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Convergent Synthesis of Fully Functionalized Ring C Allocolchicinoids. Benzannulation Approach

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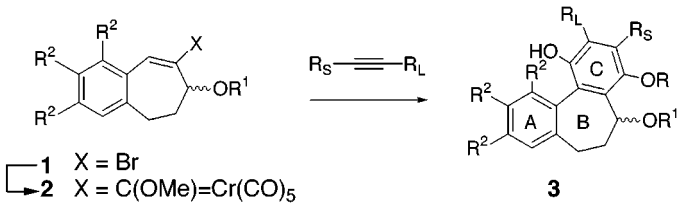
ABSTRACT



A novel convergent approach to fully functionalized ring C allocolchicinoids is developed which is based on the benzannulation reaction of Fischer carbene complexes with alkynes. The efficacy of this strategy was established with the conversion of bromide 1a (R^1 = Me, R^2 = H) to the biaryl phenol 3a (R = Me, R_L = Pr, R_S = H) via the carbene complex 2a. Bromide 1b (R^1 = *t*-Bu, R^2 = OMe) was then used for the analogous preparation of the diastereomeric allocolchicinoids 3b (R = Me, R_L = Pr, R_S = H).

(−)-Colchicine **4** (Figure 1), the major alkaloid from *Colchicum autumnale*, is one of the oldest known natural products.[1] It binds to the cytoskeletal protein tubulin, therefore interfering with the normal microtubule assembly−disassembly in the cell and thereby suppressing the cell division process.[2] Several other active colchicine analogues have been developed or found in nature, including C10-functionalized colchicinoids,[3] C7-functionalized colchicinoids,[3] and also colchicine analogues with ring systems different from that of colchicine: the family of compounds with an aryl ring C, such as allocolchicine **5**, *N*-acetylcolchinyl-*O*-methyl ether **6**, and their derivatives.[4,5] Several active allocolchicine-like biaryl compounds, which do not have ring B, for example, TCB **7**, have been developed, but their activity is usually lower than that of the corresponding allocolchicinoids.[6] Some other allocolchicine analogues with a five-membered[7] and eight-membered[8] ring B, as well as

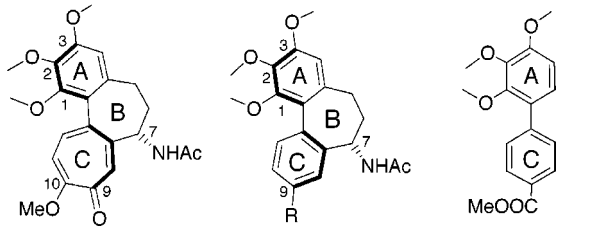


Figure 1. (−)-Colchicine and its active analogues.

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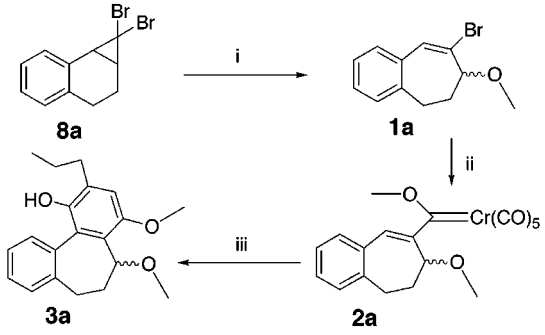
compounds with the functionality at C7 moved to C5,[9] have been recently prepared but found not to affect the tubulin polymerization process, despite their narrow structural similarity with the active allocolchicinoids. It was also shown that any alteration to the trioxygenated moiety of ring A leads to compounds with decreased tubulin-binding ability.[10] In contrast, the biological activity of ring C substituted allocolchicinoids varies with size, position, and nature of the substituents.[6,11]

It was found that only natural (−)-(7*S*)-colchicine, which adopts an a*R* biaryl configuration, binds effectively to tubulin. The a*S*,7*R*-enantiomer does not interfere with the tubulin polymerization process. Although 7*S*-allocolchicinoids prefer an a*R* biaryl configuration, they exist in solvent-dependent equilibrium between a*R* and a*S* forms and several active 7*R* allocolchicinoids are known.[5] It is still not clear whether the a*R*,7*S* form or the small amount of the a*S*,7*S* form, present in solution in equilibrium, is active in the tubulin-binding process. Because of its high toxicity, colchicine cannot be used as a therapeutic drug for treatment of human cancers. Despite the amount of work that has been directed to structural modification and synthesis of new colchicinoids and allocolchicinoids, greatly improved active compounds have not been identified, mainly because of the difficulties associated with the construction of highly functionalized ring C derivatives. To date, only a limited number of reports describe synthetic pathways toward the preparation of allocolchicinoids,[11,12] and the vast majority of these compounds are still being prepared from natural (−)-colchicine. No general methodology exists for the efficient construction of different ring C functionalized allocolchicinoids, which would be desirable in the search to find more active and less toxic antimitotic agents and to acquire structure−activity information about the requirements for binding to tubulin.

We now report a novel approach toward the highly convergent construction of allocolchicinoids of type **3** which have the natural substitution pattern on ring A and which provide for a controlled variability of functionalization on ring C. This family of allocolchicinoids should be accessible in one step from Fischer carbene complexes of type **2** by their benzannulation reaction[13] with acetylenes, where the regiochemistry of the acetylene incorporation is controlled by the steric size of large (R_L) and small (R_S) groups on the acetylene. This methodology will provide for a rapid introduction of a variety of different substituents in the C-9 and C-10 positions of allocolchicinoids from a common starting material, namely, carbene complexes of type **2b**. Furthermore, the presence of oxygen functionalities in the C-8 and C-11 positions on ring C of the allocolchicinoids of type **3b** allows for the preparation of the corresponding triflates, which can be either catalytically coupled with organometallic reagents[14] or reduced,[15] giving a variety of C-8 and C-11 functionalized allocolchicinoids. In addition, it should be possible to readily access optically pure substrates of type **1b**. A straightforward approach would be an oxidation−asymmetric reduction sequence[16] on the corresponding alcohol, followed by alkylation. The presence of a C-11 substituent, which is introduced in the ring C annulation process, will stop the epimerization about the chiral axis. Therefore, aR and aS forms of such allocolchicinoids could be isolated and separately subjected to biological testing. The development of a successful protection−deprotection routine for the hydroxy group at C-7 will be critical for the introduction of other functional groups at C-7 which are not compatible with the carbene complex preparation conditions. This would include the acyl, aroyl, or acetamido groups that occur in natural allocolchicinoids.

The proposed reaction sequence was first tested on the unsubstituted ring C model compounds **1a**−**3a** (Scheme 1).

Scheme 1. Synthesis of Biaryl Phenol **3a**[a]



[a] (i) $AgBF_4$, MeOH, reflux 24 h, 92%; (ii) (1) *t*-BuLi, −78 °C, ether, 15 min, (2) $Cr(CO)_6$, ether, 0 °C 0.5 h, 25 °C, 1.5 h, (3) MeOTf, CH_2Cl_2, 25 °C, 1.5 h, 66%; (iii) (1) 3 equiv of 1-pentyne, hexane, 50 °C, 24 h, (2) air, 25 °C, 12 h, 65%.

Access to **1a** was achieved by electrophilic ring opening of the known[17] dibromocyclopropane **8a** mediated by a silver salt in methanol which readily provided bromide **1a**. Application of the modified Fischer procedure to the substrate

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(14) For successful coupling, in situ triflation of the intermediate chromium tricarbonyl complex of **3** must be performed, which can be isolated and subjected to Suzuki or Stille coupling conditions as we have previously reported. The free allocolchicinoids can then be generated by oxidative removal of the $Cr(CO)_3$ group using iodine. Gilbert, A. M.; Wulff, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 7449.

(15) For example, HCOOH in the presence of $Pd(dppf)Cl_2$ catalyst and Et_3N has previously been used in a synthesis of the tricyclic core of olivin. Miller, R. A.; Gilbert, A. M.; Xue, S.; Wulff, W. D. *Synthesis* **1998**, 80.

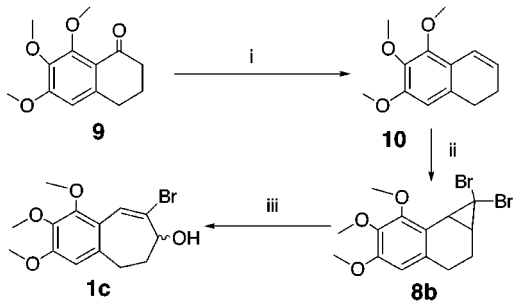
(16) For asymmetric catalytic reduction of α-bromoenones with the CBS reagent, see: Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, Ch.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

(17) Riley, P. E.; Davis, R. E.; Allison, N. T.; Jones, W. M. *J. Am. Chem. Soc.* **1980**, *102*, 2458.

1a results in the preparation of chromium pentacarbonyl complex **2a**. The pentacarbonyl complex **2a** (orange-red) was observed to slowly undergo conversion in solution or as a neat solid to a tetracarbonyl complex (dark-red) in which a methoxy group is coordinated to the chromium. For purposes of characterization, it was found most convenient to completely drive this process to the tetracarbonyl complex by heating in vacuo at 60 °C. Since it has been previously shown that chelated complexes and nonchelated complexes give identical results upon reactions with alkynes,[18] the mixture of pentacarbonyl complex **2a** and its tetracarbonyl chelated complex (5−10%) was reacted directly with 1-pentyne. The reaction gave the expected phenol **3a**, establishing the viability of allocolchicine ring system construction via the benzannulation reaction.

Preparation of the trimethoxy-substituted dibromocyclopropane **8b** was achieved starting from the known[19] tetralone **9**, which was prepared by a modified route[20] from ethyl 3,4,5-trimethoxybenzoyl acetate. Reduction of **9**, followed by the dehydration of the intermediate alcohol, readily afforded dihydronaphthalene **10** (Scheme 2). Dibromocarbene addition

Scheme 2. Preparation of Alcohol **1c**[a]

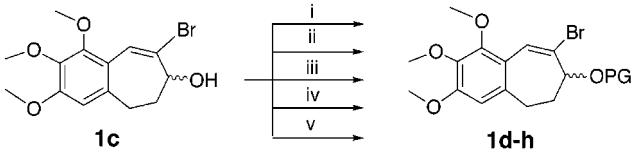


[a] (i) (1) $NaBH_4$, EtOH, 25 °C, 0.5 h, reflux 40 min, (2) $MgSO_4$, benzene, reflux 1.5 h, 89%; (ii) $CHBr_3$, NaOH, CTMAC, hexane, reflux 5 h, 55%; (iii) $AgBF_4$, DME/H_2O, 80 °C 36 h, 82.5%.

to **10** under phase-transfer conditions gave the expected dibromocyclopropane **8b**. Electrophilic ring opening of **8b** led to the alcohol **1c**, which was then protected with various protecting groups to give the substrates **1d**−**h** (Scheme 3).

Unfortunately, all of the substrates **1d**−**h** failed to form the expected carbene complexes under the conditions developed for the preparation of **2a**. Attempts to optimize the procedure for carbene complex formation with conditions more appropriate for substrates **1d**−**h** also failed. In this situation, utilization of an alkyl group as the protecting group seemed appropriate, given the fact that the alkyl protection

Scheme 3. Preparation of the Protected Substrates **1d**−**h**[a]

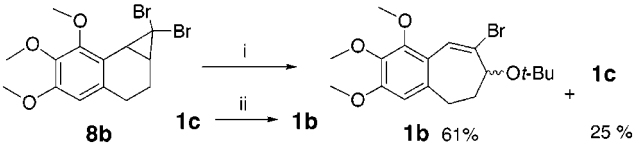


[a] (i) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 96%, PG = MOM; (ii) (1) NaH, NaI, THF, (2) MTMCl, 60%, PG = MTM; (iii) TMSCl, Et_3N, ether, 70%, PG = TMS; (iv) TBSCl, imidazole, DMF, 99%, PG = TBS; (v) Ph_3CCl, DBU, CH_2Cl_2, 36%, PG = Ph_3C.

is usually compatible with organolithium reagents. The success of this approach of course depends on whether the alkyl protecting group can be easily removed. Therefore, we decided to use the *tert*-butyl protecting group since there are known methods for its efficient and selective cleavage.

The *tert*-butyl-protected substrate **1b** was prepared from **8b** by an electrophilic ring opening in *t*-BuOH, similar to the one used for the preparation of **1a**, but with the following modifications: (a) higher temperature and longer reaction time must be applied to improve the conversion; (b) a 10-fold excess of $CaCO_3$ per mole of **8b** must be added to quench the acid formation and suppress the elimination of *tert*-butyl alcohol (Scheme 4). A significant amount of the

Scheme 4. Electrophilic Ring Opening Reaction of **8b** in *t*-BuOH[a]



[a] (i) $AgBF_4$, $CaCO_3$, *t*-BuOH, 80 °C, 36 h; (ii) $CCl_3C(NH)O$-*t*-Bu, CH_2Cl_2/Cy, catalytic $BF_3{\cdot}Et_2O$, 25 °C, 17 h, 32%.

free alcohol **1c** is also formed in this reaction. Fortunately **1c** can be easily separated and *tert*-butylated using *tert*-butyl 2,2,2-trichloroacetimidate and catalytic amounts of $BF_3{\cdot}Et_2O$.[21] Although the yield is not high for the *tert*-butylation of **1c**, 88% of unreacted starting material **1c** can be recovered and recycled. As expected, the desired carbene complex **2b** could be prepared from **1b** under the conditions developed for **2a** (Scheme 5). Here again we observed the formation of small amounts of the tetracarbonyl chelated complex (dark-red) from the pentacarbonyl complex **2b** (orange-red). However, the chelated complex in this case is too unstable to be isolated by column chromatography. It was most convenient to characterize the carbene complex in the form of the tetramethylammonium salt of its metal acylate precursor.

The pentacarbonyl complex **2b** (containing ~5% chelated complex) was subjected to the benzannulation reaction with

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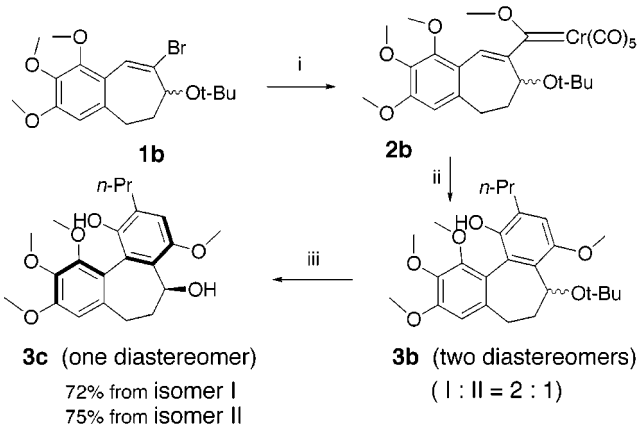
(19) Haworth, R. W.; Moore, B. P.; Pauson, P. L. *J. Chem. Soc.* **1949**, 3271.

(20) The sequence from ref 19 was modified in the following way: for the reduction of 3-(3,4,5-trimethoxybenzoyl)propionic acid , Et_3SiH[20a] was used instead of N_2H_4; for the cyclization of 4-(3,4,5-trimethoxyphenyl)-butanoic acid, polyphosphoric acid (PPA)[20b] was used instead of P_2O_5 or PCl_5. (a) Hamada, A.; An Chang, Y.; Uretsky, N.; Miller, D. D. *J. Med. Chem.* **1984**, *27*, 675. (b) Koo, J. *J. Am. Chem. Soc.* **1953**, *75*, 1891.

(21) Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483.

Scheme 5. Synthesis of the *t*-Bu-Protected Allocolchicinoids **3b** and Their Deprotection[a]



[a] (i) (1) *t*-BuLi, ether, −78 °C 15 min, (2) $Cr(CO)_6$, ether, 0 °C 0.5 h, 25 °C, 1.5 h, (3) MeOTf, CH_2Cl_2, 25 °C, 1.5 h, 54%; (ii) (1) 3 equiv of 1-pentyne, benzene, 55 °C, 24 h, (2) air, 25 °C, 12 h, 48%; (iii) (1) Ac_2O, catalytic $FeCl_3$, 0 °C, (2) LAH, THF, 25 °C, 1 h.

1-pentyne under the conditions developed for the preparation of **3a**. In this reaction, it is expected that two diastereomers of the phenol product **3b** would be possible given that the hydroxy and methoxy groups ortho to the biaryl linkage should prevent epimerization about the chiral axis. As anticipated, the phenol **3b** was produced as a mixture of diastereomers. The 2:1 mixture of isomers could be separated and each obtained in pure form. The difficulty encountered in the deprotection of the *tert*-butyl ether group in **3b** is likely due to the fact that the unsymmetrical ether linkage at the C-7 group is both tertiary and benzylic. Competing elimination is possible, which will install a double bond in ring B. To find a useful deprotection routine, we screened two known methods which do not involve the use of equimolar amounts or excess amounts of acidic reagents. The first involves treatment of the major diastereomer of **3b** with catalytic amounts of TBDMSOTf [22] which led to the formation of more than five products. The second provides a solution to the problem via the in situ trapping of the *tert*-butyl ether cleavage product by acetate in a procedure that involves treatment of the ether with Ac_2O in the presence of catalytic amounts of $FeCl_3$.[23] The acetyl group in the intermediate acetates can then be easily liberated to give an alcohol either reductively or by hydrolysis. Thus, the major diastereomer of **3b** was subjected to the acetylation conditions described above, followed by the reductive removal of the acetyl groups using $LiAlH_4$ to give the alcohol **3c** as a single diastereomer in 72% yield. Interestingly, upon similar treatment, the minor diastereomer of **3b** also gives a single diastereomer of **3c**, and furthermore, it was found to be indentical with that obtained from the major diastereomer of **3b**. The ^{1}H NMR spectrum of **3c** correlates with the major diastereomer of **3b** and differs from that of the minor isomer of **3b**.

Therefore, it is concluded that the major isomer of **3b** is cleaved to the alcohol **3c** with retention and the minor isomer **3b** gives the alcohol **3c** with inversion. The relative stereochemistry of **3c** is assigned as shown (a*R*,7*S*; a*S*,7*R*) on the basis of a comparison with the ^{1}H NMR spectra of related known compounds.[4]

In conclusion, this work has demonstrated the feasibility of a highly convergent construction of the fully functionalized ring C in the potentially biologically relevant allocolchicinoids via the benzannulation reaction of chromium carbene complexes. A successful method for the protection of the C-7 hydroxyl has been identified as well as a method for its deprotection, providing for access to the allocolchicinoid alcohol **3c** which presents possibilities for further modifications of the C7 position in this and related compounds.

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Supporting Information Available: Full experimental details and characterization data for compounds **1a**−**h**, **2a**,**b**, **3a**−**c**, **8b**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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