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Rafiq A. Taj

Anusha Abhayawardhana

James R. Green
University of Windsor

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Rafiq A. Taj, Anusha Abhayawardhana, James R. Green*

Department of Chemistry and Biochemistry, University of Windsor, Windsor, ON, Canada, N9B 3P4

Fax: 519-973-7098

E-mail: jgreen@uwindsor.ca

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Abstract: Nicholas reactions on 2,7-dioxygenated naphthalenes give C-1 monosubstitution and C-1/C-8 disubstitution in most cases. From γ- carbonyl cation monocondensation product **3b** or alkyne- unsubstituted dicondensation product **4a**, cyclohepta[de]naphthalenes bearing no substituents, gem- dimethyl substituents, and a ketone function, and the rearranged abietane framework of microstegiol may be prepared.

Key words: Carbocations, alkyne complexes, transition metals, electrophilic aromatic substitution, ring closure, tautomerism.

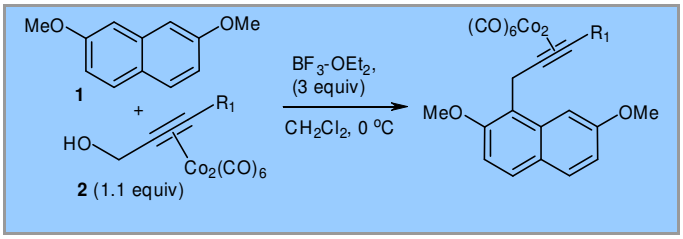
We have a long standing interest in the synthesis of seven membered ring systems, particularly involving the chemistry of alkyne dicobalt complexes and propargyldicobalt cations.[1,2] In particular, we have developed chemistry to incorporate nucleophiles, including electron rich arenes, γ- to electron withdrawing groups,[3] in an umpolung fashion,[4-6] and have used this chemistry to get access to seven membered ring systems.[1a]

In this context we were drawn to cyclohepta[de]naphthalenes, featured in the rearranged abietanes such as microstegiol[7] and salvibretol,[8] and their oxygenated analogues (Figure 1).[8,9] These compounds are isolated from a number of plants of the *salvia* species that have long seen use as folk remedies and whose crude extracts have demonstrated antibacterial and anticancer activities;[10] microstegiol itself is known to possess antileukemic activity[7,11] and modest antibacterial activity.[10b] Surprisingly, these compounds have not received synthetic attention. Therefore we considered it worthy goal to investigate our Nicholas reaction- and γ-carbonyl cation chemistry towards the construction of the cyclohepta[de]naphthalene nucleus, with a particular view to the tautomerized 2-naphthol framework of microstegiol.

Figure 1 Rearranged abietanes containing cyclohepta[de]naphthalene nucleus.

As a starting point to test reactivity, 2,7-dimethoxynaphthalene (**1**) was chosen, by virtue of its ready availability, its ability to direct monosubstitution to C-1 over C-3 in most cases[12] and disubstitution to C-1/C-8 over C-1/C-6 in many cases, and the potential for one alkoxy to serve as the masked version of the ketone function in microstegiol or salvibretol. Compound **1** showed sufficient nucleophilicity to react with propargyldicobalt cations; propargyl alcohol complex **2a** underwent BF_3-OEt_2 mediated reaction to give **3a** in excellent yield (93%) (Table 1). Use of γ- carbonyl cation precursor **2b** (R_1 = CO_2Me) gave good yields of condensation product **3b** (76%), while substitution on the remote alkyne carbon with methyl (**2c**) and trimethylsilyl (**2d**) functions also allowed formation of condensation products (**3c-d**) successfully (**3c**, 84%; **3d**, 71%).[13] Polyalkylation of the naphthalene nucleus did not appear to be a significant problem.[14]

Table 1 Monocondensation reactions of **1**



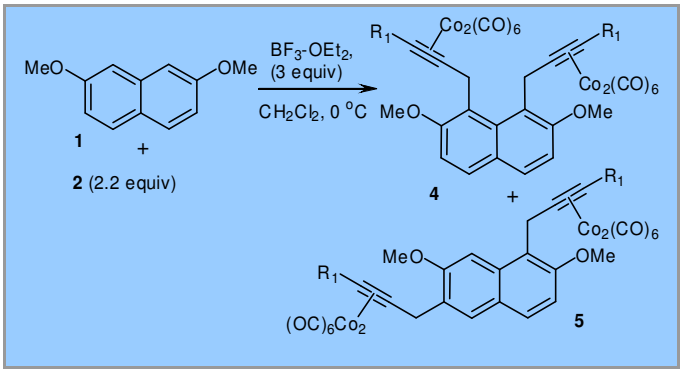
Complex	R_1	Product	Yield (%)
2a	H	**3a**	93
2b	CO_2Me[a]	**3b**	76
2c	Me	**3c**	84
2d	$SiMe_3$[b]	**3d**	71

[a] Compound **2b** was employed as the methyl ether

[b] Reaction conducted at 0 °C – RT.

Disubstitution reactions on **1** could also be accomplished, by increasing the amount of propargyldicobalt cation precursors (**2**) to 2.2 equiv. For these reactions, the predominant 1,8-disubstitution pattern (**4**) was observed only for the unsubstituted (R_1 = H) and electron withdrawing group substituted (R_1 = CO_2Me) propargyl cation complex precursors **2a** and **2b** (Table 2).[15] In the case of other R_1 substituents (R_1 = Me, Me_3Si), the second substitution occurred at C-6, giving **5c** and **5d**. In the case of **2d** (R_1 = Me_3Si), the second condensation was somewhat sluggish, and substantial amounts of **3d** were isolated in addition to **5d** despite allowing the reaction to warm to room temperature.

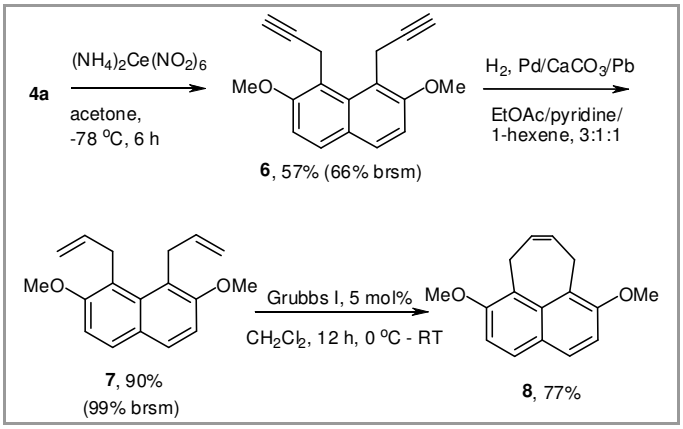
Table 2 Dicondensation reactions of **1**



Complex	R_1	Product	Yield (**4,5**) (%)
2a	H	**4a, 5a**	69, 9
2b	CO_2Me[a]	**4b**	86, 0
2c	Me	**5c**	0, 86
2d	$SiMe_3$	**3d, 5d**	0, 40[b]

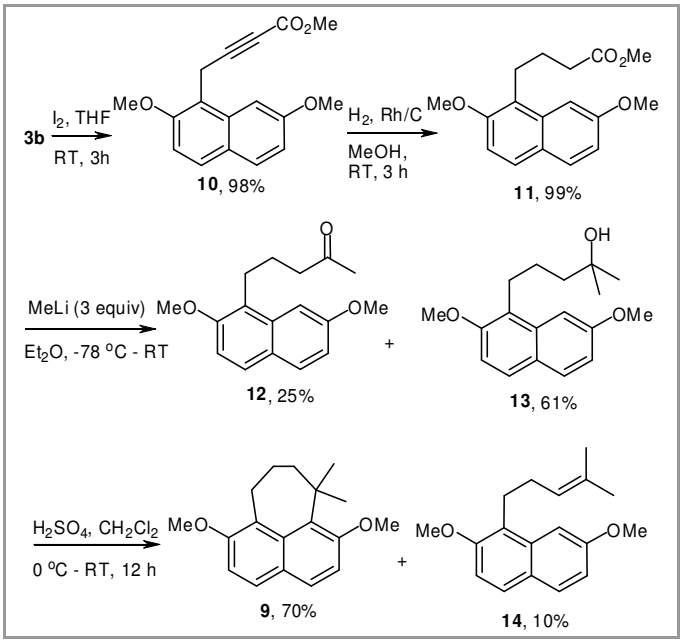
[a] Compound **2b** was employed as the methyl ether
[b] Reaction conducted at 0 °C – RT. In addition, 59 % of **3d** was isolated.

Given a basic understanding of the reactivity of 2,7-dioxygenated naphthalenes to propargyldicobalt cations, we considered γ-carbonyl cation adduct **3b** and 1,8-dicondensation product **4a** viable intermediates in the synthesis of cyclohepta[de]naphthalenes, and this possibility was explored. The unsubstituted cyclohepta[de]naphthalene nucleus was approached beginning with **4a** (Scheme 1). Decomplexation of the alkyne functions could be effected by $(NH_4)_2Ce(NO_3)_6$, affording diyne **6** in 57% yield (64% based on recovered starting **4a**). Hydrogenation of the alkynes using the Lindlar catalyst gave the diallylated naphthalene **7** (90% yield), and subsequent ring closing metathesis using $(Cy_3P)_2Cl_2Ru$=CHPh (Grubbs 1 catalyst, 5 mol%) afforded **8** in 77% yield.[16] After the viability of this approach had been demonstrated, it was reported that the corresponding diacetoxy compound also has been prepared by ring closing metathesis chemistry.[17]



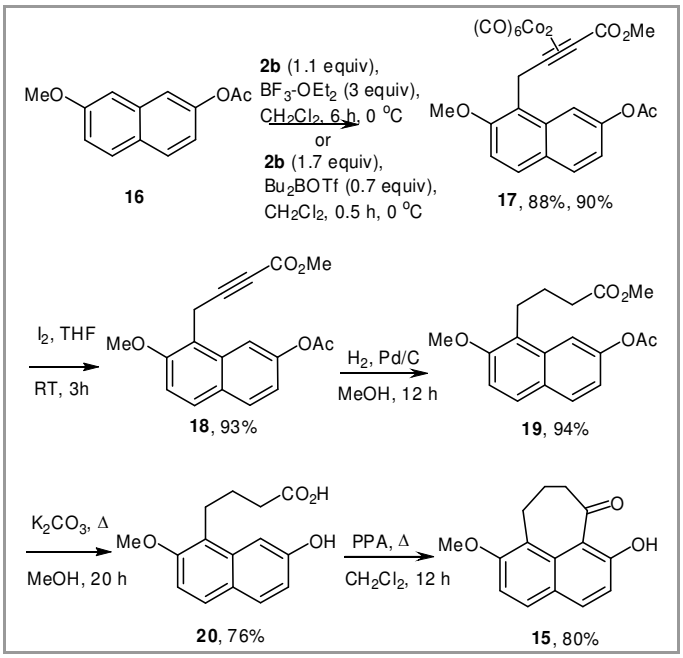
Scheme 1 Dihydrocyclohepta[de]naphthalene preparation from **4a** via ring closing metathesis.

As opposed to **8**, other cyclohepta[de]naphthalene model systems were best approached from **3b**. For dimethyl substituted cyclohepta[de]naphthalene **9**, **3b** was readily decomplexed by I_2 in THF to give **10** in excellent yield (98%) (Scheme 2). Catalytic hydrogenation of the alkyne function was sluggish over Pd/C, but proceeded well over Rh/C to afford **11** (99% yield). Subsequent addition of excess MeLi to the ester gave tertiary alcohol **13** (61% yield) along with an amount of methyl ketone **12** (25% yield). Finally, treatment of tertiary alcohol **13** with H_2SO_4 (1 drop) gave cyclohepta[de]naphthalene **9** (70% yield), contaminated with a small amount (10%) of elimination product **14.**[18]



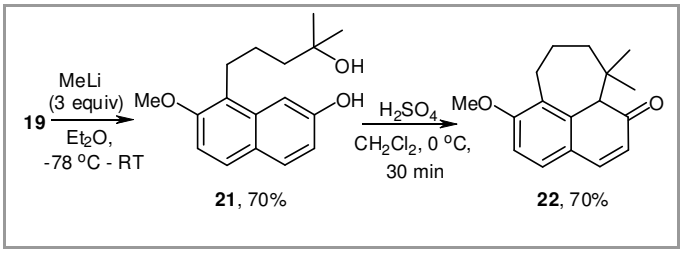
Scheme 2 Conversion of **3b** to 7,7-dimethyltetrahydrocyclohepta[de]naphthalene.

Similarly, cyclohepta[de]naphthalenone **15** was best approached via a monocondensation route employing γ-carbonyl cation precursor **2b**. In this case, unsymmetrically substituted **16**, bearing a more readily deprotected acetate function, was chosen as the starting point (Scheme 3)**.** Lewis acid mediated (either BF_3-OEt_2 (88%) or Bu_2BOTf (90%)) reaction of **16** with propargyl methyl ether complex **2b** gave monocondensation product **17** in excellent yield. After removal of the hexacarbonyldicobalt unit (I_2, THF, 93%) to give **18**, catalytic hydrogenation (H_2, Pd/C) of the alkyne function afforded **19** (94%). Hydrolysis of both the methyl ester and acetate functions was rather sluggish, but in K_2CO_3/MeOH at reflux, **19** gradually was converted to phenolic acid **20** (76%). Subjecting **20** to polyphosphoric acid (CH_2Cl_2, reflux, 12h) then resulted in closure of the seven- membered ring to give **15** in good yield (80%).[19] The phenolic ring of compound **15** existed entirely in the enolic/phenolic tautomer, as expected based on the existence of 1-hydroxy-7,12-pleiadenedione in its phenolic form.[20]



Scheme 3 Preparation of tetrahydrocyclohepta[de]naphthalene-7-one.

Finally, we deemed it important to determine whether the combination of the seven- membered ring system and latent carbonyl function would be sufficient to drive the naphthol ring tautomer to the keto form. To this end, decomplexed and reduced adduct **19** was subjected to reaction with MeLi, affording tertiary alcohol **21** in 70% yield (Scheme 4). Exposure of **21** to a single drop of H_2SO_4 in CH_2Cl_2 promoted rapid cyclization at 0 °C, giving **22** in 70% yield. Compound **22** existed entirely in the dehydro- β-tetralone tautomeric structure present in microstegiol; no evidence of the enol tautomer could be observed spectroscopically.[21] To our knowledge, this constitutes the first preparation of this ring system.



Scheme 4 Preparation of rearranged abietane framework of microstegiol.

In conclusion, we have demonstrated the viability of Nicholas reaction chemistry in the assembly of cyclohepta[de]naphthalene rings, and in the construction of the rearranged abietane framework of microstegiol. Future work, which involves installation of the γ- carbonyl cation equivalent ortho- to a less donating (methyl) substituent, and introduction of a hydroxyl function α- to the keto function, is in progress and will be reported in due course.

Experimental Section

To a solution of 2,7-dimethoxynaphthalene **1** in CH_2Cl_2 (0.05 M) at 0 °C was added propargyl alcohol complex **2** (1.1 equiv for monocondensations, 2.2 equiv for dicondensations) and BF_3-OEt_2 (3 equiv). After 3 h of stirring at 0 °C, $NH_4Cl_{(aq)}$ was added, and the mixture subjected to a conventional extractive workup. Purification by flash chromatography afforded **3** (monocondensation) or **4/5** (dicondensation).

Acknowledgment

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(13) Selected compounds: **(3a)** IR (KBr) υ_{max} 3003, 2960, 2090, 2055 cm^{-1}; ^1H NMR δ 7.71 (d, J = 8.9, 1H), 7.70 (d, J = 8.9, 1H), 7.22 (d, J = 2.4, 1H), 7.10 (d, J = 8.9, 1H), 7.04 (dd, J = 8.9, 2.4, 1H), 5.95 (s, 1H), 4.60 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H); ^{13}C NMR 199.6, 158.4, 154.7, 133.9, 130.2, 128.6, 124.6, 120.1, 116.1, 109.7, 101.6, 96.1, 73.5, 55.4, 55.1, 29.5; MS 484 (M^+-CO), 456 (M^+-2CO), 428 (M^+-3CO), 372 (M^+-5CO); HRMS m/e for $C_{21}H_{14}Co_2O_8$ calcd (M^+-2CO) 455.9454, found 455.9441. **(3b)** IR (KBr) υ_{max} 3003, 2951, 2097, 2063, 2028, 1708; H NMR δ 7.72 (d, J = 8.9, 1H), 7.68 (d, J= 8.9, 1H), 7.18 (d, J = 2.3, 1H), 7.10 (d, J = 8.9, 1H), 7.02 (dd, J= 8.9, 2.3, 1H), 4.64 (s, 2H), 3.96 (s, 3H), 3.95 (s, 3H), 3.53(s,3H); ^{13}C NMR 198.4, 171.7, 158.5, 154.7, 133.9, 130.1, 128.8, 124.4, 119.1, 116.2, 109.3, 101.1, 99.4, 79.3, 55.2, 54.9, 52.4, 29.0; MS m/e 570 (M^+), 542 (M^+-1CO), 514 (M^+-2CO), 486 (M^+-3CO), 458 (M^+-4CO), 430 (M^+-5CO), 402 (M^+-6CO); HRMS m/e for $C_{23}H_{16}Co_2O_{10}$ calcd (M^+-CO) 541.9458, found 541.9455.

(14) However, substitution at the propargylic site in **2** resulted in condensation reactions at C-3 in preference to C-1.

(15) Selected compounds: **(4a)**. IR (KBr) υ_{max} 2917, 2090, 2051, 2021; cm^{-1}; H NMR δ 7.70 (d, J = 8.9, 2H), 7.12 (d, J = 8.9, 2H), 5.83 (s, 2H), 5.22 (d, J = 16.4, 2H), 4.50 (d, J = 16.4, 2H), 3.99 (s, 6H); ^{13}C NMR 199.6, 156.1, 131.9, 130.7, 126.5, 121.3, 110.1, 97.5, 73.8, 55.9, 30.6; MS m/e 808 (M^+-1CO), 780 (M^+-2CO), 752 (M^+-3CO), 724(M^+-4CO), 696(M^+-5CO), 668(M^+-6CO), 640(M^+-7CO), 612(M^+-8CO); HRMS m/e for $C_{30}H_{16}Co_4O_{14}$ calcd. (M^+-CO) 807.7917, found 807.7904. **(4b)** IR (KBr) υ_{max} 3004, 2950, 2097, 2067, 1710 cm^{-1}; 7.71 (d, J = 9.0, 2H), 7.10 (d, J = 9.0, 2H), 5.19 (d, J = 16.5, 2H), 4.69 (d, J = 16.5, 2H), 3.40 (s, 6H), 3.46 (s, 6H); ^{13}C NMR 198.2, 170.6, 156.1, 132.1, 131.0, 126.3, 120.3, 109.8, 99.9, 80.3, 55.7, 52.4, 30.9; MS m/e 896 (M^+-2CO), 840 (M^+-4CO), 784 (M^+-6CO), 728 (M^+-8CO), 700 (M^+-9CO).

(16) **(6)** IR (KBr) υ_{max} 3291, 2932, 2107, 1618 cm^{-1}; ^1H NMR δ 7.72 (d, J = 9.0, 2H), 7.18 (d, J = 9.0, 2H), 4.31 (d, J = 2.6, 4H), 4.03 (s, 6H), 2.16 (t, J = 2.6, 2H); ^{13}C NMR 156.7, 133.5, 130.1, 126.2, 117.3, 111.0, 84.7, 69.1, 56.9, 17.3; MS m/e 264 (M^+); HRMS m/e for $C_{18}H_{16}O_2$, calcd (M^+) 264.1150, found 264.1153. (**7**) IR (KBr) υ_{max} 3077, 2934, 1614 cm^{-1}; ^1H NMR δ 7.72 (d, J = 8.9, 2H), 7.18 (d, J = 8.9, 2H), 6.23 (m, 2H), 5.09 (dd J= 10.3, 1.9, 2H), 4.84 (dd, J= 17.3, 1.9, 2H), 3.93 (s, 6H), 3.91 (m, 4H); ^{13}C NMR 156.7, 139.0, 134.9, 129.4, 126.3, 120.4, 114.5, 111.0, 56.8, 30.9; MS m/e 268 (M^+); HRMS m/e for $C_{18}H_{20}O_2$ calcd (M^+) 268.1463, found 268.1466. (**8**) IR (KBr) υ_{max} 3033, 2934, 1616 cm^{-1}; ^1H NMR δ 7.59 (d, J = 9.0, 2H), 7.11 (d, J = 9.0, 2H), 6.19 (m, 2H), 4.02 (d, J= 5.6, 4H), 3.92 (s, 6H); ^{13}C NMR 153.9, 134.8, 130.9, 128.3, 126.8, 120.2, 111.9, 57.2, 24.2; MS m/e 240 (M^+), HRMS m/e for $C_{16}H_{16}O_2$ calcd (M^+) 240.1150, found 240.1150.

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(18) (**10**) IR (KBr) υ_{max} 2956, 2233, 1712, 1628; ^1H NMR δ 7.72 (d, J = 9.0, 1H), 7.69 (d, J = 8.9, 1H), 7.22 (d, J = 2.4, 1H), 7.11 (d, J = 9.0, 1H), 7.05 (dd, J = 8.9, 2.4, 1H), 4.11 (s, 2H), 3.97 (s, 3H), 3.96 (s, 3H), 3.70 (s, 3H); ^{13}C NMR 158.4, 154.6, 154.0, 133.7, 129.9, 128.9, 124.3, 116.1, 113.6, 110.1, 101.2, 87.7, 71.9, 56.1, 55.0, 52.2, 14.5; MS m/e 284 (M^+); HRMS m/e for $C_{17}H_{16}O_4$ calcd (M^+) 284.1049, found 284.1033. (**11**) IR (KBr) υ_{max} 2954, 1740, 1628; ^1H NMR δ 7.69 (d, J = 8.9, 1H), 7.66 (d, J = 8.9, 1H), 7.32 (d, J = 2.0, 1H), 7.12 (d, J = 8.9, 1H), 7.03 (dd, J= 8.9, 2.0, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.70 (s, 3H), 3.11 (t, J= 7.6, 2H), 2.44 (t, J = 7.1, 2H), 2.00 (m, 2H); ^{13}C NMR 174.0, 158.1, 154.8, 134.1, 129.8, 127.3, 124.5, 121.2, 115.7, 110.2, 101.6, 55.9, 55.1, 51.2, 33.4, 24.2, 24.1; MS m/e 288 (M^+); HRMS m/e for $C_{17}H_{20}O_4$ calcd (M^+) 288.1362, found 288.1360. (**13**) IR (KBr) υ_{max} 3422 br, 2966, 1627; H NMR δ 7.70 (d, J = 8.9, 1H), 7.66 (d, J = 8.9, 1H), 7.24 (d, J = 2.3, 1H), 7.13 (d, J = 8.9, 1H), 7.05 (dd, J = 8.9, 2.3, 1H), 3.952 (s, 3H), 3.945 (s, 3H), 3.09 (t, J = 7.6, 2H), 1.75 (m, 2H), 1.69 (m, 2H) 1.38 (br s, 1H), 1.23 (s, 6H); ^{13}C NMR 158.0, 154.8, 134.1, 130.0, 127.1, 124.7, 122.6, 115.5, 110.8, 102.0, 70.9, 56.3, 55.1, 43.8, 29.1, 25.4, 24.4; MS m/e 288 (M^+), HRMS m/e for $C_{18}H_{24}O_3$ calcd (M^+) 288.1725, found 288.1713. (**9**) IR (KBr) υ_{max} 2929, 1612; ^1H NMR δ 7.54 (d, J = 8.9, 1H), 7.52 (d, J= 8.8, 1H), 7.09 (d, J = 8.9, 1H), 7.07 (d, J = 8.8, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.00 (br m, 2H), 1.96 (m, 2H), 1.70 (m, 2H), 1.52 (s, 6H); ^{13}C NMR 158.8, 154.5, 137.6, 131.7, 127.3, 126.9, 125.4, 122.9, 112.1, 111.6, 84.6, 57.4, 56.0, 41.1, 39.4, 25.5, 22.1; MS m/e 270 (M^+); HRMS m/e for $C_{18}H_{22}O_2$ calcd (M^+) 270.1620, found 270.1614.

(19) (**17**) IR (KBr) υ_{max} 3004, 2952, 2099, 2063, 2029,1765, 1709; ^1H NMR δ 7.82 (d, J = 9.0, 1H), 7.81 (d, J = 8.8, 1H) 7.61 (d, J = 2.2, 1H), 7.26 (d, J = 9.0, 1H), 7.11 (dd, J = 8.8, 2.2, 1H), 4.60 (s, 2H), 3.96 (s, 3H), 3.75 (s, 3H), 2.33 (s, 3H); ^{13}C NMR 198.0, 170.5, 169.4, 154.7, 149.3, 133.2, 130.0, 128.8, 126.8, 120.0, 118.6, 114.1, 111.8, 98.5, 93.9, 55.2, 52.5, 28.2, 20.8; MS m/e 542(M^+-2CO), 514(M^+-3CO), 486 (M^+-4CO), 458(M^+-5CO), 430(M^+-6CO); HRMS m/e for $C_{24}H_{16}Co_2O_{11}$ calcd (M^+-3CO) 513.9509, found 513.9511. (**18**) IR (KBr) υ_{max} 2917, 2234, 1761, 1712; ^1H NMR δ 7.81 (d, J = 8.9, 2H), 7.62 (d, J = 2.1, 1H), 7.26 (d, J = 8.9, 1H), 7.15 (dd. J = 8.8, 2.1, 1H), 4.08 (s, 2H), 3.99 (s, 3H), 3.71 (s, 3H), 2.38 (s, 3H); ^{13}C NMR 169.4, 154.7, 154.0, 149.4, 133.1, 129.9, 129.2, 126.9, 118.8, 114.8, 113.7, 112.7, 87.4, 72.0, 56.3, 52.3, 21.0, 14.6; MS m/e 312 (M^+); HRMS m/e for $C_{18}H_{16}O_5$ calcd (M^+) 312.0998, found 312.0991. (**19**) IR (KBr) υ_{max} 3067, 2950, 1759, 1734; ^1H NMR δ 7.75 (d, J = 8.8, 1H), 7.67 (d, J = 1.9, 1H), 7.65 (d, J = 9.0, 1H), 7.16 (d, J = 9.0, 1H), 7.09 (dd, J = 8.8, 1.9, 1H), 3.85 (s, 3H), 3.64 (s, 3H), 3.08 (t, J = 17.6, 2H), 2.39 (t, J = 7.4, 2H), 2.33 (s, 3H), 1.99 (m, 2H); ^{13}C NMR 173.9, 169.5, 154.9, 149.1, 133.6, 129.9, 127.6, 127.1, 122.3, 118.4, 114.0, 112.7, 56.1, 51.2, 33.5, 24.7, 24.0, 21.1; MS m/e 316 (M^+); HRMS m/e for $C_{18}H_{20}O_5$ calcd (M^+) 316.1311, found 316.1316. (**20**) . IR (KBr) υ_{max} 3385 br, 2924, 1703, 1626; ^1H NMR (acetone-d_6) δ 7.63 (d, J = 8.8, 1H), 7.62 (d, J = 9.0, 1H), 7.28 (br s,1H), 7.11 (d, J = 9.0, 1H), 6.93 (dd, J = 8.8, 2.1, 1H), 3.87 (s, 3H), 2.99 (t, J = 7.7, 2H), 2.35 (m, 2H), 1.85 (m, 2H); ^{13}C NMR (acetone-d_6) 174.5, 156.0, 155.1, 134.8, 130.2, 127.7, 124.5, 120.7, 115.7, 110.3, 104.8, 55.8, 33.3, 24.8, 24.1; MS m/e 260 (M^+); HRMS m/e for $C_{15}H_{16}O_4$ calcd (M^+) 260.1049, found 260.1045. (**15**) IR (KBr) λ_{max} 3009, 2970, 1616 cm^{-1}; ^1H NMR δ 12.73 (s, 1H), 7.71 (d, J = 8.9, 1H), 7.63 (d, J = 8.8, 1H), 7.12 (d, J = 8.8, 1H), 6.93 (d, J = 8.9, 1H), 3.95 (s, 3H), 3.01 (t, J = 7.1, 2H), 2.71 (t, J = 7.4, 2H), 2.39 (m, 2H); ^{13}C NMR 207.4, 162.5, 157.3, 136.2, 135.7, 128.6, 123.2, 122.3, 116.5, 115.2, 110.3, 56.2, 42.3, 29.5, 25.4; MS m/e 242 (M^+); HRMS for $C_{15}H_{14}O_3$ calcd (M^+) 242.0943, found 242.0931.

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(21) (**21**) IR (KBr) υ_{max} 3358, 2967 cm^{-1}; ^{1}H NMR δ 8.10 (br s, 1H), 7.65 (d, J = 8.8, 1H), 7.61 (d, J = 8.9, 1H), 7.33 (d, J = 2.2, 1H), 7.08 (d, J = 8.9, 1H), 7.01 (dd, J = 8.8, 2.2, 1 H), 3.91 (s, 3H), 2.95 (br t, J = 7.0, 2H), 2.60 (br s, 1H), 1.65 (m, 4H), 1.21 (s, 6H); ^{13}C NMR 154.6, 154.5, 134.4, 130.3, 127.3, 124.5, 122.1, 115.6, 110.7, 105.3, 72.0, 56.4, 43.5, 29.1, 25.4, 24.3; MS m/e 274 (M^+); HRMS m/e for $C_{17}H_{22}O_3$ calcd 274.1569, found 274.1574. (**22**) IR (KBr) υ_{max} 2934, 1653, 1615 cm^{-1}; ^{1}H NMR δ 7.29 (d, J = 9.7, 1H), 7.13 (d, J = 8.4, 1H), 6.79 (d, J = 8.4, 1H), 5.97 (d, J = 9.7, 1H), 3.84 (s, 3H), 3.63 (s, 1H), 3.36 (m, 1H), 2.42 (m, 1H), 1.84 (m, 1H), 1.51 (m, 1H), 1.38 (m, 1H), 1.27 (m, 1H), 1.17 (s, 3H), 0.66 (s, 3H); ^{13}C NMR 203.2, 157.7, 145.5, 140.8, 129.4, 127.9, 124.4, 123.5, 108.9, 58.3, 55.7, 43.2, 37.0, 27.4, 24.2, 21.5, 20.2; MS m/e 256 (M^+); HRMS m/e for $C_{17}H_{20}O_2$ calcd 256.1463, found 256.1457.