Published in final edited form as:

Tetrahedron. 2015 September 2; 71(35): 5979–5984. doi:10.1016/j.tet.2015.04.039.

Synthesis of Substituted Tropones by Sequential Rh-Catalyzed [5+2] Cycloaddition and Elimination

Wangze Song^a, Bao-min Xi^{a,b,*}, Ka Yang^a, and Weiping Tang^{a,c,*}

^a School of Pharmacy, University of Wisconsin, 777 Highland Avenue, Madison, WI 53705-2222, USA

^b Guangdong Provincial Key Laboratory of New Drug Screening, School of Pharmaceutical Sciences, Southern Medical University, Guangzhou, Guangdong Province, 510515, P. R. China

^c Department of Chemistry, University of Wisconsin, Madison, WI 53706, USA

Abstract

Highly substituted tropones are prepared from cycloheptatrienes derived from Rh-catalyzed intermolecular [5+2] cycloaddition of 3-acyloxy-1,4-enynes and propargylic alcohols. The intermolecular [5+2] cycloaddition is highly regioselective for a variety of propargylic alcohols. Elimination of the cycloaddition products afforded various substituted tropones.

Graphical Abstract

Keywords

tropones; cycloaddition; rhodium; 1,4-enynes; alkynes

1. Introduction

Tropone **1** and its derivatives such as tropolone **2** are non-benzenoid seven-membered aromatic compounds. The structures of tropones were first proposed 1940s.¹ To date, over two hundred of naturally occurring tropone derivatives have been identified.² They have

* Corresponding author. Tel.: +86-20-6164-8549; fax: +86-20-6164-8533; xibaomin@sohu.com. * Corresponding author. Tel.: +1-608-890-1846; fax: +1-608-262-5345; wtang@pharmacy.wisc.edu.

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Supplementary Data

NMR spectra for all new compounds. Supplementary data associated with this article can be found at <http://dx.doi.org/10.1016/j.tet.xxx>.

broad pharmacological activities ranging from anti-bacterial, anti-fungal, anti-tumor to anti-viral activities.³ Many of them have complex structural architectures, such as tropone-containing natural products hainanolidol **3**⁴ and harringtonolide **4**⁵ (Figure 1).

Numerous methods have been developed for the synthesis of tropones and their derivatives.⁶ Many of them were recently reviewed by us in the context of natural product synthesis.⁷ However, efficient synthesis of highly substituted tropones is a still challenging problem.⁸ For example, only the parent non-substituted tropone was used as the substrate in many of the cycloaddition methods involving tropones including some very recent reports.⁹

We have recently completed the first total synthesis of harringtonolide **4** via a [5+2] cycloaddition¹⁰ of oxidopyrylium ion **6** and alkene (Scheme 1).⁵ Although we were able to assemble the carbon skeleton of **4** very efficiently, it took us a number of steps to remove the extra oxygen bridge in **7** for the formation of tropone in target **4**. Clearly, the development of new types of [5+2] cycloadditions is highly desirable.

We have recently reported intra-¹¹ and intermolecular¹² Rh-catalyzed [5+2] cycloadditions for the synthesis of highly substituted cycloheptatrienes by using 3-acyloxy-1,4-enyne as a novel 5-carbon component (Scheme 2).¹³ The high degree of unsaturation and the enol ester functionality in cycloaddition product **9** are ideally set up for the synthesis of substituted tropone **10**. We herein report our efforts along this direction for the first time.

Efforts for the conversion of cycloheptatriene product **9** directly to tropones by oxidation were fruitless. Although we were able to remove the ester group in **9** by reduction or hydrolysis, we could not convert the hydrolyzed products to tropones by oxidative reagents. During the development of the intermolecular [5+2] cycloadditions,¹² we learned that high regioselectivity could be observed when propargylic alcohols **12** were employed as the substrates (Scheme 3). With the hydroxyl group handle in product **13**, we thought we might be able to prepare tropones by elimination reaction instead of oxidation reaction.

Previously, we mainly used the pivalate ester of 3-hydroxy-1,4-enyne as the 5-carbon component for Rh-catalyzed [5+2] cycloadditions.¹² It generally provided higher yields of the product compared to other esters such as acetate or benzoate. We imagine that the acetate in **13** or **14** can be easily hydrolyzed under milder conditions. We first examined the scope of the Rh-catalyzed [5+2] cycloaddition using 3-acyloxy-1,4-enyne **11a** and **11b** with a variety of propargylic alcohols. Ester **11a** was prepared in just one step from commercially available 3-methyl-1-penten-4-yn-3-ol.¹² Ester **11b** is available in three steps from commercially available 1-octyn-3-ol.¹⁴

Product **13a** was prepared as a single isomer (Scheme 3) in the presence of Wilkinson's catalyst. The same condition worked for most of the terminal alkynes. The addition of electron-poor phosphine can improve the yield for products **13c** and **13h**. When internal alkynes are employed, much better yields were obtained for products **13i** and **13j/13j'** under condition b. High regioselectivity was observed for product **13i**, while a ratio of 2:1 was obtained for products **13j** and **13j'**. The R¹ group can be methyl or other alkyl groups, such

as *n*-pentyl in **14**. When R¹ was switched phenyl group, the acetate substrate isomerized to conjugated 1,3-enyne **15**¹⁵ under the reaction condition.

We next examined the possibility of synthesizing tropones by eliminating the hydroxyl group in products **13** and **14**. We envisioned that conversion of allylic alcohols **13** or **14** to mesylate **17** followed by base-mediated elimination should yield tetraene intermediate **18**, which could be hydrolyzed to aromatic tropone product **16** via enol intermediate **19** (Scheme 4). Indeed, a three-step sequence converted **13a** to tropone **16a** in a 61% isolated yield. We also tried to treat mesylate intermediate **17a** with potassium carbonate in methanol to complete both elimination and hydrolysis in one step. However, the yield was much lower using the two step sequence.

We then examined the scope of the three-step sequence. A variety of disubstituted tropones could be prepared from the corresponding cycloheptatrienes. Tropones **16d** and **16f** were obtained in lower yields from substrates bearing a benzylic or a tertiary alcohol, respectively. The TBS-protected primary alcohol in substrate **13h** can be tolerated and tropone **16h** was prepared in a 56% isolated yield. Trisubstituted tropone **16i** was prepared from the corresponding alcohol **13i** in a 63% isolated yield. Trisubstituted tropones **16j** and **16j'** could be isolated in 47% and 24% yields, respectively, from a mixture of non-separable alcohols **13j** and **13j'**. Cycloheptatriene **14** was also converted to tropone **20** under the same condition.

We further functionalized tropone products **16b**, **16d**, and **16e** to amino-tropones **21** (Scheme 5). The amino group was introduced to the α' -position of tropones by treating them with hydrazine following literature procedures.^{3a} Since the α -position is blocked by methyl substituent, regioselectivity is not a concern for the amination reaction.

We also explored the [4+2] cycloaddition between tropone **16b** and anhydride **22**. Under thermal conditions, cycloaddition product **23** was obtained in high regio- and diastereoselectivity. The less substituted diene in tropone **16b** selectively reacted with the dienophile and afforded only the endo-product.

In summary, we have developed an efficient sequence to convert products derived from Rh-catalyzed [5+2] cycloaddition of 3-acyloxy-1,4-enynes and alkynes to substituted tropones. High regioselectivity was observed for all terminal alkynes in the Rh-catalyzed [5+2] cycloaddition. For internal alkynes, high regioselectivity could also be obtained when there were two electronically differentiated substituents on the two termini of the internal alkynes. Various di- and tri-substituted tropones were synthesized efficiently from the cycloheptatriene cycloaddition product by a three-step mesylation, elimination and hydrolysis sequence.

2. Experimental section

Esters **11a** and **11b** were prepared from the corresponding alcohols by esterification reactions following our previously reported procedures.^{12,14}

General procedures for the Rh-catalyzed intermolecular [5+2] cycloaddition

Method A—To a flask containing 1,4-enyne (1 mmol) and alkyne (2 mmol) was added $\text{RhCl}(\text{PPh}_3)_3$ (5 mol%) and chloroform (0.4 M). The flask was flushed with argon and allowed to stir at 65 °C. The reaction was monitored by TLC until the 1,4-enyne was completely consumed (approximately 12 h). The solvent was evaporated and the resulting residue was purified via flash chromatography on silica gel using ethyl acetate and hexanes to yield [5+2] cycloaddition products.

Method B—To a flask containing 1,4-enyne (1 mmol) and alkyne (2 mmol) was added $[\text{Rh}(\text{COD})\text{Cl}]_2$ (5 mol%), tris[4-(trifluoromethyl)phenyl] phosphine (30 mol%) and chloroform (0.4 M). The flask was flushed with argon and allowed to stir at 65 °C. The reaction was monitored by TLC until the 1,4-enyne was completely consumed (approximately 12 h). The solvent was evaporated and the resulting residue was purified via flash chromatography on silica gel using ethyl acetate and hexanes to yield [5+2] cycloaddition products

2.1 4-(1-hydroxyethyl)-7-methylcyclohepta-1,3,6-trien-1-yl acetate (13a)

Oil. Method A, 66% yield. ^1H NMR (500Mz, CDCl_3) δ 6.22 (d, J = 6.5 Hz, 1H), 6.07 (d, J = 6.5 Hz, 1H), 5.25 (t, J = 7.5 Hz, 1H), 4.44 (q, J = 6.5 Hz, 1H), 2.58-2.54 (m, 1H), 2.28-2.24 (m, 1H), 2.21 (s, 3H), 1.78 (s, 3H), 1.31 (d, J = 8.5 Hz, 3H); ^{13}C NMR (100Mz, CDCl_3) δ 169.6, 151.9, 142.1, 130.8, 120.8, 119.5, 117.5, 71.1, 27.9, 23.6, 21.0, 17.9. IR (film): 2926, 1730, 1637, 1440, 1370, 1218, 1056, 830 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{12}\text{H}_{16}\text{O}_3$ ($\text{M} + \text{Na}$) $^+$ 231.0997, found 231.0993.

2.2 4-(1-hydroxyhexyl)-7-methylcyclohepta-1,3,6-trien-1-yl acetate (13b)

Oil. Method A, 71% yield. ^1H NMR (500Mz, CDCl_3) δ 6.22 (d, J = 6.5 Hz, 1H), 6.02 (d, J = 6.5 Hz, 1H), 5.22 (t, J = 7.0 Hz, 1H), 4.22-4.19 (m, 1H), 2.58-2.54 (m, 1H), 2.24-2.20 (m, 1H), 2.20 (s, 3H), 1.78 (s, 3H), 1.72 (s, 1H), 1.57-1.53 (m, 2H), 1.35-1.24 (m, 6H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100Mz, CDCl_3) δ 169.6, 151.8, 141.0, 130.7, 120.8, 119.4, 118.5, 75.5, 37.0, 31.9, 27.7, 25.7, 22.7, 21.0, 17.9, 14.2. IR (film): 2930, 1728, 1637, 1370, 1210, 1062, 834, 777 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{16}\text{H}_{24}\text{O}_3$ ($\text{M} + \text{Na}$) $^+$ 287.1623, found 287.1618.

2.3 4-(1-hydroxy-3-phenylpropyl)-7-methylcyclohepta-1,3,6-trien-1-yl acetate (13c)

Oil. Method A, 55% yield. Method B, 69% yield. ^1H NMR (400Mz, CDCl_3) δ 7.30-7.26 (m, 2H), 7.20-7.16 (m, 3H), 6.22 (d, J = 6.4 Hz, 1H), 6.05 (d, J = 6.4 Hz, 1H), 5.24 (t, J = 6.0 Hz, 1H), 4.25-4.23 (m, 1H), 2.70-2.62 (m, 2H), 2.60-2.57 (m, 1H), 2.24-2.19 (m, 4H), 1.91-1.84 (m, 2H), 1.79 (s, 3H), 1.67 (s, 1H); ^{13}C NMR (100Mz, CDCl_3) δ 169.6, 152.0, 142.0, 140.5, 130.9, 128.68, 128.66, 126.1, 120.8, 119.4, 118.8, 74.8, 39.7, 32.4, 27.7, 21.0, 17.9. IR (film): 3027, 2923, 1749, 1637, 1454, 1369, 1213, 1120, 1056, 833 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{19}\text{H}_{22}\text{O}_3$ ($\text{M} + \text{Na}$) $^+$ 321.1461, found 321.1461.

2.4 4-(hydroxy(phenyl)methyl)-7-methylcyclohepta-1,3,6-trien-1-yl acetate (13d)

Oil. Method A, 68% yield. ^1H NMR (400Mz, CDCl_3) δ 7.38-7.25 (m, 5H), 6.25 (s, 2H), 5.34 (s, 1H), 5.00 (t, $J = 7.2$ Hz, 1H), 2.41-2.36 (m, 1H), 2.28-2.23 (m, 1H), 2.18 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100Mz, CDCl_3) δ 169.6, 152.0, 142.4, 140.3, 130.7, 128.6, 128.0, 126.9, 121.7, 119.3, 119.1, 77.1, 28.5, 21.0, 17.9. IR (film): 2935, 1750, 1632, 1441, 1142, 1060, 924, 770, 697 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{17}\text{H}_{18}\text{O}_3$ ($\text{M}+\text{Na}$) $^+$ 293.1154, found 293.1151.

2.5 4-(1-hydroxy-2,2-dimethylpropyl)-7-methylcyclohepta-1,3,6-trien-1-yl acetate (13e)

Oil. Method A, 73% yield. ^1H NMR (500Mz, CDCl_3) δ 6.22 (d, $J = 6.5$ Hz, 1H), 6.00 (d, $J = 6.5$ Hz, 1H), 5.26 (t, $J = 7.5$ Hz, 1H), 3.97 (s, 1H), 2.68-2.64 (m, 1H), 2.20-2.16 (m, 4H), 1.80 (s, 3H), 1.70 (s, 1H), 0.93 (s, 9H); ^{13}C NMR (125Mz, CDCl_3) δ 169.6, 151.7, 139.0, 131.0, 121.1, 120.4, 119.5, 83.6, 36.0, 26.5, 25.6, 25.5, 21.0, 17.9. IR (film): 2981, 2874, 2341, 1747, 1637, 1480, 1266, 1005, 896. cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{15}\text{H}_{22}\text{O}_3$ ($\text{M}+\text{Na}$) $^+$ 273.1461, found 273.1460.

2.6 4-(2-hydroxypropan-2-yl)-7-methylcyclohepta-1,3,6-trien-1-yl acetate (13f)

Oil. Method A, 62% yield. ^1H NMR (400Mz, CDCl_3) δ 6.25 (d, $J = 6.8$ Hz, 1H), 6.17 (d, $J = 6.4$ Hz, 1H), 5.26 (t, $J = 7.2$ Hz, 1H), 2.42 (d, $J = 7.6$ Hz, 2H), 2.21 (s, 3H), 1.78 (s, 3H), 1.41 (s, 6H); ^{13}C NMR (100Mz, CDCl_3) δ 169.7, 151.4, 145.4, 130.6, 120.9, 119.7, 115.5, 73.0, 30.0, 29.9, 21.0, 17.8. IR (film): 3450, 2979, 1740, 1637, 1438, 1367, 1215, 1115, 1062, 957. cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{13}\text{H}_{18}\text{O}_3$ ($\text{M}+\text{Na}$) $^+$ 245.1148, found 245.1153.

2.7 4-(1-hydroxy-2-methylpentyl)-7-methylcyclohepta-1,3,6-trien-1-yl acetate (13g)

Oil. Method A, 64% yield (dr 1:1). ^1H NMR (500Mz, CDCl_3) δ 6.23 (dd, $J = 9.0, 6.0$ Hz, 1H), 6.02 (dd, $J = 15.0, 6.0$ Hz, 1H), 5.23-5.21 (m, 1H), 4.01 (dd, $J = 45.5, 6.0$ Hz, 1H), 2.48-2.44 (m, 1H), 2.30-2.27 (m, 1H), 2.21 (s, 3H), 1.78 (s, 3H), 1.67-1.65 (m, 1H), 1.34-1.25 (m, 4H), 1.10-1.07 (m, 1H), 0.92-0.85 (m, 5H), 0.79 (d, $J = 7.0$ Hz, 1H); ^{13}C NMR (100Mz, CDCl_3) δ 169.6, 166.6, 151.8, 151.6, 140.3, 140.2, 130.9, 130.8, 121.0, 120.7, 119.8, 119.5, 119.4, 119.1, 80.4, 79.2, 37.6, 37.3, 36.1, 34.2, 27.9, 21.0, 20.5, 20.4, 17.907, 17.899, 16.7, 14.6, 14.5, 14.3. IR (film): 3426, 2922, 1727, 1456, 1371, 1216, 1123, 1037, 924 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{16}\text{H}_{24}\text{O}_3$ ($\text{M}+\text{Na}$) $^+$ 287.1617, found 287.1615.

2.8 4-(2-((tert-butyldimethylsilyl)oxy)-1-hydroxyethyl)-7-methylcyclohepta-1,3,6-trien-1-yl acetate (13h)

Oil. Method B, 90% yield. ^1H NMR (500Mz, CDCl_3) δ 6.26 (d, $J = 6.5$ Hz, 1H), 6.14 (d, $J = 6.5$ Hz, 1H), 5.21 (t, $J = 7.0$ Hz, 1H), 4.30 (d, $J = 8.5$ Hz, 1H), 3.63 (dd, $J = 10.0, 3.5$ Hz, 1H), 3.39 (dd, $J = 10.0, 8.5$ Hz, 1H), 2.76 (d, $J = 2.5$ Hz, 1H), 2.59-2.55 (m, 1H), 2.21 (s, 3H), 2.17-2.13 (m, 1H), 1.78 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125Mz, CDCl_3) δ 169.6, 152.1, 135.6, 131.0, 119.8, 119.7, 119.6, 75.2, 67.3, 28.0, 26.1, 21.0, 18.5, 17.9, -5.0, -5.1. IR (film): 2970, 2858, 2349, 1738, 1436, 1374, 1110, 1060, 834 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{18}\text{H}_{30}\text{O}_4\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 361.1805, found 361.1802.

2.9 4-(hydroxymethyl)-3,7-dimethylcyclohepta-1,3,6-trien-1-yl acetate (13i)

Oil. Method B, 76% yield. ^1H NMR (500Mz, CDCl_3) δ 6.18 (s, 1H), 5.40 (t, $J = 9.0$ Hz, 1H), 4.23 (s, 2H), 2.44 (d, $J = 7.5$ Hz, 2H), 2.20 (s, 3H), 2.06-2.01 (m, 1H), 1.87 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100Mz, CDCl_3) δ 169.5, 151.0, 130.2, 129.9, 127.4, 124.7, 122.3, 62.8, 30.4, 20.9, 17.8, 17.6. IR (film): 3405, 2950, 1752, 1637, 1321, 1131, 1061, 1016, 873 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{12}\text{H}_{16}\text{O}_3$ ($\text{M}+\text{Na}$) $^+$ 231.0991, found 231.0989.

2.10 3-(((tert-butyldimethylsilyl)oxy)methyl)-4-(hydroxymethyl)-7-methylcyclohepta-1,3,6-trien-1-yl acetate (13j and 13j')

Oil. Method B, 79% yield (2:1) mixture. Major ^1H NMR (500Mz, CDCl_3) δ 6.29 (s, 1H), 5.34 (t, $J = 7.5$ Hz, 1H), 4.36-4.34 (m, 2H), 4.30-4.26 (m, 2H), 2.40 (s, 2H), 2.20 (s, 3H), 1.77 (s, 3H), 0.89 (s, 9H), 0.08 (s, 6H); Major ^{13}C NMR (100Mz, CDCl_3) δ 169.5, 151.7, 131.8, 130.2, 122.3, 120.1, 63.7, 63.5, 31.7, 26.0, 21.0, 18.5, 17.6, -5.0. IR (film): 2930, 2858, 1728, 1472, 1370, 1135, 1062, 834 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{18}\text{H}_{30}\text{O}_4\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 361.1805, found 361.1808.

2.11 4-(hydroxymethyl)-7-pentylcyclohepta-1,3,6-trien-1-yl acetate (14)

Oil. Method A, 62% yield. ^1H NMR (500Mz, CDCl_3) δ 6.26 (d, $J = 6.0$ Hz, 1H), 6.06 (d, $J = 6.5$ Hz, 1H), 5.28 (t, $J = 7.0$ Hz, 1H), 4.24 (s, 2H), 2.42 (d, $J = 7.5$ Hz, 2H), 2.19 (s, 3H), 2.08 (t, $J = 8.0$ Hz, 2H), 1.68 (s, 1H), 1.38-1.32 (m, 2H), 1.29-1.24 (m, 2H), 1.20-1.16 (m, 2H), 0.85 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125Mz, CDCl_3) δ 169.7, 151.6, 137.9, 135.5, 120.24, 120.15, 118.3, 66.2, 32.2, 31.7, 29.1, 29.0, 22.6, 21.0, 14.2. IR (film): 3431, 2928, 1750, 1436, 1364, 1122, 1020, 928 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{15}\text{H}_{22}\text{O}_3$ ($\text{M}+\text{Na}$) $^+$ 273.1467, found 273.1471.

General procedures for the synthesis of tropones from cycloheptatrienes—To a solution of the cycloheptatriene substrate (0.2 mmol) in dry dichloromethane (4 mL) was added triethylamine (85 μL) and MsCl (31 μL) at -78°C . The reaction was warmed to room temperature and stirred for 1h. The solution was quenched with saturated aqueous NaHCO_3 (10 mL) solution and extracted with dichloromethane (3×10 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 , concentrated under vacuum to give the crude mesylation product.

To a solution of the crude mesylation product in dry THF (4 mL) was added DBU (44 μL) at room temperature. After stirring at this temperature for 10-30 min, it was concentrated to give the crude tetraene product. To a solution of this crude product in MeOH (4 mL) was added K_2CO_3 (13 mg) at room temperature. After stirring at this temperature for 5-10 min, the product was concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate and hexanes to give the final tropone product.

2.12 5-ethyl-2-methylcyclohepta-2,4,6-trienone (16a)

Oil. 18 mg, 61% yield. ^1H NMR (500Mz, CDCl_3) δ 7.25 (d, $J = 9.5$ Hz, 1H), 7.04 (s, 2H), 6.78 (d, $J = 9.5$ Hz, 1H), 2.55 (q, $J = 7.5$ Hz, 2H), 2.25 (s, 3H), 1.21 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100Mz, CDCl_3) δ 187.2, 150.1, 149.4, 139.6, 138.5, 136.0, 131.2, 33.0, 22.7, 15.3.

IR (film): 3417, 3055, 2854, 1728, 1573, 1266, 1080, 957 cm⁻¹. HRMS (ESI) *m/z* calc. For C₁₀H₁₂O (M+Na)⁺ 171.0780, found 171.0779.

2.13 5-hexyl-2-methylcyclohepta-2,4,6-trienone (16b)

Oil. 28 mg, 67% yield. ¹H NMR (500Mz, CDCl₃) δ 7.24 (d, *J* = 9.0 Hz, 1H), 7.03 (s, 2H), 6.76 (d, *J* = 9.0 Hz, 1H), 2.49 (t, *J* = 7.5 Hz, 2H), 2.25 (s, 3H), 1.57-1.55 (m, 2H), 1.34-1.27 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (100Mz, CDCl₃) δ 187.2, 150.1, 148.2, 139.5, 138.7, 135.9, 132.0, 40.0, 31.8, 31.0, 29.0, 22.8, 22.7, 14.3. IR (film): 3040, 2925, 1737, 1581, 1664, 1360, 1220, 962 cm⁻¹. HRMS (ESI) *m/z* calc. For C₁₄H₂₀O (M+Na)⁺ 227.1412, found 227.1416.

2.14 2-methyl-5-(3-phenylpropyl)cyclohepta-2,4,6-trienone (16c)

Oil. 29 mg, 60% yield. ¹H NMR (400Mz, CDCl₃) δ 7.31-7.29 (m, 2H), 7.24-7.21 (m, 2H), 7.19-7.16 (m, 2H), 7.02 (s, 2H), 6.76 (d, *J* = 9.2 Hz, 1H), 2.66 (t, *J* = 7.6 Hz, 2H), 2.53 (t, *J* = 9.5 Hz, 2H), 2.27 (s, 3H), 1.96-1.88 (m, 2H); ¹³C NMR (100Mz, CDCl₃) δ 187.2, 150.4, 147.5, 141.7, 139.6, 138.5, 135.7, 132.2, 128.7, 128.6, 126.3, 39.4, 35.4, 32.5, 22.7. IR (film): 3053, 2927, 2858, 1730, 1573, 1456, 1265, 1097, 733, 700 cm⁻¹. HRMS (ESI) *m/z* calc. For C₁₇H₁₈O (M+H)⁺ 239.1430, found 239.1436.

2.15 5-benzyl-2-methylcyclohepta-2,4,6-trienone (16d)

Oil. 21 mg, 51% yield. ¹H NMR (500Mz, CDCl₃) δ 7.33-7.30 (m, 3H), 7.26-7.24 (m, 1H), 7.17-7.15 (m, 2H), 6.99 (s, 2H), 6.81 (d, *J* = 9.0 Hz, 1H), 3.85 (s, 2H), 2.25 (s, 3H); ¹³C NMR (100Mz, CDCl₃) δ 187.1, 150.6, 146.0, 139.5, 139.1, 138.5, 135.6, 132.7, 129.2, 129.1, 127.1, 45.5, 22.7. IR (film): 3055, 2987, 2361, 1726, 1575, 1422, 1265, 896. cm⁻¹. HRMS (ESI) *m/z* calc. For C₁₅H₁₄O (M+Na)⁺ 233.0937, found 233.0945.

2.16 2-methyl-5-neopentylcyclohepta-2,4,6-trienone (16e)

Oil. 28 mg, 72% yield. ¹H NMR (500Mz, CDCl₃) δ 7.26 (d, *J* = 9.0 Hz, 1H), 7.00 (s, 2H), 6.72 (d, *J* = 9.5 Hz, 1H), 2.41 (s, 2H), 2.27 (s, 3H), 0.93 (s, 9H); ¹³C NMR (100Mz, CDCl₃) δ 187.2, 150.5, 145.5, 140.5, 138.3, 135.4, 134.3, 53.6, 32.8, 29.6, 22.7. IR (film): 3060, 2964, 1730, 1587, 1403, 1264, 1080, 1026 cm⁻¹. HRMS (ESI) *m/z* calc. For C₁₃H₁₈O (M+Na)⁺ 213.1255, found 213.1259.

2.17 5-isopropyl-2-methylcyclohepta-2,4,6-trienone (16f)

Oil. 14 mg, 42% yield. All spectra data are in accordance with literature.¹⁶

2.18 2-methyl-5-(2-methylpentyl)cyclohepta-2,4,6-trienone (16g)

Oil. 31 mg, 75% yield. ¹H NMR (400Mz, CDCl₃) δ 7.24 (d, *J* = 9.2 Hz, 1H), 7.05-6.98 (m, 2H), 6.73 (d, *J* = 9.2 Hz, 1H), 2.55-2.51 (m, 1H), 2.25 (s, 3H), 2.25-2.20 (m, 1H), 1.72-1.67 (m, 1H), 1.41-1.25 (m, 3H), 1.19-1.13 (m, 1H), 0.90-0.85 (m, 6H); ¹³C NMR (100Mz, CDCl₃) δ 187.2, 150.2, 147.1, 139.2, 139.0, 135.7, 133.0, 47.6, 39.1, 34.5, 22.7, 20.3, 19.4, 14.5. IR (film): 2455, 2360, 2254, 1737, 1625, 1565, 1421, 1230, 1095, 904. cm⁻¹. HRMS (ESI) *m/z* calc. For C₁₄H₂₀O (M+Na)⁺ 227.1406, found 227.1409.

2.19 5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-methylcyclohepta-2,4,6-trienone (16h)

Oil. 32 mg, 56% yield. ^1H NMR (500Mz, CDCl_3) δ 7.27 (d, $J = 9.5$ Hz, 1H), 7.19-7.03 (m, 2H), 6.83 (d, $J = 9.0$ Hz, 1H), 3.83 (t, $J = 6.0$ Hz, 2H), 2.71 (t, $J = 6.5$ Hz, 2H), 2.28 (s, 3H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100Mz, CDCl_3) δ 187.1, 150.7, 145.0, 139.20, 139.18, 135.6, 133.4, 63.6, 43.1, 26.1, 22.7, 18.5, -5.2. IR (film): 2953, 2895, 1730, 1631, 1577, 1374, 1254, 1095. cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{16}\text{H}_{26}\text{O}_2\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 301.1594, found 301.1597

2.20 2,5,6-trimethylcyclohepta-2,4,6-trienone (16i)

Oil. 19 mg, 63% yield. ^1H NMR (500Mz, CDCl_3) δ 7.14-7.11 (m, 2H), 6.81 (d, $J = 9.5$ Hz, 1H), 2.27 (s, 3H), 2.25 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100Mz, CDCl_3) δ 186.3, 149.0, 147.1, 144.1, 140.2, 134.9, 132.1, 26.0, 25.5, 22.1. IR (film): 2923, 2855, 1738, 1566, 1372, 1216, 950, 894, 713 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{10}\text{H}_{12}\text{O}$ ($\text{M}+\text{H}$) $^+$ 149.0960, found 149.0966

2.21 6-(((tert-butyldimethylsilyl)oxy)methyl)-2,5-dimethylcyclohepta-2,4,6-trienone (16j)

Oil. 27 mg, 47% yield. ^1H NMR (500Mz, CDCl_3) δ 7.28 (d, $J = 9.5$ Hz, 1H), 7.14 (d, $J = 10.0$ Hz, 1H), 7.07 (s, 1H), 4.53 (s, 2H), 2.25 (s, 6H), 0.94 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (100Mz, CDCl_3) δ 186.5, 150.0, 145.3, 145.0, 140.8, 134.9, 129.1, 65.2, 26.15, 26.11, 23.2, 22.3, 18.6, -5.1. IR (film): 3055, 2955, 1729, 1626, 1265, 1063, 1017, 838. cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{16}\text{H}_{26}\text{O}_2\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 301.1594, found 301.1600

2.22 5-(((tert-butyldimethylsilyl)oxy)methyl)-2,6-dimethylcyclohepta-2,4,6-trienone (16j')

Oil. 13 mg, 24% yield. ^1H NMR (500Mz, CDCl_3) δ 7.36 (s, 1H), 7.14 (d, $J = 9.0$ Hz, 1H), 6.77 (d, $J = 9.5$ Hz, 1H), 4.53 (s, 2H), 2.24 (s, 6H), 0.93 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (100Mz, CDCl_3) δ 187.1, 149.4, 147.8, 142.0, 136.5, 134.8, 132.9, 66.5, 26.1, 22.7, 22.1, 18.6, -5.0. IR (film): 3055, 2954, 2858, 1738, 1625, 1265, 1177, 1060, 940. cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{16}\text{H}_{26}\text{O}_2\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 301.1594, found 301.1601

2.23 5-methyl-2-pentylcyclohepta-2,4,6-trienone (20)

Oil. 23 mg, 60% yield. ^1H NMR (400Mz, CDCl_3) δ 7.12 (d, $J = 9.2$ Hz, 1H), 6.99 (s, 2H), 6.80 (d, $J = 9.2$ Hz, 1H), 2.62-2.58 (m, 2H), 2.30 (s, 3H), 1.56-1.50 (m, 2H), 1.36-1.31 (m, 4H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100Mz, CDCl_3) δ 186.8, 153.9, 143.3, 139.7, 139.0, 135.3, 132.3, 35.4, 32.0, 28.8, 25.8, 22.8, 14.2. IR (film): 2955, 2925, 1729, 1633, 1574, 1462, 1190, 1040, 844. cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{13}\text{H}_{18}\text{O}$ ($\text{M}+\text{Na}$) $^+$ 213.1249, found 213.1256

General procedures for the amination of tropones—To a solution of α -methyl-tropone (0.1 mmol) in EtOH (0.5 ml) was added 65% hydrazine monohydrate (0.12 mL). The solution was allowed to stir at 60°C until all starting material was consumed by monitoring the reaction by TLC (~2h). The reaction was concentrated under vacuum and then taken up in EtOAc (4 mL) and washed with H_2O (3×4 mL). The organic layer was then washed with brine, dried over Na_2SO_4 , filtered and concentrated under vacuum. The crude

residue was purified by flash column chromatography on silica gel using ethyl acetate and hexanes to provide the desired α -amino-tropones.

2.24 2-amino-4-hexyl-7-methylcyclohepta-2,4,6-trienone (21a)

Oil. 17 mg, 79% yield. ^1H NMR (500Mz, CDCl_3) δ 7.37 (d, $J = 9.5$ Hz, 1H), 6.80 (s, 1H), 6.57 (d, $J = 10.0$ Hz, 1H), 5.80 (bs, 2H), 2.54-2.51 (m, 2H), 2.40 (s, 3H), 1.62-1.57 (m, 2H), 1.35-1.25 (m, 6H), 0.89 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (125Mz, CDCl_3) δ 175.2, 154.1, 150.5, 139.0, 137.5, 123.9, 115.3, 41.2, 32.1, 31.9, 29.1, 23.4, 22.8, 14.3. IR (film): 3055, 2987, 1730, 1530, 1422, 1265, 839. cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{14}\text{H}_{21}\text{NO}$ ($\text{M}+\text{Na}$) $^+$ 242.1515, found 242.1584.

2.25 2-amino-4-benzyl-7-methylcyclohepta-2,4,6-trienone (21b)

Oil. 19 mg, 85% yield. ^1H NMR (500Mz, CDCl_3) δ 7.39 (d, $J = 10.0$ Hz, 1H), 7.32-7.29 (m, 2H), 7.24-7.22 (m, 1H), 7.18 (d, $J = 7.0$ Hz, 2H), 6.76 (s, 1H), 6.62 (d, $J = 10.0$ Hz, 1H), 5.76 (bs, 2H), 3.90 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (125Mz, CDCl_3) δ 175.5, 153.9, 148.0, 140.3, 139.5, 137.4, 129.1, 128.9, 126.9, 124.5, 115.3, 46.5, 23.4. IR (film): 3319, 3282, 2382, 1728, 1609, 1521, 1276, 969, 740. cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{15}\text{H}_{15}\text{NO}$ ($\text{M}+\text{Na}$) $^+$ 248.1045, found 248.1048.

2.26 2-amino-4-(tert-butyl)-7-methylcyclohepta-2,4,6-trienone (21c)

Oil. 16 mg, 79% yield. ^1H NMR (500Mz, CDCl_3) δ 7.37 (d, $J = 10.0$ Hz, 1H), 6.76 (s, 1H), 6.52 (d, $J = 10.0$ Hz, 1H), 5.79 (bs, 2H), 2.46 (s, 2H), 2.41 (s, 3H), 0.94 (s, 9H); ^{13}C NMR (125Mz, CDCl_3) δ 175.2, 153.3, 147.3, 139.2, 136.8, 126.0, 117.3, 54.8, 32.8, 29.8, 23.4. IR (film): 3419, 3281, 2952, 1730, 1605, 1524, 1424, 1363, 1163, 962, 829 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{13}\text{H}_{19}\text{NO}$ ($\text{M}+\text{Na}$) $^+$ 228.1358, found 228.1365.

Procedure for the synthesis of 23 via [4+2] cycloaddition—To a solution of tropone **16b** (0.06 mmol) in xylene (0.3 mL) was added furan-2,5-dione (29.5 mg). The solution was allowed to stir at 120 $^{\circ}\text{C}$ overnight. The reaction was concentrated under vacuum and purified by flash column chromatography on silica gel using ethyl acetate and hexanes to provide the desired cycloaddition product in 65% yield.

2.27 9-hexyl-6-methyl-3a,4,8,8a-tetrahydro-1H-4,8-ethenocyclohepta[c]furan-1,3,5-trione (23)

Oil. 12 mg, 65% yield. ^1H NMR (400Mz, CDCl_3) δ 6.98 (d, $J = 6.8$ Hz, 1H), 5.79 (d, $J = 6.0$ Hz, 1H), 3.99 (dd, $J = 6.0, 1.2$ Hz, 1H), 3.69 (dd, $J = 7.2, 2.0$ Hz, 1H), 3.60-3.58 (m, 1H), 3.53 (dd, $J = 7.2, 1.2$ Hz, 1H), 2.12-2.08 (m, 2H), 1.76 (s, 3H), 1.37-1.33 (m, 2H), 1.30-1.23 (m, 6H), 0.87 (t, $J = 9.6$ Hz, 3H); ^{13}C NMR (125Mz, CDCl_3) δ 193.4, 171.0, 152.5, 144.2, 137.7, 118.1, 53.9, 47.9, 43.1, 42.2, 36.7, 31.7, 28.9, 26.8, 22.8, 18.4, 14.3. IR (film): 3055, 2930, 2359, 1785, 1674, 1265, 1076, 928, 832 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{18}\text{H}_{22}\text{O}_4$ ($\text{M}+\text{Na}$) $^+$ 325.1410, found 325.1424.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

W. T. thanks University of Wisconsin and National Institute of Health (R01GM088285) for funding. B.-m. Xi thanks Southern Medical University for funding.

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Figure 1.
Tropones, tropolones and tropone-containing natural products

Scheme 1.
Total synthesis of (±)-harringtonolide

Scheme 2.

Rh-catalyzed intermolecular [5+2] cycloaddition and formation of tropones

a) $\text{RhCl}(\text{PPh}_3)_3$ (5 mol%), CHCl_3 , 65 °C
 b) $[\text{Rh}(\text{COD})\text{Cl}]_2$ (5 mol%), $p\text{-(CF}_3\text{C}_6\text{H}_4)_3\text{P}$, CHCl_3 , 65 °C

Scheme 3.
 Synthesis of substituted cycloheptatrienes

^a Isolated yield after three steps.

Scheme 4.
Synthesis of substituted tropones

Scheme 5.
Amination and cycloaddition of substituted tropones