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A Route to 1,4-Disubstituted Aromatics and Its Application to the Synthesis of the Antibiotic Culpin

Rajesh Sunasee and Derrick L. J. Clive*

Chemistry Department, University of Alberta, Edmonton, Alberta T6G 2G2, Canada

derrick.clive@ualberta.ca

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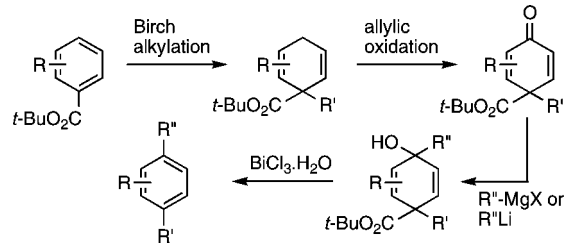


A method is described for converting *tert*-butyl benzoates or *tert*-butyl 1-naphthoates into derivatives having an alkyl or substituted alkyl group in a 1,4-relationship to an alkyl, aryl, alkenyl, or alkynyl group. Key steps in the sequence are (i) addition of an organometallic species to a cross-conjugated cyclohexadienone obtained by Birch alkylation of a *tert*-butyl benzoate or a *tert*-butyl 1-naphthoate, followed by allylic oxidation, and (ii) treatment with $BiCl_3 \cdot H_2O$, which results in removal of the *tert*-butyl group and spontaneous decarboxylative aromatization. The method was applied to the synthesis of the antimicrobial fungal metabolite culpin.

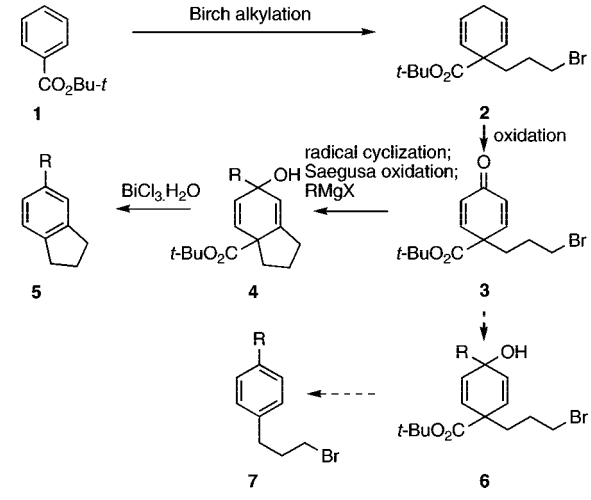
Introduction

Although many approaches are available for the synthesis of substituted aromatics,[1] the general importance of such compounds leaves considerable room for the development of new synthetic procedures, and we report a method that starts with *tert*-butyl benzoates or *tert*-butyl 1-naphthoates and allows the introduction of two substituents in a 1,4-relationship.

Results and Discussion

Numerous cross-conjugated dienones of type **3** have been prepared in this laboratory by alkylative Birch reduction (**1** → **2**), followed by allylic oxidation (**2** → **3**) (Scheme 1).[2] Some of these dienones were then elaborated into the alcohols **4**, which underwent aromatization (**4** → **5**) on heating (70−80 °C) with $BiCl_3 \cdot H_2O$, a reagent known[3] to be useful for deprotection of *tert*-butyl carbamates but which we had found to be equally effective for deprotection of *tert*-butyl esters.[2] This earlier work was aimed specifically at the preparation of benzo-fused carbocycles (such as **5**), but the facility of the decarboxylative aromatization step (**4** → **5**) suggested that monocyclic compounds of type **6**, which would be readily available from the cross-conjugated dienones **3** by Grignard or organolithium addition, might likewise be aromatized to afford para-disubsti-

SCHEME 1. Principle of the Method



(1) (a) *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933. (c) Donohoe, T. J.; Orr, A. J.; Bingham, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2–9.

(2) (a) Clive, D. L. J.; Sunasee, R. *Org. Lett.* **2007**, *9*, 2677–2680. (b) Clive, D. L. J.; Sunasee, R.; Chen, Z. *Org. Biomol. Chem.* **2008**, 2434–2441. (c) Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893–5901. (d) Schultz, A. G.; Lavieri, F. P.; Macielag, M.; Plummer, M. *J. Am. Chem. Soc.* **1987**, *109*, 3991–4000. (e) Schultz, A. G.; Taveras, A. G.; Harrington, R. E. *Tetrahedron Lett.* **1988**, *29*, 3907–3910.

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TABLE 1. Formation of 1,4-Disubstituted Aromatics

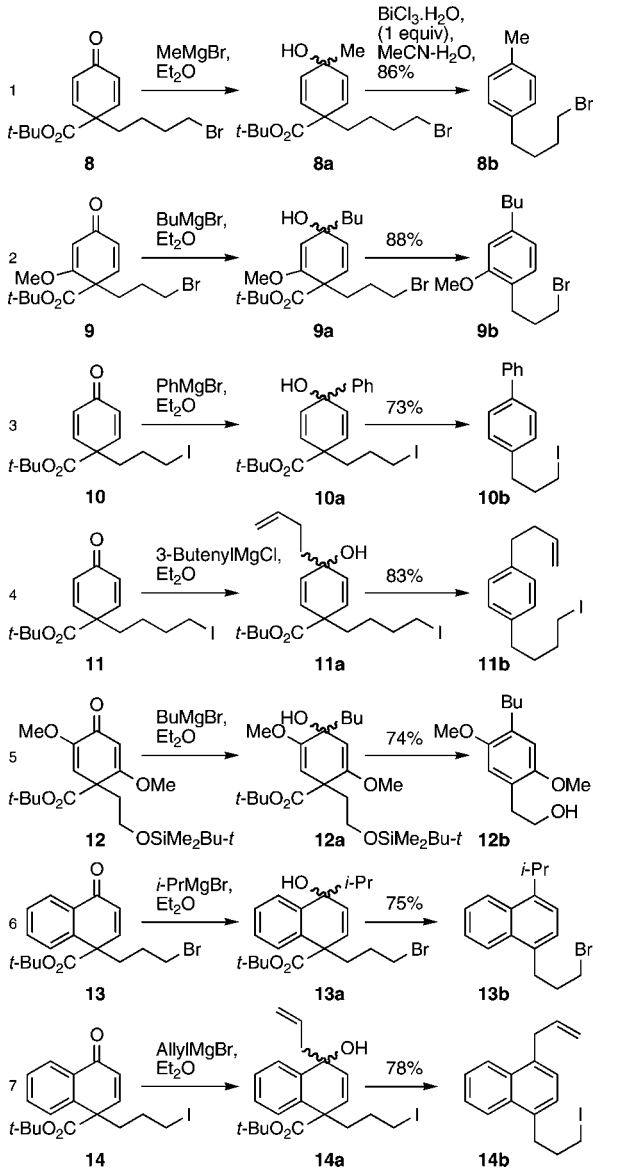
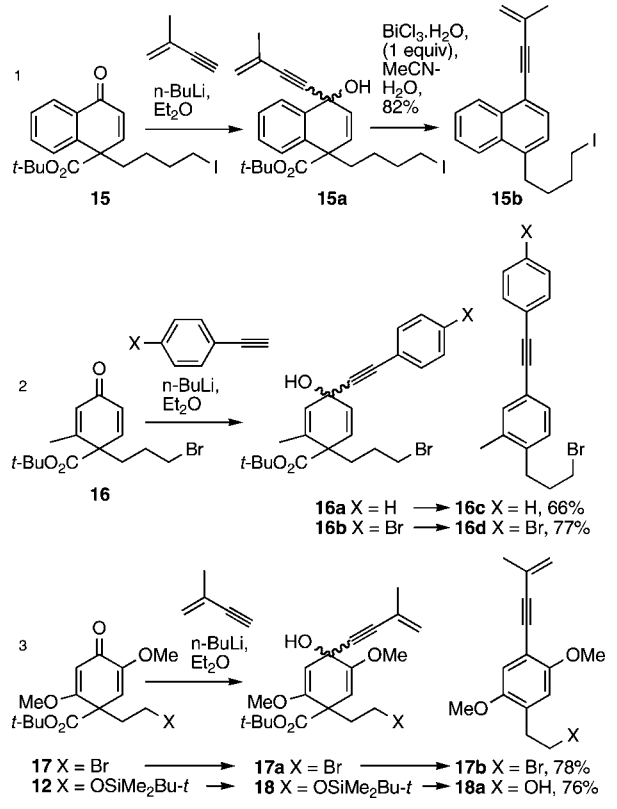
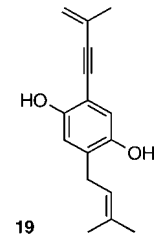


TABLE 2. Formation of Acetylenic Compounds



tuted benzenes **7**. We have now established that the short sequence **3** → **6** → **7** is general, and we describe several examples of this route as well as its application to the synthesis of the antibiotic culpin (**19**).[4]

Most of the cross-conjugated ketones we have examined are listed in Tables 1 and 2; several were available from our earlier study[2] (hence the presence of a bromine or iodine atom at the end of the first alkyl chain), but we have also prepared some new examples. All were made by a Birch reduction/alkylation sequence, followed by oxidation with CrO_3−AcOH or PDC−*t*-BuOOH, using procedures described earlier.[2] The cross-conjugated ketones react efficiently with Grignard reagents and organolithiums to produce the expected alcohols as a mixture of diastereoisomers. The formation of a mixture is of no consequence, however, because treatment with 1 equiv of $BiCl_3 \cdot H_2O$[2,3] in MeCN−water at 70−80 °C converts the alcohols smoothly into the desired aromatized products. The overall yield for the two steps—carbanion addition and aromatization—is generally above 75%. We did not establish if the bismuth salt plays a role in the decarboxylation or is involved only in removal of the *tert*-butyl group.



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Entry 5 of Table 1 and entry 3 of Table 2 show that a *tert*-butyldimethylsilyl group is removed by the bismuth reagent, which we use in stoichiometric amounts; other bismuth salts, such as $Bi(OTf)_3$[5] (in MeOH) and $BiBr_3$[6] (in wet MeCN), are known to cleave *tert*-butyldimethylsilyl ethers, but $BiCl_3$ (in catalytic amounts) in MeOH is reported[5] to have no effect on this protecting group.

The overall sequence is applicable to naphthalenes (Table 1, entries 6 and 7; Table 2, entry 1) and can be used to introduce an alkyl, alkenyl, aryl, or alkynyl group. As the examples show, the presence of halogens is tolerated (Table 2, entry 2) as well as those substituents on the starting *tert*-butyl benzoate that are

(3) Cf. (a) Navath, R. S.; Pabbisetty, K. B.; Hu, L. *Tetrahedron Lett.* **2006**, *47*, 389–393. (b) Review on applications of Bi(III) compounds: Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373–8397.

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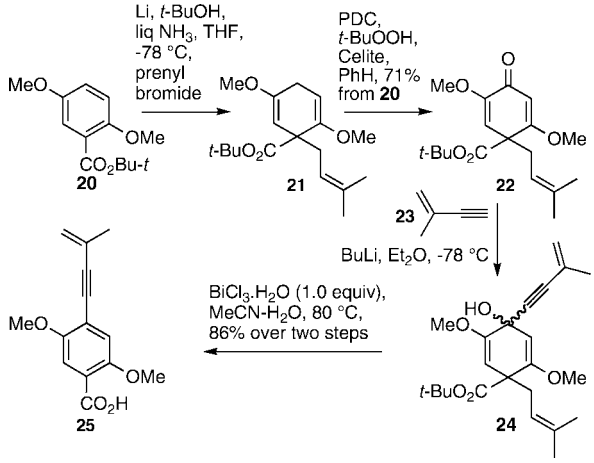
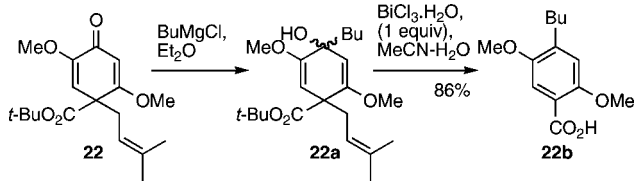
(5) Firouzabadi, H.; Mohammadpoor-Baltork, I.; Kolagar, S. *Synth. Commun.* **2001**, *31*, 905–909.

(6) Bajwa, J. S.; Vivelo, J.; Slade, J.; Repic, O.; Blacklock, T. *Tetrahedron Lett.* **2000**, *41*, 6021–6024.

SCHEME 2. Initial Approach to Culpin



SCHEME 3. Additional Example of Loss of a Prenyl Substituent



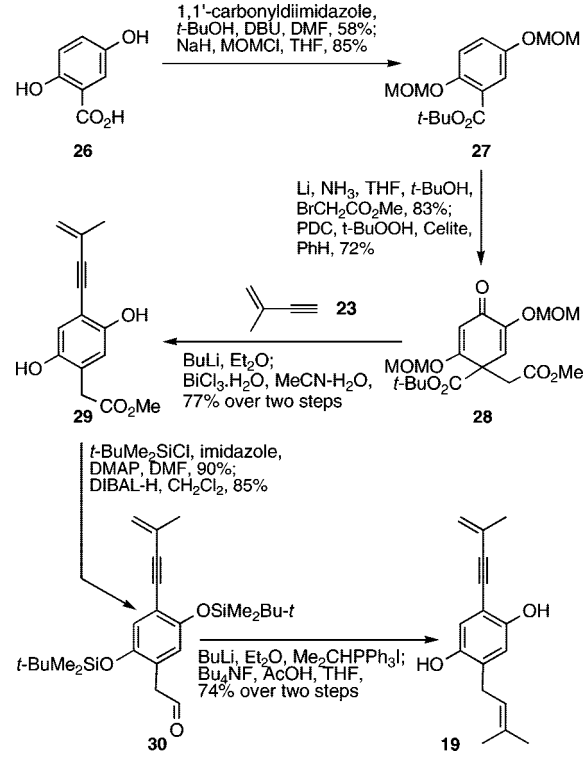
compatible with conditions of the Birch reduction (Table 1, entry 5, Table 2, entry 2).

In none of the cases did we observe a 1,2-alkyl shift[7] during the aromatization step mediated by $BiCl_3 \cdot H_2O$, but one unexpected limitation was identified when we attempted to apply the method to the synthesis of the antibiotic culpin (**19**),[4] which is a member of a small group of phenolic natural products[8] having an isopentenyne unit, some of which have weak antimicrobial and/or phytotoxic activity.

Our initial approach to culpin is summarized in Scheme 2. The first three steps (**20** → **24**) proceeded normally, but the attempted decarboxylative aromatization resulted in loss of the prenyl group rather than the carboxyl. This preference for loss of a prenyl unit (we did not test other allylic substituents), rather than decarboxylation, appears to be general, as compound **22a** behaved in a similar way to afford the acid **22b** (Scheme 3).

This unexpected result necessitated a different approach in which the prenyl unit of culpin was elaborated *after* the rearomatization step. However, once this problem had been solved, we found that the sensitivity of the culpin structure imposed severe restrictions on the types of protecting group that could be used for the phenolic oxygens,[9] and our optimized route to culpin is that summarized in Scheme 4. Gentisic acid (**26**) was converted into its *tert*-butyl ester and then protected

SCHEME 4. Synthesis of Culpin



as a bis-MOM ether (**27**). Birch alkylation with $BrCH_2CO_2Me$, followed by allylic oxidation, gave the cross-conjugated ketone **28**. Reaction with the lithium salt of acetylene **23** and treatment with $BiCl_3 \cdot H_2O$ under our standard conditions resulted not only in aromatization but also in loss of the MOM groups. Accordingly, the resulting bis-phenol **29** was silylated, and the ester side chain was elaborated to the required prenyl unit by standard reactions (DIBAL reduction and Wittig olefination). Finally, desilylation produced culpin (**19**). While we expect that culpin should be more easily accessible by transition-metal-catalyzed coupling reactions, using a suitably protected 2,5-dihalo-1,4-benzenediol, our study shows that the present method is not limited to simple alkyl substituents, and a potentially useful characteristic is that it is applicable to cases where the substructure that is incorporated does itself bear a metal-sensitive substituent such as a halogen (Table 2, entry 2). The work on culpin also served to identify a limitation in the nature of the groups that survive the decarboxylative aromatization in the presence of $BiCl_3 \cdot H_2O$.

Experimental Section

General Procedure for Rearomatization. $BiCl_3 \cdot H_2O$[2] (1 equiv) was added to a solution of the intermediate tertiary alcohol in a mixture of MeCN (5 mL) and water (0.1 mL), and the mixture was stirred at 75−80 °C for 1−12 h until reaction was complete (TLC control). The mixture was filtered through Celite, using CH_2Cl_2, and the filtrate was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel gave the aromatized product.

***tert*-Butyl 1-(3-Bromopropyl)-4-butyl-4-hydroxy-2-methoxycyclohexa-2,5-dienecarboxylate (9a).** BuMgBr (2 M in THF, 0.09 mL, 0.2 mmol) was added at a fast dropwise rate to a stirred and cooled (−78 °C) solution of **9** (54.3 mg, 0.160 mmol) in Et_2O (10 mL). The cold bath was removed, and stirring was continued for 1.5 h. The mixture was cooled to 0 °C, quenched slowly with water,

(7) Cf. (a) Newman, M. S.; Eberwein, J.; Wood, L. L., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 6454–6456. (b) Summermatter, W.; Heimgartner, H. *Helv. Chim. Acta* **1984**, *67*, 1298–1309. (c) Lakác, J.; Heimgartner, H. *Helv. Chim. Acta* **1985**, *68*, 355–370.

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(9) We tried *O*-methyl and *O*-*tert*-butyldimethylsilyl groups. When the phenolic oxygens were protected as methyl ethers, attempts to carry out the final demethylation [BBr_3, BCl_3, $(NH_4)_2Ce(NO_2)_6$ under various conditions, $CeCl_3 \cdot H_2O \cdot 7H_2O$/NaI, Me_3SiI, EtSNa] that would have released culpin gave complex mixtures or recovered starting material. In the case of silicon-protected intermediates, the bismuth reagent resulted in loss of the protecting groups.

and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The crude product (**9a**) was used directly in the next step.

1-(3-Bromopropyl)-4-butyl-2-methoxybenzene (9b). The general procedure for rearomatization was followed, using $BiCl_3 \cdot H_2O$ (52.5 mg, 0.160 mmol) and **9a** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL) and a reaction time of 6 h. Flash chromatography of the crude product over silica gel (1 × 12 cm), using 10% EtOAc−hexane, gave **9b** (39.4 mg, 88%) as an oil: FTIR (microscope, cast) 2999, 2956, 2856, 1612, 1580, 1509, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, J = 7.3 Hz, 3 H), 1.36−1.41 (m, 2 H), 1.54−1.62 (m, 2 H), 2.11−2.16 (m, 2 H), 2.59 (t, J = 7.6 Hz, 2 H), 2.72 (t, J = 7.2 Hz, 2 H), 3.40 (t, J = 6.8 Hz, 2 H), 3.82 (s, 3 H), 6.67 (s, 1 H), 6.71 (d, J = 7.5 Hz, 1 H), 7.04 (d, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 22.4 (t), 28.5 (t), 32.7 (t), 33.6 (t), 33.7 (t), 35.6 (t), 55.1 (q), 110.5 (d), 120.1 (d), 125.9 (s), 129.8 (d), 142.4 (s), 157.2 (s); exact mass m/z calcd for $C_{14}H_{21}{}^{79}Br$ 284.07758, found 284.07763.

***tert*-Butyl 4-[(4-Bromophenyl)ethynyl]-1-(3-bromopropyl)-4-hydroxy-2-methylcyclohexa-2,5-dienecarboxylate (16b).** (4-Bromophenyl)acetylene (227.0 mg, 1.250 mmol) was added to a stirred and cooled (−78 °C) solution of LDA [from *n*-BuLi (2.5 M in hexane), 0.55 mL, 1.4 mmol) and *i*-Pr_2NH (0.19 mL, 1.4 mmol) in THF (3.0 mL)]. The resulting mixture was stirred at −78 °C for 1 h. A solution of **16** (495 mg, 1.51 mmol) in THF (2 mL) was added dropwise, and stirring was continued for 2 h. The mixture was quenched by slow addition of saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The crude product (**16b**) was used directly in the next step.

4-[(4-Bromophenyl)ethynyl]-1-(3-bromopropyl)-2-methylbenzene (16d). The general procedure for rearomatization was followed, using $BiCl_3 \cdot H_2O$ (418.1 mg, 1.250 mmol) and **16b** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL) and a reaction time of 2 h. Flash chromatography of the crude product over silica gel (1.5 × 11 cm), using 90% EtOAc−hexane, gave **16d** (438.5 mg, 77% over two steps) as an oil: FTIR ($CDCl_3$, microscope) 2925, 2868, 2211, 1502, 1484 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.05−2.18 (m, 2 H), 2.33 (s, 3 H), 2.79 (t, J = 7.3 Hz, 2 H), 3.45 (t, J = 6.5 Hz, 2 H), 7.15 (d, J = 7.8 Hz, 1 H), 7.28−7.39 (m, 4 H), 7.46−7.49 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5 (q), 31.8 (t), 33.1 (t), 33.5 (t), 88.0 (s), 90.8 (s), 120.9 (s), 122.4 (s), 122.6 (s), 129.3 (d), 129.4 (d), 131.8 (d), 133.1 (d), 133.6 (d), 136.4 (s), 139.9 (s); exact mass m/z calcd for $C_{18}H_{16}{}^{79}Br_2$ 389.96188, found 389.96176.

***tert*-Butyl 1-[(Methoxycarbonyl)methyl]-2,5-bis(methoxymethoxy)-4-oxocyclohexa-2,5-dienecarboxylate (28). (a) *tert*-Butyl 1-[(Methoxycarbonyl)methyl]-2,5-bis(methoxymethoxy)cyclohexa-2,5-dienecarboxylate.** The apparatus consists of a three-necked round-bottomed flask containing a magnetic stirring bar and fitted with a coldfinger condenser fused onto one of the necks. The exit of the condenser carried a drying tube filled $CaSO_4$. An external mark on the flask indicated the level corresponding to the desired volume of liquid NH_3. The central neck was closed by a septum carrying a nitrogen inlet. The flask was cooled in a dry ice−acetone bath and the coldfinger condenser was charged with dry ice−acetone. Another round-bottomed flask was half-filled with liquid NH_3 and several small pieces of Na were added, so as to form a permanently blue solution. This flask was connected via bent adaptors and dry Tygon tubing to the third neck of the other flask. A solution of **27** (1.77 g, 5.94 mmol) in dry THF (20 mL) and *t*-BuOH (0.60 mL, 5.9 mmol) was injected into the three-necked flask, and liquid NH_3 (40 mL) was allowed to condense into the flask. Lithium wire (0.17 g, 24 mmol), cut into small pieces, was added rapidly to the vigorously stirred solution. Stirring at −78 °C was continued for 1 h, by which time a dark blue color persisted. A solution of $BrCH_2CO_2CH_3$ (1.70 mL, 17.8 mmol) in THF (5 mL) was then added dropwise from a syringe over ca. 2 min, and the resulting solution was stirred for 2 h at −78 °C. The cooling bath was removed and the NH_3 was allowed to evaporate under a stream of N_2 (2−3 h). Water was added and the mixture was extracted with Et_2O (3 times). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 × 18 cm), using 50% EtOAc−hexane, gave *tert*-butyl 1-[(methoxycarbonyl)methyl]-2,5-bis(methoxymethoxy)cyclohexa-2,5-dienecarboxylate (1.83 g, 83%) as an oil: FTIR ($CDCl_3$, microscope) 2954, 2902, 1731, 1665, 1392, 1368, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9 H), 2.82−2.87 (m, 3 H), 3.39 (s, 3 H), 3.41 (s, 3 H), 3.60 (s, 3 H), 3.66−3.68 (m, 1 H), 4.93−4.97 (m, 5 H), 5.10−5.18 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.7 (q), 27.9 (t), 40.4 (t), 51.1 (q), 51.3 (s), 55.7 (q), 55.8 (q), 81.0 (s), 93.4 (t), 94.1 (t), 96.5 (d), 98.9 (d), 150.0 (s), 152.1 (s), 171.2 (s), 171.3 (s); exact mass m/z calcd for $C_{18}H_{28}NaO_8$ (M + Na) 395.16764, found 395.16751.

(b) *tert*-Butyl 1-[(Methoxycarbonyl)methyl]-2,5-bis(methoxymethoxy)-4-oxocyclohexa-2,5-dienecarboxylate (28). Celite (1.0 g) and then PDC (2.18 g, 5.81 mmol) were added to a stirred solution of *tert*-butyl 1-[(methoxycarbonyl)methyl]-2,5-bis(methoxymethoxy)cyclohexa-2,5-dienecarboxylate (540 mg, 1.45 mmol) in PhH (15 mL). *t*-BuOOH (7.76 M in decane, 0.75 mL, 5.8 mmol) was added, and stirring at room temperature was continued for 4 h. The mixture was filtered through Celite, and the solid was washed CH_2Cl_2 (2 × 30 mL) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 18 cm), using first hexane and then EtOAc−hexane mixtures up to 1:1 EtOAc−hexane, gave **28** (403 mg, 72%) as an oil: FTIR ($CDCl_3$, microscope) 2978, 2832, 1737, 1665, 1615, 1370, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 9 H), 3.06−3.10 (m, 2 H), 3.42 (s, 3 H), 3.43 (s, 3 H), 3.60 (s, 3 H), 5.10−5.12 (m, 4 H), 5.95 (s, 1 H), 6.10 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.7 (q), 39.8 (t), 51.7 (q), 53.6 (s), 56.0 (q), 56.9 (q), 83.3 (s), 94.4 (t), 94.9 (t), 106.7 (d), 115.2 (d), 149.2 (s), 167.2 (s), 169.3 (s), 169.7 (s), 182.0 (s); exact mass m/z calcd for $C_{18}H_{26}NaO_9$ (M + Na) 409.14690, found 409.14688.

2-[2,5-Dihydroxy-4-(3-methylbut-3-en-1-ynyl)phenyl]acetic Acid Methyl Ester (29). (a) *tert*-Butyl 4-Hydroxy-1-[(methoxycarbonyl)methyl]-2,5-bis(methoxymethoxy)-4-(3-methylbut-3-en-1-ynyl)cyclohexa-2,5-dienecarboxylate. *n*-BuLi (2.5 M in hexane, 0.35 mL, 0.88 mmol) was added at a fast dropwise rate to a stirred and cooled (−78 °C) solution of 2-methyl-1-buten-3-yne (0.08 mL, 0.9 mmol) in Et_2O (5 mL). The resulting solution was stirred at −78 °C for 1 h. A solution of **28** (169 mg, 0.440 mmol) in Et_2O (3 mL) was added dropwise, and stirring was continued for 3 h. The mixture was quenched slowly with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The crude product [*tert*-butyl 4-hydroxy1-1-[(methoxycarbonyl)methyl]-2,5-bis(methoxymethoxy)-4-(3-methylbut-3-en-1-ynyl)cyclohexa-2,5-dienecarboxylate] was used directly in the next step.

(b) 2-[2,5-Dihydroxy-4-(3-methylbut-3-en-1-ynyl)phenyl]acetic Acid Methyl Ester (29). The general procedure for rearomatization was followed, using $BiCl_3 \cdot H_2O$ (131.3 mg, 0.440 mmol) and *tert*-butyl 4-hydroxy-1-[(methoxycarbonyl)methyl]-2,5-bis(methoxymethoxy)-4-(3-methylbut-3-en-1-ynyl)cyclohexa-2,5-dienecarboxylate (total product from the previous step) in MeCN (5 mL) and water (0.1 mL) and a reaction time of 3 h. Flash chromatography of the crude product over silica gel (1 × 10 cm), using 30% EtOAc−hexane, gave **29** (82.9 mg, 77%) as an oil: FTIR ($CDCl_3$, microscope) 3398, 2954, 2924, 2196, 1716, 1431, 1199 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.01 (s, 3 H), 3.64 (s, 2 H), 3.76 (s, 3 H), 5.35−5.37 (m, 2 H), 5.43 (s, 1 H), 6.71 (s, 1 H), 6.87 (s, 1 H), 6.92 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4 (q), 37.7 (t), 52.8 (q), 81.7 (s), 97.6 (s), 109.5 (s), 116.6 (d), 119.9

(d), 123.0 (s), 123.7 (s), 126.1 (s), 148.2 (t), 150.6 (s), 173.8 (s); exact mass *m/z* calcd for $C_{14}H_{14}NaO_4$ (M + Na) 269.07843, found 269.07862.

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Supporting Information Available: Experimental procedures and copies of NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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