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Nicholas Reactions in the Synthesis of Dicobalt Dibenzocyclooctyne Complexes

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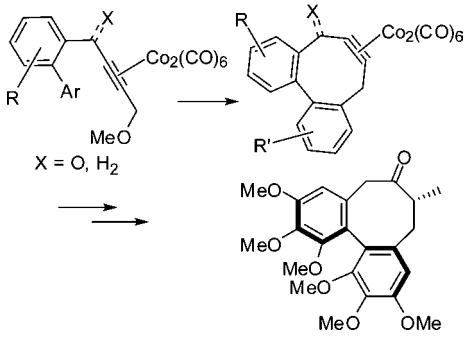
ABSTRACT



Hexacarbonyldicobalt complexes of biaryl-substituted 4-methoxybutynones and 4-methoxy-2-butynes undergo intramolecular Nicholas reactions to form dibenzocyclooctyne−$Co_2(CO)_6$ complexes in good yields. Reductive decomplexation of the cyclization products is possible, and the method has been applied to a formal synthesis of isoschizandrin.

Cyclooctyne is well-known as the smallest of the simple cycloalkynes with sufficient stability to be capable of isolation in the conventional sense.[1] This does not apply to all cyclooctyne derivatives, as increasing unsaturation in the eight-membered ring renders the compounds more marginally stable[2] or incapable of isolation.[3] In contrast, the hexacarbonyldicobalt complexes of cyclooctynes appear to have excellent stability. While direct preparation from cyclooctyne itself is known,[4] this is synthetically limited. Several scattered reports of de novo construction of cyclooctyne−$Co_2(CO)_6$ complexes have been published, including those resulting from Nicholas reaction chemistry,[5] ring-closing metathesis,[6] aldol and Michael reaction chemistry,[7] Diels−Alder reactions,[8] and epoxide ring-openings.[9] In addition, cyclic ether and amine complexes have been prepared.[10] Despite the viability of systems of this class, there has been no attempt to prepare dibenzocyclooctynedicobalt complexes (**1**, Figure 1) or to explore their applicability toward dibenzocyclooctane-containing compounds.

The dibenzocyclooctane lignans are a large group of natural products occurring widely, particularly in the Schizandraceae family.[11] Their structural features and

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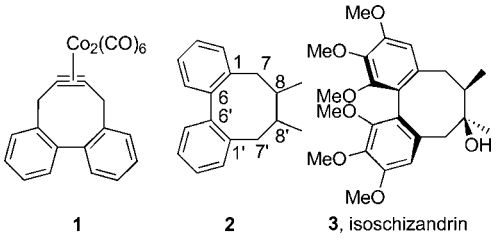
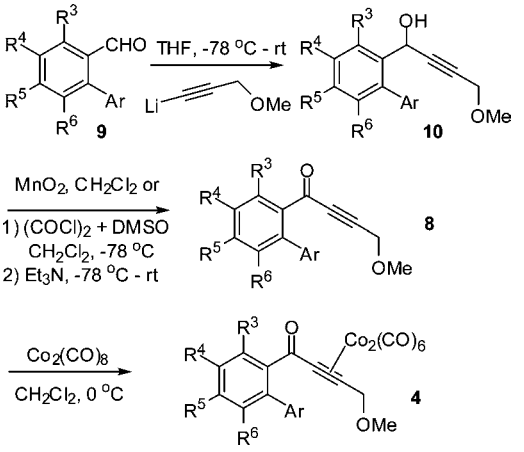


Figure 1. Dibenzocyclooctane lignan framework and **1**.

wide-ranging biological activities have made them recent attractive synthetic targets. Synthesis of the eight-membered rings of these systems is overwhelmingly accomplished either by aryl−aryl (C6−C6′) (see **2**) coupling protocols[11a,12] or by assorted condensation or coupling reactions at the homobenzylic sites (C8−C8′) of functionalized 2,2′-diethylbiphenyls. Construction by way of benzylic−bishomobenzylic bond formation (C8′−C7′) of biaryls is less common but known.[13] Their preparation by way of C1′−C7′ coupling reactions, such as by electrophilic substitution protocols, is rare and on those occasions tend to be by dienone−phenol rearrangements.[14,15]

Our group has had recent success with the use of intramolecular Nicholas reaction chemistry in the preparation of dibenzocycloheptyne−$Co_2(CO)_6$ complexes[16] and have found the method useful in allocolchicine synthesis in conjunction with reductive decomplexation reactions. As a result of these developments, we have chosen to explore a Nicholas reaction approach to such dibenzocyclooctyne complexes, with a view toward their use in dibenzocyclooctane synthesis. Isoschizandrin (**3**), an antiulcer C-8 oxygenated dibenzocyclooctane lignan, was identified as a target compound relevant to this chemistry.[17] Given the common occurrence of C7-oxygen substituted dibenzocyclooctane lignans in addition to their C8-hydroxy-substituted and nonoxygen-substituted counterparts,[11a] we considered it of importance to include both γ-carbonyl cation (**4**→**5**) and normal (**6**→**7**) versions of these Nicholas reactions.

Table 1. Preparation of **4**



9	10	8	4
9a, R^4 = OMe, Ar = 2,3,4-$(MeO)_3C_6H_2$	**10a** (86%)	**8a** (96%)[a]	**4a** (93%)
9b, R^3 = R^4 = OMe, Ar = 2,3,4-$(MeO)_3C_6H_2$	**10b** (97%)	**8b** (78%)[b]	**4b** (90%)
9c, R^4 = OMe, Ar = 3-thienyl	**10c** (94%)	**8c** (79%)[b]	**4c** (87%)
9d, R^4 = R^5 = R^6 = OMe, Ar = 2,3,4-$(MeO)_3C_6H_2$	**10d** (98%)	**8d** (92%)[a]	**4d** (93%)

[a] MnO_2, CH_2Cl_2, rt; [b] Swern conditions.

The precursors for γ-carbonyl cation complexes were selected to be 4-alkoxy-2-butynoyl-substituted biaryls (**8**) (Table 1), which were prepared from the biarylcarboxaldehydes (**9**)[16] in straightforward fashion.

Reaction of the aldehydes with the lithium acetylide derived from 3-methoxy-1-propyne (propargyl methyl ether) gave the benzylic/propargylic alcohols (**10**) in good to excellent yield (Table 1); subsequent oxidation with MnO_2, or using Swern conditions when MnO_2 performed sluggishly, gave the corresponding ketones (**8**). Complexation of the alkyne functions of these alkynones with $Co_2(CO)_8$ then afforded **4** readily.

The biaryls bearing 4-methoxy-2-butynyl functions (**11**) were also prepared from the biarylcarboxaldehydes (**9**) in three steps (Table 2). Reduction of the aldehyde function to the benzylic alcohols (**12**) occurred cleanly and in excellent yields. Substitution of bromide for the alcohol function (**13**) was accomplished with PBr_3. For tetramethoxy-substituted **13f**, reaction of the benzyl bromide with the lithium acetylide derived from propargyl methyl ether afforded **11f** in acceptable yield. In other cases, this protocol gave poor yields; conversely, use of this lithium acetylide in the presence of $InCl_3$ and catalytic amounts of $Pd(dppf)Cl_2$ gave **11c**−**e** successfully.[18] Once again, the alkyne functions underwent complexation by $Co_2(CO)_8$ to afford **6** readily.

Cyclization reactions of the aryl alkynone complexes were investigated first. While previous experience has

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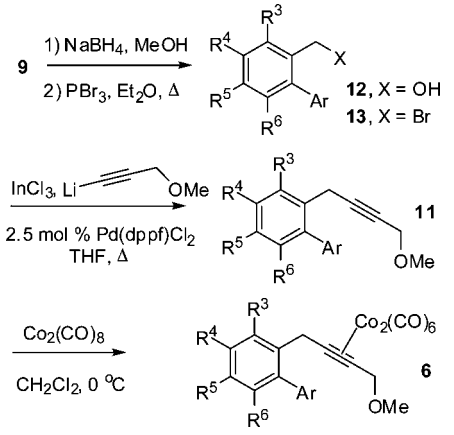
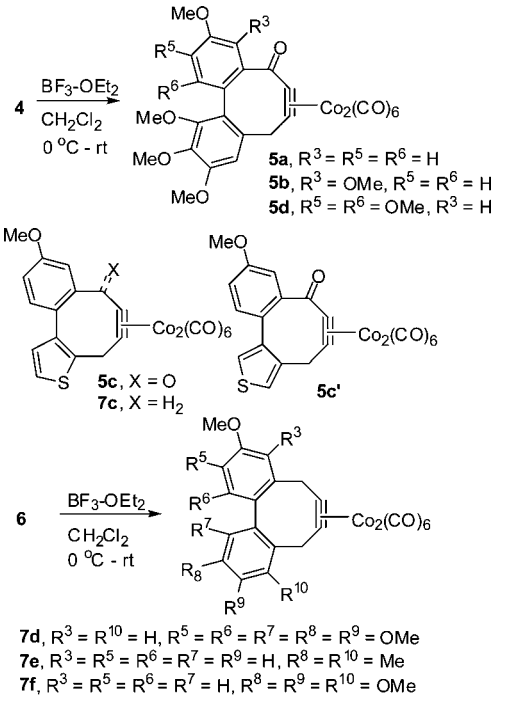
Table 2. Preparation of **6**



9	12	13	11	6
9c, R^4 = OMe, Ar = 3-thienyl	**12c** (89%)	**13c** (73%)	**11c** (61%)	**6c** (86%)
9d, $R^4 = R^5 = R^6$ = OMe, Ar = 2,3,4-$(MeO)_3C_6H_2$	**12d** (93%)	**13d** (99%)	**11d** (69%)	**6d** (99%)
9e, R^4 = OMe, Ar = 3,5-$Me_2C_6H_3$	**12e** (92%)	**13e** (63%)	**11e** (66%)	**6e** (86%)
9f, R^4 = OMe, Ar = 3,4,5-$(MeO)_3C_6H_2$	**12f** (99%)	**13f** (80%)	**11f** (61%)[a]	**6f** (78%)

[a] $InCl_3$ and $Pd(dppf)Cl_2$ omitted.

Table 3. Intramolecular Nicholas Reactions



entry	starting material	conditions[a]	time (h)	product	yield (%)
1	**4a**	A	5	**5a**	85
2	**4b**	B	6	**5b**	71
3	**4c**	B	8	**5c**	68[b]
4	**4d**	A	8	**5d**	81
5	**4d**	A[c]	8	**5d**	71
6	**6c**	A	1	**7c**	77
7	**6d**	A	2	**7d**	93
8	**6e**	A	2	**7e**	88
9	**6f**	A	1	**7f**	91

[a] A: $BF_3 \cdot OEt_2$ (3 equiv), 0 °C to rt, CH_2Cl_2 (4×10^{-3} M); B: $BF_3 \cdot OEt_2$ (4 equiv), $^iPr_2NEt$ (1.5 equiv) 0 °C to rt, CH_2Cl_2 (4×10^{-3} M). [b] **5c**:**5c'** = 14:1. [c] 8×10^{-3} M.

shown that Nicholas reaction based γ-carbonyl cations are more reliably generated using Bu_2BOTf as Lewis acid,[19] $BF_3 \cdot OEt_2$ (3 equiv, 0 °C) gave good rates of reaction in the case of **4** (Table 3). Reactions were conducted at 4×10^{-3} M; doubling the concentration reduced yield modestly (entry 4 versus entry 5). The addition of *i*-Pr_2NEt (1.5 equiv, with 4 equiv $BF_3 \cdot OEt_2$) occasionally resulted in lesser amounts of decomposition due to presumed scavenging of liberated acid and consequently gave greater yields. Ultimately, tetramethoxy **4a** afforded **5a** in 85% yield, whereas hexamethoxy substrate **4d** gave **5d** in 81% yield. In the case of pentamethoxy substrate **4b** and thiophene-containing **4c**, the reactions were conducted in the presence of *i*-Pr_2NEt; the former afforded **5b** in 71% yield, whereas the latter gave **5c** in in 68% yield, as a 14:1 mixture of products reacting at C-2 and C-4 (**5c'**) of the thiophene ring.

Cyclization reactions involving the benzyl alkyne complexes **6** succeeded under similar conditions. In none of the cases was the presence of additional *i*-Pr_2NEt necessary, and the reactions were somewhat more rapid than for **4**. We attributed this to the lack of a competitively Lewis basic and electron-withdrawing carbonyl in **6**. In the event, hexamethoxy-substituted **6d** gave dibenzocyclooctyne **7d** in 93% yield in 1 h, whereas tetramethoxy-substituted **6f** afforded **7f** in 91% yield over the same period. The substrates with less electron rich arene nucleophiles also underwent cyclization rapidly, as thiophene-substituted **6c** afforded **7c** in 77% yield over 2 h, while dimethyl-substituted **6e** gave **7e** in 88% over 2 h. In the **6c**→**7c** case, there was no evidence of C-4 reactivity on the thiophene ring competing with the C-2 substitution.

Decomplexation reactions of the cyclooctynones were studied using **5d** as a model compound (Scheme 1). Use of Bu_3SnH[20] resulted in the successful removal of the $Co_2(CO)_6$ unit with predominant overreduction of the alkyne function to give cyclooctanone **14** (82% yield), along with a small amount of cyclooctenone **15** (9% yield). The cyclooctenone **15** could be obtained as the predominant product (44% yield, 51% based on recovered starting material) by employing 2 equiv of NaH_2PO_2 in 2-methoxyethanol;[21] this was accompanied by 13% of cyclooctanone **14** and 14% of unreacted **5d**. The use of the conventionally employed 5 equiv of hypophosphite gave greater amounts of cyclooctanone **14** (29%), at the expense of **15** (36%).[22]

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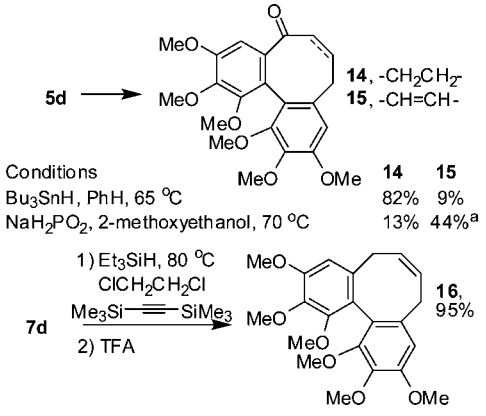
Scheme 1. Reductive Decomplexations

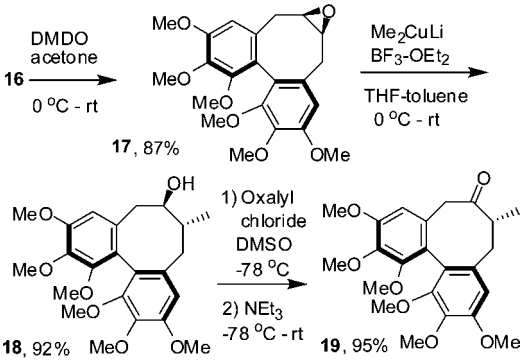


[a] 51% based on recovered starting material.

In the case of dibenzocyclooctyne complex **7d**, the reductive decomplexation was much more straightforward. Employing our hydrosilylation–protodesilylation modification of the Isobe protocol,[16,23] **7d** afforded **16** cleanly (95% yield).

Alkene **16** is well suited for use in the synthesis of isoschizandrin. Epoxidation of the alkene function occurred readily with dimethyldioxirane (DMDO), giving **17** in 87% yield (Scheme 2). Lewis acid mediated cuprate attack of the epoxide gave alcohol **18** with complete diastereoselectivity (92% yield). Swern oxidation of the alcohol then afforded **19** in 95% yield. The Meyers group has previously converted enantioenriched **19** into (−)-isoschizandrin (79% yield, along with 9% (−)-schizandrin) by methyllithium addition;[17a] consequently, this constitutes a formal synthesis of racemic isoschizandrin.

Scheme 2. Completion of Isoschizandrin Formal Synthesis



In summary, we have found that intramolecular Nicholas reactions of both biaryl-4-methoxybutynonedicobalt complexes and biaryl-4-methoxy-2-butynedicobalt complexes afford the corresponding dibenzocyclooctyne–$Co_2(CO)_6$ complexes in good yields. Reductive decomplexation of these cyclization products is possible, and the process may be applied to the formal synthesis of isoschizandin.

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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.

The authors declare no competing financial interest.

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