Vinylogous Nicholas Reactions in the Synthesis of Icetexane, Faveline, and Related Ring Systems

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Abstract: The intramolecular vinylogous Nicholas reactions of aryl substituted acetoxy enyne–$Co_2(CO)_6$ complexes afford tricyclic 6,7,6-ring systems and related systems in good yield.

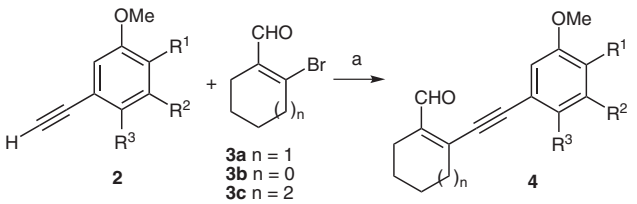
Key words: carbocations, alkyne complexes, electrophilic aromatic substitution, cyclization, fused ring systems

The reactions of alkynedicobalt complexes have proven useful in the synthesis of seven-membered ring systems[1] by way of ring-closing metathesis,[2] carbonylative Heck reactions,[3] Diels–Alder reactions,[4] Hosomi–Sakurai and Mukaiyama aldol reactions,[5] Michael reaction,[6] and particularly by Nicholas reactions.[7,8] In the latter case, the combination of ready generation of the propargyldicobalt cations with the sufficient reactivity of the cations for electron-rich arenes has allowed the preparation of benzo- and dibenzocycloheptyne complexes.[9] By contrast, a more limited amount is known regarding vinylogous Nicholas reactions, which are the reactions of cations generated from dicobalt complexes of propargyl-allyl alcohol derivatives. Although the preference for attack by carbon nucleophiles at the allyl terminus remote to cobalt is known,[10] and they have been shown to be useful in dehydrooxepane synthesis (through proximal attack)[8a] and a macrocyclization,[10b] vinylogous Nicholas reactions have never been employed in the formation of cycloheptynedicobalt ring systems.

The 6,7,6-systems of the icetexane diterpenes and related compounds such as the favelines have become the object of recent increased synthetic attention.[11] In addition to both modified and traditional Friedel–Crafts approaches to the system,[12] successful access to these systems have been accomplished by way of Brønsted or Lewis acid mediated conjugate additions,[13] Diels–Alder, carbonyl ylide and benzopyrylium ion cycloadditions,[14] radical cyclization chemistry,[15] palladium-catalyzed Heck and enolate arylation reactions,[16] aldol-type ring closures,[17] Barbier-type reactions,[18] and cycloisomerization and ring-expansion reactions.[19]

Given the normal reactivity pattern of vinylogous propargyldicobalt cations and the fact that cyclopentynedicobalt complexes appear to be prohibitively strained, we considered it a reasonable possibility that intramolecular vinylogous Nicholas reaction chemistry would readily give access to these 6,7,6-systems and other 6,7,n-systems. This letter reports our preliminary findings in this effort.

The precursors to the cyclization reactions were envisioned as allylic acetate complexes **1**, the endocyclic alkene being advantageous in imposing an *anti* geometry on any resulting allyl cation. The complexes could be prepared beginning with ethynylarenes **2**[20] and 2-bromocycloalkenecarboxaldehydes **3**, which were subjected to Sonogashira coupling to afford alkynals **4** (Scheme 1, Table 1). Reduction of the aldehyde function in **4** with acetylation of the alcohol gave acetates **5** in good yield, which then underwent complexation with $Co_2(CO)_8$ to give **1** in straightforward fashion (Table 1).[21] For compound **4d**, an additional case involving replacement of the reduction step by a PhMgBr reaction with the aldehyde afforded benzylic acetates **5e** and **1e** without incident.



	R^1	R^2	R^3	n	R^4
1a	H	H	H	1	H
1b	H	H	OMe	1	H
1c	OMe	H	H	1	H
1d	OMe	OMe	H	1	H
1e	OMe	OMe	H	1	Ph
1f	OMe	OMe	H	0	H
1g	H	H	OMe	2	H
1h	OMe	OMe	H	2	H

Scheme 1 *Reagents and conditions*: (a) $Pd(PPh_3)_4$ (3 mol%), CuI (6 mol%), Et_3N–THF, 40–80 °C; (b) DIBAL-H, Et_2O, –78 °C (PhMgBr, THF, –78 °C for **5e**); (c) Ac_2O, pyridine; (d) $Co_2(CO)_8$, CH_2Cl_2.

Compound **1a** was tested for its ability to undergo Lewis acid based Nicholas-type cyclization reactions. An excess of $BF_3{\cdot}OEt_2$ (3 equiv) mediated a relatively rapid consumption of **1a** at 0 °C. After 1 hour, this compound had disappeared completely, and separable compounds **8a** and **8a′** could be isolated in a combined 81% yield (**8a/**

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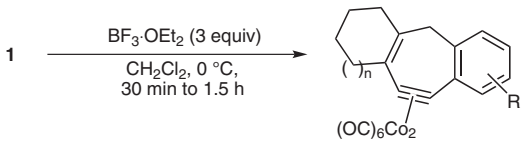
Table 1 Preparation of Allyl Acetate Complexes **1**

2	R^1	R^2	R^3	**3**	R^4	Yield of **4** (%)	Yield of **5** (%)	Yield of **1** (%)
2a	H	H	H	**3a** n = 1	H	**4a** 74	**5a** 88	**1a** 92
2b	H	H	OMe	**3a** n = 1	H	**4b** 76	**5b** 82	**1b** 82
2c	OMe	H	H	**3a** n = 1	H	**4c** 81	**5c** 80	**1c** 85
2d	OMe	OMe	H	**3a** n = 1	H	**4d** 85	**5d** 83	**1c** 86
2d	OMe	OMe	H	**3a** n = 1	Ph	–	**5e** 80	**1e** 87
2d	OMe	OMe	H	**3b** n = 0	H	**4f** 80	**5f** 80	**1f** 85
2b	H	H	OMe	**3c** n = 2	H	**4g** 76	**5g** 83	**1g** 84
2d	OMe	OMe	H	**3c** n = 2	H	**4h** 79	**5h** 84	**1h** 83

8a′ = 4.9:1, Table 2, Figure 1). The addition of *i*-Pr_2NEt, which was beneficial in Nicholas-based cyclizations toward dibenzocycloheptyne complexes, showed no advantage in the reaction of **1a**. Reducing the reaction temperature to –40 °C still allowed the reaction to progress (1.5 h), giving an enhanced amount of the substitution *para* to the methoxy function (79% yield, **8a/8a′** = 6.8:1).[22] 2,6-Dimethoxy-substituted **1b** reacted at a similar rate to **1a** and at 0 °C and afforded **8b** in 78% yield. 3,4-Dimethoxy-substituted **1c** afforded a separable mixture of regioisomeric products **8c** and **8c′** favoring the less sterically hindered site and in overall excellent yield (90% yield, **8c/8c′** = 8:1). Trimethoxy-substituted **1d** gave the corresponding 6,7,6-system in a straightforward fashion (**8d**, 82%), in 0.5 hours. Substitution at the reacting center, however, was detrimental to the Nicholas reaction; benzylic acetate complex **1e** afforded **8e** in modest yield (40%, Table 2, entry 6) due to competitive elimination (**9**, 40%).

The size of the cycloalkene ring in **1** could be varied with no noticeable effect on the cyclization. Cyclopentene-containing **1f** transformed to 6,7,5-tricycle **8f** under the standard conditions (87% yield, Table 2, entry 7) in 45 minutes, while cycloheptene-containing **1g** and **1h** similarly afforded 6,7,7-tricycles **8g** and **8h** in 81% yield (Table 2, entry 8) and 77% yield (Table 2, entry 9), respectively, each over 1 hour (Scheme 2).[23]



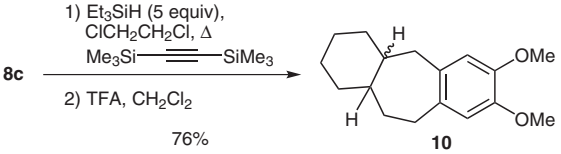
Scheme 2

In order to demonstrate the ability to remove the $Co_2(CO)_6$ unit from the cyclization products, compound **8c** was chosen for study. Reductive decomplexation was facile on this compound. Subjecting **8c** to the hydrosilylation conditions developed by Isobe,[24] followed by in situ protodesilylation with TFA,[9b] gave an overall reductive decomplexation that included reduction of the alkene functions, to give benzocycloheptene **10** in 76% yield (1:1 diastereomeric mixture, Scheme 3).

Table 2 Vinylogous Nicholas Reaction Based Cyclizations

Entry	R^1	R^2	R^3	n	R^4	Yield of **8** (%)
1	H	H	H	1	H	**8a** + **8a′** 81 (4.9:1)[a]
2	H	H	H	1	H	**8a** + **8a′** 79 (6.8:1)[b]
3	H	H	OMe	1	H	**8b** 78
4	OMe	H	H	1	H	**8c** + **8c′** 90 (8.0:1)
5	OMe	OMe	H	1	H	**8d** 82
6	OMe	OMe	H	1	Ph	**8e** 40[c]
7	OMe	H	H	0	H	**8f** 87
8	H	H	OMe	2	H	**8g** 81
9	OMe	OMe	OMe	2	H	**8h** 77

[a] Product ratios in parentheses.
[b] Reaction conducted at –40 °C.
[c] In addition, 40% of **9** was isolated.



Scheme 3

In summary, aryl-substituted allylic acetoxy enyne–$Co_2(CO)_6$ complexes readily undergo intramolecular vinylogous Nicholas reactions to afford 6,7,6-, 6,7,5-, and 6,7,7-ring systems. Yields are in general good, and removal of the $Co_2(CO)_6$ unit is facile, although the possibility for competitive elimination compromises the cyclization yields in some cases. Work on biasing the re-

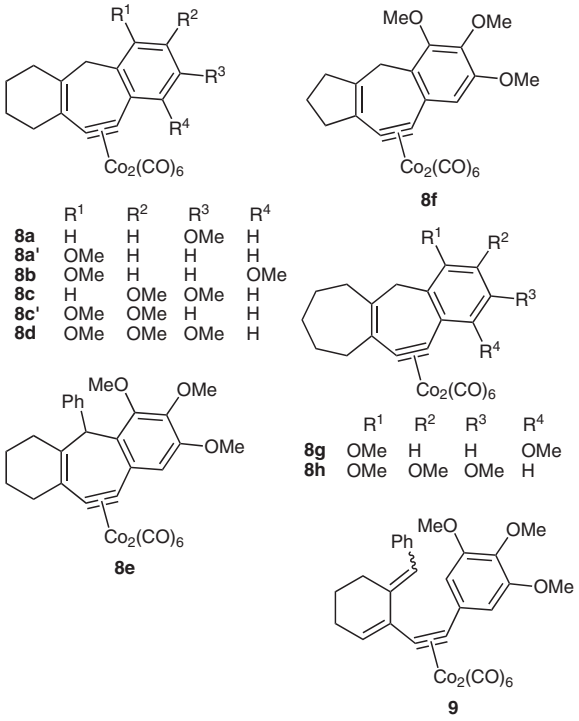


Figure 1

gioselectivity of cyclization onto the aryl ring, the use of other nucleophilic functions, and on systems with A-ring substitution leading to specific icetexanes or faveline is in progress and will be reported in due course.

Acknowledgment

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(21) **Analytical Data for Selected Compounds**

Compound **4g**: IR (KBr): ν_{max} = 2954, 2833, 2187, 1673 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.35 (s, 1 H), 6.96 (d, *J* = 3.1 Hz, 1 H), 6.90 (dd, *J* = 9.1, 3.1 Hz, 1 H), 6.83 (d, *J* = 9.1 Hz, 1 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 2.73 (m, 2 H), 2.55 (m, 2 H), 1.83 (m, 2 H), 1.70 (m, 1 H), 1.48 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.0, 154.9, 153.2, 148.2, 145.9, 117.5, 116.8, 112.0, 111.9, 96.7, 91.9, 56.4, 55.8, 37.4, 32.3, 25.7, 24.2. MS: *m/e* = 284 [M^+]. HRMS: *m/e* calcd for $C_{18}H_{20}O_3$ [M^+] 284.1412; found: 284.1412.

Compound **5g**: IR (KBr): ν_{max} = 2964, 1746 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.93 (d, *J* = 2.9 Hz, 1 H), 6.81 (d of 0.5 ABquart, *J* = 2.9, 8.9 Hz, 1 H), 6.78 (0.5 ABquart, *J* = 8.9 Hz, 1 H), 4.97 (s, 2 H), 3.84 (s, 3 H), 3.77 (s, 3 H), 2.51 (m, 2 H), 2.32 (m, 2 H), 2.09 (s, 3 H), 1.79 (m, 2 H), 1.62 (m, 2 H), 1.53 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 154.4, 153.1, 145.1, 126.0, 117.4, 115.4, 113.3, 111.9, 94.9, 89.9, 68.0, 56.4, 55.8, 34.6, 32.3, 31.2, 26.1, 26.0, 21.0. MS: *m/e* = 328 [M^+]. HRMS: *m/e* calcd for $C_{20}H_{24}O_4$ [M^+]: 328.1675; found: 328.1683.

Compound **1g**: IR (KBr): ν_{max} = 2926, 2085, 2058, 2013, 1741 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 3.1 Hz, 1 H), 6.86 (dd, *J* = 8.9, 3.1 Hz, 1 H), 6.75 (d, *J* = 8.9 Hz, 1 H), 4.53 (s, 2 H), 3.81 (s, 3 H), 3.75 (s, 3 H), 2.61 (m, 2 H), 2.31 (m, 2 H), 1.95 (s, 3 H), 1.83 (m, 2 H), 1.55–1.64 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.8, 170.9, 153.5, 150.1, 139.1, 138.6, 127.7, 117.2, 113.5, 110.2, 95.8, 91.0, 65.6, 58.7, 54.4, 37.5, 32.6, 32.3, 26.6, 26.3, 20.8. MS: *m/e* = 558 [M^+ – 2CO], 530 [M^+ – 3CO], 446 [M^+ – 5CO]. HRMS: *m/e* calcd for $C_{26}H_{24}Co_2O_{10}$ [M – $2CO^+$]: 558.0106; found: 558.0117.

(22) Compound **8a**: IR (KBr): ν_{max} = 2930, 2087, 2046, 2017 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 2.7 Hz, 1 H), 7.04 (d, *J* = 8.4 Hz, 1 H), 6.84 (dd, *J* = 8.4, 2.7 Hz, 1 H), 3.85 (s, 3 H), 3.20 (s, 2 H), 2.33–2.38 (m, 2 H), 2.26–2.30 (m, 2 H), 1.73–1.78 (m, 2 H), 1.66–1.72 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.0, 159.0, 139.1, 137.2, 130.1, 129.9, 129.3, 117.4, 113.6, 94.9, 89.5, 55.3, 42.1, 33.7, 30.5, 23.0, 22.7. MS: *m/e* = 510 [M^+], 482 [M^+ – CO], 454 [M^+ – 2CO], 426 [M^+ – 3CO], 398 [M^+ – 4CO]. HRMS: *m/e* calcd for $C_{22}H_{16}Co_2O_7$ [M – CO^+]: 481.9611; found: 481.9634.

Compound **8a′**: IR (KBr): ν_{max} = 2933, 2087, 2046, 2017 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.28 (dd, obscured, 1 H), 7.23 (apparent t, *J* = 7.8 Hz, 1 H), 6.90 (dd, *J* = 8.0, 1.1 Hz, 1 H), 3.86 (s, 3 H), 3.33 (s, 2 H), 2.30–2.38 (m, 4 H), 1.73–1.79 (m, 2 H), 1.65–1.71 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.1, 155.8, 139.5, 137.5, 130.8, 127.5, 125.3, 124.7, 110.5, 95.1, 89.9, 55.9, 33.7, 32.2, 30.4, 23.0, 22.7. MS: *m/e* = 510 [M^+], 482 [M^+ – CO], 454 [M^+ – 2CO], 426 [M^+ – 3CO], 398 [M^+ – 4CO]. HRMS: *m/e* calcd for $C_{22}H_{16}Co_2O_7$ [M^+ – CO]: 481.9611; found: 481.9624.

Compound **8b**: IR (KBr): ν_{max} = 2964, 2085, 2046, 2026 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.92 (d, *J* = 8.9 Hz, 1 H), 6.75 (d, *J* = 8.9 Hz, 1 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.34 (s, 2 H), 2.29–2.37 (m, 4 H), 1.73–1.79 (m, 2 H), 1.65–1.72 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.5, 153.9, 150.2, 136.2, 131.4, 127.3, 126.5, 112.0, 108.6, 95.9, 84.7, 56.6, 54.7, 33.5, 32.7, 30.5, 23.0, 22.6. MS: *m/e* = 512 [M^+ – CO], 484 [M^+ – 2CO], 428 [M^+ – 4CO]. HRMS: *m/e* calcd for $C_{23}H_{18}Co_2O_8$: 539.9666; found: 539.9669.

Compound **8c**: IR (KBr): ν_{max} = 2935, 2085, 2043, 2012 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.13 (s, 1 H), 6.64 (s, 1 H), 3.92 (s, 6 H), 3.19 (s, 2 H), 2.34–2.39 (m, 2 H), 2.26–2.31 (m, 2 H), 1.74–1.79 (m, 2 H), 1.68–1.73 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.1, 149.2, 148.4, 136.3, 130.4, 129.7, 114.6, 112.3, 95.1, 90.5, 56.0, 42.6, 33.8, 30.5, 23.0, 22.7. HRMS: *m/e* calcd for $C_{23}H_{18}Co_2O_8$ [M^+ – CO]: 511.9716; found: 511.9711.

Compound **8d**: IR (KBr): ν_{max} = 2936, 2085, 2045, 2016 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.98 (s, 1 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.25 (s, 2 H), 2.36 (m, 2 H), 2.31 (m, 2 H), 1.77 (m, 2 H), 1.70 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.1, 152.4, 150.4, 142.8, 137.0, 133.7, 130.8, 123.3, 111.0, 95.2, 90.3, 61.6, 60.8, 56.0, 33.7, 32.8, 30.4, 23.0, 22.7. MS: *m/e* = 458 [M^+ – 4CO], 430 [M^+ – 5CO], 402 [M^+ – 6CO]. HRMS: *m/e* calcd for $C_{24}H_{20}Co_2O_9$ [M^+ – CO]: 541.9822; found: 541.9821.

Compound **8e**: IR (KBr): ν_{max} = 2931, 2084, 2049, 2015, 1638 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.14 (apparent t, *J* = 7.7 Hz, 2 H), 7.09 (s, 1 H), 7.06 (t, *J* = 6.9 Hz, 1 H), 6.89 (d, *J* = 8.2 Hz, 2 H), 5.32 (s, 1 H), 3.98 (s, 3 H), 3.92 (s, 3 H), 3.86 (s, 3 H), 2.63–2.72 (m, 1 H), 2.50–2.60 (m, 1 H), 2.27–2.48 (m, 2 H), 1.82–1.95 (m, 2 H), 1.68–1.77 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.7, 152.7, 151.6, 142.8, 141.0, 138.3, 132.7, 131.4, 128.4, 126.8, 126.3, 125.0, 112.2, 91.6, 61.7, 60.8, 55.7, 47.6, 35.8, 31.4, 23.4, 22.8. MS: *m/e* = 562 [M^+ – 3CO], 534 [M^+ – 4CO], 478 [M^+ – 6CO]. HRMS: *m/e* calcd for $C_{30}H_{24}Co_2O_9$ [M^+ – 3CO]: 562.0237; found: 562.0240.

Compound **8f**: IR (KBr): ν_{max} = 2938, 2087, 2048, 2019 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.99 (s, 1 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 3.48 (s, 2 H), 2.71 (m, 2 H), 2.56 (m, 2 H), 2.06 (apparent quin, *J* = 7.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.7, 152.3, 150.8, 142.9, 141.5, 135.2, 133.4, 121.5, 112.2, 90.9, 87.9, 61.2, 60.8, 55.9, 39.2, 35.4, 27.4, 22.5. MS: *m/e* = 472 [M^+ – 3CO], 444 [M^+ – 4CO], 416 [M^+ – 5CO], 388 [M^+ - 6CO]. HRMS: *m/e* calcd for $C_{23}H_{18}Co_2O_9$ [M^+ – CO]: 527.9654; found: 527.9666.

Compound **8g**: IR (KBr): ν_{max} = 2937, 2085, 2051, 2029 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.92 (d, *J* = 8.9 Hz, 1 H), 6.74 (d, *J* = 8.9 Hz, 1 H), 3.86 (s, 3 H), 3.81 (s, 3 H), 3.40 (s, 2 H), 2.76 (m, 1 H), 2.51–2.57 (m, 4 H), 2.29 (m, 1 H), 1.75–1.81 (m, 2 H), 1.61–1.72 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.0, 153.8, 150.1, 141.6, 136.7, 130.9, 126.7, 112.2, 108.5, 97.6, 56.8, 54.6, 38.5, 35.5, 34.6, 31.4, 29.7, 26.2. MS: *m/e* = 526 [M^+ – CO], 498 [M^+ – 2CO], 442 [M^+ – 4CO]. HRMS: *m/e* calcd for $C_{24}H_{20}Co_2O_8$ [M^+]: 553.9822; found: 553.9802.

Compound **8h**: IR (KBr): ν_{max} = 2918, 2085, 2046, 2016 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.97 (s, 1 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.31 (s, 2 H), 2.56 (m, 4 H), 1.79 (m, 2 H), 1.65 (m, 2 H), 1.59 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.1, 152.4, 150.3, 142.89, 142.85, 136.3, 133.5, 123.3, 110.7, 97.1, 90.9, 61.7, 60.9, 56.0, 39.0, 35.4, 34.9, 31.6, 26.24, 26.19. MS: *m/e* = 584 [M^+], 556 [M^+ – CO], 528 [M^+ – 2CO], 500 [M^+ – 3CO], 472 [M^+ – 4CO], 444 [M^+ – 5CO], 414 [M^+ – 6CO]. HRMS: *m/e* calcd for $C_{25}H_{22}Co_2O_9$ [M^+ – 2CO]: 528.0029; found: 528.0030.

Compound **10**: IR (KBr): ν_{max} = 3035, 2919, 1607, 1516 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.66 (s, 1 H), 6.65 (s, 1 H), 6.64 (s, 1 H), 6.60 (s, 1 H), 3.861 (s, 3 H), 3.860 (s, 6 H), 3.85 (s, 3 H), 2.86 (apparent t, *J* = 13.1 Hz, 1 H), 2.76 (dd, *J* = 14.2, 10.6 Hz, 1 H), 2.62–2.75 (m, 3 H), 2.61 (dd, *J* = 14.2, 6.9 Hz, 1H), 2.32 (d, *J* = 14.2 Hz, 1 H), 1.97 (m, 1 H), 1.89 (m, 1 H), 1.80 (m, 1 H), 0.95–1.75 (m, 22 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.51, 146.45, 146.44, 146.3, 135.4, 135.1, 134.3, 113.8, 113.1, 112.5, 112.4, 56.00, 55.95, 55.90, 48.5, 43.9, 43.7, 38.0, 36.3, 35.8, 35.4, 34.9, 26.7, 26.4. MS: *m/e* = 260 [M^+]. HRMS: *m/e* calcd for $C_{17}H_{24}O_2$: 260.1776; found: 260.1775.

(23) **Typical Experimental Procedure**

To a solution of **1f** (0.406 g, mmol) in CH_2Cl_2 (9 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (25 μL, 0.20 mmol). After stirring for 45 min, aq NH_4Cl was added and the mixture subjected to a

conventional extractive workup (CH_2Cl_2). Flash chromatography (PE–Et_2O = 1:1) afforded **8f** (0.0319 g, 87% yield) as a viscous red-brown oil.

(24) (a) Kira, K.; Tanda, H.; Hamajima, A.; Baba, T.; Takai, S.; Isobe, M. *Tetrahedron* **2002**, *58*, 6485. (b) For related examples, see: Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609. (c) Takai, S.; Ploypradith, P.; Hamajima, A.; Kira, K.; Isobe, M. *Synlett* **2002**, 588.