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The Synthesis of Velloziolide via Nicholas Reaction Based γ-Carbonyl Cations

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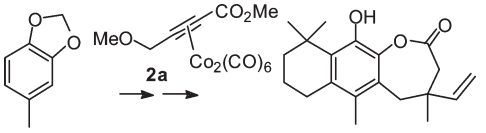

velloziolide, **1**

The total synthesis of the 9,11-seco-rosane diterpene velloziolide (**1**) has been accomplished by employing the Nicholas reaction chemistry of **2a** as a γ-carbonyl cation equivalent. An initial model study demonstrated the utility of Nicholas reactions of **2** in the generation of 4-arylalkynoate-$Co_2(CO)_6$ complexes, and in conjunction with Gilman cuprate addition and Johnson−Claisen rearrangement chemistry, the preparation of a 3-methyl-3-vinyl-4-arylalkanoate model for velloziolide. The Nicholas reaction/γ-carbonyl cation methodology was then employed twice in the total synthesis to incorporate onto 3,4-methylenedioxytoluene the 4-carbon unit that became the *gem*-dimethyltetralin portion of the velloziolide and, subsequently, to incorporate the γ-arylalkanoate function of the ε-lactone.

Introduction

Velloziolide (**1**) is a diterpene isolated from the Brazilian plant *Vellozia candida* Mikan,[1] which possesses an unusual 9,11-seco-rosane skeleton. Its biological activity is unreported, although the crude extracts of this plant and other seco-rosanes isolated from *Vellozia candida* show activity in bioassays as DNA-damaging agents.[2] Velloziolide is also noteworthy for the benzo-fused ε-lactone unit contained within its structure; this function is encountered more frequently, being present in the floresolides,[3] in amarulone,[4] and in urdamycin L.[5] Velloziolide has never been synthesized successfully; Marco and Rodriguez have prepared a bicyclic ester analogue with the correct carbon connectivity but were unable to remove the phenolic methyl ether protecting groups.[6]

Our group was attracted to velloziolide by virtue of our continued interest in the chemistry of γ-carbonyl cation equivalents,[7−10] normally based on transition-metal-stabilized cations.[7,8] Of particular relevance is our work on the Nicholas reaction chemistry[11] of 4-hydroxyalkynoate-$Co_2(CO)_6$

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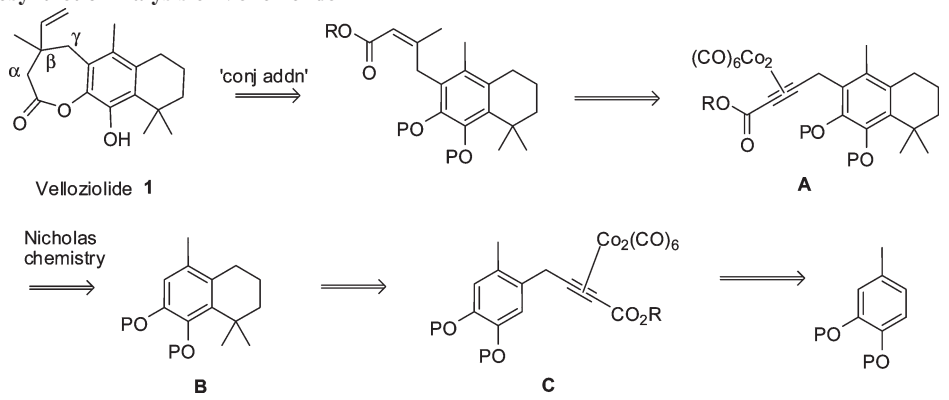
SCHEME 1. Retrosynthetic Analysis of Velloziolide

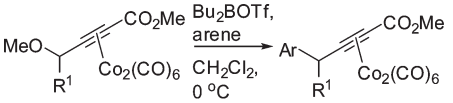


derivatives,[7] as the derived propargyldicobalt cations possess sufficient stability despite the remote electron-withdrawing group substitution and yet have sufficient electrophilicity to undergo reaction with electron-rich arenes.[12] Since we consider the most compelling structural feature of velloziolide to be the β,β-disubstituted γ-aryl lactone unit, retrosynthetically the Nicholas reaction/γ-carbonyl cation chemistry is well positioned for the incorporation of this portion of velliozioliide (**A**, Scheme 1). There is additional relevance of this chemistry to velloziolide by virtue of the *gem*-dimethyltetralin also present in the natural product. This structural unit (**B**) is one which also is expected to be readily accessible by γ-carbonyl cation chemistry, based on the assumption that the *gem*-dimethyl function could be derived from a tertiary alcohol, whose source would in turn be an ester function (**C**).

Results and Discussion

As the necessity of ultimately incorporating a γ-carbonyl cation equivalent ortho to a para-substituted phenol derivative is an essential consideration in the synthesis of velloziolide, we considered it of importance to investigate the Lewis acid induced substitution reactions of simple para-substituted phenol derivatives with 4-methoxyalkynoate-$Co_2(CO)_6$ complexes (**2a**−**c**) (Table 1). Our initial choice of substrate, 4-methoxytoluene, underwent condensation with **2a** only sluggishly in the presence of $BF_3{-}OEt_2$ (rt, 24 h, 22% yield), as has been observed in our group in related cases of Nicholas reaction precursors bearing remote Lewis basic functions.[7b] Conversely, in the presence of Bu_2BOTf (0 °C, CH_2Cl_2, 1 h), reaction occurred rapidly and without complication, affording **3a** in 81% yield using a modest excess (1.5 equiv) of arene (Table 1). While the yield of **3a** could be increased further using a greater excess of arene (91% at 2.5 equiv of 4-methylanisole) under otherwise identical reaction conditions, we made the choice to impose a limit of 1.5 equiv in further experiments. Alternatives to methyl substitution on the phenol were less successful; while acetoxy and methoxymethyl derivatives of 4-methylphenol gave no condensation product whatsoever, 4-benzyloxytoluene afforded **3b** in moderate yield (64%). Use of the more electron-deficient *p*-nitrobenzyl (PNB)-protected 4-(4-nitrobenzyloxy)-toluene did not improve the results for condensation; in fact,

TABLE 1. Reactions of 2 with Aromatic Nucleophiles[a]



2a-c **3a-l**

2	nucleophile	product, yield (%)
2a	4-methoxytoluene	**3a**, 81
2a	4-methoxytoluene	**3a**, 91[b]
2a	4-benzyloxytoluene	**3b**, 64
2a	4-(4-nitrobenzyloxy)toluene	**3c**, 39
2a	4-(4-triisopropylsiloxy)toluene	**3d**, 53[c]
2a	1-hexyl-4-methoxybenzene	**3e**, 61
2a	1,4-dimethoxybenzene	**3f**, 57
2a	1,3,5-trimethoxybenzene	**3g**, 68
2b	4-methoxytoluene	**3h**, 61
2b	1,3,5-trimethoxybenzene	**3i**, 77
2b	1,4-dimethoxybenzene	**3j**, 52
2c	4-methoxytoluene	**3k**, 78
2a	3,4-dimethoxytoluene	**3l**, 65

[a]Reactions carried out with **2a**−**c**, arene (1.5 equiv), Bu_2BOTf (1.0 equiv), at 0 °C in CH_2Cl_2 for 1 h. [b]Carried out using 2.5 equiv of arene. [c]Reaction conducted in the presence of molecular sieves with inverse addition of **2a** to a solution of Lewis acid and arene.

the condensation product **3c** appeared to be somewhat unstable to the reaction conditions and could be isolated only in poor yield (**3c**, 39%). Conversely, reaction of TIPS-protected 4-(triisopropylsiloxy)toluene did give a fair yield of condensation product **3d** under slightly modified conditions involving the presence of molecular sieves, but the silyl function was lost from the phenol (**3d**, 53% yield). The additional of a base (iPr_2NEt) did not suppress this loss of the phenolic silyl function.[13]

Since neither benzyl, PNB, nor TIPS phenolic protecting groups were superior to a methyl group for the Nicholas reaction chemistry of **2a**, the remaining methodological examples were examined on phenolic methyl ethers. Replacing the *para*-methyl function by *n*-hexyl- (1-hexyl-4-methoxybenzene) or methoxy (1,4-dimethoxybenzene) functions allowed the formation of **3e** (61%) and **3f** (57%) in acceptable yields, while use of 1,3,5-trimethoxybenzene as nucleophile gave a reasonable yield of **3g** (68%). Substitution of the alkynedicobalt complex with a methyl function at the

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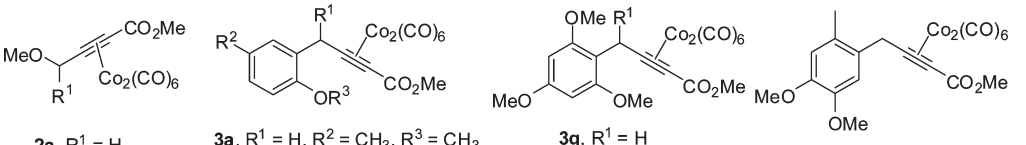
(13) TMS or TBS protecting groups gave lower yields of condensation products.



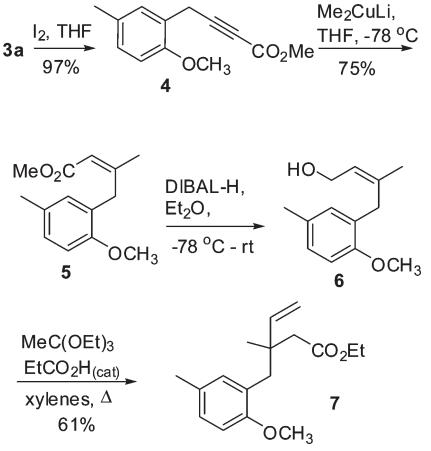
2a, R^1 = H
2b, R^1 = CH_3
2c, R^1 = Ph

3a, R^1 = H, R^2 = CH_3, R^3 = CH_3
3b, R^1 = H, R^2 = CH_3, R^3 = Bn
3c, R^1 = H, R^2 = CH_3, R^3 = PNB
3d, R^1 = H, R^2 = CH_3, R^3 = OH
3e, R^1 = H, R^2 = $^nC_6H_{13}$, R^3 = CH_3
3f, R^1 = H, R^2 = OCH_3, R^3 = CH_3
3h, R^1 = CH_3, R^2 = CH_3, R^3 = CH_3
3j, R^1 = CH_3, R^2 = OCH_3, R^3 = CH_3
3k, R^1 = Ph, R^2 = CH_3, R^3 = CH_3

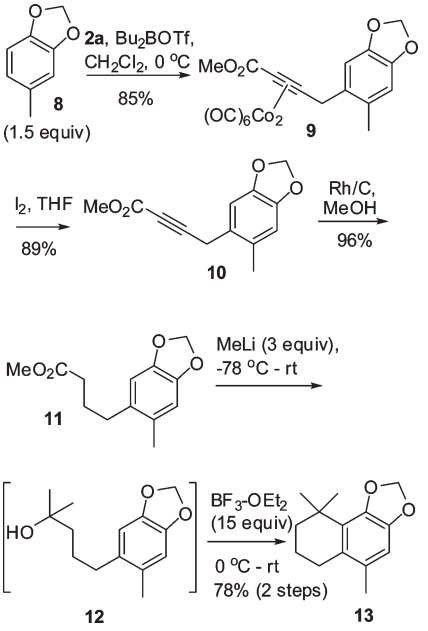
3g, R^1 = H
3i, R^1 = CH_3

3l

SCHEME 2. Preparation of Model γ-Arylalkanoate 7



SCHEME 3. Preparation of *gem*-Dimethyltetralin 13



propargylic reaction site (**2b**) resulted in only trace amounts of competition from methanol elimination from **2b**; consequently, the adducts with 4-methoxytoluene (**3h**, 61%), 1,3,5-trimethoxybenzene (**3i**, 77%), and 1,4-dimethoxybenzene (**3j**, 52%) were formed in acceptable yields. In addition, phenyl-substituted alkynedicobalt complex **2c** reacted with 4-methoxytoluene to give **3k** without complication (78%). Finally, 3,4-dimethoxytoluene, which we considered to be a model substrate for the *gem*-dimethyltetralin unit of velloziolide, reacted with **2a** to give **3l** in 65% yield.

We chose 4-methoxytoluene condensation product **3a** as a model to study the creation of the γ-aryl, β,β-disubstituted ester function of velloziolide. Removal of the dicobalt unit from the alkyne function proceeded poorly with several of the conventional decomplexation reagents (CAN, Me_3NO) but was readily accomplished with I_2 in THF (**4**, 97%) (Scheme 2). Conjugate addition to **4** with Gilman cuprate Me_2CuLi incorporated the β-methyl group cleanly, giving **5** as its *Z*-isomer (75%). The identification of **5** as the *Z*-isomer was supported by the ^{1}H NMR NOESY cross-peak between the vinylic proton (δ 5.81) and the methyl function β to the ester (δ 1.78). Conversely, **5** was not susceptible to conjugate addition by either vinylcuprate[14] or rhodium-catalyzed alkenylborane chemistry[15] and was recovered unchanged upon these attempted reactions. As a result, a synthetic equivalent of β-vinylation was accomplished by reduction of the ester function to allylic alcohol **6**; when **6** was subjected to heating with triethyl orthoacetate and a catalytic amount of propionic acid in xylenes at reflux, it underwent a Johnson−Claisen rearrangement[16] to give **7** (61% yield from **5**).

With this protocol in hand, attention was turned to the synthesis of velloziolide itself. Given the difficulty in phenolic methyl ether deprotection in the Marco and Rodriguez approach,[6] we chose to employ 3,4-methylenedioxytoluene (**8**) as a starting material. Under the previously outlined conditions, compound **8** underwent Nicholas reaction chemistry with **2a** in good yield (**9**, 85%) (Scheme 3). Decomplexation of **9** with I_2/THF was straightforward, affording **10** in excellent yield (89%). Catalytic hydrogenation of the alkyne function was sluggish under catalysis with Pd/C but proceeded cleanly over Rh/C to give **11** (96%). Reaction with excess methyllithium gave tertiary alcohol **12**, which as the crude reaction product was subjected to reaction with excess

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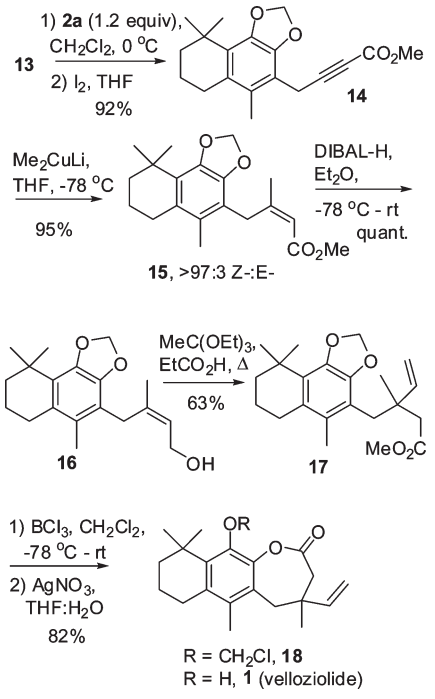
SCHEME 4. Synthesis of Velloziolide



$BF_3{-}OEt_2$, resulting in cyclization to the *gem*-dimethyltetrahydronaphthalene **13** (78% yield from **11**).

With the carbocyclic ring system constructed, attention was now turned to the incorporation of the β-arylalkanoate/ε-lactone portion of velloziolide. Since the prospect of polyalkylation by **13** no longer existed, it was subjected to Bu_2-BOTf-mediated reaction with slight excess (1.2 equiv) of **2a**, and the crude reaction mixture was subjected to the oxidative decomplexation conditions (I_2, THF). Under this protocol, compound **14** was formed in excellent yield (92% from **13**) (Scheme 4). Conjugate addition of Me_2CuLi occurred to give **15** cleanly (95% yield), with the *Z*-isomer present exclusively within the ^{1}H NMR detection limits, provided the reaction was conducted in THF.[17] Compound **15** behaved similarly to **5** in its reluctance to undergo conjugate addition, while reduction of **15** (*Z*-isomer) with DIBAL-H gave the allyl alcohol readily (**16**, quantitative). While use of the exact conditions previously employed for Johnson−Claisen reaction only gave small amounts of **17** when applied to **16**, the use of triethyl orthoacetate as solvent afforded **17** in acceptable yield (63%).

Final removal of the methylenedioxy protecting group required slightly specialized conditions. Attempted deprotection of **17** with BBr_3 gave nonproductive decomposition. The use of BCl_3 in reaction with **17** gave a mixture of velloziolide (**1**) and chloromethylated **18**, the latter as evidenced by an additional δ 6.09 singlet in the ^{1}H NMR spectrum, and presence of *m*/*e* 362/364 in the mass spectrum of the crude reaction product. Consequently, the final protocol involved the reaction of **17** with BCl_3, followed by subjecting the crude reaction product to wet $AgNO_3$;[18] under these conditions, velloziolide could be isolated in 82% yield. Synthetic **1** was found to be identical to natural velloziolide based on a comparison of physical and spectral data, save for the optical activity of the natural product.

In conclusion, velloziolide has been prepared from **2a** and 3,4-methylenedioxytoluene (**8**) in 10 steps in 25% overall yield. The Nicholas reaction chemistry of 4-methoxy-2-alkynoate-$Co_2(CO)_6$ complexes **2** is effective in condensation reactions with electron-rich aromatic nucleophiles, requiring only a modest excess of nucleophile to give acceptable yields when multiple arene C−H are present, and giving excellent yields when only one substitution is possible. As a result, **2a** is useful in the construction of both the dimethylcyclohexene and ε-lactone rings of velloziolide, without the need for the one-carbon extension reactions often required for umpolung functional group relationships.

Experimental Section

Hexacarbonyl[μ-η^4-(methyl 4-(2-methoxy-5-methylphenyl)-2-butynoate)]dicobalt (3a). General Procedure A:. To a solution of **2a** (0.4909 g, 1.19 mmol) and 4-methoxytoluene (0.23 mL, 1.8 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added dibutylboron triflate (1 M in CH_2Cl_2, 1.20 mL, 1.2 mmol) slowly. The reaction mixture was stirred at 0 °C for 1 h. Addition of saturated $NH_4Cl_{(aq)}$ and a conventional extractive workup (CH_2Cl_2), followed by column chromatography (10:1 petroleum ether/diethyl ether), gave **3a** (0.4870 g, 81% yield) as a red-brown oil: IR (KBr) ν_{max} 2952, 2098, 2062, 2029, 1710 cm^{-1}; ^{1}H NMR δ 7.05 (dd, J = 1.9, 8.3 Hz, 1H), 7.00 (d, J = 1.9 Hz, 1H), 6.76 (d, J = 8.3 Hz, 1H), 4.11 (s, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 2.29 (s, 3H); ^{13}C NMR δ 198.2, 170.8, 154.8, 131.6, 129.6, 128.7, 127.5, 110.0, 101.1, 78.5, 54.6, 52.8, 33.4, 20.3; MS *m*/*e* 476 (M − CO$^+$), 448 (M − 2CO$^+$), 420 (M − 3CO$^+$), 392 (M − 4CO$^+$), 364 (M − 5CO$^+$); HRMS *m*/*e* for $C_{19}H_{14}Co_2O_9$ calcd 475.9353 (M − CO$^+$), found 475.9365.

Methyl 4-(2-methoxy-5-methylphenyl)-2-butynoate (4): To a solution of **3a** (0.3698 g, 0.0.733 mmol) in THF (30 mL) was added excess iodine (1.5 g). The solution was stirred for 10 h at room temperature. The solution was treated with $NaHSO_{3(aq)}$ and subjected to a conventional extractive workup (Et_2O). Radial chromatography (15:1 petroleum ether/Et_2O) gave **4** (0.1554 g, 97% yield) as a colorless oil: bp 90−95 °C (0.2 Torr) (bulb-to-bulb); IR (KBr) ν_{max} 3003, 2925, 2240, 1717 cm^{-1}; ^{1}H NMR δ 7.23 (d, J = 1.6 Hz, 1H), 7.08 (dd, J = 1.6, 8.3 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.71 (s, 2H), 2.33 (s, 3H); ^{13}C NMR δ 154.5, 154.2, 129.8, 129.6, 128.6, 122.1, 110.1, 87.4, 74.0, 55.4, 52.5, 20.4, 19.3; MS *m*/*e* 218 (M$^+$); HRMS *m*/*e* for $C_{13}H_{14}O_3$ calcd 218.0943 (M$^+$), found 218.0945.

(*Z*)-Methyl 4-(2-methoxy-5-methylphenyl)-3-methyl-2-butenoate (5): To a suspension of CuI (0.248 g, 1.30 mmol) in THF (10 mL) at 0 °C was added MeLi (1.6 mL of a 1.6 M solution in Et_2O). After stirring for 15 min, the solution was cooled to −78 °C, and a solution of **4** (0.1895 g, 0.868 mmol) in THF (10 mL) was added slowly. Following stirring at −78 °C for 2 h, saturated $NH_4Cl_{(aq)}$ was added, and a conventional extractive workup (Et_2O) was performed. Preparative TLC (20:1 hexanes/Et_2O) afforded **5** (0.1521 g, 75% yield) as a colorless oil: bp 95−100 °C (0.1 Torr) (bulb-to-bulb); IR (KBr) ν_{max} 2948, 1716, 1652 cm^{-1}; ^{1}H NMR δ 6.99 (d, J = 8.0 Hz, 1H), 6.96 (s, 1H), 6.76 (d, J = 8.0 Hz, 1H), 5.81 (d, J = 1.3 Hz, 1H), 4.06 (s, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 2.26 (s, 3H), 1.78 (d, J = 1.3 Hz, 3H); ^{13}C NMR δ 166.9, 158.9, 155.5, 130.6, 129.7, 127.7, 126.9, 116.5, 110.3, 55.4, 50.8,

(17) The use of Et_2O as solvent also allowed the conjugate addition process to proceed (89% yield) but gave an isomeric mixture of **15** (*Z*:*E* = 14:86).

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32.2, 24.4, 20.5; MS *m/e* 234 (M^+); HRMS *m/e* for $C_{14}H_{18}O_3$ calcd 234.1256 (M^+), found 234.1253.

Ethyl 3-(2-methoxy-5-methylbenzyl)-3-methyl-4-pentenoate (7): To a solution of **5** (0.1405 g, 0.600 mmol) in Et_2O (15 mL) at −78 °C was added DIBAL-H (1.8 mL of a 1 M solution in hexanes). The solution was allowed to warm to rt for 1 h, at which time the solution was recooled to −78 °C and H_2SO_4 (1 M) was added. Following a conventional extractive workup (Et_2O), the residue was dissolved in xylenes (15 mL), and propionic acid (10 μL) and triethyl orthoacetate (0.44 mL, 2.4 mmol) were added. The solution was heated to reflux for 15 h, and after cooling, the volatiles were removed under reduced pressure. Preparative TLC (10:1 hexanes/Et_2O) afforded **7** (0.1016 g, 61% yield) as a colorless oil: bp 105−110 °C (0.2 Torr) (bulb-to-bulb); IR (KBr) ν_{max} 3083, 2960, 1732 cm^{-1}; ^1H NMR δ 6.99 (d, J = 8.3 Hz, 1H), 6.93 (s, 1H), 6.75 (d, J = 8.3 Hz, 1H), 5.99 (dd, J = 10.8, 17.5 Hz, 1H), 4.98 (d, J = 10.8 Hz, 1H), 4.89 (d, J = 17.5 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 2.79 (1/2 of ABquartet, J = 13.0 Hz, 1H), 2.74 (1/2 of ABquartet, J = 13.0 Hz, 1H), 2.42 (1/2 of ABquartet, J = 13.9 Hz, 1H), 2.31 (1/2 of ABquartet, J = 13.9 Hz, 1H), 2.28 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.15 (s, 3H); ^{13}C NMR δ 172.0, 156.0, 145.6, 133.3, 128.8, 127.8, 126.0, 111.4, 110.3, 59.8, 55.1, 44.4, 40.6, 40.2, 22.6, 20.4, 14.3; MS *m/e* 276 (M^+); HRMS *m/e* for $C_{17}H_{24}O_3$ calcd (M^+) 276.1725, found 276.1731.

Hexacarbonyl[μ-η^4-(methyl 4-(6-methylbenzo[*d*][1,3]dioxol-5-yl)-2-butynoate)]dicobalt (9): Subjecting a solution of **2a** (0.9721 g, 2.35 mmol) and 3,4-methylenedioxytoluene (0.42 mL, 3.5 mmol) in CH_2Cl_2 (60 mL) with Bu_2BOTf (2.4 mL of 1 M solution in CH_2Cl_2) according to General Procedure A, followed by flash chromatography (20:1 petroleum ether/Et_2O), gave **9** (1.0396 g, 85% yield) as a red-brown oil: IR (KBr) ν_{max} 2954, 2100, 2060, 2029, 1709 cm^{-1}; ^1H NMR δ 6.71 (s, 1H), 6.64 (s, 1H), 5.89 (s, 2H), 4.07 (s, 2H), 3.85 (s, 3H), 2.30 (s, 3H); ^{13}C NMR δ 198.0, 170.6, 146.6, 145.9, 131.0, 128.7, 110.3, 110.0, 100.8, 99.9, 78.6, 53.0, 36.5, 19.2; MS *m/e* 490 ($M - CO^+$), 462 ($M - 2CO^+$), 434 ($M - 3CO^+$), 416 ($M - 4CO^+$); HRMS *m/e* for $C_{19}H_{12}$ Co_2O_{10} calcd 517.9094 (M^+), found 517.9092.

Methyl 4-(6-methylbenzo[*d*][1,3]dioxol-5-yl)-2-butynoate (10): To a solution of **9** (1.0396 g, 2.006 mmol) in THF (25 mL) was added I_2 (1.5 g). The solution was stirred 12 h. Following the addition of saturated $Na_2SO_{3(aq)}$ and a conventional extractive workup (Et_2O), flash chromatography (18:1 petroleum ether/Et_2O) gave **10** (0.4140 g, 89% yield) as a colorless oil: bp 125−130 °C (0.1 Torr) (bulb-to-bulb); IR (KBr) ν_{max} 2954, 2237,1714 cm^{-1}; ^1H NMR δ 6.85 (s, 1H), 6.66 (s, 1H), 5.92 (s, 2H), 3.77 (s, 3H), 3.57 (s, 2H), 2.24 (s, 3H); ^{13}C NMR δ 154.1, 146.7, 145.9, 129.1, 125.0, 110.5, 108.9, 100.9, 86.5, 74.3, 52.6, 22.8, 19.2; MS *m/e* 232 (M^+); HRMS *m/e* for $C_{13}H_{12}$ O_4 calcd 232.0736 (M^+), found 232.0737.

Methyl 4-(6-methylbenzo[*d*][1,3]dioxol-5-yl)butanoate (11): To a solution of **10** (0.4140 g, 0.178 mmol) in MeOH (20 mL) was added 5% Rh/C (0.1 g). H_2 was bubbled through solution, while stirring for 10 h. The mixture was filtered and concentrated under reduced pressure. The crude reaction mixture was filtered through a plug of neutral alumina and again concentrated under reduced pressure. Bulb-to-bulb distillation gave **11** (0.4048 g, 96% yield) as a colorless oil: bp 105−100 °C (0.1 Torr) (bulb-to-bulb); IR (KBr) ν_{max} 2952, 1738 cm^{-1}; ^1H NMR δ 6.62 (apparent s, 2H), 5.86 (s, 2H), 3.68 (s, 3H), 2.54 (m, 2H), 2.36 (t, J = 7.3 Hz, 2H), 2.21 (s, 3H), 1.86 (m, 2H); ^{13}C NMR δ 173.7, 145.5, 132.4, 128.6, 110.2, 109.0, 100.4, 51.3, 33.3, 32.2, 25.4, 18.9; MS *m/e* 236 (M^+); HRMS *m/e* for $C_{13}H_{16}$ O_4 calcd 236.1049 (M^+), found 236.1048.

5,9,9-Trimethyl-6,7,8,9-tetrahydronaphtho[1,2-*d*][1,3]dioxole (13): To a solution of **11** (0.5106 g, 2.16 mmol) in Et_2O was added MeLi (5.0 mL, 1.53 M in Et_2O, 7.7 mmol) at −78 °C. The cooling bath was removed and the solution allowed to warm to rt; stirring was continued for 2 h. Saturated $NH_4Cl_{(aq)}$ was added and the reaction mixture subjected to a conventional extractive workup (Et_2O). The crude reaction product was dissolved in CH_2Cl_2 (35 mL) and cooled to 0 °C. BF_3-OEt_2 (4.0 mL, 15 equiv) was added, and the solution was stirred at 0 °C for 0.5 h followed by rt for 1 h. Following the addition of H_2O and a conventional extractive workup (CH_2Cl_2), preparative TLC (50:1 hexanes/Et_2O) gave **13** (0.3703 g, 78% yield) as a colorless oil: bp 90−95 °C (0.1 Torr) (bulb-to-bulb); IR (KBr) ν_{max} 2927, 1625,1605 cm^{-1}; ^1H NMR δ 6.60 (s, 1H), 5.90 (s, 2H), 2.55 (t, J = 6.3 Hz, 2H), 2.19 (s, 3H), 1.82 (m, 2H), 1.66 (m, 2H), 1.39 (S, 6H); ^{13}C NMR δ 144.8, 143.4, 128.9, 128.50, 128.47, 108.1, 99.7, 40.0, 33.3, 28.4, 27.9, 20.1, 19.9; MS *m/e* 218 (M^+); HRMS *m/e* for $C_{14}H_{18}$ O_2 calcd 218.1307 (M^+), found 218.1305.

Methyl 4-(5,9,9-trimethyl-6,7,8,9-tetrahydronaphtho[1,2-*d*][1,3]-dioxol-4-yl)-2-butynoate (14): To a solution of **13** (0.3703 g, 1.70 mmol) and **2a** (0.843 g, 2.04 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added Bu_2BOTf (2.0 mL of 1 M solution in CH_2Cl_2). The mixture was stirred for 1 h, saturated $NH_4Cl_{(aq)}$ was added, and the mixture was subjected to a conventional extractive workup. The residue was dissolved in THF (25 mL), I_2 (1 g) added, and the solution stirred for 12 h. Saturated $Na_2SO_{3(aq)}$ was added, and the mixture was subjected to a conventional extractive workup (Et_2O). Preparative TLC (15:1 hexanes/Et_2O) afforded **14** (0.4904 g, 92% yield) as a colorless oil; bp 150−155 °C (0.1 Torr) (bulb-to-bulb); IR (KBr) ν_{max} 2959, 2233,1706 cm^{-1}; ^1H NMR δ 5.90 (s, 2H), 3.74 (s, 3H), 3.64 (s, 2H), 2.55 (t, J = 6.3 Hz, 2H), 2.17 (s, 3H), 1.78 (m, 2H), 1.61 (m, 2H), 1.34 (s, 6H); ^{13}C NMR δ 154.1, 143.6, 143.0, 129.3, 127.9, 127.6, 111.9, 99.9, 86.5, 72.4, 52.4, 39.8, 33.2, 28.5, 28.4, 19.9, 16.6, 15.0; MS *m/e* 314 (M^+); HRMS *m/e* for $C_{19}H_{22}O_4$ calcd 314.1518 (M^+), found 314.1504.

(*Z*)-Methyl 3-methyl-4-(5,9,9-trimethyl-6,7,8,9-tetrahydronaphtho[1,2-*d*][1,3]dioxol-4-yl)-2-butenoate (15): To a suspension of CuI (0.229 g, 1.20 mmol) in THF (10 mL) at 0 °C was added MeLi (1.50 mL of a 1.6 M solution in Et_2O). The solution was stirred for 15 min and then added slowly to a solution of **14** (0.1892 g, 0.602 mmol) in THF at −78 °C. The solution was stirred for 2 h at −78 °C, at which time saturated $NH_4Cl_{(aq)}$ was added and the mixture allowed to warm to rt. Following a conventional extractive workup (Et_2O), preparative TLC (20:1 hexanes/Et_2O) afforded **15** (0.1880 g, 95% yield) as a viscous colorless oil: bp 130−135 °C (0.1 Torr) (bulb-to-bulb); IR (KBr) ν_{max} 2929, 1717, 1645 cm^{-1}; ^1H NMR δ 5.87 (s, 2H), 5.79 (br s, 1H), 4.16 (s, 2H), 3.75 (s, 3H), 2.52 (t, J = 6.5 Hz, 2H), 2.02 (s, 3H), 1.77 (m, 2H), 1.72 (s, 3H), 1.61 (m, 2H), 1.35 (s, 6H); ^{13}C NMR δ 166.8, 158.6, 144.5, 142.4, 128.8, 128.5, 126.9, 116.6, 115.9, 99.4, 50.8, 39.8, 33.2, 30.0, 28.53, 28.50, 23.9, 20.0, 14.6; MS *m/e* 330 (M^+); HRMS *m/e* for $C_{20}H_{26}$ O_4 calcd 330.1831 (M^+), found 330.1830.

(*Z*)-3-Methyl-4-(5,9,9-trimethyl-6,7,8,9-tetrahydronaphtho-[1,2-*d*][1,3]dioxol-4-yl)-2-buten-1-ol (16): To a solution of **15** (0.1161 g, 0.352 mmol) in Et_2O (15 mL) at −78 °C was added DIBAL-H (1.5 mL of a 1 M solution in hexanes). The solution was stirred at −78 °C for 1 h and allowed to warm to rt for 1 h. Following the addition of H_2SO_4 (1 M) and a conventional extractive workup (Et_2O), preparative TLC (2:1 hexanes/Et_2O) gave **16** (0.1059 g, 100%) as an undistillable glass: IR (KBr) ν_{max} 3346, 2928, 1666 cm^{-1}; ^1H NMR δ 5.86 (s, 2H), 5.52 (dt, J = 1.2, 7.1 Hz, 1H), 4.30 (d, J = 7.1 Hz, 2H), 3.46 (s, 2H), 2.54 (t, J = 6.3 Hz, 2H), 2.09 (s, 3H), 1.92 (br s, 1H), 1.78 (m, 2H), 1.62 (s, 3H), 1.61 (m, 2H), 1.35 (s, 6H); ^{13}C NMR 144.0, 142.5, 137.8, 128.9, 127.8, 126.8, 124.5, 117.2, 99.4, 58.9, 39.8, 33.2, 28.9, 28.7, 28.5, 22.8, 20.0, 15.0; MS *m/e* 302 (M^+); HRMS *m/e* for $C_{19}H_{26}O_3$ calcd 302.1882 (M^+), found 302.1882.

Ethyl 3-methyl-3-((5,9,9-trimethyl-6,7,8,9-tetrahydronaphtho-[1,2-*d*][1,3]dioxol-4-yl)methyl)-4-pentenoate (17): To a solution of (*Z*)-allyl alcohol **16** (0.0543 g, 0.180 mmol) in triethyl orthoacetate (4 mL) was added propionic acid (2 μL). The mixture was heated to reflux for 47 h. The solvent was removed

under reduced pressure, and preparative TLC (10:1 petroleum ether/ether) gave **17** (0.0423 g, 63% yield): bp 160−165 °C (0.15 Torr) (bulb-to-bulb); IR (KBr) ν_{max} 3083, 2928, 1733 cm^{-1}; ^{1}H NMR δ 5.98 (dd, J = 17.5, 11.0 Hz, 1H), 5.83 (d, J = 1.4 Hz, 1H), 5.81 (d, J = 1.4 Hz, 1H), 4.97 (d, J = 11.0 Hz, 1H), 4.94 (d, J = 17.5 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 2.80 (1/2 AB quartet, J = 14.0 Hz, 1H), 2.78 (1/2 AB quartet, J = 14.0 Hz, 1H), 2.50 (t, J = 6.3 Hz, 2H), 2.47 (1/2 AB quartet, J = 14.0 Hz, 1H), 2.38 (1/2 AB quartet, J = 14.0 Hz, 1H), 2.05 (s, 3H), 1.77 (m, 2H), 1.60 (m, 2H), 1.343 (s, 3H), 1.339 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.20 (s, 3H); ^{13}C NMR δ 172.0, 145.4, 144.8, 142.3, 129.1, 128.7, 126.9, 116.3, 111.6, 99.1, 59.9, 44.9, 41.7, 39.9, 38.2, 33.2, 28.8, 28.5, 22.6, 20.0, 16.6, 14.3; MS m/e 372 (M^+); HRMS m/e for $C_{23}H_{32}O_4$ calcd 372.2301 (M^+), found 372.2282.

Velloziolide (1):. To a solution of **17** (0.0423 g, 0.114 mmol) in CH_2Cl_2 (5 mL) cooled to −78 °C was added BCl_3 (0.5 mL of 1 M solution in heptane). The mixture was allowed to stir 1 h at −78 °C and subsequently warmed to rt and stirred for 12 h. Following a conventional extractive workup (CH_2Cl_2) and concentration under reduced pressure, the residue was dissolved in H_2O (1 mL)/THF (2 mL) and $AgNO_3$ (25 mg) added. The mixture was shielded from light and stirred for 24 h at rt. Following a conventional extractive workup (Et_2O), the crude reaction was subjected to preparative TLC (9:1 hexanes/Et_2O) to give **1** (velloziolide, 0.0292 g, 82% yield): mp 137−139 °C (CH_2Cl_2/hexanes), lit.[1] mp 138−140 °C; IR (KBr) ν_{max} 3445 (br), 3085, 2926, 1761 cm^{-1}; ^{1}H NMR δ 5.93 (dd, J = 10.7, 17.4 Hz, 1H), 5.62 (s, 1H), 5.12 (d, J = 17.4 Hz, 1H), 5.08 (d, J = 10.7 Hz, 1H), 2.79 (1/2 AB quartet, J = 14.2 Hz, 1H), 2.69 (1/2 AB quartet, J = 14.2 Hz, 1H), 2.58 (t, J = 6.3 Hz, 2H), 2.48 (1/2 AB quartet, J = 12.1 Hz, 1H), 2.29 (1/2 AB quartet, J = 12.1 Hz, 1H), 2.10 (s, 3H), 1.77 (m, 2H), 1.62 (m, 2H), 1.43 (s, 6H), 1.23 (s, 3H); ^{13}C NMR δ 170.0, 144.0, 142.5, 137.3, 134.3, 131.6, 125.7, 124.0, 112.5, 44.1, 42.6, 41.5, 36.9, 34.4, 29.6, 28.1, 28.0, 25.1, 19.6, 15.3; MS m/e 314 (M^+); HRMS m/e for $C_{20}H_{26}O_3$ calcd 314.1882 (M^+), found 314.1869.

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Supporting Information Available: Experimental details for the preparation of 1-hexyl-4-methoxybenzene, **2a**−**2c**, **3b**−**3k**, and **6**, ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.