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738. Ru catalyst = {[(1*S*,2*S*)-TsDPEN]RuCl(η^6-*p*-cymene)}.

(16) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.

(17) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 1797. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(18) Murray, R. W.; Singh, M. *J. Org. Chem.* **1993**, *58*, 5076.

(19) (a) Henbest, H. B. *Proc. Chem. Soc.* **1963**, 159. (b) Chamberlin, P.; Roberts, M. L.; Whitham, G. H. *J. Chem. Soc. (B)* **1970**, 1374.

(20) For a steric model of allene oxidation, see: (a) Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348. (b) Crandall, J. K.; Batal, D. J.; Sebesta, D. P.; Lin, F. *J. Org. Chem.* **1991**, *56*, 1153.

(21) Crandall, J. K.; Batal, D. J.; Lin, F.; Reix, T.; Nadol, G. S.; Ng, R. A. *Tetrahedron* **1992**, *48*, 1427.

(22) The TBDPS protecting group, in contrast to TBS and MOM, was found to be optimal for the sequence **14**→**21**.

(23) The SDE was stable to analytical thin-layer chromatography and standing in solution for three days, whereas flash column chromatography induced decomposition of the SDE to several products.

(24) Minor products were observed but do not appear to be simple diastereomeric pyrans. The methanol adduct was observed as a minor product (<5%) when the reaction was run on a large scale (~3 g).

(25) Evans, D.; Clark, J.; Metternich, R.; Novack, V.; Sheppard, G. *J. Am. Chem. Soc.* **1990**, *112*, 866.

(26) When dry THF was used, the tosylate was obtained.

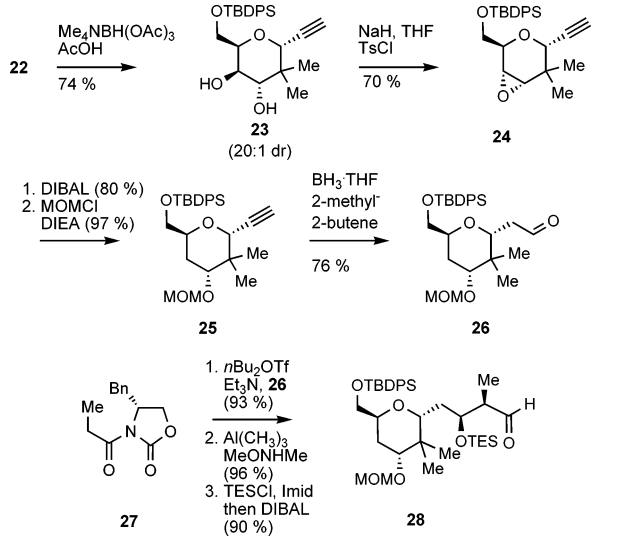
(27) Kim, S.; Ko, H.; Lee, T.; Kim, D. *J. Org. Chem.* **2005**, *70*, 5756.

(28) Evans, D. A.; Takacs, J. M.; Mcgee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartolli, L. *Pure Appl. Chem.* **1981**, *53*, 1109.

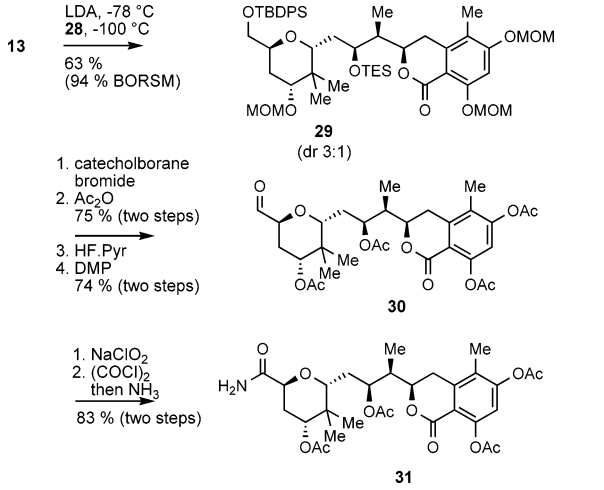
(29) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

(30) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

Scheme 6. Elaborated Pyran Synthesis



Scheme 7. Formal Synthesis



Completion of the synthesis is presented in Scheme 7. The anion derived from **13** smoothly added to **28**, and the adduct spontaneously cyclized to give dihydroisocumarin **29**.[31] Although both isomers are of interest, the product that matches psymberin was favored (dr 3:1) and taken on to complete the synthesis. The protecting groups were consolidated by treatment with catecholborane[32] and then acetic anhydride followed by silyl ether cleavage and oxidation (**29**→**30**). Further oxidation and subsequent conversion to the amide gave **31**, which proved identical to earlier reports,[7] as judged by optical rotation and ^{1}H and ^{13}C NMR.

The strategy presented here enables a flexible synthesis of psymberin from allene, arene, and amide subunits. Both highly oxygenated and simpler pyrans have been prepared (**19**−**28**). Notable features of this study include: (1) the chemo-, regio-, and stereoselective oxidation of 1,3-disubstituted allenes; (2) an unexpected configuration-dependent SDE opening; (3) the efficient synthesis of a functionalized trans-2,6-disubstituted pyran from an SDE; and (4) union of a highly functionalized aldehyde with a pentasubstituted aryl homoenolate to give a dihydroisocumarin. Studies to further develop these transformations and this strategy toward designed hybrid targets and related analogues are ongoing.

Acknowledgment. Financial support from Merck & Co., Johnson & Johnson (Discovery Award), donors of the American Chemical Society Petroleum Research Fund, and Rutgers, The State University of New Jersey, is gratefully acknowledged.

Supporting Information Available: Synthetic methods and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) This appears to be among the most sophisticated couplings of this sort to date. See: (a) Hauser, F. M.; Rhee, R. *Synthesis* **1977**, 245. (b) Hauser, F. M.; Rhee, R.; Prasanna, S. *Synthesis* **1980**, *1*, 72. (c) Leeper, F. J.; Staunton, J. *J. Chem. Soc., Chem. Commun.* **1979**, 205. (d) Carpenter, T. A.; Evans, G. E.; Leeper, S. J.; Staunton, J.; Wilkinson, M. R. *J. Chem. Soc., Perkin 1* **1984**, 1043. (e) Ward, R. A.; Procter, G. *Tetrahedron* **1995**, *51*, 12301. (f) Barber, J. A.; Staunton, J.; Wilkinson, M. R. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2101. (g) Chevenier, E.; Lucatelli, C.; Pandya, U.; Wang, W.; Gimbert, Y.; Greence, A. E. *Synlett* **2004**, *15*, 2693. (h) Zhang, Z.; Yu, B. *J. Org. Chem.* **2003**, *68*, 6309.

(32) Cao, B.; Park, H.; Joullié, M. *J. Am. Chem. Soc.* **2002**, *124*, 520.