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Allocolchicines via Intramolecular Nicholas Reactions: The Synthesis of NSC 51046

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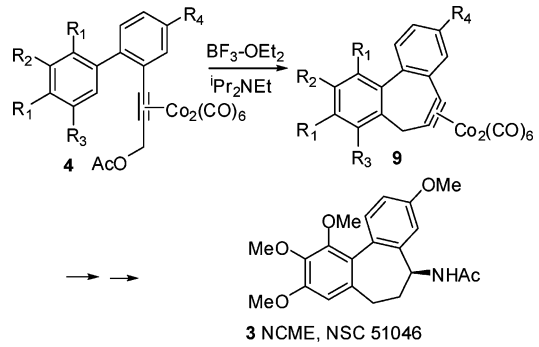
ABSTRACT



Biaryl propargyl acetate hexacarbonyldicobalt complexes (4) undergo Lewis acid mediated Nicholas reactions with a remote arene function to afford dibenzocycloheptyne complexes (9). Reductive decomplexation based on a hydrosilylation–protodesilylation protocol is facile, and the 1,2,3,9-tetramethoxy case can be converted to NSC 51046 ((*S*)-*N*-acetylcolchicinol methyl ether, 3).

The allocolchicines are a series of compounds featuring a 6,7,6-ring system and a highly oxygenated A ring. Several of these compounds have been found to be active against a variety of cancer cell lines, including drug-resistant ones, operating by inhibition of tubulin assembly and polymerization, resulting in the arrest of cell mitosis.[1] Individual members of this class of compounds have been the subject of increased recent synthetic interest. Examples include Wulff's Diels−Alder C ring construction approach to (*S*)-allocolchicine (**1**),[2a] Fagnou's formal (*S*)-allocolchicine synthesis featuring formation of the B ring by palladium-catalyzed direct C−H arylation,[2b] Chong's,[2c] Kocienski's,[2d] and Leonard's[2e] (*S*)-*N*-acetylcolchinol (**2**) syntheses based on inter-[3] or intramolecular oxidative coupling protocols, and DeShong's siloxane coupling−ring expansion route to racemic *N*-acetylcolchinol-*O*-methyl ether (**3**).[4] By contrast, all preparations of enantiomerically pure **3** (NSC 51046) derive from oxidative degradation of colchicine itself[5] or rely upon resolution (Figure 1).[6]

We[7] and others[8] have developed several methods to construct seven-membered ring systems featuring cyclohep-

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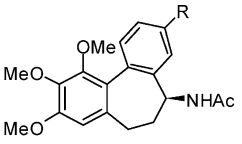
tyne−$Co_2(CO)_6$ complexes, based on propargyl cation−$Co_2(CO)_6$ (Nicholas reaction) chemistry and other reactions on intact alkyne−$Co_2(CO)_6$ complexes.[9] Most pertinently, we

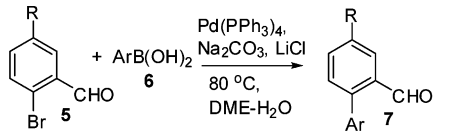


1, R = CO_2Me allocochicine
2, R = OH N-acetylcolchicinol
3, R = OMe NCME, NSC 51046

Figure 1. Selected allocolchicines.

have demonstrated that aryl (*Z*)-enyne propargyl acetate−$Co_2(CO)_6$ complexes undergo ready Lewis acid mediated cyclization onto electronically neutral or electron-rich arenes to afford benzocycloheptyne complexes.[7a]

Scheme 1. Suzuki−Miyaura Synthesis of **7**



5a, R = OMe
5b, R = H

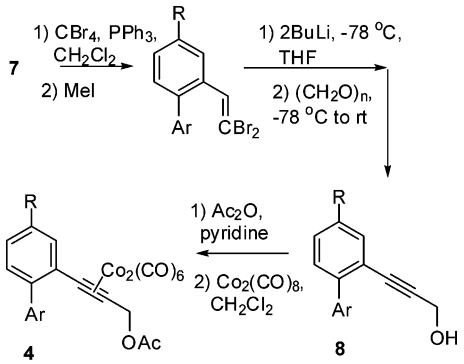
6a, Ar = 2,3,4-$(MeO)_3C_6H_2$
6b, Ar = 3,5-$Me_2C_6H_3$
6c, Ar = 3-thienyl

7a, Ar = 2,3,4-$(MeO)_3C_6H_2$, R = OMe
7b, Ar = 2,3,4-$(MeO)_3C_6H_2$, R = H
7c, Ar = 3,5-$Me_2C_6H_3$, R = OMe
7d, Ar = 3-thienyl, R = OMe

Given this facile ring closing process and the electron-rich A ring of the allocolchicines, we viewed the intramolecular Nicholas reaction protocol on biaryl-2-propargyl acetate−$Co_2(CO)_6$ complexes (**4**) as an attractive choice for a general approach to the 6,7,6-ring system. Moreover, our interest was drawn to **3**, given its limited synthetic attention and the ready availability of precursors by way of Suzuki−Miyaura coupling and Corey−Fuchs reaction chemistry.

For all but one of the cyclization substrates (**4**), the synthesis therefore commenced with 2-bromobenzaldehydes (**5**). Suzuki−Miyaura cross-coupling occurs readily with arylboronic acids (**6**) under conventional conditions as reported by Fürstner,[10] affording biaryl-2-carboxaldehydes (**7**) in good to excellent yields (Scheme 1 and Table 1). In addition to the precedented cases with 2,3,4-trimethoxyphenylboronic acid (**6a** → **7a**, **7b**),[10] analogous cross-coupling reactions were similarly successful with 3,5-dimethylphenylboronic acid (**6b** → **7c**) and 3-thiopheneboronic acid (**6c** → **7d**).

Scheme 2. Preparation of Propargyl Acetate Complexes **4**[a]



7/8/4a, Ar = 2,3,4-$(MeO)_3C_6H_2$, R = OMe
7/8/4b, Ar = 2,3,4-$(MeO)_3C_6H_2$, R = H
7/8/4c, Ar = 3,5-$Me_2C_6H_3$, R = OMe
7/8/4d, Ar = 3-thienyl, R = OMe
8/4e[a], Ar = Ph, R = H

[a] Compound **8e** was prepared by Sonogashira reaction of 2-iodobiphenyl with propargyl alcohol.

The aldehyde function on the biaryl system was central to the attachment of the propargyl acetate cobalt complex. The Corey−Fuchs protocol was accomplished without purification of the dibromoalkene intermediate; quenching the BuLi-derived acetylide ion with paraformaldehyde ultimately resulted in the conversion of the biaryl-2-carbox-

Table 1. Preparation of Propargyl Acetate Complexes **4**

compd	yield (%)	compd	yield (%)	compd	yield (%)
7a	84[a]	**8a**	82	**4a**	86
7b	92[b]	**8b**	78	**4b**	84
7c	72	**8c**	57	**4c**	91
7d	80	**8d**	38[c]	**4d**	77
		8e	87	**4e**	86

[a] Literature yield, 89%.[10] [b] Literature yield, 85%.[10] [c] 7-Methoxynaphtho[2,1-*b*]thiophene was isolated in 50% yield.

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(9) For recent reviews on the Nicholas reaction, see: (a) Diaz, D. D.; Betancort, J. M.; Martin, V. S. *Synlett* **2007**, 343. (b) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133. (c) Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809.
(10) Mamane, V.; Hannen, P.; Fürstner, A. *Chem.—Eur. J.* **2004**, *10*, 4556.

aldehydes (**7**) into the corresponding propargyl alcohols (**8**) in good yields (Scheme 2 and Table 1), except in the thienyl case (**8d**), which was formed in modest yield.[11] In addition, unsubstituted biphenyl case **8e** was prepared by Sonogashira coupling of 2-iodobiphenyl with propargyl alcohol in 87% yield. Straightforward acetylation of the alcohol and complexation of the alkyne function with $Co_2(CO)_8$ then afforded the propargyl acetate−$Co_2(CO)_6$ complexes (**4**) in good yields (Table 1).[12]

With the precursor propargyl acetate complexes (**4**) in hand, attention was turned to the cyclization reactions. At 5 × 10^{-3} M concentration (CH_2Cl_2), tetramethoxy-substituted complex **4a** underwent reaction mediated by BF_3−OEt_2 (3 equiv) to give tricyclic product **9a** in 56% yield after 2.5 h at room temperature (Table 2, entry 1). With the intent to

Table 2. Intramolecular Nicholas Reactions of **4**

entry	biaryl	rxn time	product	yield[a] (%)
1	**4a**	2.5 h	**9a**	56[b]
2	**4a**	6 h	**9a**	71
3	**4b**	16 h	**9b**	59 (66)
4	**4c**	6 h	**9c**	85
5	**4d**	5 h	**9d/9d′**	82[c]
6	**4e**	16 h	**9e**	59

[a] Number in parentheses is the yield based on recovered starting material. [b] No ^{i}Pr$_2$NEt added. [c] **9d**/**9d′** = 45:55.

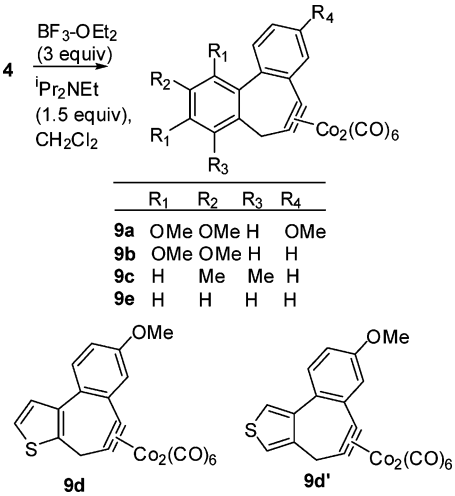
scavenge acid liberated during the reaction process, 1.5 equiv of ^{i}Pr$_2$NEt was added to the mixture in addition to the Lewis acid. While a slightly longer reaction time (6 h) was required for complete consumption of **4a**, compound **9a** was formed in increased yield (71%, entry 2). This 3 equiv of BF_3−OEt_2/1.5 equiv of ^{i}Pr$_2$NEt (CH_2Cl_2, 5 × 10^{-3} to 1 × 10^{-2} M) protocol was therefore adopted as the standard one for **4b**−**e**. Each substrate gave the corresponding dibenzocycloheptyne (**9b**−**e**) in synthetically useful yields (Scheme 3 and Table 2).

There are several significant points for these Nicholas reaction based cyclizations. The 3-thienyl-substituted substrate **4d** afforded **9d** as an approximately 1:1 ratio of regioisomers resulting from attack at the 2- and 4-positions of the thiophene ring (entry 5). In addition, it is also worthy of note that there was very limited correlation between the nucleophilicity of the ring at which reaction occurs (i.e., entry 3 vs 4), and that all the cyclizations were considerably slower than the analogous benzocycloheptenyne formation reactions.[7a] Taken together, it is clear that the rate at which ring closing occurs in the current system is dependent upon the proportion

(11) In this case, the major product was 7-methoxynaphtho[2,1-*b*]-thiophene (50% yield), consistent with vinyl carbene insertion into the thiophene C(2)−H bond. For related chemistry, see: (a) Imamura, K.; Hirayama, D.; Yoshimura, H.; Takimiya, K.; Aso, Y.; Otsubo, T. *Tetrahedron Lett.* **1999**, *40*, 2789. (b) Merlic, C. A.; Pauly, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 11319.

(12) Acetates were chosen over alcohol leaving groups due to their superiority in benzocycloheptenyne complex syntheses; see ref 7a.

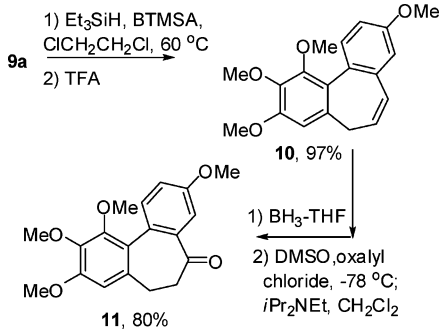
Scheme 3. Intramolecular Nicholas Reactions of **4**



of cations derived from **4** in a reactive rotamer in addition to the degree that the reacting arene is electron-rich. Nevertheless, formation of dibenzocycloheptyne complexes was possible in all cases and included both electron-rich and unactivated arenes as the nucleophilic fragment.[13]

As the transformation of **9a** into NSC 51046 required conversion of the cycloheptynedicobalt unit into an appropriate synthetic handle, a number of reductive decomplexation reaction protocols were investigated. It was quite gratifying to find that employing the hydrosilylation conditions developed by Isobe,[14] followed by in situ desilylation by the addition of CF_3CO_2H, resulted in the formation of dibenzocycloheptene **10** in excellent yield (97%) (Scheme 4). A

Scheme 4. Conversion of **9a** to Dibenzosuberone **11**

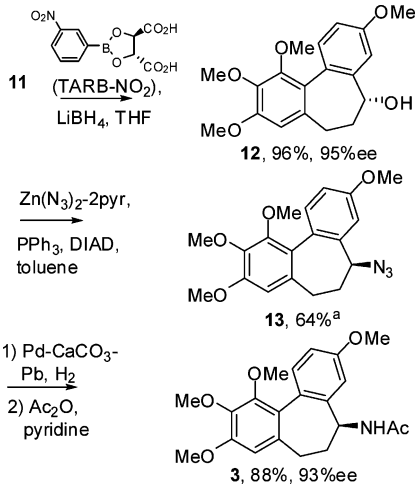


conventional hydroboration/oxidation reaction, followed by further oxidation under Swern conditions, gave ketone **11** (80% yield), with only a trace of the isomeric hydroboration−oxidation product observable in the crude reaction product.[15]

(13) The complexes with substitution *ortho* to the biaryl juncture or to the cycloheptyne on the A ring (**4a**,**b**, **9a**−**c**) possess a diastereotopic methylene in the ^{1}H NMR spectrum, reflecting biaryl restricted rotation.

(14) Kira, K.; Tanda, H.; Hamajima, A.; Baba, T.; Takai, S.; Isobe, M. *Tetrahedron* **2002**, *58*, 6485.

Scheme 5. Completion of Synthesis of NSC 51046[a]



[a] Isolated with 7% of alkene **10**.

While **11** has been converted previously to racemic **3**,[4,6] no fully synthetic enantioselective approach has been reported. Therefore, adapting Wulff's approach to (*S*)-allocolchicine to the current system, we subjected ketone **11** to reaction with $LiBH_4-TARB-NO_2$, giving **12** in good yield (96%) and enantiomeric purity (95% ee) (Scheme 5). Substitution of the alcohol function with zinc azide[16] and diisopropyl azodicarboxylate (DIAD) gave **13** (64%), and subsequent reduction of the azide and acetylation of the intermediate amine afforded target NSC 51046 (**3**) (88% yield, 93% ee). A single recrystallization of **3** resulted in its isolation in >99% ee.

In summary, we have demonstrated that biaryl-2-propargyl acetate$-Co_2(CO)_6$ complexes (**4**) undergo cyclization to afford dibenzocycloheptyne$-Co_2(CO)_6$ complexes (**9**) under mild, Lewis acid mediated conditions in fair to good yields. The appropriate dibenzocycloheptyne complex (**9a**) may be converted readily into allocolchicine NSC 51046 (**3**); to our knowledge, this is the first de novo synthesis of this allocolchicine in enantiomerically enriched form. The application of the cyclization protocol to other allocolchicine natural products is in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Both **10** and **11** themselves also have significant tubulin assembly inhibitory activity. See refs 1b,c and: (a) Polański, J. *Acta Biochim. Pol.* **2000**, *47*, 37. (b) Han, S.; Hamel, E.; Bastow, K. F.; McPhail, A. T.; Brossi, A.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2851.

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