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Application of Aryl Siloxane Cross-Coupling to the Synthesis of Allocolchicinoids

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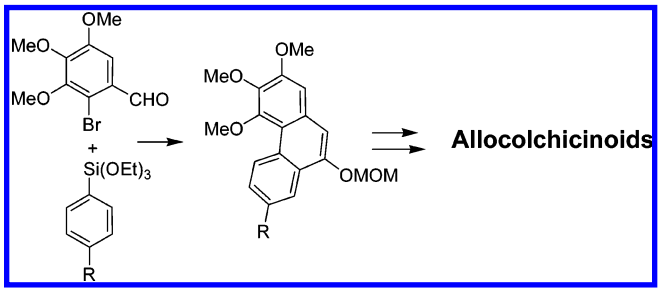
ABSTRACT



In this communication, we report a new approach to the allocolchicine carbocyclic skeleton based upon an aryl siloxane coupling reaction and a phenanthrol ring expansion. These key steps allow for the selective functionalization of every carbon within the carbocyclic framework. The siloxane coupling–phenanthrol sequence was applied to the synthesis of two allocolchicinoids, including the first fully synthetic approach to *N*-acetyl colchinol-*O*-methyl ether (NCME).

Allocolchicine (**1**) and *N*-acetyl colchinol-*O*-methyl ether (NCME) (**2**) possess a 6-7-6 carbocyclic framework, related to the 6-7-7 tricylic system present in colchicine (**3**). Like colchicine, the allocolchicinoids are potent tubulin inhibitors.[1] The majority of the synthetic work related to allocolchicine has relied on chemical degradation of colchicine to provide allocolchicine and its analogues, and this has limited access to novel derivatives possessing reduced toxicity. Several approaches have been reported for the partial synthesis of allocolchicine or derivatives.[2] Additionally, several total syntheses of allocolchicine exist;[3] however, there are no reported total syntheses of NCME (**2**). This allocolchicinoid possesses tubulin inhibition activity that is greater than that of colchicine itself.[1a]

It has been demonstrated that the A and C allocolchicinoid rings are required to maintain full biological activity.[3a,4]

(1) (a) Nakagawa-Goto, K.; Jung, M. K.; Hamel, E.; Wu, C.-C.; Bastow, K. F.; Brossi, A.; Ohta, S.; Lee, K.-H. *Heterocycles* **2005**, *65*, 541−550. (b) Shi, Q.; Chen, K.; Chen, X.; Brossi, A.; Verdier-Pinard, P.; Hamel, E.; McPhail, A. T.; Tropsha, A.; Lee, K.-H. *J. Org. Chem.* **1998**, *63*, 4018−4025. (c) Bergemann, S.; Brecht, R.; Buttner, F.; Guenard, D.; Gust, R.; Seitz, G.; Stubbs, M. T.; Thoret, S. *Bioorg. Med. Chem.* **2003**, *11*, 1269−1281. (d) Brecht, R.; Seitz, G.; Guenard, D.; Thoret, S. *Bioorg. Med. Chem.* **2000**, *8*, 557−562. (e) Roesner, M.; Capraro, H.-G.; Jacobson, A. E.; Atwell, L.; Brossi, A.; Iorio, M. A.; Williams, T. H.; Sik, R. H.; Chignell, C. F. *J. Med. Chem.* **1981**, *24*, 257−261. (f) Brossi, A.; Sharma, P. N.; Atwell, L.; Jacobson, A. E.; Iorio, M. A.; Molinari, M.; Chignell, C. F. *J. Med. Chem.* **1983**, *26*, 1365−1369. (g) Han, S.; Hamel, E.; Bastow, K. F.; McPhail, A. T.; Brossi, A.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2851−2853. (h) Shi, Q.; Chen, K.; Brossi, A.; Verdier-Pinard, P.; Hamel, E.; McPhail, A. T.; Lee, K.-H. *Helv. Chim. Acta* **1998**, *81*, 1023−1037.

(2) (a) Banwell, M. G.; Fam, M.-A.; Gable, R. W.; Hamel, E. *J. Chem. Soc., Chem Commun.* **1994**, 2647−2649. (b) Banwell, M. G.; Cameron, J. M.; Corbett, M.; Dupuche, J. R.; Hamel, E.; Lambert, J. N.; Lin, C. M.; Mackay, M. F. *Aust. J. Chem.* **1992**, *45*, 1967−1982. (c) Itoh, Y.; Brossi, A.; Hamel, E.; Lin, C. M. *Helv. Chim. Acta* **1988**, *71*, 1199−1209. (d) Boye, O.; Itoh, Y.; Brossi, A. *Helv. Chim. Acta* **1989**, *72*, 1690−1696. (e) Boye, O.; Brossi, A.; Yeh, H. J. C.; Hamel, E.; Wegrzynski, B.; Toome, V. *Can. J. Chem.* **1992**, *70*, 1237−1249.

(3) (a) Sawyer, J. S.; Macdonald, T. L. *Tetrahedron Lett.* **1988**, *29*, 4839−4842. (b) Buettner, F.; Bergemann, S.; Guenard, D.; Gust, R.; Seitz, G.; Thoret, S. *Bioorg. Med. Chem.* **2005**, *13*, 3497−3511. (c) Vorogushin, A. V.; Predeus, A. V.; Wulff, W. D.; Hansen, H.-J. *J. Org. Chem.* **2003**, *68*, 5826−5831. (d) Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849−2852.

(4) (a) Rossi, M.; Gorbunoff, M. J.; Caruso, F.; Wing, B.; Perez-Ramirez, B.; Timasheff, S. N. *Biochemistry* **1996**, *35*, 3286−3289. (b) Perez-Ramirez, B.; Gorbunoff, M. J.; Timasheff, S. N. *Biochemistry* **1998**, *37*, 1646−1661.

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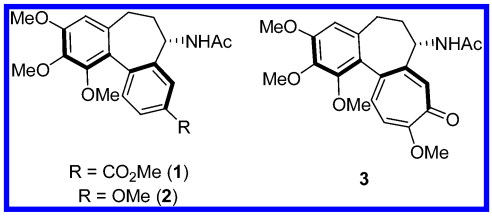
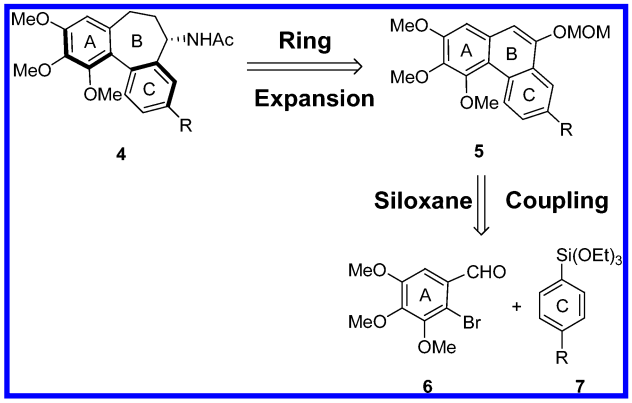


However, the B ring can be manipulated to generate analogues that retain the antitumor activity, while moderating the toxicity of these compounds. The existing total syntheses do not readily provide access to B ring analogues. Accordingly, a synthetic approach that would allow for the facile construction of the A, B, and C rings, while also permitting functionalization of all of the rings, would have great synthetic value. Our approach seeks to satisfy this goal by utilizing an aryl siloxane coupling reaction developed within our laboratory to form the A−C biaryl core[5] and a phenanthrol ring expansion to provide the seven-membered B ring (Scheme 1).

Scheme 1. Retrosynthesis

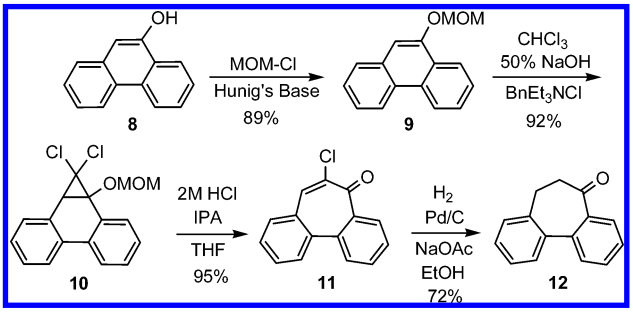


Our first task was to explore the phenanthrol ring expansion. The one-carbon expansion of phenanthrene has been studied,[6] but the corresponding ring expansion of phenanthrol has not been investigated. Accordingly, a model system utilizing 9-phenanthrol (**8**) as the substrate was examined. Protection of the hydroxyl moiety of 9-phenanthrol (**8**) as a MOM ether proceeded smoothly to provide ether **9** (Scheme 2). Reaction of this compound under optimized conditions ($CHCl_3$, 50% NaOH, $BnEt_3NCl$, room temperature, 5 h) led to the formation of the dichlorocyclopropyl adduct **10** in excellent yield. Treatment of compound **10** with dilute acid removed the MOM ether and induced cyclopropane ring opening to provide the ring-expanded chloroenone **11**. Hydrogenation of the chloroenone, using conditions developed by Jones and Coburn,[6a] provided aryl ketone **12**.

(5) (a) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137−2140. (b) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684−1688. (c) McElroy, W. T.; DeShong, P. *Org. Lett.* **2003**, *5*, 4779−4782. (d) Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 1137−1143.

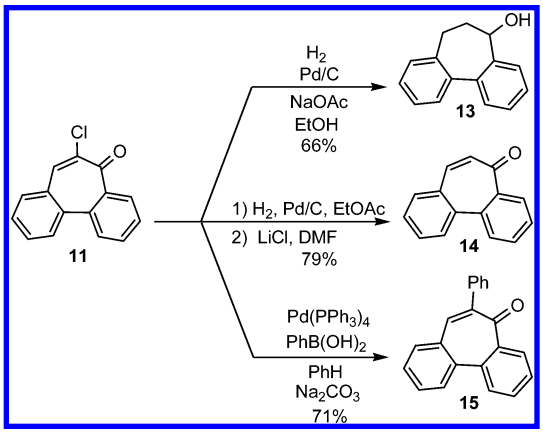
(6) (a) Coburn, T. T.; Jones, W. M. *J. Am. Chem. Soc.* **1974**, *96*, 5218−5227. (b) Joshi, G. C.; Singh, N.; Pande, L. M. *Synthesis* **1972**, 317. (c) Halton, B.; Officer, D. L. *Aust. J. Chem.* **1983**, *36*, 1167−1175. (d) Nerdel, F.; Buddrus, J.; Brodowski, W.; Windhoff, J.; Klamann, D. *Tetrahedron Lett.* **1968**, *9*, 1175−1179.

Scheme 2. Annulation Model System



Having successfully generated the allocolchicine carbocyclic framework in ketone **12**, our attention focused on derivatization of chloroenone **11** (Scheme 3). This compound

Scheme 3. Functionalization of α-Chloro Ketone **11**



possesses a high degree of functionalization which could be utilized to generate allocolchicine B ring analogues. Accordingly, enone **11** was hydrogenated to benzyl alcohol **13**. Alternatively, by switching the hydrogenation solvent from EtOH to EtOAc,[6a] hydrogenation was stopped at the chloroketone, which was eliminated to generate the Michael acceptor **14**.

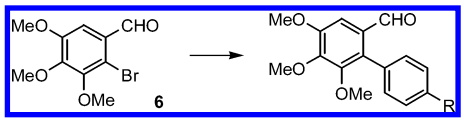
The palladium-catalyzed cross-coupling of the chloride moiety of α-chloroenone **11** was also investigated. Gratifyingly, when chloroenone **11** was subjected to standard Suzuki coupling conditions,[7] a good yield of the coupled product **15** was obtained. This result is particularly noteworthy because it constitutes only the second example of the cross-coupling of an α-chloroenone. The coupling of iodides and bromides has been studied previously,[8] but until recently, there was not an example of the coupling of a chloride substrate.[9]

Having established that the α-chloroenone would be suitable for derivatization, we sought to apply the ring expansion protocol to the synthesis of several allocolchici-

(7) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, pp 41−124.

noids. An aryl siloxane coupling reaction would be used to generate the unsymmetrical A−C biaryl bond. Under optimized conditions, the siloxane coupling reaction provided several unsymmetrical biaryls, including substrates that can be utilized for the synthesis of NCME (**2**), and allocolchicine (**1**) (Table 1, entries 2 and 4, respectively). This coupling

Table 1. Synthesis of Biaryl Derivatives Using Palladium-Catalyzed Siloxane Coupling[a]



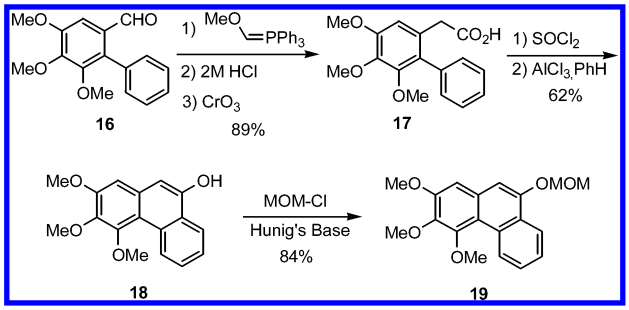
entry	R	yield[b]
1	H	94
2	OMe	93
3	Me	87
4	CO_2Et	94

[a] Conditions: 5% $Pd(OAc)_2$, 25% PPh_3, 1.5 equiv of aryl siloxane, 1.5 equiv of TBAF, THF. [b] Isolated yield of purified product.

reaction could be used to synthesize a variety of A−C ring modified allocolchicinoid precursors.

The first allocolchicinoid assembled was derived from biaryl **16** (Table 1, entry 1) (Scheme 4). The biaryl was

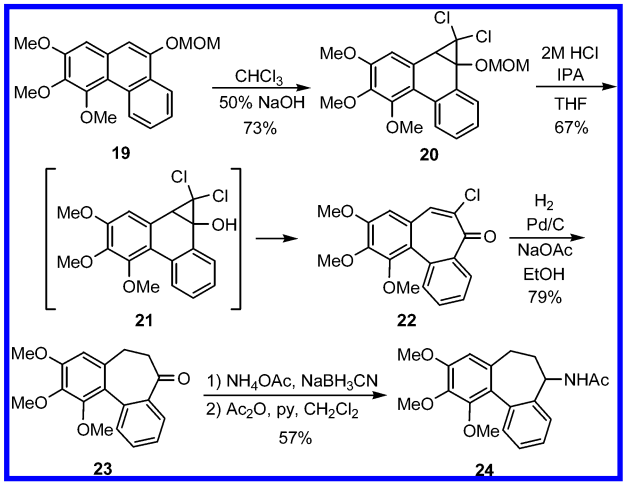
Scheme 4. Synthesis of MOM-Protected Phenanthrol



homologated by Wittig reaction, followed by oxidation, to provide acid **17** (Scheme 4). Friedel−Crafts ring closure generated air-sensitive phenanthrol **18** which was immediately protected to provide MOM ether **19**.

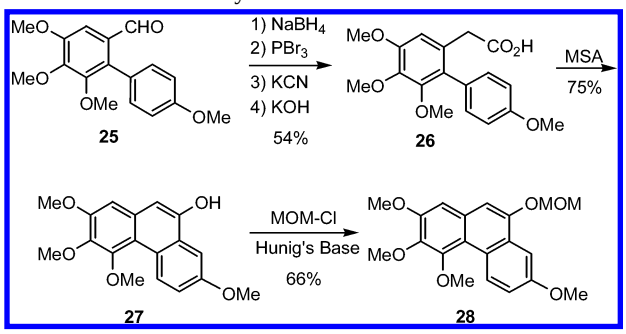
Cyclopropanation of MOM ether **19** provided dichlorocyclopropyl adduct **20** (Scheme 5). Ring expansion, presumably occurring via deprotected alcohol **21**, proceeded to provide chloroenone **22**. Hydrogenation of enone **22** gave saturated ketone **23**. Reductive amination followed by acylation provided the known[3d] allocolchicinoid **24**.

Scheme 5. Phenanthrol Ring Expansion



Having successfully generated allocolchicinoid **24**, our attention turned to the synthesis of NCME (**2**) (Scheme 6).

Scheme 6. Synthesis of NCME Phenanthrol



Biaryl **25** (Table 1, entry 2) was homologated to acid **26**. Ring closure was effected in good yield by stirring in neat methanesulfonic acid (MSA) for 2.5 h at room temperature.[10] Formation of the MOM ether proceeded smoothly to give protected phenanthrol **28**.[11]

Conversion of protected phenanthrol **28** to ketone **29** was accomplished as described above (Scheme 7). Additionally, it was found that only a single purification step was needed to provide aryl ketone **29** in good yield for the three-step procedure. Reductive amination of ketone **29** followed by acylation provided the first fully synthetic NCME (**2**).

In summary, a short and versatile synthesis of the allocolchicinoid carbon skeleton has been presented. It is

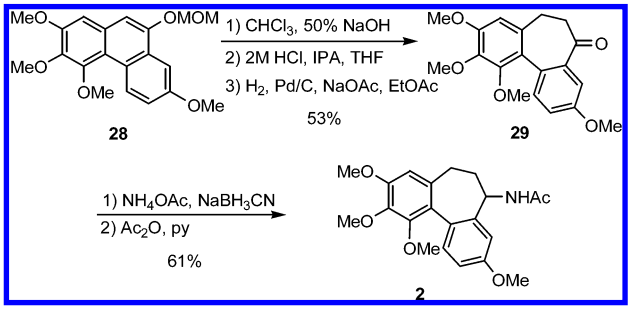
(8) (a) Negishi, E.-i. *J. Organomet. Chem.* **1999**, *576*, 179−194. (b) Dyker, G.; Markwitz, H.; Henkel, G. *Eur. J. Org. Chem.* **2001**, 2415−2423. (c) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628−4641. (d) Scott, T. L.; Soderberg, B. C. G. *Tetrahedron Lett.* **2002**, *43*, 1621−1624. (e) Scott, T. L.; Soderberg, B. C. G. *Tetrahedron* **2003**, *59*, 6323−6332. (f) Ohshima, T.; Xu, Y.; Takita, R.; Shimizu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546−14547. (g) Banwell, M. G.; Kelly, B. D.; Kokas, O. J.; Lupton, D. W. *Org. Lett.* **2003**, *5*, 2497−2500. (h) Ruel, R. S.; Braun, M. P.; Johnson, C. R. *Org. Synth.* **1997**, *75*, 69−77. (i) Furness, M. S.; Robinson, T. P.; Goldsmith, D. J.; Bowen, J. P. *Tetrahedron Lett.* **1999**, *40*, 459−462. (j) Felpin, F.-X. *J. Org. Chem.* **2005**, *70*, 8575−8578.

(9) Banks, J. C.; Van Mele, D.; Frost, C. G. *Tetrahedron Lett.* **2006**, *47*, 2863−2866.

(10) Leon, A. A.; Daub, G.; Silverman, I. R. *J. Org. Chem.* **1984**, *49*, 4544−4545.

(11) Attempts to close the ring using a Friedel−Crafts approach (as for **18**, Scheme 4) yielded complex mixtures, presumably due to the increased reactivity of the activated C ring. Conversely, MSA proved ineffective for the synthesis of **18**.

Scheme 7. Final Stage of NCME Synthesis



based upon a siloxane coupling reaction to form the A−C biaryl ring system and a phenanthrol ring expansion reaction to provide the seven-membered B ring. In combination, these protocols allow for the potential selective functionalization of every carbon present in the allocolchicine skeleton. Full disclosure of our results, as well as the synthesis of novel allocolchicinoids, will be reported in due course.

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Supporting Information Available: Detailed experimental procedures and characterization information for all compounds including copies of ^{1}H NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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