Published in final edited form as:

Tetrahedron. 2008 May 19; 64(21): 4758–4767. doi:10.1016/j.tet.2008.01.129.

A Rh(II)-catalyzed cycloaddition approach towards the synthesis of komaroviquinone

Albert Padwa^{*}, Majid J. Chughtai, Jutatip Boonsombat, and Paitoon Rashatasakhon

Department of Chemistry, Emory University, Atlanta GA 30322, USA

Abstract

Using a rhodium(II)-catalyzed cyclization/cycloaddition sequence as the key reaction step, the icetexane core of komaroviquinone was constructed by an intramolecular dipolar-cycloaddition of a carbonyl ylide dipole across a tethered π -bond. The ylide was arrived at by cyclization of a rhodium carbenoid intermediate onto a proximal ester group. Efforts towards the preparation of the required precursor for elaboration to the natural product are discussed.

Keywords

diterpene; icetexane; komaroviquinone; diazo carbonyl; rhodium(II); catalyst; carbonyl ylide; intramolecular; dipolar-cycloaddition

1. Introduction

Dried whole plants of a perennial semishrub that is referred to as 'buzbosh' (*Dracocephalum komarovi*) in Uzbekistan were extracted and fractionated to give several icetexane diterpenes whose structures were elucidated by extensive analysis of their NMR data.^{1,2} The major fraction isolated from the plant was assigned structure **1** and was named komaroviquinone. This compound showed strong *in vitro* trypanocidal activity against epimastigotes of *Trypanosoma cruzi*, the causative agent of Chagas' disease in Central and South America.³ In addition to compound **1**, a minor diterpene **2** was also isolated from the same plant which possesses a novel spiro-octahydroindene skeleton and was named komarovispiron (2).⁴ Biogenetically, komarovispiron (2) may be derived from komaroviquinone (1) through a novel ring-contraction sequence as outlined in Scheme 1. The stereochemistry of **2** was tentatively assigned as indicated in the scheme.

The total syntheses of several related diterpenes which incorporate a functionalized 6-7-6 fused tricyclic framework have appeared in the literature^{5–7} and involve generation of the basic skeleton mainly through acid-catalyzed cyclalkylation reactions.⁸ More recently, the first total synthesis of ($\pm$)-komaroviquinone (**1**) was reported by Banerjee and coworkers in 2005.⁹

Construction of the critical *trans*-10-hydroxy-1,1-dimethyloctahydrodibenzo[*a,d*]cyclohepten-7-one core was achieved by employing an intramolecular Heck reaction for the

© 2008 Elsevier Ltd. All rights reserved.

^{*}Corresponding author. Tel.: +1 404 727 0283; fax: +1 404 727 6629; e-mail: chemap@emory.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

crucial carbon-carbon bond forming step.¹⁰ Thus, cyclization of the olefinic intermediate **3** with Pd(OAc)₂, K₂CO₃ and PPh₃ in acetonitrile under reflux was followed by oxidation of the methylene group to produce ketone **5**, which was found to be in equilibrium with the hemiketal form **6** in solution. Further oxidation of the equilibrating mixture with silver oxide in dilute HNO₃ afforded (±)-komaroviquinone (**1**) as the major product in 68% yield for this last step (Scheme 2).

Based on prior work in our laboratory using the intramolecular dipolar-cycloaddition reaction of carbonyl ylides for the synthesis of various natural products,^{11–14} we felt that the Rh(II)-catalyzed reaction of a diazo-dione precursor (*i.e.*, **7**) might allow for a facile entry to the icetexane core of komaroviquinone (**1**). The eventual formation of the oxa-tricyclo[6.3.1.0^{0,0}] dodecane skeleton of **1** was envisioned to come about from cyclization of the rhodium carbenoid intermediate **8** with the adjacent carbomethoxy group.¹³ The ensuing dipole **9** was expected to undergo an intramolecular [3+2]-cycloaddition across the tethered π-bond. The resulting cycloadduct **10** would then be converted to (±)-komaroviquinone in several steps *via* sequential reduction of the keto groups, oxidation to the benzoquinone core and acid hydrolysis of the ketal moiety (Scheme 3).¹⁵

2. Results and Discussion

1,3-Dicarbonyl compounds represent a basic building block in organic chemistry and consequently many procedures have been developed for their synthesis.¹⁶ Among these methods, the condensation of ethyl diazoacetate with aldehydes employing a variety of Lewis and Bronsted acids as catalysts¹⁷ represents a facile and efficient way to prepare 1,3-diones.¹⁸ Another approach involves the condensation of an aldehyde with an α-diazo ketone and the resulting aldol product is then subjected to a metal-catalyzed decomposition.¹⁹ In order to test the feasibility of the retrosynthetic strategy outlined in Scheme 3, our initial efforts were focused on several model substrates. According to our design, we hoped to employ a tandem cyclization/cycloaddition reaction of a rhodium carbenoid intermediate to rapidly generate the 9,10-benzo-12-oxa-tricyclo[6.3.1.0^{0,0}]dodecane-dione skeleton from a relatively simple precursor (*i.e.*, **13**).

Our synthesis of the key diazo-dione **13** commenced with *o*-carbomethoxy diazoketone **11** which is readily available in high yield from phthalic acid monomethyl ester. We anticipated that under suitable reaction conditions, **11** would react with hex-5-enal to give diketone **12** following a protocol developed by Holmquist and Roskamp for β-keto esters.²⁰ These authors have found that aldehydes can be converted into β-keto esters by the addition of ethyl diazoacetate in the presence of tin(II) chloride. In our hands, a modest (but unoptimized) yield of **12** (ca 40%) was obtained from the reaction of **11** with hex-5-enal. A subsequent Regitz diazo transfer reaction²¹ using nosyl azide and Et₃N furnished diazo-dione **13** in 98% yield. Treating a sample of **13** with Rh₂(OAc)₄ in benzene at 80 °C afforded cycloadduct **16** in 75% yield (Scheme 4). Interestingly, when the Rh(II)-catalyzed reaction was carried out at room temperature, the major product isolated corresponded to epoxy-indanone **15** (71%) with only a small amount (<10%) of cycloadduct **16** being formed. Heating a sample of **15** at 80 °C in benzene gave **16** in 78% isolated yield. This reaction presumably occurs *via* thermal C-C bond cleavage of the epoxide ring to generate dipole **14** which undergoes a subsequent intramolecular [3+2]-cycloaddition to give **16**. Most noteworthy, when a sample of the methoxy substituted cycloadduct **16** was treated with aqueous acid it was smoothly converted into the corresponding hemiketal **17**. We assume that the hydrolytic conversion of **16** to **17** occurs by oxabicyclic ring opening under the acidic conditions to produce a hydroxy-tricarbonyl as a transient species which subsequently cyclizes to hemiketal **17**.

Many studies support the intermediacy of carbonyl ylides in reactions involving the interaction of a metallocarbenoid with a carbonyl oxygen.²² The great majority of literature reports on carbonyl ylides are dominated by 1,3-dipolar cycloaddition reactions rather than cyclization of the dipole to produce the oxirane ring system.^{11–14} Huisgen was the first to report the formation of an epoxide from the reaction of dimethyl diazomalonate with benzaldehyde, but only in 7% yield when the reaction was carried out at 125 °C in the presence of 1 mol% of Cu (acac)₂.²³ More recently, the Doyle²⁴ and Davies²⁵ groups have reported on stereospecific epoxide formation by Rh₂(OAc)₄ catalyzed reactions of aryl, heteroaryl, and vinyl diazoacetates with α,β -unsaturated aldehydes or ketones. Later, a similar epoxidation process was used to prepare spiroindoloxiranes with cyclic diazoamides by the Mathusamy group.²⁶ When dimethyl diazomalonate was used as the carbenoid source, a competition between dioxolane and epoxide formation was noted. Doyle was able to direct the decomposition of the diazomalonate system to produce either epoxide or dioxolane by influencing the stability of the intermediate carbonyl ylide dipole.²⁷ When the electron rich *p*-anisaldehyde was used as the trapping reagent, only epoxide formation was observed. Stabilization of the intermediate ylide was suggested to account for its diminished reactivity toward cycloaddition with a second molecule of the added aldehyde. The fact that we were able to isolate epoxide **15** in 71% yield from the cyclization of dipole **14** is perfectly consistent with the Doyle observations (Scheme 4). Thus, stabilization of the positive center of the dipole by interaction with the adjacent methoxy group diminishes the rate of the dipolar cycloaddition reaction and promotes cyclization of the ylide to the epoxide ring.

The Rh(II)-catalyzed reaction of the related dimethyl substituted diazo ester **25** was also studied since this system contained the required substituent groups needed for the eventual synthesis of komaroviquinone (**1**). The rate of an intramolecular reaction is often increased when alkyl groups are placed on a chain between the two reacting centers.²⁸ This is known as the gem-dialkyl effect and is often exploited to promote difficult cyclization reactions.²⁹

The required side chain for the Rh(II)-catalyzed reaction was prepared using standard chemistry starting from ethyl 2,2-dimethylpent-4-enoate **18** (Scheme 5). Hydroboration-oxidation followed by protection of the resulting hydroxyl group gave ester **20**. Adjustment of the oxidation state was followed by Wittig methylenation in 80% yield. The hydroxyl group was unmasked and oxidized to give aldehyde **23** which was coupled with α -diazoketone **11** and further elaborated to diazo dione **25** as before to give the key substrate needed for the cyclization/cycloaddition sequence. Indeed, the reaction of diazo dione **25** with a Rh(II) catalyst gave cycloadduct **26** in 92% yield, Scheme 6. Most importantly, when **26** was treated with aqueous acid it was readily converted to **27** in essentially quantitative yield. The conversion of **25** to **27** via this method suggests that a similar approach could be used in our planned synthesis of komaroviquinone (**1**).

Accordingly, we set out to prepare the diazo dicarbonyl precursor **7** which is essential for our planned synthetic route. After the cycloaddition chemistry, oxidation of the aromatic portion would be expected to provide the *para*-benzoquinone moiety found in the natural product. Thus, the challenge became the preparation of a hexa-substituted aromatic carboxylic acid (*i.e.* **30**) which could be coupled via α -diazo ketone **29** to a suitable olefinic tether to give the necessary diazo dicarbonyl precursor **7** (Scheme 7).

Our approach towards carboxylic acid **30** initially centered on the thermal rearrangement of cyclobutenones.³⁰ Moore and co-workers have shown this to be an expedient route for the preparation of phenols.³¹ Starting from squaric acid (**31**), methylation with diazomethane gave dimethyl squarate (Scheme 8).³² Treatment with *iso*-propyl magnesium bromide at –78 °C followed by hydrolysis produced cyclobutenedione **32** in 89% yield. The thermal rearrangement precursor was formed by addition of 2-lithiopropene to a solution of **32** in THF

at -78°C followed by trapping with methyl triflate. The mixture was then heated at reflux in hexane to give phenol **33** as the only isolable product in 45% yield. The addition of the organolithium reagent to dione **32** was completely regioselective and resulted in the formation of only one of the two possible regiomer phenols. The identification of phenol **33** was confirmed by NMR spectroscopy studies and is consistent with reports made elsewhere.³¹

Prior to elaboration of the 2-*H* position of phenol **33**, protection of the phenolic hydroxy group was carried out using sodium hydride/methyl triflate in 90% yield. Our initial attempts to introduce functionality into this position employing lithiation chemistry were unsuccessful. *ortho*-Lithiation under a range of conditions (*n*-BuLi, *n*-BuLi/TMEDA, *s*-BuLi/TMEDA) at a variety of temperatures followed by quenching with methyl chloroformate resulted only in recovered starting material. We next turned our attention to a mild bromination protocol developed by Kulkarni and co-workers.³³ They reported on the use of KBr/oxone® as a facile method for the bromination of a variety of aromatic compounds. In our hands using methanol as the solvent, the brominated derivative **35** was obtained in 67% yield. Both lithium-halogen exchange and carbonyl insertion chemistry were examined without success. We suspect that steric crowding around the carbon atom bearing the bromo atom is responsible for the difficulty in converting the aryl bromide into the corresponding carbomethoxy group.

Despite the congestion about the aromatic scaffold, we decided to develop another approach towards the synthesis of carboxylic acid **30**. Introduction of a primary alcohol in place of the methyl group should result in a better directing group for the subsequent *ortho*-lithiation reaction since an electron lone pair on the oxygen atom would coordinate to the lithium ion thereby enhancing the stability of the complex. The cyclobutanone/thermolysis chemistry still appeared worth carrying out since the use of lithiopropynes had been reported earlier.³¹ With this in mind, the tetrahydropyranyl protected propargyl alcohol **37** was treated with *n*-BuLi followed by reaction with cyclobutenedione **32** in a manner analogous to that described above, Scheme 9. Disappointingly, the expected phenol **39** could not be observed in the crude reaction mixture after heating in toluene. Therefore, we embarked on an alternative strategy for the synthesis of the related alcohol **44** starting from 1,2,4-trimethoxybenzene (see Scheme 10). Treatment of this compound with *n*-BuLi at -78°C resulted in the selective lithiation at the 3-position of the aromatic ring by virtue of lithiate coordination with the adjacent methoxy groups. Quenching with methyl chloroformate followed by methyl Grignard addition afforded tertiary alcohol **41** which was subsequently dehydrated and hydrogenated in a one pot procedure to give **42**.³⁴ This compound was then subjected to a regiospecific bromination by following a procedure described by Carreño³⁵ which resulted in the formation of compound **43** in excellent yield. Next, lithium-halogen exchange followed by reaction with *N,N'*-dimethyl formamide provided the expected aldehyde which was readily reduced with sodium borohydride to furnish alcohol **44** in 78% over the final two steps.

At this point we anticipated that lithiation at the remaining aromatic ring position would provide a nucleophilic site which could be subsequently treated with a suitable electrophile to supply ester **46** (see Scheme 11). Unfortunately, this could not be borne out in practice as the steric congestion around the local environment proved prohibitory.

Consequently, we turned our attention to still another approach designed to alleviate the steric crowding by preparing a penta-substituted aromatic ring with the expectation that the final substituent could be introduced by an oxidation reaction to give the desired *para*-quinone (see Scheme 12).

Starting from 2,3-dimethoxybenzoic acid (**49**), methyl esterification followed by Grignard addition of methyl magnesium bromide delivered alcohol **50** in 89% for the two step sequence (Scheme 13). Once again, the dehydration-hydrogenation protocol proceeded uneventfully to

give isopropyl veratrole **51** in 65% yield. This compound was subsequently treated with *n*-BuLi followed by reaction with *N,N'*-dimethylformamide to give aldehyde **52** in 82% yield.^{36,37}

Further functionalization of the aromatic framework was not possible using either Comins³⁸ lithiation chemistry or by electrophilic substitution chemistry. Therefore, the aldehydic carbonyl group was reduced with sodium borohydride and protected as its MOM ether derivative **53**. Lithiation of **53** returned only starting material and so instead, **53** was exposed to *N*-bromosuccinimide which successfully delivered the bromo compound **54**, albeit as a mixture of regioisomers and with the desired aryl bromide **54** being formed in only 24% yield. The two regioisomeric bromides could be distinguished from the respective nOe's of the aromatic proton. A minor improvement in the regiomer ratio could be obtained by changing the reaction conditions, but at the expense of a lower overall reaction yield. The rather low yield of the desired bromide led to the abandonment of this particular route. Further approaches toward the necessary aromatic framework are currently under investigation.

In conclusion, the Rh(II)-catalyzed intramolecular dipolarcycloaddition described herein allows for a facile access to the icetexane core of komaroviquinone. Completion of the synthesis of the natural product requires the preparation of a highly substituted aromatic system which has thus far proved elusive. Efforts are currently underway to address this issue in order to enable the completion of the synthesis.

3. Experimental

3.1 General

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry argon. All solids were recrystallized from ethyl acetate/hexane for analytical data.

α -Methoxycarbonyl- α -diazoacetophenone (11)—To a 5.0 g (28 mmol) sample of phthalic acid monomethyl ester was added 24 mL (0.28 mol) of thionyl chloride at rt. The mixture was stirred at 25 °C for 3 h and then the excess thionyl chloride was removed under reduced pressure. The crude residue was dissolved in 200 mL of Et₂O and an ethereal solution of diazomethane, prepared by the addition of 32 g (0.15 mol) of diazald (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) in 60 mL of Et₂O to 7.7 g (0.14 mol) of potassium hydroxide in 12 mL of water and 37 mL of ethanol, was added to the above acid chloride solution at 0 °C. After the addition was complete, the reaction mixture was allowed to warm to room temperature. Excess silica gel was added, the mixture was stirred for 5 min, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 40% EtOAc/hexane mixture as the eluent to provide 5.1 g (99%) of the titled compound as a yellow solid: mp 61–62 °C (lit³⁹ mp 62–63 °C); IR (neat) 3094, 2100, 1726, 1619 and 1352 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 3.88 (s, 3H), 5.58 (brs, 1H), 7.39 (dd, 1H, *J* = 7.2 and 2.0 Hz), 7.44–7.52 (m, 2H) and 7.80 (brs, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 52.5, 56.1, 126.8, 129.8, 130.3, 130.8, 131.5, 139.6, 167.4 and 188.7.

Methyl 2-(3-oxo-oct-7-enoyl)benzoate (12)—To a solution containing 0.09 g (0.88 mmol) of hex-5-enal and 0.01 g of SnCl₂ (0.1 mmol) in 1 mL of CH₂Cl₂ was added 0.15 g (0.74 mmol) of the above diazo ketone **11** in 2 mL of CH₂Cl₂. The mixture was stirred at room temperature for 1 h, diluted with CH₂Cl₂ and washed with water. The organic phase was dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 30% EtOAc/hexane mixture as the eluent to provide 0.04 g (41%) of the titled compound as a yellow oil which exists

predominantly in the enol form: IR (neat) 1734, 1727, 1545, 1396, 1292 and 1063 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.81–1.90 (m, 2H), 2.15 (q, 2H, $J = 6.7$ Hz), 2.62 (q, 2H, $J = 7.6$ Hz), 3.87 (s, 3H), 5.00–5.08 (m, 2H), 5.70–5.82 (m, 1H), 6.28 (s, 1H), 7.57–7.66 (m, 3H) and 7.82–7.86 (m, 1H), and 15.6 (bs, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 24.8, 32.9, 37.2, 53.0, 100.2, 116.3, 129.0, 130.4, 131.4, 132.2, 132.8, 133.3, 136.9, 167.2, 186.4 and 196.8; HRMS Calcd for $[(\text{C}_{16}\text{H}_{18}\text{O}_4) + \text{H}^+]$: 275.1278. Found: 275.1274.

Methyl 2-(2-diazo-3-oxo-oct-7-enoyl)benzoate (13)—To a solution containing 0.09 g (0.33 mmol) of the above 1,3-dione **12** in 3.0 mL of CH_3CN was added 0.14 mL (0.98 mmol) of Et_3N and 0.07 g (0.39 mmol) of *p*-nitrobenzenesulfonyl azide⁴⁰ at room temperature. The mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 0.1 g (98%) of the titled compound as a pale yellow oil: IR (neat) 2120, 1721, 1656 and 1195 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.71–1.77 (m, 2H), 2.09 (q, 2H, $J = 6.7$ Hz), 2.83 (brs, 2H), 3.87 (s, 3H), 4.95 (d, 1H, $J = 10.5$ Hz), 5.00 (d, 1H, $J = 17.1$ Hz), 5.71–5.81 (m, 1H), 7.34 (d, 1H, $J = 7.6$ Hz), 7.54 (td, 1H, $J = 7.6$ and 1.0 Hz), 7.62 (td, 1H, $J = 7.6$ and 1.0 Hz) and 8.03 (d, 1H, $J = 7.6$ Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ 23.1, 33.0, 40.2, 52.6, 85.8, 115.2, 126.3, 127.6, 130.1, 130.6, 132.9, 137.6, 140.5, 165.8, 186.4 and 191.8.

8-Methoxy-12-oxatricyclo[6.3.1.0.^{0,0}]octahydrodibenzo-[a,d]-4,11-dione (16)—

To a solution containing 0.13 g (0.43 mmol) of the above diazo-dione in 5 mL of benzene was added 0.01 g (0.02 mmol) of $\text{Rh}_2(\text{OAc})_4$ at room temperature. The mixture was heated for 30 min at 80 °C, cooled to room temperature and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 50% EtOAc/hexane mixture as the eluent to provide 0.03 g (75%) of the titled compound as a pale yellow solid: mp 165–166 °C; IR (neat) 3025, 2910, 1726, 1693, 1600, 1305 and 1281 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.39–1.52 (m, 1H), 1.92–2.12 (m, 4H), 2.32 (dd, 1H, $J = 12.4$ and 5.6 Hz), 2.51–2.63 (m, 2H), 2.84–2.95 (m, 1H), 3.50 (s, 3H), 7.42–7.50 (m, 2H), 7.63 (td, 1H, $J = 7.3$ and 1.3 Hz) and 7.99 (dd, 1H, $J = 8.3$ and 1.3 Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ 21.7, 28.4, 37.2, 41.9, 42.0, 52.8, 90.1, 106.5, 123.5, 127.5, 128.9, 129.9, 134.5, 144.7, 193.0 and 205.8; Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_4$: C, 70.56; H, 5.93. Found: C, 70.13; H, 5.74.

6a-Hex-5-enoyl-1a-methoxy-1a,6a-dihydro-1-oxa-cyclopropa[a]inden-6-one (15)—

To a solution containing 0.1 g (0.33 mmol) of the above diazo-dione in 3 mL of benzene was added 0.01 g (0.02 mmol) of $\text{Rh}_2(\text{OAc})_4$ at room temperature. The mixture was stirred at room temperature for 30 min, the solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography to provide 0.054 g (71%) of the titled compound as a pale yellow solid, mp 113–115 °C; IR (neat) 1737, 1724, 1541, 1290 and 1061 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.67–1.87 (m, 2H), 2.05–2.20 (m, 2H), 2.80–2.99 (m, 2H), 3.42 (s, 3H), 4.94–5.08 (m, 2H), 5.76–5.88 (m, 1H), 7.28 (td, 1H, $J = 7.9$ and 1.3 Hz), 7.41 (ddd, 2H, $J = 15.9$, 7.9 and 1.0 Hz) and 7.58 (td, 1H, $J = 7.9$ and 1.3 Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ 23.0, 33.0, 40.3, 51.9, 90.3, 99.5, 115.0, 125.6, 127.2, 129.5, 130.1, 134.7, 137.4, 138.3, 187.0 and 197.8; Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_4$: C, 70.56; H, 5.93. Found: C, 69.96; H, 5.95.

In addition, 0.009 g (10%) of cycloadduct **16** was also isolated from the chromatographic column. Heating a sample of epoxide **15** in benzene at 100 °C for 2 h afforded cycloadduct **16** in 78% yield.

8-Hydroxy-12-oxa-tricyclo[6.3.1.0.^{0,0}]octahydrodibenzo-[a,d]-4,11-dione (17)—

To a solution containing 0.1 g of cycloadduct **16** in a 1:2:1-mixture of THF/MeOH/ H_2O (2 mL) was added 0.5 mL of conc. HCl. The mixture was heated at reflux for 6 h, cooled to rt and

extracted with EtOAc. The combined organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the crude mixture was purified by flash silica gel column chromatography using a 50% EtOAc/hexane mixture as the eluent to provide 0.08 g (84%) of the titled compound as a yellow solid: mp 156–158 °C; IR (KBr) 3425, 2939, 1721, 1692 and 1289 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.32 (qd, 1H, *J* = 12.7 and 4.8 Hz), 1.86–2.06 (m, 3H), 1.96 (dd, 1H, *J* = 12.0 and 6.7 Hz), 2.32 (dd, 1H, *J* = 12.0 and 8.6 Hz), 2.38–2.47 (m, 1H), 2.53 (ddd, 1H, *J* = 16.8, 9.5 and 6.0 Hz), 2.85 (ddd, 1H, *J* = 16.8, 11.1 and 4.8 Hz), 5.79 (s, 1H), 7.28 (td, 1H, *J* = 7.6 and 1.0 Hz) and 7.43–7.55 (m, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 21.8, 28.1, 36.7, 41.9, 43.2, 90.6, 103.6, 123.1, 127.1, 127.5, 128.4, 134.8, 146.7, 192.6 and 207.2; Anal. Calcd. for C₁₅H₁₄O₄: C, 69.74; H, 5.47. Found: C, 69.70; H, 5.34.

Ethyl 5-hydroxy-2,2-dimethylpentanoate (19)—To a stirred solution of 24 mL (12.0 mmol) of 9-BBN (0.5 M in THF) was added a solution of 2.0 g (12.0 mmol) of 2,2-dimethylpent-4-enoic acid ethyl ester⁴¹ in 6 mL of THF at rt. After stirring for 2 h, the reaction was cooled to 0 °C and 8 mL of ethanol, 2.4 mL of 6 M aqueous NaOH solution, and 4.8 mL of 30% aqueous H₂O₂ were added consecutively. The mixture was heated at 50 °C for 1 h, cooled to room temperature and extracted with EtOAc. The combined organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 8% EtOAc/hexane mixture as the eluent to provide 1.2 g (55%) of the titled compound as a clear oil^{15,42}; IR (neat) 3437, 2971 and 1634 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.15 (s, 6H), 1.22 (t, 3H, *J* = 7.2 Hz), 1.50–1.65 (m, 4H), 3.60 (brt, 2H, *J* = 6.0 Hz) and 4.15 (q, 2H, *J* = 7.2 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 13.9, 24.8, 27.9, 36.4, 41.6, 60.1, 62.4 and 177.9.

Ethyl 5-(*tert*-butyldimethylsilyloxy)-2,2-dimethylpentanoate (20)—To a solution containing 0.75 g (4.0 mmol) of the above alcohol **19** in 2 mL of DMF was added 0.77 g (10.7 mmol) of imidazole and a crystal of 4-dimethylaminopyridine. The mixture was cooled to 0 °C for 15 min and then 0.77 g (5.0 mmol) of *tert*-butyldimethylsilyl chloride was added in one portion. The reaction was stirred for 2 h, quenched with H₂O and extracted with Et₂O. The combined organic layer was dried over MgSO₄ and the crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 1.0 g (95%) of the titled compound as a clear oil^{15,42}; IR (neat) 2650, 2925, 2889, 2848 and 1726 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.05 (s, 6H), 0.84 (s, 9H), 1.12 (s, 6H), 1.20 (t, 3H, *J* = 7.4 Hz), 1.40–1.47 (m, 2H), 1.49–1.54 (m, 2H), 3.54 (t, 2H, *J* = 6.2 Hz) and 4.08 (q, 2H, *J* = 7.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ -5.3, 14.2, 18.3, 25.1, 25.9, 28.4, 36.8, 41.8, 60.2, 63.4 and 177.9.

5-(*tert*-Butyldimethylsilyloxy)-2,2-dimethylpentanal (21)—To a suspension of 0.13 g (3.0 mmol) of lithium aluminum hydride in 25 mL of Et₂O at 0 °C was added 0.99 g (3.0 mmol) of the above ester **20** in 10 mL of Et₂O. After stirring for 30 min at 0 °C, the reaction was quenched by the slow addition of 30 mL of H₂O. The aqueous layer was extracted with Et₂O, the solvent was dried and then removed under reduced pressure and the crude alcohol was taken up in 15 mL of CH₂Cl₂. This solution was added to a stirred solution of 1.1 g (4.5 mmol) of pyridinium chlorochromate in 10 mL of CH₂Cl₂ at room temperature. The mixture was stirred overnight, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 0.59 g (70%) of the titled compound as a clear oil^{15,42}; IR (neat) 2960, 2925, 1726, 1701, 1470 and 1255 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.04 (s, 6H), 0.85 (s, 9H), 1.15 (s, 6H), 1.35–1.50 (m, 4H), 3.60 (t, 2H, *J* = 6.0 Hz) and 9.40 (s, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ -5.4, 18.3, 21.2, 25.9, 27.6, 33.3, 45.4, 63.1 and 206.2.

tert-Butyl-4,4-dimethylhex-5-enyloxyl dimethylsilane (22)—To a stirred solution of 0.48 g (1.2 mmol) of methyltriphenylphosphonium iodide in 5 mL of THF at 0 °C was slowly added 0.6 mL (1.2 mmol) of *n*-BuLi (2.1 M in THF). After stirring for 30 min, the solution was warmed to rt and was stirred for an additional 1 h. The mixture was then cooled to 0 °C and a solution of 0.29 g (1.1 mmol) of the above aldehyde **21** in 2 mL of THF was added dropwise and the mixture was allowed to warm to rt and was stirred overnight. The reaction mixture was quenched with H₂O and extracted with Et₂O. The combined organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 6% EtOAc/hexane mixture as the eluent to provide 0.23 g (80%) of the titled compound as a clear oil^{15,42}: IR (neat) 3083, 2960, 2930, 2852, 1634 and 1096 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.04 (s, 6H), 0.08 (s, 9H), 0.99 (s, 6H), 1.23–1.29 (m, 2H), 1.40–1.48 (m, 2H), 3.47 (t, 2H, *J* = 6.8 Hz), 4.88 (dd, 1H, *J* = 4.8 and 1.2 Hz); 4.92 (q, 1H, *J* = 1.2 Hz) and 5.76 (dd, 1H, *J* = 17.6 and 10.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ -5.3, 18.3, 26.0, 26.7, 28.1, 36.1, 38.6, 63.9, 110.3 and 148.4.

4,4-Dimethylhex-5-enal (23)—To a solution containing 0.45 g (1.9 mmol) of the above alkene **22** in 8 mL of THF was added 2.3 mL (2.3 mmol) of *tetra*-butyl ammonium fluoride (1.0 M in THF) at 0 °C. The reaction mixture was stirred for 2 h after which time a 1:1-mixture of H₂O and Et₂O was added to the solution. The aqueous layer was extracted with Et₂O and the combined organic layer was dried over MgSO₄. The solvent was removed under reduced pressure and the crude alcohol was redissolved in 3 mL of CH₂Cl₂. The mixture was added to a stirred solution of 0.6 g (2.7 mmol) of pyridinium chlorochromate in 2 mL of CH₂Cl₂ at room temperature. The solution was stirred overnight, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 6% EtOAc/hexane mixture as the eluent to provide 0.19 g (80%) of the titled compound^{15,42} as a clear oil: IR (neat) 3084, 2955, 2852, 2807, 2709, 1726 and 1639 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.96 (s, 6H), 1.60 (t, 2H, *J* = 8.0 Hz), 2.34 (td, 2H, *J* = 8.0 and 1.6 Hz), 4.91 (dd, 1H, *J* = 17.2 and 1.2 Hz), 4.95 (dd, 1H, *J* = 10.8 and 1.2 Hz); 5.68 (dd, 1H, *J* = 17.2 and 10.8 Hz) and 9.74 (t, 1H, *J* = 1.6 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 26.5, 33.9, 36.0; 39.8; 111.6, 147.0 and 202.8.

Methyl 2-(6,6-dimethyl-3-oxo-oct-7-enyl)benzoate (24)—To a solution containing 0.34 g (1.6 mmol) of diazo ketone **11** and 0.03 g (0.16 mmol) of anhydrous SnCl₂ in 4 mL of CH₂Cl₂ was added a solution of 0.25 g (1.9 mmol) of the above aldehyde **23** in 4 mL of CH₂Cl₂ and the mixture was stirred at rt for 18 h. The solution was quenched with H₂O and extracted with Et₂O. The combined organic layer was dried over MgSO₄ and the crude residue was purified by flash silica gel column chromatography using a 20% EtOAc/hexane mixture as the eluent to provide 1.0 g (20%) of the titled compound as a clear oil¹⁵ which exists primarily in the enol form: IR (neat) 3500, 1721, 1701, 1588 and 1265 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.02 (s, 6H), 1.62–1.70 (m, 2H), 2.28–2.35 (m, 2H), 3.83 (s, 3H), 4.90–5.00 (m, 2H), 5.75 (dd, 1H, *J* = 17.6 and 10.8 Hz), 5.84 (s, 1H) 7.47–7.53 (m, 3H) and 7.72–7.77 (m, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 26.5, 34.0, 36.4, 38.0, 52.5, 99.0, 111.5, 127.9, 129.5, 130.5, 131.0, 131.1, 137.5, 147.1, 168.4, 188.4 and 194.4; HRMS Calcd for [(C₁₈H₂₂O₄) + H⁺] : 303.1591. Found: 303.1591.

Methyl 2-(2-diazo-6,6-dimethyl-3-oxooct-7-enyl)benzoate(25)—To a solution containing 1.0 g (0.32 mmol) of the above diketo-ester **24** and 0.11 g (0.44 mmol) of *p*-nitrobenzenesulfonyl azide⁴⁰ in 3 mL of CH₃CN at 0 °C was added 0.09 g (0.65 mmol) of Et₃N. The reaction mixture was stirred for 3 h, the solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography using a 50% EtOAc/hexane mixture as the eluent to provide 0.4 g (38%) of the titled compound as a clear oil: IR (neat) 3078 , 2955, 2120, 1716, 1650 and 1280 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ

0.95 (s, 6H), 1.55–1.65 (m, 2H), 2.65 (brs, 2H), 3.85 (s, 3H), 4.87 (dd, 1H, $J = 17.2$ and 1.2 Hz), 5.69 (dd, 1H, $J = 17.2$ and 10.8 Hz), 7.33 (dd, 1H, $J = 7.6$ and 0.8 Hz), 7.53 (td, 1H, 8.0 and 0.8 Hz), 7.62 (td, 1H, $J = 8.0$ and 1.6 Hz) and 8.03 (dd, 1H, $J = 7.6$ and 0.8 Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ 26.5, 36.0, 36.2, 36.9, 52.6, 86.1, 111.3, 126.4, 127.7, 130.1, 130.6, 133.0, 140.7, 147.2, 1658, 186.5 and 192.2.

1,1-Dimethyl-8-methoxy-12-oxa-tricyclo[6.3.1.0.^{0,0}]-octahydrodibenzo

[a,d]-4,11-dione (26)—To a solution containing 0.04 g (0.12 mmol) of diazo-dione **25** in 1 mL of benzene was added 0.004 g (0.01 mmol) of $\text{Rh}_2(\text{OAc})_4$. The mixture was heated at 80 °C for 18 h, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 6% EtOAc/hexane mixture as the eluent to provide 0.012 g (92%) of the titled compound as a clear oil; IR (neat) 2955, 1721, 1690, and 1270 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 0.93 (s, 3H), 0.95 (s, 3H), 1.81 (ddd, 1H, $J = 14.0$, 9.2 and 1.6 Hz), 1.93 (dt, 1H, $J = 14.0$ and 9.6 Hz), 2.03–2.22 (m, 2H), 2.40 (t, 1H, $J = 8.8$ Hz), 2.65 (dt, 1H, $J = 18.8$ and 9.6 Hz), 2.81 (ddd, 1H, $J = 19.2$, 9.6 and 1.6 Hz), 3.49 (s, 3H), 7.48 (d, 2H, $J = 7.6$ Hz), 7.63 (td, 1H, $J = 7.6$ and 1.2 Hz) and 7.98 (dd, 1H, $J = 8.4$ and 1.2 Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ 20.3, 29.8, 32.9, 35.7, 36.1, 36.5, 51.5, 52.7, 88.7, 106.5, 123.6, 127.5, 128.9, 129.6, 134.4, 144.6, 193.1 and 206.7; HRMS (FAB) Calcd for $[(\text{C}_{18}\text{H}_{20}\text{O}_4)+\text{Li}^+]$: 300.1361. Found 300.1373.

2-Isopropyl-1,3,4-trimethoxy-5-methyl-benzene (34)—To a solution of 1.2 g (5.7 mmol) sample of the penta-substituted arene **33**³¹ in 30 mL of THF at –78 °C was added 1.52 g (23 mmol) of NaH (60% in mineral oil) in one portion. The mixture was warmed to 0 °C and stirred for 30 min. At the end of this time, the solution was cooled to –78 °C, and 0.97 mL (8.6 mmol) of MeOTf was added dropwise. The solution was warmed to rt, stirred for an additional 2 h, and then quenched with H_2O and extracted with Et_2O . The combined organic layer was dried over Na_2SO_4 and the crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 1.15 g (90%) of the titled compound as a pale yellow solid: mp 26–27 °C; IR (neat) 1582, 1455, 1403, 1231, 1135, 1073 and 840 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.29 (d, 6H, $J = 7.2$ Hz), 2.24 (s, 3H), 3.47 (sept, 1H, $J = 7.2$ Hz), 3.76 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 6.20 (s, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 15.9, 21.3, 25.0, 55.6, 60.1, 60.9, 108.5, 127.9, 128.9, 145.5, 151.6, and 154.2; HRMS Calcd for $[(\text{C}_{13}\text{H}_{20}\text{O}_3) + \text{H}^+]$: 225.1491. Found: 225.1487.

1-Bromo-3-isopropyl-2,4,5-trimethoxy-6-methylbenzene(35)—To a solution of 0.09 g (0.4 mmol) of the above penta-substituted arene **34** in 4 mL of THF at rt was added 0.05 g (0.44 mmol) of KBr followed by 0.27 g (0.44 mmol) of oxone®. The reaction mixture was allowed to stir at rt for 1 h. The mixture was then passed through a filter funnel and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 0.08 g (67%) of the titled compound as a yellow oil: IR (neat) 2935, 1454, 1398, 1231, 1120 and 1030 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.32 (d, 6H, $J = 7.2$ Hz), 2.30 (s, 3H), 3.43 (sept, 1H, $J = 7.2$ Hz), 3.72 (s, 3H), 3.73 (s, 3H), and 3.80 (s, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ 16.3, 22.1, 26.7, 60.1, 60.5, 61.4, 114.7, 130.5, 133.6, 148.5, 151.0, and 151.9.

2-Isopropyl-3,4-dimethoxy-4-[3-(tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-cyclobut-2-enone (38)—To a solution of 0.25 mL (1.8 mmol) of 2-[(propyl-2-yn-1yl)oxy]-tetrahydropyran in 3 mL of THF at –78 °C was added 0.84 mL (2.1 mmol) of *n*-BuLi (2.5 M in hexane) dropwise. The solution was stirred for 1 h at –78 °C and transferred to a –78 °C solution of 0.25 g (1.6 mmol) of 3-isopropyl-4-methoxy-cyclobut-3-ene-1,2-dione (**31**)³¹ in 3 mL of THF *via* cannula, followed by the addition of 0.24 mL (2.1 mmol) of MeOTf. The solution was warmed to 0 °C and was stirred for additional 30 min. After quenching with

aqueous NH_4Cl , the solution was extracted with Et_2O . The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by silica gel flash chromatography using a 10% EtOAc /hexane mixture as the eluent to provide 0.14 g (29%) of the titled compound as an orange oil: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.07 (d, 6H, $J = 7.2$ Hz), 1.40–1.80 (m, 6H), 2.43 (sept, 1H, $J = 7.2$ Hz), 3.50 (s, 3H), 3.45–3.50 (m, 1H), 3.72–3.79 (m, 1H), 4.05 (s, 3H), 4.30 (dd, 2H, $J = 3.0$ and 1.2 Hz), and 4.72 (t, 1H, $J = 2.0$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 18.8, 19.9, 23.9, 25.2, 30.0, 54.1, 54.2, 59.4, 61.8, 78.3, 87.6, 96.8, 135.6, 177.4 and 184.3.

(3-Isopropyl-2,4,5-trimethoxy-phenyl)-methanol (44)—To a solution of 4.0 g (13.8 mmol) of 1-bromo-3-isopropyl-2,4,5-trimethoxybenzene (**43**)^{34,35} in 55 mL of THF at -78°C was added 6.1 mL (15.2 mmol) of *n*-BuLi (2.5 M in hexane) dropwise. The solution was stirred for 1 h, then 1.3 mL (17.3 mmol) of DMF was slowly added to the reaction flask. After stirring the mixture at -78°C for 2 h, aqueous NH_4Cl was added. The mixture was extracted with EtOAc , dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was then purified by flash silica gel chromatography using a 20% EtOAc /hexane mixture as the eluent to provide 2.9 g (87%) of 3-isopropyl-2,4,5-trimethoxybenzaldehyde as a white solid: mp $45\text{--}47^\circ\text{C}$; IR (neat) 2955, 2842, 1685, 1583, and 1083 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.33 (d, 6H, $J = 7.1$ Hz), 3.43 (sept, 1H, $J = 7.1$ Hz), 3.81 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 7.22 (s, 1H), and 10.24 (s, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 21.6, 25.4, 55.8, 60.8, 65.4, 107.7, 124.4, 135.4, 150.0, 154.8, 156.8 and 189.1.

To a solution of 2.6 g (10.9 mmol) of the above aldehyde in MeOH at 0°C was added 0.5 g (13 mmol) of NaBH_4 in portions. The mixture was stirred for 1 h at 0°C , and then water was added. The MeOH was removed under reduced pressure and the residue was extracted with EtOAc . The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel chromatography using a 25% EtOAc /hexane mixture as the eluent to provide 2.4 g (90%) of the titled compound as a yellow oil: IR (neat) 3416, 2955, 1598, 1480, 1224, 1107 and 1040 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.35 (d, 6H, $J = 7.1$ Hz), 2.13 (t, 1H, $J = 5.7$ Hz), 3.40 (sept, 1H, $J = 7.1$ Hz), 3.71 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 4.68 (d, 2H, $J = 5.7$ Hz), and 6.79 (s, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 21.8, 25.8, 55.7, 60.6, 61.0, 62.3, 110.0, 128.7, 135.0, 148.2, 149.3 and 149.6; HRMS Calcd for $[(\text{C}_{13}\text{H}_{20}\text{O}_4) + \text{H}^+]$: 241.1440. Found: 241.1438.

2-(2,3-Dimethoxyphenyl)propan-2-ol (50)—To a solution of 9.1 g (50 mmol) of 2,3-dimethoxybenzoic acid in 100 mL methanol was slowly added 6.3 mL (50 mmol) of chlorotrimethylsilane at 0°C and the mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure to afford 9.3 g (95%) of the titled ester as a white solid; mp $47\text{--}48^\circ\text{C}$ (Et_2O) [lit. 47°C]⁴³; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 3.88 (s, 3H), 3.91 (s, 6H), 7.05–7.11 (m, 2H), and 7.31–7.33 (m, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 52.4, 56.3, 61.7, 116.0, 122.4, 124.0, 126.3, 149.3, 153.4 and 167.0.

To a solution of 9.3 g (47.5 mmol) of the above ester in 100 mL of THF at 0°C was slowly added 50 mL (3.0 M) of methyl magnesium bromide. The solution was heated at reflux for 6 h. After cooling to 0°C , the reaction mixture was quenched by the cautious addition of 50 mL of 1M HCl and was then extracted with ether. The organic phase was washed successively with water and brine, dried, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography using a 20% EtOAc /hexane mixture as the eluent to provide 8.75 g (94%) of the titled compound³⁶ as a clear oil; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.61 (s, 6H), 3.88 (s, 3H), 4.00 (s, 3H), 4.30 (s, 1H), 6.86 (dd, 1H, $J = 8.0$ and 2.0 Hz), 6.94 (dd, 1H, $J = 8.0$ and 2.0 Hz), and 7.02 (t, 1H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 31.0, 56.0, 61.2, 73.0, 111.8, 118.2, 123.9, 141.4, 147.0 and 152.9.

1-Isopropyl-2,3-dimethoxy-4-((methoxymethoxy) methyl)benzene (53)—To a solution of 2.2 g (10.1 mmol) of (4-isopropyl-2,3-dimethoxyphenyl)methanol⁴⁴ in 50 mL of CH₂Cl₂ was added 5.3 mL (30 mmol) of Hünig's base. To this mixture was slowly added 1.5 mL (20 mmol) of chloromethyl methyl ether at 0 °C and the reaction mixture was allowed to warm to room temperature and was stirred for 15 h. The reaction was then quenched by the addition of a saturated NH₄Cl solution and was extracted with CH₂Cl₂. The organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford a pale yellow residue. Purification by flash silica gel column chromatography using a 90% EtOAc/hexane mixture as the eluent afforded 1.3 g (90%) of the titled compound as a clear liquid; IR (thin film) 2961 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.22 (d, 6H, *J* = 7.0 Hz), 3.33 (sept, 1H, *J* = 7.0 Hz), 3.44 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 4.60 (s, 2H), 4.74 (s, 2H), 6.98 (d, 1H, *J* = 8.0 Hz), and 7.09 (d, 1H, *J* = 8.0 Hz); ¹³C-NMR (100 MHz) 23.7, 27.0, 55.5, 60.9, 61.0, 64.5, 96.0, 121.5, 125.0, 129.4, 143.2, 150.5 and 151.5; HRMS Calcd for [(C₁₄H₂₂O₄) + H⁺]: 255.1596. Found: 255.1598.

1-Bromo-5-isopropyl-3,4-dimethoxy-2-((methoxymethoxy)methyl)benzene (54)—To a stirred solution of 0.5 g (2.0 mmol) of 1-isopropyl-2,3-dimethoxy-4-((methoxymethoxy) methyl)benzene (**53**) in 5 mL of DMF was added 0.35 g (2.0 mmol) of *N*-bromosuccinimide at room temperature. After stirring for 12 h at rt, the reaction mixture was quenched by the addition of NaHCO₃ and was extracted with Et₂O. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography using a 66% CH₂Cl₂/hexane mixture as the eluent to afford 0.16 g (24%) of the titled compound as a clear oil; IR (thin film) 2962 cm⁻¹; ¹H-NMR (600 MHz, CDCl₃) δ 1.29 (d, 6H, *J* = 6.7 Hz), 3.28 (sept, 1H, *J* = 6.7 Hz), 3.47 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 4.70 (s, 2H), 4.77 (s, 2H), and 7.21 (s, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 23.4, 27.1, 55.7, 60.8, 61.5, 64.3, 96.6, 120.0, 126.0, 129.1, 145.0, 150.2 and 153.4.

Acknowledgements

We greatly appreciate the financial support provided by the National Science Foundation (CHE-0450779). We thank Dr. Jerremey Willis for some experimental assistance.

References

1. Vvedenski, AI. *Editio Academiae Scientiarum UzSSR*. Vol. Vol 5. Tashkent: 1961. Flora Uzbekistana; p. 313
2. Uchiyama N, Kiuchi F, Ito M, Honda G, Takeda Y, Khodzhimatov OK, Ashurmetov OA. *J. Nat. Prod* 2003;66:128. [PubMed: 12542361]
3. Bastien, JW. *The Kiss of Death, Chagas' Disease in the Americas*. Salt Lake City: The University of Utah Press; 1998.
4. Uchiyama N, Ito M, Kiuchi F, Honda G, Takeda Y, Khodzhimatov OK, Ashurmetov OA. *Tetrahedron Lett* 2004;45:531.
5. (a) Matsumoto T, Imai S, Yoshinari T, Matsuno S. *Bull. Chem. Soc. Jpn* 1986;59:3103. (b) Kametani T, Kondoh H, Tsubuki M, Honda T. *J. Chem. Soc., Perkin Trans. 1* 1990:5. (c) Majetich G, Hicks R, Zhang Y, Tian X, Feltman TL, Fang J, Duncan S Jr. *J. Org. Chem* 1996;61:8169. [PubMed: 11667805]
6. Deb S, Bhattacharjee G, Ghatak UR. *J. Chem. Soc., Perkin Trans. 1* 1990:1453.
7. (a) Koft ER. *Tetrahedron* 1987;43:5775. (b) Majetich G, Zhang Y, Feltman TL, Duncan S Jr. *Tetrahedron Lett* 1993;34:445.
8. Ghosh AK, Ray C, Ghatak UR. *Tetrahedron Lett* 1992;33:655.
9. Sengupta S, Drew MGB, Mukhopadhyay R, Achari B, Banerjee AK. *J. Org. Chem* 2005;70:7694. [PubMed: 16149801]
10. Dounay AB, Overman LE. *Chem. Rev* 2003;103:2945. [PubMed: 12914487]

11. (a) Padwa A, Carter SP, Nimmesgern H. *J. Org. Chem* 1986;51:1157. (b) Padwa A, Carter SP, Nimmesgern H, Stull PD. *J. Am. Chem. Soc* 1988;110:2894.
12. (a) Padwa A, Fryxell GE, Zhi L. *J. Org. Chem* 1988;53:2875. (b) Padwa A, Fryxell GE, Zhi L. *J. Am. Chem. Soc* 1990;112:3100.
13. (a) Padwa A, Hornbuckle SF. *Chem. Rev* 1991;91:263. (b) Padwa A, Weingarten MD. *Chem. Rev* 1996;96:223. [PubMed: 11848752] (c) Padwa A. *Top. Curr. Chem* 1997;189:121.
14. (a) Padwa A, Sandanayaka VP, Curtis EA. *J. Am. Chem. Soc* 1994;116:2667. (b) Padwa A, Curtis EA, Sandanayaka VP. *J. Org. Chem* 1996;61:73.
15. Padwa A, Boonsombat J, Rashatasakhon P, Willis J. *Org. Lett* 2005;7:3725. [PubMed: 16092860]
16. Milan M, Viktor M, Rudolf K, Dusan I. *Curr. Org. Chem* 2004;8:695.
17. (a) Dhavale DD, Patil PN, Mali RS. *J. Chem. Res. (S)* 1994:152. (b) Balaji BS, Chanda BM. *Tetrahedron* 1998;54:13237. (c) Bandgar BP, Pandit SS, Sadavarte VS. *Green Chem* 2001;3:247. (d) Dudley ME, Morshed MM, Brennan CL, Islam MS, Ahmad MS, Atuu M-R, Branstetter B, Hossain MM. *J. Org. Chem* 2004;69:7599. [PubMed: 15497987] (e) Yadav JS, Reddy BVS, Eeshwaraiah B, Reddy PN. *Tetrahedron* 2005;61:875.
18. Ye T, McKervey MA. *Chem. Rev* 1994;94:1091.
19. Pellicciari R, Fringuelli R, Ceccherelli P, Sisani E. *J. Chem. Soc., Chem. Commun* 1979:959.
20. (a) Holmquist CR, Roskamp EJ. *J. Org. Chem* 1989;54:3258.. see also: (b) Padwa A, Hornbuckle SF, Zhang Z, Zhi L. *J. Org. Chem* 1990;55:5297.
21. (a) Regitz M. *Chem. Ber* 1966;99:3128. (b) Regitz M, Hocker J, Liedhegener A. *Org. Synth* 1973;5:179.
22. Doyle, MP.; McKervey, MA.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*. New York: John Wiley and Sons; 1998.
23. de March P, Huisgen R. *J. Am. Chem. Soc* 1982;104:4952.
24. Doyle MP, Hu W, Timmons DJ. *Org. Lett* 2001;3:933. [PubMed: 11263919]
25. Davies HML, DeMeese J. *Tetrahedron Lett* 2001;42:6803.
26. Muthusamy S, Gunanathan C, Nethaji M. *Synlett* 2004;4:639.
27. Russell AE, Brekan J, Gronenberg L, Doyle MP. *J. Org. Chem* 2004;69:5269. [PubMed: 15287769]
28. Bruice TC, Pandit UK. *J. Am. Chem. Soc* 1960;82:5858.
29. (a) Jung ME, Gervay J. *J. Am. Chem. Soc* 1991;113:224. (b) Jung ME, Trifunovich ID, Lensen N. *Tetrahedron Lett* 1992;33:6719.
30. Danheiser RL, Gee SK. *J. Org. Chem* 1984;49:1674.
31. Tomooka CS, Liu H, Moore HW. *J. Org. Chem* 1996;61:6009.
32. Miles DH, Payne M. *Tetrahedron* 2001;57:5769.
33. Narender N, Srinivasu P, Prasad MR, Kulkarni SJ, Raghavan KV. *Synth. Commun* 2002;32:2313.
34. Carreño MC, García Ruano JL, Toledo MA, Urbano A. *Tetrahedron: Asymmetry* 1997;8:913.
35. Carreño MC, García Ruano JL, Sanz G, Toledo MA, Urbano A. *J. Org. Chem* 1995;60:5328.
36. Majetich G, Liu S. *Synth. Commun* 1993;23:2331.
37. Simmons EM, Sarpong R. *Org. Lett* 2006;8:2883. [PubMed: 16774281]
38. Comins DL. *Synlett* 1992:615.
39. (a) Duggleby PM, Holt G. *J. Chem. Soc* 1962:3579. (b) Udea K, Ibata T, Takebayashi M. *Bull. Chem. Soc. Jpn* 1972:2799. (c) Hodson D, Holt G, Wall DK. *J. Chem. Soc. C* 1970:971.
40. Reagan MT, Nickon A. *J. Am. Chem. Soc* 1968;90:4096.
41. Baldwin JE, Walker JA. *J. Chem. Soc., Chem. Comm* 1973:117.
42. Kossanyi J, Guiard B, Furth B. *Bull. Soc. Chem. Fr* 1974:305.
43. Perkin WH, Robinson R. *J. Chem. Soc., Trans* 1914;105:2376.
44. Majetich G, Hicks R, Zhang Y, Tian X, Feltman TL, Fang J, Duncan S. *J. Org. Chem* 1996;61:8169. [PubMed: 11667805]

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Scheme 6.

Scheme 7.

Scheme 8.

Scheme 9.

Scheme 10.

Scheme 11.

Scheme 12.

Scheme 13.