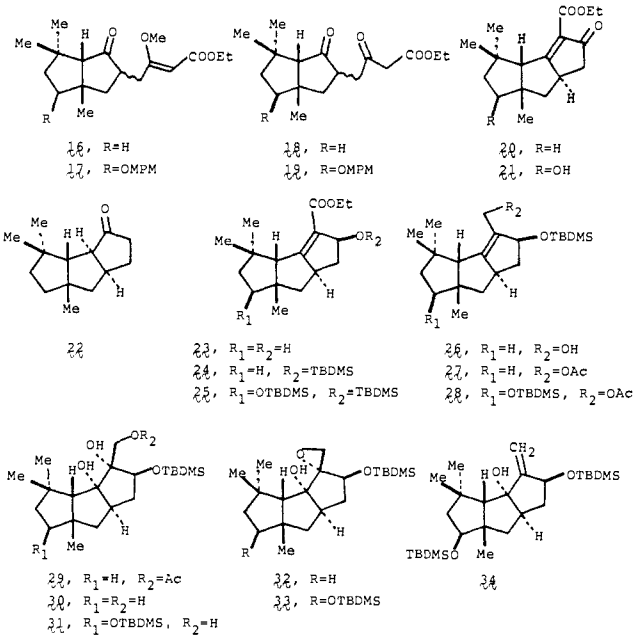

The stereochemistry of **20** was unequivocally determined by converting to the known **22**.[2b]

Likewise the intermediate **21** was also obtained in ca. 20% overall yield from **15** by using the above strategy. Under the cyclization conditions deprotection of the MPM group occurred simultaneously to give **21**.

Transformation of **20** to (±)-$\Delta^{9(12)}$-capnellene-8β,10α-diol (**1**) was first investigated. Reduction of **20** with $NaBH_4$–$CeCl_3$[13] gave **23** exclusively,[14] which underwent silylation (*tert*-butyldimethylsilyl chloride and imidazole) to give **24** in 98% overall yield. DIBAH reduction of **24** (63%) followed by acetylation (92%) provided **27**. The acetate **27** was then converted to **29** in 94% yield on exposure to 2.5 equiv of osmium tetraoxide in pyridine at 30 °C for 14 h followed by reducitve workup (saturated aqueous $NaHSO_3$, 50 °C for 9 h). Treatment of **29** with K_2CO_3 in MeOH gave **30** (98%). Reaction of **30** with 1.2 equiv of CH_3SO_2Cl and 1.2 equiv of triethylamine in CH_2Cl_2 gave the monomesylate, which was immediately converted to **32** by treatment with DBU in benzene (98% overall yield). Reaction of **32** with (trimethylsilyl)lithium in HMPA–THF followed by exposure to $Bu_4N^+F^-$ provided (±)-**1** in 53% yield, whose spectral data were identical with those reported (^1H NMR, IR, mass).[1,15]

With the first total synthesis of **1** completed, we next investigated the total synthesis of (±)-$\Delta^{9(12)}$-capnellene-3β,8β,10α-triol (**3**) using similar strategy. Reduction of **21** with $NaBH_4$-$CeCl_3$ followed by silylation gave **25** in a good yield. DIBAH reduction and subsequent acetylation afforded **28**, which was then converted to **31** in a two-step process (OsO_4, then K_2CO_3 in MeOH) (ca. 35% overall yield from **25**). Epoxide formation (88%) followed by treatment with (trimethylsilyl)lithium gave **34** (75%). Exposure to $Bu_4N^+F^-$ in THF accomplished the first total synthesis of (±)-**3** (78%), whose spectal data were identical with those reported.[1] Furthermore the spectral data of $\Delta^{9(12)}$-8-oxocapnellene-3β,10α-diol derived from **3** by MnO_2 oxidation were also identical with those reported.[1]

In summation, the first total syntheses of (±)-**1** and (±)-**3** have been accomplished by a general strategy that hopefully will allow the synthesis of other members of the capnellane family. The novel TMSOTf–Et_3N-induced aldol cyclizations of keto esters developed during these syntheses are expected to find other applications in complex synthetic situation and are under further exploration. Biological investigations with **1**, **3**, and related compounds as well as asymmetric approaches to these natural products are currently in progress.

Supplementary Material Available: Full NMR data for compounds **8–21**, **23–34**, and ii (3 pages). Ordering information is given on any current masthead page.

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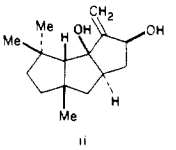
(14) The stereochemistry of **23** was unequivocally proven by the fact that **23** was converted to **1** without producing the 8-epimer of **1** (i). For the synthesis of i, see: Pattenden, G.; Teague, S. J. *Tetrahedron Lett.* **1983**, *23*, 547.

(15) Another route to (±)-**1** from **26** [(i) CCl_4–HMPT, (ii) Me_3SiLi in HMPA–THF, (iii) *m*-CPBA, (iv) $Bu_4N^+F^-$) was also investigated. However, surprisingly, this synthetic route provided the bisallylic alcohol ii in 38% overall yield from **26**. The structure of ii was presumed to be the 10-epimer of **1** on



ii

the basis of the mass and ^1H NMR. The X-ray crystallographic analysis is under way.

Cobalt-Mediated [2 + 2 + 2] Cycloadditions of Alkynes to the Indole 2,3-Double Bond: An Extremely Facile Entry into the Novel 4a,9a-Dihydro-9*H*-carbazole Nucleus

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Because of the extremely diverse physiological activity exhibited by the indole nucleus[1] and its presence in a multitude of natural products[2] selective alteration of its structure has commanded a considerable amount of synthetic attention. Part of this effort has involved the utilization of the 2,3-double bond in Diels–Alder[3] and other cycloadditions.[4] We report a novel mode of reactivity of this bond in the presence of η^5-CpCo reagents: the [2 + 2 + 2] cycloaddition to two alkynes to provide the hitherto unknown[5] 4a,9a-dihydro-9*H*-carbazole nucleus as incorporated in a variety of complex polycyclic dienes. This methodology demonstrates for the first time the feasibility of activating aromatic double bonds in CpCo-mediated cyclizations[6] and provides a powerful means by which to fuse several rings onto the indole moiety in one step.

The starting materials **1** were prepared in one or two steps from known indole derivatives by adaptation of literature procedures,[7-9] using the appropriate acyl chloride[10a-c] or iodoalkane (Table I).[10d]

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(8) N-Acylation: Kikugawa, Y. *Synthesis* **1981**, 460.

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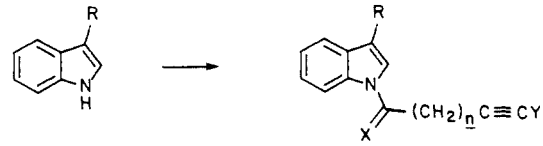
Table I. Syntheses of Cyclization Precursors **1**



1

product **1**	R	X	Y	*n*	yield, %	mp or bp, °C/mm	method (ref)
1a	H	O	H	2	63	87–88	8
1b	H	O	H	3	91	200/0.05	8
1c	CH_3	O	H	2	81	112–114	8
1d	H	H_2	H	2	90	150/0.5	7
1e	CH_2CH_2NHAc	O	H	2	80	131–133	8
1f	CH_2CH_2NPhth	O	H	2	57[a]	168–169	9
1g	$CH_2CH_2OSi(CH_3)_2$-*t*-Bu	O	H	2	56[b]	89–90	8
1h	$CH_2CH_2N(CH_2C{\equiv}CH)(CH_2Ph)$	O	H	2	65	90–92	8
1i	H	O	$(CH_2)_4C{\equiv}CH$	2	62	73–74	8
1j[c]	$COCH_2CH_2C{\equiv}CH$	O	H	2	25	115–121	

[a] Overall yield from tryptamine. [b] Overall yield from tryptophol. [c] From indole-*N*-magnesium bromide and 4-pentynoyl chloride.

The results of the various cyclizations are shown in Table II.

Several comments are in order concerning our observations. (1) All cyclizations are unoptimized (but give reproducible results) and were run under standard conditions[6] [$CpCo(CO)_2$, Δ, *hν* (GE-ENH slide projector lamp)] in order to provide comparative data. However, we have noted that, depending on the system, yields can be improved by changing solvents, temperature, and catalyst.[13] Most dramatically, employment of η^5-$C_5H_5Co(CH_2{=}CH_2)_2$[14] at room temperature completely avoids cyclobutadiene **3** formation with (in some cases) a corresponding increase of the yield of indole cycloaddition product. It also enhances the regioselectivity observed in cocyclizations with unsymmetrical alkynes (e.g., **1f** → **4f**:**5f** = 16:1). It appears, however, that each system under investigation commands its own specific optimized conditions for formation. (2) The cocyclization is stereo- and extensively regiospecific. Stereochemical assignments were made in analogy to other systems[6] utilizing the anisotropy of cobalt in ^1H NMR spectra. (3) The complexes in Table II are readily demetalated by $CuCl_2$ or $Fe(NO_3)_3$ (3–5 equiv, 0 °C, THF, or CH_3CN, 5–15 min) to the free ligands in excellent yield (80–90%). To our knowledge, this method constitutes the first construction of the 4a,9a-dihydro-9*H*-carbazole nucleus. These compounds are surprisingly stable with respect to dehydrogenation. Thus, the liberated ligand in **2a** is left unchanged after exposure to 10% Pd–C in boiling *m*-xylene. (3) Demetalation with concomitant aromatization to the corresponding carbazole can be achieved with Ce^{4+} [e.g., **2a**, $(NH_4)_2Ce(NO_3)_6$ (6 equiv), THF-CH_3CN, −78 °C, 0.5 h, 54%]. (4) In the cyclizations of **1e** and **1f** some free ligand is formed directly, indicating the feasibility of a catalytic approach[15] to the organic fragments. (5) The identity of the ligands in **8i** and **9i** was ascertained by decomplexation to the same compound. (6) Recomplexation of the free ligand in **2a** to CpCo gives mainly (30:1 selectivity) the isomer of opposite configuration to **2a**, indicating kinetic product formation in the cyclization. (7)

Table II. Results of the Inter- and Intramolecular Cocyclizations of **1**[11]

start. mater.	cocyclization partner	products (% yield)		
1a–d	$(CH_3)_3SiC{\equiv}CSi(CH_3)_3$	**2a** (64) **2b** (2) **2c** (8) **2d** (0)	**3a** (7) **3b** (24) **3c** (44) **3d** (30)	
	$(CH_3)_3SiC{\equiv}CX$ X = CH_3O[12a] or CO_2CH_3[12b]			5-free ligand
1e	X = CH_3O	**4e** (46)	**5e** (trace)	(0)
1e	X = CO_2CH_3	**4e'** (32)	**5e'** (11)	(4)
1f	X = CO_2CH_3	**4f** (35)	**5f** (19)	(5)
1g	X = CH_3O	**4g** (50)	**5g** (1.2)	(0)
1h		**6h** (20)	**7h** (20)	
1i		**8i** (52)	**9i** (7)	
1j		**10j** (15)		

Preliminary chemistry of the dihydrocarbazole moiety shows useful reactivity. Thus, the free ligand derived from **2a** undergoes Diels–Alder cycloaddition with *o*-chloranil (23 °C, 3 days, 69%) to give **11** or with *N*-phenyltriazolinedione to furnish **12** (82%).[11] Exo addition was assumed on the basis of the CpCo-recomplexation results on the same ligand. Similarly the free ligand in **4e** hydrolyzes to the protodesilylated α,β-unsaturated ketone, a crucial intermediate in a projected total synthesis of strychnine.[16] (8)

(10) (a) The known (Schulte, K. E.; Rejsch, J. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1952**, *292*, 51) 4-pentynoyl chloride was prepared (80%) by a modification of the method of ref 10b. (b) 5-Hexynoyl chloride: Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 4786. (c) 4,10-Undecadiynoyl chloride was synthesized without isolation from the acid ($SOCl_2$, catalytic DMF, 25 °C, 0.5 h), in turn prepared from lithio-4-pentynol dimethyl-*tert*-butylsilyl ether and 1-iodo-5-(trimethylsilyl)-4-pentyne followed by desilylation and oxidation (CrO_3, H^+) in 22% overall yield. (d) 5-Iodopentyne: Büchi, G.; Wüest, H. *J. Org. Chem.* **1979**, *44*, 546.

(11) All new compounds isolated gave satisfactory analytical and/or spectroscopic data (see supplementary material).

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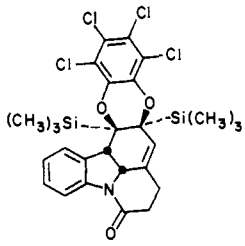
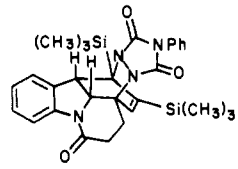


11



12

The complexes **2a–c** and **4e–g** exhibit hindered rotation of the trimethylsilyl group on the ^1H NMR time scale (300 MHz), only the second observation of such a phenomenon.[17] In contrast, neither the isomer of **2a**, free ligands of **2a**, **4e**, and **4e'**, nor the corresponding carbazole derived from **2a** have this property. (9) 3,3-Dialkylindole systems as observed in the ligands of **2c**, **4e–g**, **5e–g**, **6h**, **7h**, and **10j** may be of particular importance in medicinal applications.[18]

In short, the described chemistry opens up the way to utilizing the indole 2,3 and perhaps other aromatic double bonds in cobalt-mediated cyclizations, providing novel synthetic flexibility in polyheterocycle construction.

Acknowledgment. This work was supported by NIH-GM22479. K.P.C.V. is a Miller Professor in Residence (1985–1986).

Supplementary Material Available: Melting point, boiling point, spectral, and analytical data on 37 new compounds reported (21 pages). Ordering information is given on any current masthead page.

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^1H and ^{13}C Assignments from Sensitivity-Enhanced Detection of Heteronuclear Multiple-Bond Connectivity by 2D Multiple Quantum NMR

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We present a new and sensitive method for determining long-range (two- and three-bond) ^1H–^{13}C connectivity. The method is a modified version of the ^1H-detected heteronuclear multiple quantum experiment,[1-3] previously used for obtaining high-sensitivity ^1H–^{15}N shift correlation spectra.[4-7]

[†]National Institutes of Health.
[‡]Food and Drug Administration.

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Table I. Phases, ϕ and ψ, of the First Two 90°(^{13}C) Pulses and the Receiver Phase in the Eight Steps of the Long-Range Multiple Quantum Shift Correlation Experiment

step	ϕ	ψ	receiver	step	ϕ	ψ	receiver
1	x	x	x	5	x	y	y
2	x	$-x$	$-x$	6	x	$-y$	$-y$
3	$-x$	x	x	7	$-x$	y	y
4	$-x$	$-x$	$-x$	8	$-x$	$-y$	$-y$

Recently, it has been demonstrated convincingly that detection of long-range ^1H–^{13}C connectivity provides a wealth of structural and assignment information.[8-12] Unfortunately, the 2D COLOC experiment[8,9] proposed for this purpose suffers from low sensitivity and yields spectral intensities that are modulated by the size of both the one-bond J_{CH} coupling and the homonuclear proton couplings. The other possible method, the one-dimensional selective INEPT experiment,[10] has the disadvantage of requiring exact adjustment of pulse widths and being time consuming if a large number of connectivities are to be investigated.

Here, we demonstrate that a simple extension of the ^1H-detected heteronuclear multiple quantum experiment can be used successfully to circumvent the problems mentioned above. The sequence we propose is

$$\begin{array}{lllllll} ^1H & 90°_x\text{–}\Delta_1\text{–} & & \text{–}\Delta_2\text{–} & & -t_1/2\text{–}180°_x\text{–}t_1/2\text{–} & \text{–Acq}(t_2) \\ ^{13}C & & 90°_\phi & & 90°_\psi & & 90°_x \end{array}$$

where $\Delta_1 = 1/2^1J_{CH}$, and the duration of Δ_2 is about 60 ms. The phase cycling employed is given in Table I. The first 90°(^{13}C) pulse serves as a low-pass J filter[11] and suppresses one-bond correlations in the 2D spectrum. This pulse creates heteronuclear multiple quantum coherence for protons that are directly coupled to a ^{13}C nucleus, which is removed from the 2D spectrum by alternating the phase of the ^{13}C pulse along the $\pm x$ axis without changing the receiver phase. Removal of these direct connectivities from the 2D spectrum is not essential but it simplifies the final spectrum at a very small cost in sensitivity. The second 90°(^{13}C) pulse creates the ^1H–^{13}C multiple (zero and double) quantum coherence of interest. The 180°(^1H) pulse interchanges the zero and double quantum components and thus removes the effect of ^1H chemical shift from the t_1 modulation frequency. Consequently, after the final 90°(^{13}C) pulse, the ^1H signals that originate from ^1H–^{13}C multiple quantum coherence are modulated by ^{13}C chemical shifts and homonuclear proton couplings. Signals from protons that do not have a long-range coupling to ^{13}C are removed by phase cycling of the second 90°(^{13}C) pulse.

Because the detected signal is also phase-modulated by the homonuclear scalar coupling, absorptive 2D spectra cannot be recorded and the spectra are presented most conveniently in the absolute value mode. Very recently, Frey et al.[12] proposed the use of purge pulses and z filters to allow the recording of absorptive ^1H–^{113}Cd shift correlation spectra. Unfortunately, in the application to ^{13}C these modifications degrade the sensitivity unacceptably and they also make the suppression of signals not coupled to ^{13}C more difficult.

As an example, we illustrate the multiple-bond shift correlation method for a 4-mg sample of (5'-deoxyadenosyl)cobalamin (coenzyme B_{12}, MW 1580), dissolved in 0.35 mL of phosphate-

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