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Synthesis of Terpene and Steroid Dimers and Trimers Having Cyclobutadienyl−Co and Aromatic Tethers

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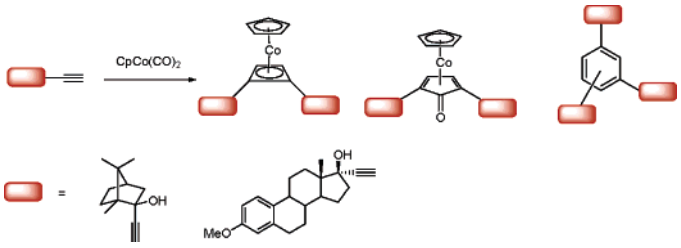

The reaction of natural product derived propargylic alcohols with $CpCo(CO)_2$ produces three new types of natural product hybrids having two or three terpene or steroid fragments. The tether joining the natural product subunits is built during the reaction. Type 1 hybrids have two terpene or steroid moieties joined by a CpCo−cyclobutadiene tether, with the two units disposed in a 1,2-arrangement (**9**, **14**, **22**). Type 2 hybrids have a Co−cyclopentadienone tether (**10**). Type 3 has three units of terpene or steroid joined to a benzene ring (**11**, **12**, **15**). An unusual Co-mediated β-carbon elimination pathway of propargylic alcohols leading to ketones (an unknown process in this chemistry) has been observed.

Introduction

The preparation of bio-organometallic compounds[1] and natural product hybrids[2] share the common goal of preparing new molecular entities having structural diversity. The merge of both approaches open doors to prepare bio-organometallic natural product hybrids within the idea of diversity oriented synthesis.[3] In this field we have reported the preparation of several ferrocenyl-β-lactams **1**[4] and, among other derivatives, the dicobalthexacarbonyl complexes from alkaloid- and steroid-terpene hybrids **2** and **3** as bio-organometallic natural product derivatives.[5] An alternate approach to the building of bio-organometallic natural product hybrids is to join two moieties by an organometallic tether. To the best of our knowledge, the single example of this approach is the stepwise preparation of dimeric terpene **4** recently reported by us.[6]

† Laboratorio de Difracción de Rayos X. To whom inquires regarding the determination of the structure of compounds **9** and **10** should be addressed.

(1) For an overview of this field, see: (a) Fish, R. H.; Jaouen, G. *Organometallics* **2003**, *22*, 36. (b) Dagani, R. *Chem. Eng. News* **2002**, *80*, 23. (c) Special issue on bioorganometallic chemistry: *J. Organomet. Chem.* **1999**, 589, Issue 1.

(2) (a) Tietze, L. F.; Bell, H. P.; Chandrasekhar, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3996. (b) Mehta, G.; Singh, V. *Chem. Soc. Rev.* **2002**, *31*, 324.

(3) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Schreiber, S. L. *Chem. Eng. News* **2003**, *81*, 51. (c) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.

(4) Sierra, M. A.; Mancheño, M. J.; Vicente, R.; Gómez-Gallego, M. *J. Org. Chem.* **2001**, *66*, 8920.

(5) Álvaro, E.; de la Torre, M. C.; Sierra, M. A. *Chem.—Eur. J.* **2006**, *12*, 6403.

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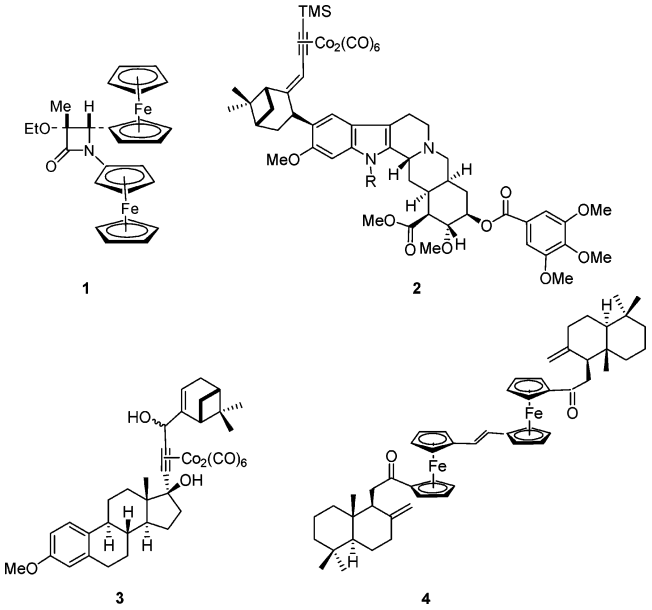
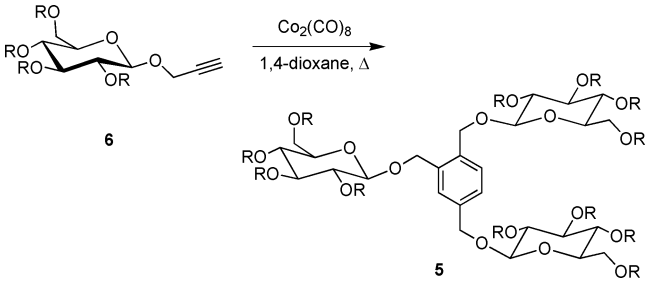


The metal catalyzed [2+2+2] cycloaddition of alkynes (Reppe's reaction)[7] offers a paramount opportunity to create either hybrids incorporating three units of natural product across an aromatic nucleus or two units across a cyclobutadieneCoCp spacer, depending on the reaction conditions. This approach is different from the one reported before by us because now the organometallic tether is built during the joining of the fragments. The $CpCoL_2$-catalyzed [2+2+2] cycloaddition of alkynes has been used to synthesize different natural products like, for example, morphinanes,[8] sesqui- and diterpenes,[9] and strychnine.[10] Furthermore, the use of nitriles as components of the cycloadditions allowed the access to different pyridine containing heterocyclic natural products like LSD and lysergenes.[11] However, the synthesis of natural product trimers tethered to an aromatic nucleus is restricted to the synthesis of sugar derivatives **5** by cyclotrimerization of alkynyl sugars **6** (Scheme 1).[12]

SCHEME 1



Reported herein is the use of terpene- and steroid-derived alkynes to prepare three novel classes of sophisticated terpene or steroid dimers and trimers. Furthermore, the unusual fragmentation of a Co-coordinated propargyl alcohol complex to yield a ketone has been discovered during these investigations.

Results and Discussion

Propargylic alcohol **7** was prepared by the reaction of (1*R*)-(+)-camphor **8**, following the procedure reported by Palomo et al.[13] Alcohol **7** was reacted with a stoichiometric amount of $CpCo(CO)_2$ in boiling toluene. A mixture of four compounds

SCHEME 2

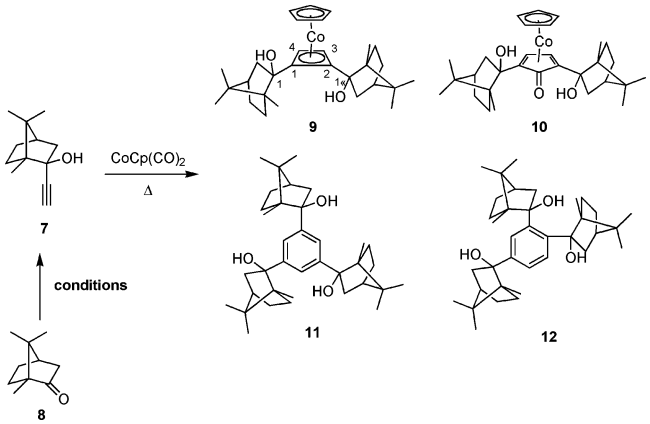


TABLE 1. Reaction of 7 with $CpCo(CO)_2$

entry	alkyne/Co equivalents	solvent (*T*)	yield[a] (%) **9**	**10**	**11**+**12**
1	1:1	toluene (120 °C)	21	5	30
2	2:1	xylenes (140 °C)	39	3	28
3	1:0.05	xylenes (140 °C)	3	1	18
4	2:1	decalin (160 °C)	38	4	35

[a] Isolated yield of chromatographically pure product.

9−**12** was obtained (Scheme 2). Compounds **9** (21%) and **10** (5%) retain the Co moiety, while compounds **11** and **12** (30% combined yield) were aromatic compounds derived from the cyclotrimerization of alcohol **7**. The structures of complexes **9** and **10** were unambiguously determined by X-ray diffraction analysis as the CpCo−cyclobutadiene complex **9** and the CpCo−cyclopentadienone complex **10**, respectively (Figure 1). The ^1H and ^{13}C NMR data of **10** showed signals characteristic to the terpene fragment, together with new signals attributable to the CpCo−cyclobutadiene moiety, instead of the signals corresponding to the triple bond of alcohol **7**. Extensive 2D-NMR experiments allowed the assignment of signals at δ_C 85.2, 89.2, 56.3, and 60.0 to carbons C-1 to C-4 of the cyclobutadiene fragment and two singlets, one proton each, at δ_H 3.67 and 4.02 to the cyclobutadiene protons H-3 and H-4, respectively. Increasing the alkyne/$CpCo(CO)_2$ ratio to 2:1 and the reaction temperature (boiling xylenes or decalin, Table 1, entries 2 and 4, respectively) resulted in an increased yield of cyclobutadiene complex **9**, while the use of catalytic amounts of $CoCp(CO)_2$ makes trimers **11** and **12** the main reaction products (Table 1, entry 3).[14]

Mestranol **13** was used next as the substrate for these reactions. Now a mixture of three compounds was obtained. CpCo−cyclobutadiene complex **14** was identified as the minor product (8−13%), while the 1,2,5-trisubstituted aromatic compound **15** was the main product (30−44%) in all the conditions tested (Scheme 3), even in the presence of high excesses (up to 10 equiv) of $CpCo(CO)_2$ for each equivalent of mestranol (see Table 2). Finally, methoxyestrone **16** was identified in all cases in variable yields (7−12%).

The structure of the Co complex **14** was established by a comparison of its spectroscopic data with those of CpCo−cyclobutadiene **9**, whose structure has been unambiguously determined by X-ray diffraction analysis. ^1H and ^{13}C NMR

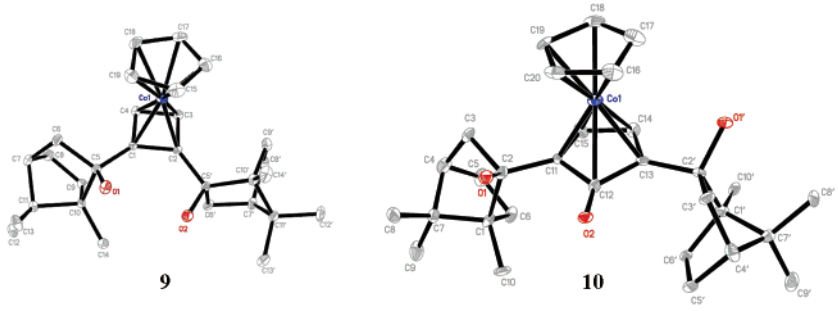


FIGURE 1. ORTEP diagrams of the crystal structures of compounds **9** and **10**.

SCHEME 3

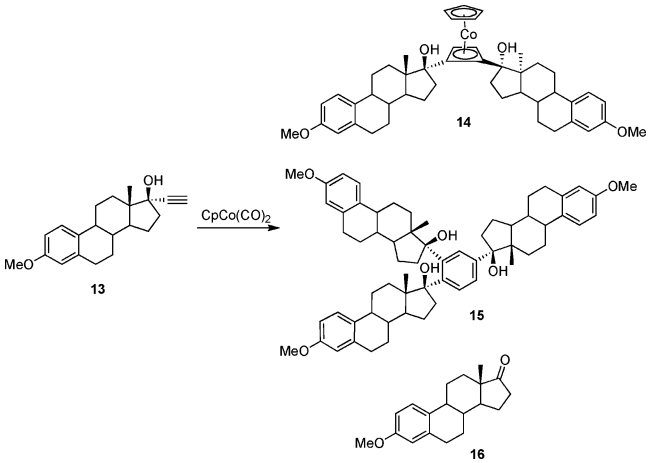


TABLE 2. Reaction of Mestranol 13 with $CpCo(CO)_2$

entry	alkyne/Co equivalents	solvent (*T*)	time (h)	yield[a] (%) 14	15	16
1	2:1	decalin (160 °C)	2	10	32	7
2	2:1	decalin (160 °C)	12	8	32	8
3	1:3	xylenes (140 °C)	7	5	30	8
4	1:10	xylenes (140 °C)	2.5	13	44	12

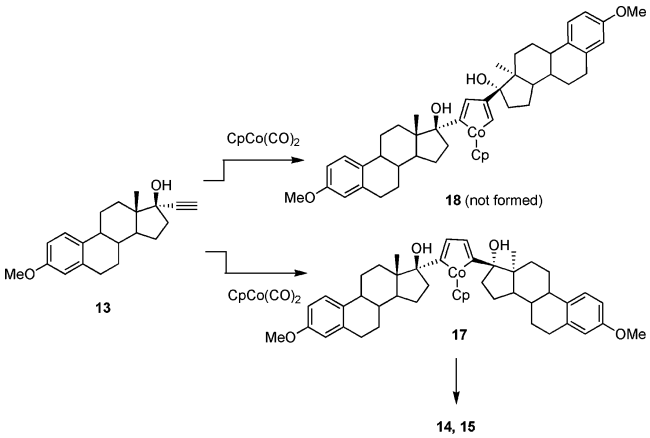
[a] Isolated yield of chromatographically pure product.

spectra of **14** showed signals attributable to the CpCo−1,2-disubstituted cyclobutadiene moiety (δ_H 3.98 and 3.95, δ_C 59.3 and 57.1, one CH each, and 88.8 and 88.4, one C each). The regiochemistry of **14** was confirmed by 2D-NMR spectroscopy. The *g*-HMBC spectra showed cross-peaks between each cyclobutadiene hydrogen at 3.95 and 3.98 ppm, with just one single C-17 steroid quaternary carbon at 81.8 and 82.8 ppm, respectively. Should the obtained compound be the 1,3-isomer, the aforementioned correlation would occur between each cyclobutadiene hydrogen with both C-17 steroid carbons.

The structure of compound **15** as 1,2,5-trisubstituted benzene was established by extensive NMR studies. ^{13}C NMR spectra of **15** showed signals for three aromatic CH carbons (δ_C 124.4, 128.3, and 128.4) and three quaternary carbons (δ_C 141.6, 142.2, and 142.7), apart from the signals attributable to the three steroid fragments, accounting for the formation of a trisubstituted benzene ring. In addition, ^1H NMR spectra of compound **15** showed three singlet signals attributable to the three steroid methoxy groups (δ_H 3.73, 3.76, and 3.78) and three singlet signals, one methyl C-18 each (δ_H 1.03, 1.06, and 1.07). The nonequivalence of the signals of the benzene ring and of the steroidic fragment is consistent with a 1,2,5-substitution pattern in the aromatic ring.[15]

Compounds **14** and **15** should arise from a common cobaltacyclopentadiene **17** having the bulky steroid groups farther away. Because neither the 1,3-disubstituted cyclobutadiene complex nor the 1,3,5-substituted benzene derivatives were obtained, the formation of the alternate cobaltacyclopentadiene **18** should be strongly disfavored due in principle to steric reasons (see below; Scheme 4).[16]

SCHEME 4



Results above pointed to steric hindrance as the controlling factor for the regioselectivity of these processes. However, the

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(8) Pérez, D.; Siesel, B. A.; Malaska, M. J.; David, E.; Vollhardt, K. P. C. *Synlett* **2000**, 306.

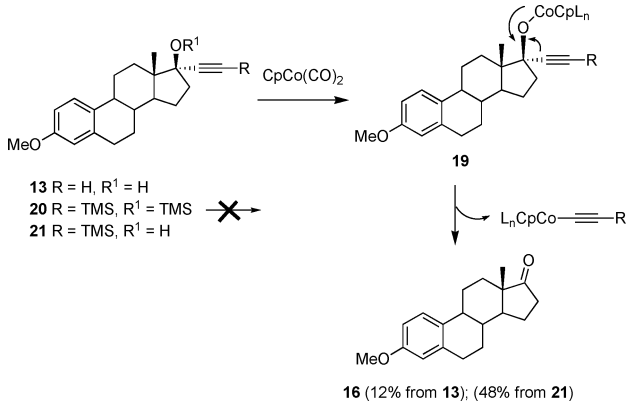
(9) (a) Johnson, E. P.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 381. (b) Germanas, J.; Aubert, C.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 4006.

(10) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **2001**, *113*, 9324.

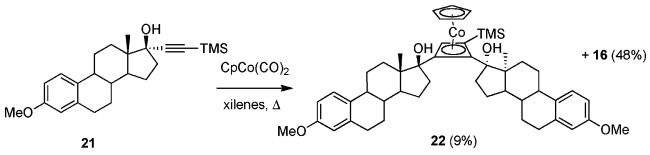
(11) Saá, C.; Crotts, D. D.; Hsu, G.; Vollhardt, K. P. C. *Synlett* **1999**, 487.

(12) Kaufman, R. J.; Sidhu, R. S. *J. Org. Chem.* **1982**, *47*, 4941.

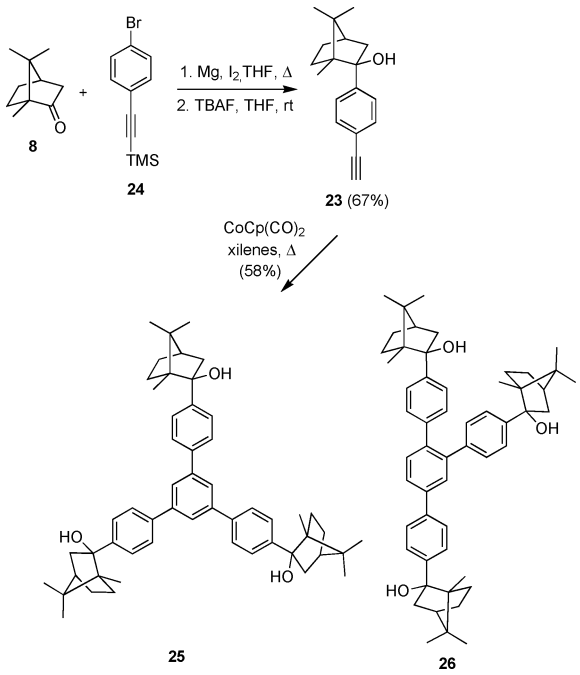
SCHEME 5



SCHEME 6



SCHEME 7



formation of methoxyestrone **16** together with compounds **14** and **15** deserves some additional comments relevant for the mechanistic interpretation of these processes. First, the question of the generality of formation of ketones from the propargylic alcohols in the presence of $CpCo(CO)_2$ was addressed. Camphor was detected by GC-mass spectrometry in the crude reaction mixtures of **7**. Therefore, it can be concluded that the fragmentation of the alkynyl group is general (see below for an additional example). Second, the origin of methoxyestrone **16** is neither the CpCo−cyclobutadiene complex **14** nor mestranol **13**. This was demonstrated by heating pure samples of both compounds for 60 h under the conditions in which **16** is formed. Ketone **16** was not detected in these experiments. Therefore, the fragmentation of the alkynyl moiety requires the presence of Co and should occur before the intermediate cobaltacyclobutadiene **17** evolves to the final products. It is well-known that the coordination to metals promotes the breakage of the propargylic alcohols to form an organometal intermediate along with a ketone.[17] Therefore, it can be proposed that the coordination of the alcohol to the $CpCo(CO)_2$ leads to the formation of **19**. This process is followed by β-carbon elimination, with liberation of either camphor or methoxyestrone, and competes with the formation of cobaltacycle **17** and its further evolution to form either trimers or Co−cyclobutadiene complexes (Scheme 5).

The importance of the coordination of the alcohol to the cobalt and the steric bulkiness in the alkyne were additionally evaluated. Reaction of the bis-TMS-derivative **20** of mestranol[18] with $CpCo(CO)_2$ resulted in recovery of starting material in all the conditions assayed, including an increase in the reaction temperature and an increase in the amount of $CoCp(CO)_2$.[19] On the contrary, compound **21**, having unblocked the C-17 hydroxyl group,[18] produces complex **22** (9%) together with methoxyestrone **16** as the main reaction product (48%; Scheme 6). The structure of cyclobutadiene−Co complex **22** was established on spectroscopic grounds. Both ^{1}H and ^{13}C NMR spectra are almost identical to those of CpCo−cyclobutadiene **14**, except for the signals attributable to the cyclobutadiene fragment. The ^{1}H NMR spectrum of **22** showed one signal singlet for only one cyclobutadiene proton at 4.27 ppm and one signal singlet at 0.30 ppm, accounting for nine hydrogens attributable to one trimethylsilyl group. The presence of the silyl group is consistent with the low field shift observed for the cyclobutadiene carbons (δ_C 93.5, 91.8, 61.8, and 66.0 for carbons C-1 to C-4, respectively) compared with the 1,2-disubstitued derivative **14** (Scheme 3). These data are in accordance with structure **22**.

Finally, to evaluate the role of the propargylic alcohol moiety into the reactions, the alkyne was spaced from the carbinol center. Thus, compound **23** was prepared by reacting the Grignard compound derived from **24** with camphor and subsequent treatment with TBAF/THF to remove the TMS-group (Scheme 7). Alkyne **23** was submitted to a reaction with 1 equiv of $CpCo(CO)_2$ in boiling toluene and simultaneous irradiation (100W, W-lamp). An inseparable mixture of 1,3,5- and 1,2,5-trisubstituted aromatic compounds **25** and **26** was

(13) Palomo, C.; González, A.; García, J. M.; Landa, C.; Oiarbide, M.; Rodríguez, S.; Lynden, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 180.

(14) This is congruent with the reported increment of cyclotrimerization/cyclobutadiene complex ratio upon increasing the reaction temperature. See: Sheppard, G. S.; Vollhardt, K. P. C. *J. Org. Chem.* **1986**, *51*, 5496.

(15) The aromatic tether of compound **11**, the 1,3,5-trisubstituted regioisomer, possesses magnetically equivalent carbons and protons, showing one signal for the three protons and two signals for the six aromatic carbons.

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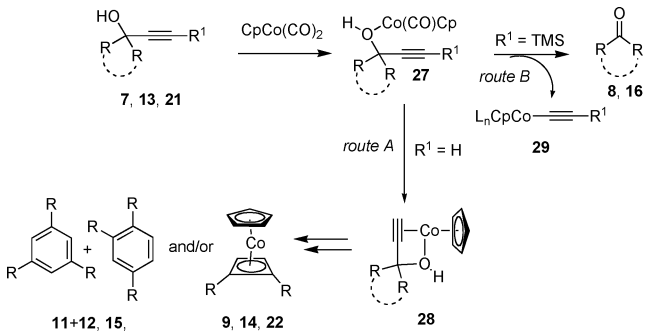
(17) Selected recent examples referred to Rh: (a) Funayama, A.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2005**, *127*, 15354. (b) Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407. (c) Terao, Y.; Wakui, H.; Nomoto, N.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 5236.

(18) Peters, R. H.; Crowe, D. F.; Tanabe, M.; Avery, M. A.; Chong, W. K. M. *J. Med. Chem.* **1987**, *30*, 646.

(19) The lack of reactivity of trimethylsilyl alkynyl carboranes has been recognized; contrary to phenyl alkynyl carboranes that render the cobaltacyclobutadiene derivatives under analogous reaction conditions. Goswami, A.; Nie, Y.; Oeser, T.; Siebert, W. *Eur. J. Inorg. Chem.* **2006**, 566.

SCHEME 8



obtained in 58% yield (Scheme 7). Neither traces of the corresponding CpCo−cyclobutadiene nor the CpCo−cyclobutadienone complexes were obtained. Camphor was not detected in the crude reaction mixtures by GC-MS analysis.

Results above show that the coordination of the propargylic alcohol to the $CpCo(CO)_2$ is crucial to determine both the composition of the reaction products and their regiochemistry. Clearly, the separation of the triple bond and the alcohol moieties as in **23** produces the usual outcome of these reactions, namely, the cyclotrimerization products, as a nearly equimolar mixture of regioisomers **25** and **26**. The propargylic alcohols **7**, **13**, and **21** produce mixtures of cobalt complexes and cyclotrimers together with the ketone derived from the breakage of the propargyl moiety. Finally, the blockage of the propargyl alcohol **20** results in the inertia of this compound, at least in the conditions investigated.

These experimental data may be rationalized by proposing the initial coordination of the alcohol moiety to the $CpCo(CO)_2$ to yield the key intermediate **27** (Scheme 8).[20] The fate of this intermediate is dictated by the bulkiness of the substituents joined to the triple bond. Coordination of the triple bond to the cobalt (route A, Scheme 8) competes favorably with the β-carbon elimination in monosubstituted alkynes (route B, Scheme 8). In this case, the additional stabilization of the 16-electron intermediate cobaltacycle **28** allowed the formation of cyclobutadiene−Co complexes (**9**, **14**, **22**) at the expense of the cyclotrimerization compounds (**11**+**12**, **15**). The regiochemistry in both cases is dictated by the steric hindrance of the alkyne. Increasing the bulkiness of the substituents at the alkyne (compound **21**) results in an increased difficulty for the coordination of the alkyne to the Co nucleus, and therefore, the β-carbon elimination reaction leading to ketones (**8**, **16**) becomes the preferred pathway (Scheme 8). It should be noted that, in this case, the Co−cyclobutadiene complex **22** is formed in low yield and with the concomitant elimination of one TMS group (Scheme 6).

In conclusion, the reaction of natural product derived propargylic alcohols with $CpCo(CO)_2$ produces three new types of natural product hybrids. These products contain two or three terpene or steroid fragments and the tether joining the natural product subunits is built during the reaction. Type 1 hybrids have two terpene or steroid moieties joined by a CpCo−cyclobutadiene tether, with the two units disposed in a 1,2-arrangement (**9**, **14**, **22**). Type 2 hybrids have been obtained as minor products in the reaction of camphor-derived propargylic alcohols and are analogous to type 1, but having a Co−cyclopentadienone tether (**10**). Type 1 and 2 are bio-organometallic hybrid natural products. Type 3 has three units of terpene or steroid joined to a benzene ring (**11**, **12**, **15**). A reasonable mechanism based on the coordination of the propargyl alcohol to the Co center, followed by two competitive reaction pathways from a common intermediate **27**, is proposed. Intermediate **28** may evolve mainly through the usual pathways to cyclotrimerization or Co−cyclobutadiene products for monosubstituted alkynes. The β-carbon elimination pathway leading to ketones (an unknown process in this chemistry) competes unfavorably in the above case, but it becomes the main reaction pathway for disubstituted alkynes. Having established the grounds to prepare three different types of natural product hybrids, further work pursuing the synthesis of more complicated structures is now in progress.

Experimental Section

See Supporting Information for general methods and procedures.

Reaction of Alcohol 7 with $CpCo(CO)_2$. Compounds 9, 10, 11, and 12: $CpCo(CO)_2$ (68 mg, 0.39 mmol) was added to a solution of **7** (140 mg, 0.78 mmol) in degassed decaline (5.6 mL) at 160 °C. The reaction mixture was boiled for 2.5 h, cooled to room temperature, filtered through a pad of celite, and concentrated in vacuo. Silica gel chromatography of the crude product (hexanes → hexanes/AcOEt 4:1) afforded **9** (72 mg, 38%), **10** (8 mg , 4%), and **11** and **12** (48 mg, 35%). Compound **9**: Yellow syrup; IR (nujol) ν_{max} 3521, 3463, 2925, 1456, 1376, 1067, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.97 (s, 5H), 4.02 (s, 1H), 3.67 (s, 2H), 3.12 (br s, 1H), 2.37 (dt, J = 13.0, 3.7 Hz, 1H), 1.95 (dt, J = 13.6, 3.9 Hz, 1H), 1.74 (d, J = 12.8 Hz, 1H), 1.67−1.49 (m, 6H), 1.35−1.21 (m, 2H), 1.34 (d, J = 13.5 Hz, 1H), 1.08 (s, 3H), 1.04 (m, 1H), 1.07 (s, 3H), 1.03 (s, 3H), 0.92 (m, 1H), 0.90 (s, 3H), 0.82 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 89.2 (C), 85.2 (C), 81.5 (C), 80.2 (5CH), 78.9 (C), 60.0 (CH), 56.3 (CH), 54.3 (2C), 53.0 (CH_2), 50.8 (C), 50.6 (C), 48.4 (CH_2), 45.9 (CH), 45.5 (CH), 32.3 (CH_2), 29.1 (CH_2), 27.8 (CH_2), 27.4 (CH_2), 22.0 (CH_3), 21.7 (CH_3), 21.5 (CH_3), 21.2 (CH_3), 12.0 (CH_3), 11.8 (CH_3); MS (EI) m/z (relative intensity) 480 [M^+] (5), 462 [$M^+ - 18$] (100), 447 [$M^+ - 15 - 18$] (25), 419 (8), 338 (10), 311 (12), 124 (14). Anal. Calcd for $C_{29}H_{41}O_2Co$: C, 72.48; H, 8.60. Found: C, 72.25; H, 8.38. Compound **10**: Orange syrup; IR (KBr) ν_{max} 3436, 2954, 1790, 1631, 1537, 1456, 1385, 1067, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.11 (s, 5H), 5.00 (d, J = 3.1 Hz, 1H), 4.81 (d, J = 3.3 Hz, 1H), 3.32 (d, J = 13.0 Hz, 1H), 2.23 (dt, J = 13.6, 3.9 Hz, 1H), 1.96 (ddd, J = 13.0, 4.4, 2.9 Hz, 1H), 1.86−1.67 (m, 4H), 1.54 (m, 1H), 1.46 (d, J = 13.4 Hz, 1H), 1.36−0.96 (m, 5H), 1.21 (s, 3H), 1.17 (s, 3H), 0.91 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4 (C), 91.3 (C), 90.5 (C), 82.2 (5CH), 81.7 (C), 81.0 (C), 72.1 (CH), 71.5 (CH), 54.5 (C), 54.2 (C), 50.4 (C), 50.0 (C), 46.7 (CH_2), 46.3 (CH), 45.4 (CH), 42.1 (CH_2), 31.6 (CH_2), 31.3 (CH_2), 27.3 (CH_2), 26.1 (CH_2), 21.5 (CH_3), 21.4 ($2CH_3$), 21.2 (CH_3), 11.6 (CH_3), 10.1 (CH_3); MS (EI) m/z (relative intensity) 508 [M^+] (28), 490 [$M^+ - 18$] (100), 421 [$M^+ - 15 - 18$] (15), 461 (10), 447 (11), 421 (39), 367 (40), 243 (36). Anal. Calcd for $C_{30}H_{41}O_3Co$: C, 70.85; H, 8.13. Found: C, 70.71; H, 7.89. Compound **11**: Pale yellow oil; IR (KBr) ν_{max} 3436, 2957, 1631, 1478, 1458, 1388, 1065 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.62 (s, 3H), 2.39−0.78 (overlapped m, 21H), 1.27 (s, 9H), 0.91 (s, 9H), 0.90 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.3 (3C), 123.9 (3CH), 83.9 (3C), 53.6 (3C), 50.6 (3C), 45.8 ($3CH_2$)*, 45.7 (3CH)*, 31.4 ($3CH_2$), 26.6 ($3CH_2$), 21.6 ($6CH_3$), 9.9 ($3CH_3$) (assignments marked with an asterisk may be interchanged); MS (EI) m/z (relative intensity) 534 [M^+] (2), 516 [$M^+ - 18$] (6), 425 (28), 406 (12), 315 (46), 204 (100), 108 (29), 95 (42). Anal. Calcd for $C_{36}H_{54}O_3$: C, 80.85; H, 10.18. Found: C,

(20) A nitrogen coordinated cobaltacyclopentadiene has been proposed by Saá et al. to explain regioselectivity in the synthesis of 3,3′-substituted 2,2′-bipyridines: Varela, J. A.; Castedeo, L.; Maestro, M.; Mahía, J.; Saá, C. *Chem.—Eur. J.* **2001**, *7*, 5203.

80.71; H, 10.41. Compound **12**: Pale yellow oil; $[\alpha]^{22}_D$ −50.0 (*c* 0.09, $CHCl_3$); IR (KBr) ν_{max} 3430, 2934, 1630, 1477, 1459, 1390, 1062 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.62 (m, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 1H), 2.45−0.82 (overlapped m), 1.27, 0.91, 0.89 (3s, 27H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.2 (3C), 131.1 (CH), 130.7 (CH), 123.5 (CH), 83.7 (3C), 55.1, 53.6, 51.3, 51.1 and 50.6 (6C), 45.7 ($3CH_2$)*, 45.5 (3CH)*, 31.7 (CH_2), 31.6 (CH_2), 31.3 (CH_2), 26.8 ($3CH_2$), 22.3, 21.7 and 21.6 ($6CH_3$), 10.0 ($3CH_3$) (assignments marked with asterisk may be interchanged); MS (EI) *m*/*z* (relative intensity) 516 [M^+ − 18] (54), 501 [M^+ − 18 − 15] (7), 445 (96), 407 (31), 335 (21), 296 (23), 186 (64), 95 (100). Anal. Calcd for $C_{36}H_{54}O_3$: C, 80.85; H, 10.18. Found: C, 80.57; H, 10.42.

Reaction of Mestranol 13 with $CpCo(CO)_2$. Compounds 14 and 15: $CpCo(CO)_2$ (5.6 mmol, 1.0 g) was added to a solution of mestranol (215 mg, 0.56 mmol) in xylenes at 140 °C. The reaction mixture was refluxed for 2.5 h until no starting material was left (TLC analysis), cooled to room temperature, and filtered through a pad of celite. The solvent was removed under reduced pressure. Silica gel chromatography of the residue yielded, in increasing order of polarity, 3-*O*-methylstrone **16** (19 mg, 12%), cyclobutadiene−Co complex **14** (28 mg, 135), and trimer **15** (77 mg, 44%). Compound **14**: Yellow oil; IR (KBr) ν_{max} 3435, 2928, 1610, 1500, 1453, 1255, 1038 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.11 (m, 4H), 6.56 (m, 6H), 4.99 (s, 5H), 3.98 (br s, 1H), 3.95 (br s, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 2.77−1.18 (overlapped m), 0.89 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 157.4, 138.1, 138.0, 132.6, 132.5, 126.4, 113.8, 111.6, 111.5, 88.7, 88.3, 82.8, 81.1, 80.2, 59.3, 57.1, 55.2, 53.8, 49.7, 49.5, 48.5, 47.7, 43.6, 43.5, 39.9, 39.3, 37.4, 35.3, 33.6, 31.7, 29.9, 29.7, 27.5, 27.4, 26.9, 26.6, 23.5, 23.1, 15.2, 14.8; MS (EI) *m*/*z* (relative intensity) 744 [M^+] (12), 726 [M^+ − 18] (100), 708 (73), 497 (23), 460 (17), 443 (17), 173 (46), 147 (35), 124 (22). Anal. Calcd for $C_{47}H_{57}O_4Co$: C, 75.78; H, 7.71. Found: C, 75.53; H, 7.44. Compound **15**: Pale yellow solid; mp 205−208 °C; $[\alpha]^{20}_D$ +64.15 (*c* 0.132, $CHCl_3$); IR (film) ν_{max} 3360, 2930, 1610, 1500, 1255, 1237, 1050, 1038, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (br s, 1H), 7.18−7.03 (m, 4H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.79−6.52 (m, 6H), 3.78 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 2.87−1.14 (overlapped m), 1.07 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2 (3C), 142.7 (C), 142.2 (C), 141.6 (C), 137.8, 137.6 (3C), 132.7, 132.2 (3C), 128.4 (CH), 128.3 (CH), 126.3, 126.2 (3CH), 124.4 (CH), 113.6 (3CH), 111.3 (3CH), 89.4 (C), 89.1 (C), 85.7 (C), 55.1 ($3CH_3$), 49.8 (CH), 49.6 (CH), 48.8 (C), 48.7 (C), 48.2 (CH), 47.4 (C), 43.4, 43.3 (3CH), 43.0, 42.7 ($2CH_2$), 39.9, 39.7, 39.4 (3CH), 39.1 (CH_2), 34.6, 34.5, 34.2 ($3CH_2$), 29.9, 29.7 ($3CH_2$), 27.5, 27.4 ($3CH_2$), 26.8, 26.7, 26.1 ($3CH_2$), 24.2, 24.0, 23.9 ($3CH_2$), 15.4, 14.7 ($3CH_3$); MS (API-ES) *m*/*z* 953 [M^+ + Na]. Anal. Calcd for $C_{63}H_{78}O_6$: C, 81.25; H, 8.44. Found: C, 81.07; H, 8.41.

Preparation of Compound 20. To a solution of mestranol (300 mg, 0.97 mmol) in THF (10 mL) at 0 °C, *n*-BuLi (0.90 mL, 1.16 mmol) was added. The mixture was allowed to reach room temperature and stirred for 30 min. The reaction mixture was cooled again at 0 °C, and trimethylsilylchloride was added (0.14 mL, 1.06 mmol). After 30 min, the process was repeated by cooling the mixture at 0 °C, adding *n*-BuLi (0.90 mL, 1.16 mmol) and trimethylsilylchloride (0.14 mL, 1.06 mmol). Finally, after 1 h of stirring at room temperature, 10% HCl aqueous solution was added and the reaction mixture was extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvents under vacuum afforded a residue that was chromatographed on silica gel with hexanes, yielding pure **20** (420 mg, 95%) as a white solid: IR (KBr) ν_{max} 2954, 2928, 2158, 1610, 1499, 1249, 1092, 903, 841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 1H), 6.72 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.63 (d, *J* = 2.6 Hz, 1H), 3.79 (s, 3H), 2.85 (m, 2H), 2.40−1.32 (m, 13H), 0.81 (s, 3H), 0.19 (s, 9H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3 (C), 138.0 (C), 132.8 (C), 126.4 (CH), 113.7 (CH), 111.4 (CH), 110.2 (C), 90.6 (C), 80.9 (C), 55.2 (CH_3), 48.4 (CH), 47.9 (C), 43.8 (CH), 40.5 (CH_2), 39.5 (CH), 32.8 (CH_2), 29.9 (CH_2), 27.3 (CH_2), 26.6 (CH_2), 23.0 (CH_2), 12.9 (CH_3), 1.9 ($3CH_3$), −0.1 ($3CH_3$); MS (IE) *m*/*z* (relative intensity) 454 [M^+] (22), 439 (6), 381 (20), 364 (18), 268 (63), 242 (57), 225 (59), 174 (37), 147 (35), 73 (100). Anal. Calcd for $C_{27}H_{42}O_2Si_2$: C, 71.30; H, 9.31. Found: C, 71.58; H, 9.04.

Preparation of Compound 21. To a solution of compound **20** (160 mg, 0.35 mmol) in MeOH (20 mL) were added dropwise 0.4 mL of concd HCl. The mixture was stirred for 5 h at this temperature and for 72 h at −20 °C until compound **20** was consumed. $NaHCO_3$ saturated aqueous solution was added to the reaction mixture, most of the methanol was removed under vacuum, and the residue was extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvents afforded a residue that was chromatographed on silica gel with hexanes/AcOEt mixtures 25:1 → 10:1, yielding pure **21**(123 mg, 91%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 1H), 6.73 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 3.78 (s, 3H), 2.87 (m, 2H), 2.40−1.10 (m, 14H), 0.88 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4 (C), 137.9 (C), 132.4 (C), 126.3 (CH), 113.7 (CH), 111.5 (CH), 109.5 (C), 90.0 (C), 80.0 (C), 55.1, (CH_3), 49.5 (CH), 47.2 (C), 43.7 (CH), 39.4 (CH_2), 38.9 (CH), 32.8 (CH_2), 29.8 (CH_2), 27.3 (CH_2), 26.4 (CH_2), 22.8 (CH_2), 12.8 (CH_3), 0.02 (3 CH_3).

Reaction of Alcohol 21 with $CpCo(CO)_2$. Compound 22: $CpCo(CO)_2$ (931 mg, 5.17 mmol) was added to a solution of alcohol **21** (198 mg, 0.52 mmol) in degassed xylenes (4 mL) at 140 °C. The reaction mixture was boiled for 12 h, cooled to room temperature, filtered through a pad of celite, and concentrated in vacuo. Silica gel chromatography of the residue (hexanes → hexanes/AcOEt 15:1) yielded in increasing order of polarity pure methoxyestrone **16** (53 mg, 48%) and **22** (19 mg, 9%) as yellow oil: IR (KBr) ν_{max} 3436, 2932, 1703, 1610, 1500, 1280, 1256, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.5 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.58 (m, 3H), 6.49 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.02 (s, 5H), 4.27 (s, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 2.83 (m, 4H), 2.17−1.28 (m overlapped), 0.93 (s, 3H,), 0.91 (s, 3H), 0.3 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4 (2C), 137.8 (2C), 132.1 (C), 132.0 (C), 126.9 (CH), 126.8 (CH), 113.7 (CH), 113.6 (CH), 111.7 (CH), 111.6 (CH), 93.5 (C), 91.8 (C), 82.7 (C), 82.6 (C), 79.3 (5CH), 66.0 (CH), 61.8 (C), 55.2 ($2CH_3$, OCH_3), 48.7 (2CH), 46.7 (C), 46.2 (C), 44.6 (CH), 44.1 (CH), 39.4 (CH), 39.2 (CH), 38.1 (CH_2), 37.1 (CH_2), 35.3 (CH_2), 35.1 (CH_2), 30.0 ($2CH_2$), 27.6 (CH_2), 27.1 (CH_2), 26.8 (CH_2), 26.5 (CH_2), 23.9 (CH_2), 23.4 (CH_2), 14.3 (CH_3), 14.1 (CH_3), 2.8 ($3CH_3$); MS (ES) *m*/*z* 816.4 [M^+]. Anal. Calcd for $C_{50}H_{65}O_4SiCo$: C, 73.50; H, 8.02. Found: C, 73.66; H, 8.32.

Preparation of Compound 24. A solution of [(4-bromophenyl)-ethynyl](trimethyl)silane (1.66 g, 4.44 mmol) in THF (13 mL) was added dropwise to a suspension of Mg (0.31 g, 12.9 mmol) in THF (3 mL), which had been previously treated with a small amount of I_2. The mixture was refluxed for 1.5 h and cooled to room temperature. Then it was treated with a solution of (*R*)-(+)-camphor (0.50 g, 3.22 mmol) in THF (4 mL) and stirred for 8 h. After quenching with NH_4Cl (saturated aqueous solution), the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Silica gel chromatography (hexanes → hexanes/AcOEt 9:1) of the crude product afforded pure **24** (0.47 g, 45%) as a clear oil: $[\alpha]^{20}_D$ −22.9 (*c* 0.14, $CHCl_3$); IR (nujol) ν_{max} 3468, 2957, 2158, 1502, 1457, 1249, 1064 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 2.28 (d, *J* = 14.1 Hz, 1H), 2.18 (dt, *J* = 13.7, 3.9 Hz, 1H), 1.90 (t, *J* = 3.9 Hz, 1H), 1.72 (m, 1H), 1.29−1.12 (m, 2H), 1.25 (s, 3H), 0.89 (s, 3H), 0.87 (s, 3H), 0.76 (m, 1H), 0.24 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5 (C), 131.1 (2CH), 126.7 (2CH), 121.5 (C), 104.9 (C), 94.2 (C), 83.5 (C), 53.6 (C), 50.4 (C), 45.5 (CH), 45.4 (CH_2), 31.1 (CH_2), 26.5 (CH_2), 21.6 ($2CH_3$), 9.7 (CH_3), 0.0 ($3CH_3$); MS (EI) *m*/*z* (relative intensity) 326 [M^+] (5), 311 [M^+ − 15] (9),

216 (100), 201 (88), 158 (11), 95 (11). Anal. Calcd for $C_{21}H_{30}OSi$: C, 77.24; H, 9.26. Found: C, 77.02; H, 9.43.

Preparation of Compound 23: A solution of TBAF (250 mg, 0.77 mmol) in THF (11 mL) was added dropwise to a solution of **24** (252 mg, 0.77 mmol) in THF (15 mL). After 10 min of stirring at room temperature, a saturated aqueous solution of NH_4Cl (10 mL) was added. The mixture was extracted with AcOEt and washed with brine. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Silica gel chromatography (hexanes/AcOEt 9:1) of the crude product gave **23** (88 mg, 67%) as a white solid: $[\alpha]^{20}_D$ −31.4 (*c* 0.21, $CHCl_3$); mp 207−210 °C; IR (nujol) ν_{max} 3498, 3298, 2925, 2103, 1502, 1457, 1388, 1371, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 8.9 Hz, 2H), 7.41 (d, J = 8.9 Hz, 2H), 3.06 (s, 1H), 2.28 (d, J = 13.9 Hz, 1H), 2.18 (dt, J = 13.9, 4.1 Hz, 1H), 1.90 (t, J = 4.3 Hz, 1H), 1.72 (m, 1H), 1.24−1.15 (m, 2H), 1.26 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9 (C), 131.2 (2CH), 126.8 (2CH), 120.4 (C), 83.5 (CH), 83.4 (C), 77.2 (C), 53.5 (C), 50.4 (C), 45.5 (CH, CH_2), 31.1 (CH_2), 26.5 (CH_2), 21.6 ($2CH_3$), 9.7 (CH_3); MS (EI) *m*/*z* (relative intensity) 254 [M^+] (2), 239 [M^+ − 15] (1), 144 (100), 129 (26), 101 (11), 95 (24). Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 85.22; H, 8.50.

Reaction of 23 with $CpCo(CO)_2$. Compounds 25 and 26: $CpCo(CO)_2$ (29 mg, 0.16 mmol) was added to a solution of **23** (41 mg, 0.16 mmol) in degassed toluene (5 mL) at 110 °C. The reaction mixture was irradiated (100 W, W lamp) for 30 min and then boiled for an additional 3.5 h period. After cooling to room temperature, it was filtered through a pad of celite and concentrated in vacuo. The crude product was purified by silica gel chromatography (hexanes → hexanes/AcOEt 10:1), which provided a mixture of **25** and **26** (24 mg, 58%) as a yellow solid: IR (nujol) ν_{max} 3461, 2923, 1458, 1376, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (s), 7.69−7.59 (m), 7.52 (d, J = 8.1 Hz), 7.35 (m), 7.12 (m), 2.24−14 (m), 1.94−1.67 (m), 1.29 (s), 1.25 (s), 0.96 (s), 0.95 (s), 0.93 (s), 0.90 (s), 0.88 (s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.5, 145.4, 144.3, 144.2, 141.8, 140.7, 140.0, 139.8, 139.6, 139.5, 139.2, 138.9, 130.8, 129.1, 127.3, 126.4, 126.2, 126.0, 124.8, 83.5, 83.4, 53.6, 53.5, 50.5, 50.3, 45.6, 45.2, 31.2, 26.6, 26.4, 21.7, 21.6, 9.9, 9.8; MS (ESI) *m*/*z* 785.3 [M^+ + Na], 801.4 [M^+ + K]. Anal. Calcd for $C_{54}H_{66}O_3$: C, 84.99; H, 8.72. Found: C, 85.23; H, 8.66.

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Supporting Information Available: Copies of the 1D- and 2D-NMR spectra of new compounds prepared through this work as well as X-ray characterization of compounds **9** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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