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Syntheses of 3,4-Benzotropolones by Ring-Closing Metatheses

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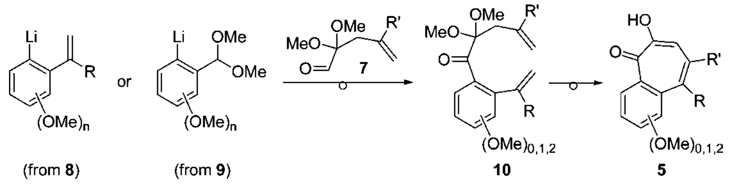
ABSTRACT



***Ortho*-lithiated styrenes or *ortho*-lithiated benzaldehyde dimethyl acetals were added to 2,2-dimethoxypent-4-enals 7. The resulting alcohols were carried on to the aromatic dienones 10. These were ring-closed by olefin metathesis. Hydrolysis of the dimethyl ketal moiety and enolization provided the 3,4-benzotropolones 5. Overall, this access comprises 4−6 steps and totaled a 22−81% yield.**

In 1945 Dewar deduced the correct structure of the fungal metabolite stipitatic acid (Figure 1) and named its hydroxycycloheptatrienone core tropolone (**1**).[1] This assignment was confirmed by Todd et al.[2] The latter also demonstrated that the mold product puberulic acid is hydroxystipitatic acid.[3] β-Thujaplicin was described as a naturally occurring tropolone at that time as well.[4] Figure 1 shows stipitatic and puberulic acid as single tautomers arbitrarily, and β-thujaplicin is depicted as a mixture of tautomers,[5] because tropolone tautomerizes quickly.[6]

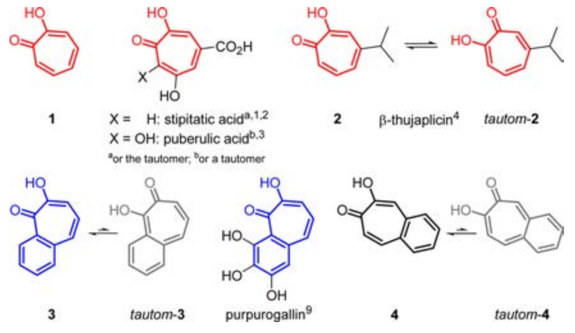


Figure 1. Tropolones (red), 3,4-benzotropolones (blue), and 6,7-(*tautom*-**3**), 4,5- (**4**), and 5,6-benzotropolone (*tautom*-**4**).

Benzannulation to the tropolone scaffold gives rise to 3,4- (**3**) and 5,6-benzotropolones (**4**) but not to 6,7-(*tautom*-**3**) or 4,5-benzotropolones (*tautom*-**4**). The latter gain a Clar electron sextet[7] if they isomerize to give the former. Only a few 5,6-benzotropolones (**4**) occur in nature,[8] but various 3,4-benzotropolones (**3**) do, e.g. purpurogallin[9] (Figure 1). In nature 3,4-benzotropolones are found in plants[10] and fungi.[11] In industry 3,4-benzotropolones have gained patent protection as antimicrobial, antiretroviral, and

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[1] Dewar, M. J. S. *Nature* **1945**, *155*, 50–51.

[2] Corbett, R. E.; Johnson, A. W.; Todd, A. R. *J. Chem. Soc.* **1950**, 147–149.

[3] Corbett, R. E.; Johnson, A. W.; Todd, A. R. *J. Chem. Soc.* **1950**, 6–9.

[4] Erdtman, H.; Gripenberg, J. *Nature* **1948**, *161*, 719–719.

[5] Two phenols cocrystallized with a given tautomer of β-thujaplicin, and a third phenol cocrystallized with the other tautomer: Tanaka, K.; Nagahiro, R.; Ohba, S.; Eishima, M. *Tetrahedron Lett.* **2001**, *42*, 925–929.

[6] Redington, R. L. *J. Chem. Phys.* **2000**, *113*, 2319–2335.

[7] Inferred from: Randić, M. *Chem. Rev.* **2003**, *103*, 3449–3605.

[8] (a) Ginda, H.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H.; Weijie, Z.; Jun, C.; Tian, G. Y. *Tetrahedron Lett.* **1988**, *29*, 4603–4606. (b) Kabouche, A.; Boutaghane, N.; Kabouche, Z.; Seguin, E.; Tillequin, F.; Benlabed, K. *Fitoterapia* **2005**, *76*, 450–452 (*CAN* 144:167135). (c) Seephonkai, P.; Sangdee, A.; Bunchalee, P.; Pyne, S. G. *J. Nat. Prod.* **2009**, *72*, 1892–1894.

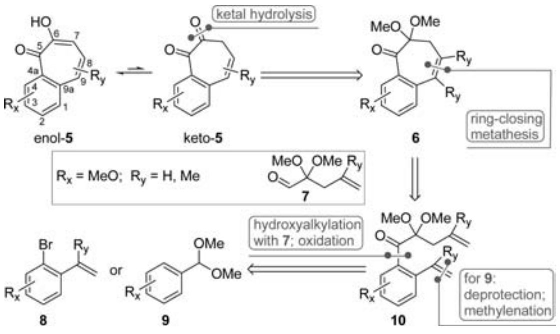
[9] Barltrop, J. A.; Nicholson, J. S. *J. Chem. Soc.* **1948**, 116–120.

[10] For example: (a) Watanabe, N.; Sekine, T.; Takagi, M.; Iwasaki, J.-i.; Imamoto, N.; Kawasaki, H.; Osada, H. *J. Biol. Chem.* **2009**, *284*, 2344–2353. (b) Mesa-Siverio, D.; Estévez-Braun, A.; Ravelo, Á. G.; Murguia, J. R.; Rodríguez-Afonso, A. *Eur. J. Org. Chem.* **2003**, 4243–4247.

[11] For example: (a) Kerschensteiner, L.; Löbermann, F.; Steglich, W.; Trauner, D. *Tetrahedron* **2011**, *67*, 1536–1539. (b) Klostermeyer, D.; Knops, L.; Sindlinger, T.; Polborn, K.; Steglich, W. *Eur. J. Org. Chem.* **2000**, 603–609.

10.1021/ol400510j

Scheme 1. Our Retrosynthetic Analysis of 3,4-Benzotropolones

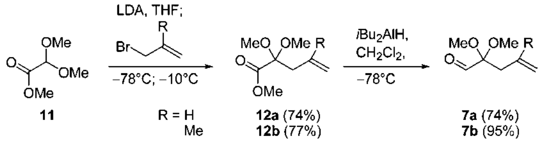


antiobesity agents, for stabilizing household, cosmetic, and nutritional products, and as UV-absorbers in sunscreens.[12] Several 3,4-benzotropolones inhibit a regulator of our immune system.[13]

A one-step synthesis of 3,4-benzotropolones from catechols and pyrogallols has been known since the 19th century.[14] It is still being used[15] but entails limited variability of the substitution pattern. Multistep routes to 3,4-benzotropolone comprise the functionalization of benzocycloheptenones[16] and ring expansions.[17] A route to ether-annulated 3,4-benzotropolones by an intramolecular 1,3-dipolar cycloaddition[18] was extended to making polycyclic 3,4-benzotropolones by hetero-Diels–Alder reactions.[19]

In our retrosynthetic analysis (Scheme 1) we perceived 3,4-benzotropolones **5** as thermodynamically favored enol tautomers *enol*-**5** of much less stable 1,2-diketones *keto*-**5**.

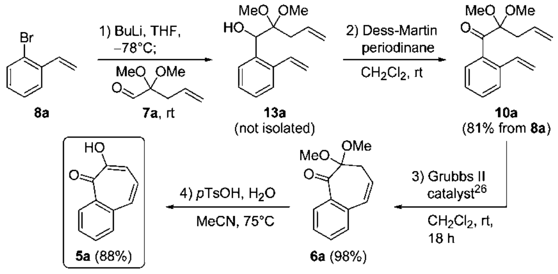
Scheme 2. Syntheses of 2,2-Dimethoxypent-4-enals **7a** and **b**



Accordingly, a synthetic plan targeting diketones *keto*-**5** should conclude with 3,4-benzotropolones *enol*-**5**. We traced back these diketones *keto*-**5** to their monoketals **6**. Constituting cycloheptenes of sorts we envisaged accessing them by ring-closing metatheses ("RCM") of benzannulated dienes **10**. The latter are aromatic ketones. This indicated that **10** could stem from the acylation[20]—or an equivalent hydroxyalkylation/oxidation sequence starting with the incorporation of 2,2-dimethoxypent-4-enals **7**—of *ortho*-metalated styrenes or *ortho*-metalated precursors of styrenes. Such reagents seemed accessible from *ortho*-bromostyrenes **8** (by Br/Li exchange) or benzaldehyde dimethyl acetals **9** (by *ortho*-lithiation), respectively.

Our syntheses of 2,2-dimethoxypent-4-enals **7a** and **b** began with the dimethoxyacetate **11** (available from glyoxylic acid in one step;[21] Scheme 2). Allylating the **11**-enolate by modifying the procedure from Conia et al.[22] delivered the ester **12a** in 74% yield (ref 22, 50%). Methallylating the **11**-enolate analogously furnished ester **12b** readily. Esters **12a** and **b** were reduced with iBu$_2$AlH[23] to provide aldehydes **7a** (74% yield) and **b** (95%).

Scheme 3. *ortho*-Lithiostyrene Approach to Benzotropolone **5d**



A Br/Li exchange reaction of *ortho*-bromostyrene (**8a**) followed by the addition of aldehyde **7a**[24] gave the benzylic alcohol **13a** (Scheme 3). Oxidation with Dess-Martin periodinane[25] led to the benzannulated dienone **10a**. In the presence of 1 mol % of the second generation Grubbs

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[12] (a) Bieler, K.; Ochs, D.; Wagner, B. WO2011048011 (A2), April 28, 2011 (CAN 154:524103). (b) Wagner, B. et al. WO2011042423 (A2), April 14, 2011 (CAN 154:443987). (c) Fukui, Y.; Asami, S.; Maeda, M. WO2010134595 (A1), November 25, 2010 (CAN 153:634903). (d) Wagner, B.; Öhrlein, R.; Herzog, B.; Eichin, K.; Baisch, G.; Portmann, S. WO2009156324 (A2), December 30, 2009 (CAN 152:97724). (e) Romanov, A. N. et al. RU2359954 (C2), June 27, 2009 (CAN 151:100921). (f) Romanov A. N. et al. RU2359955 (C2), June 27, 2009 (CAN 151:100922).

[13] (a) Cheng, K.; Wang, X.; Zhang, S.; Yin, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 12246–12249.

[14] (a) First chemical synthesis of purpurogallin (Figure 1): Girard, M. A. *C. R. Hebd. Séances Acad. Sci.* **1869**, *69*, 865–868. (b) First enzymatic synthesis of purpurogallin: Bertrand, M. G. *C. R. Hebd. Séances Acad. Sci.* **1895**, *120*, 267–269. Isolations of analogues of the putative 1,9-dihydroxy-4a,5-dihydro-9*H*-5,9-methanobenzocycloheptene-2,8,10-trione and 3,4,5-trihydroxy-5,9-dihydro-5,9-methanobenzocycloheptene-6,10-dione intermediates, respectively: (c) Dürckheimer, W.; Paulus, E. F. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 224–225. (d) Yanase, E.; Sawaki, K.; Nakatsuka, S.-i. *Synlett* **2005**, *17*, 2661–2663.

[15] For example: (a) Kawabe, Y.; Aihara, Y.; Hirose, Y.; Sakurada, A.; Yoshida, A.; Inai, M.; Asakawa, T.; Hamashima, Y.; Kan, T. *Synlett* **2013**, 479–482. (b) Reference 11a. (c) Huang, C.; Bai, H.; Li, C.; Shi, G. *Chem. Commun.* **2011**, *47*, 4962–4964. (d) Das, D.; Roy, S.; Debnath, S.; Das, P. K. *Chem.—Eur. J.* **2010**, *16*, 4911–4922. (e) Li, Y.; Shibahara, A.; Matsuo, Y.; Tanaka, T.; Kouno, I. *J. Nat. Prod.* **2010**, *73*, 33–39. (f) Baisch, G.; Wagner, B.; Öhrlein, R. *Tetrahedron* **2010**, *66*, 3742–3748.

[16] (a) Synthesis of **3**: Cook, J. W.; Somerville, A. R. *Nature* **1949**, *163*, 410–410. (b) Recent example: Daştan, A.; Güney, M.; Balci, M. *Helv. Chim. Acta* **2005**, *88*, 830–838.

[17] For example: (a) Fukui, N.; Ohmori, K.; Suzuki, K. *Helv. Chim. Acta* **2012**, *95*, 2194–2217. (b) Iwaya, K.; Tamura, M.; Nakamura, M.; Hasegawa, E. *Tetrahedron Lett.* **2003**, *44*, 9317–9320.

[18] Plüg, C.; Friedrichsen, W.; Debaerdemaeker, T. *J. Prakt. Chem.* **1997**, *339*, 205–216.

[19] Baldwin, J. E.; Mayweg, A. V. W.; Neumann, K.; Pritchard, G. J. *Org. Lett.* **1999**, *1*, 1933–1935.

[20] Attempted acylations of *ortho*-lithiostyrene (obtained from bromostyrene **8a** like in step 1 of Scheme 3) or 2-lithio-3,4-dimethoxybenzaldehyde dimethyl acetal (obtained from acetal **9a** like in step 1 of Scheme 5) failed with ester **12a** or the corresponding Weinreb amide. They also did not proceed cleanly with the corresponding acid chloride.

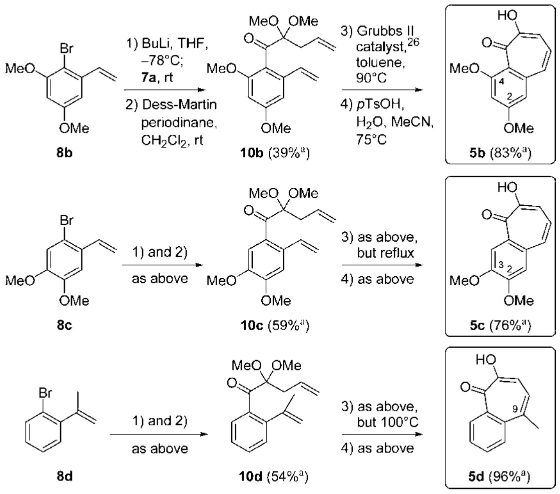
[21] (a) Cameron, A. G.; Hewson, A. T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2979–2983. (b) Griesbaum, K.; Meister, M. *Chem. Ber.* **1987**, *120*, 1573–1580.

[22] Huet, F.; Pellet, M.; Conia, J. M. *Synthesis* **1979**, 33–34.

[23] Reduction protocol: Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660–2661.

catalyst[26] ("Grubbs II catalyst") the benzocycloheptadienedione monoketal **6a** resulted in nearly quantitative yield. Hydrolysis of **6a** with excess *p*TsOH in aqueous acetonitrile required heating at 75 °C for 4 h. This sluggishness reflects the destabilization of the carboxonium ion, which precedes the hemiacetal intermediate, through the benzoyl group. Completion of hydrolysis and keto–enol tautomerism furnished the unsubstituted 3,4-benzotropolone **5a**. Altogether our synthesis comprised four steps and gave 71% of **5a**. This resembles the best previous synthesis of **5a**, which required four steps as well and totaled a 68% yield.[16b]

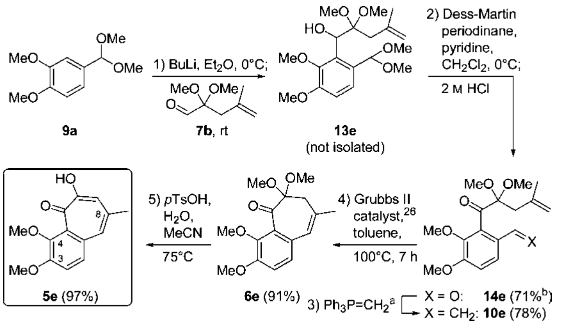
Scheme 4. Synthesis of 3,4-Benzotropolones **5b–d**: Embellishing the *ortho*-Lithiostyrene Approach of Scheme *3*,[a]



[a] Over the two steps.

We employed the strategy of Scheme 3 for synthesizing the substituted benzotropolones **5b–d** (Scheme 4). None of them nor their core **5a** is substituted such that it could be reached by the mentioned[14] co-oxidation of a catechol and a pyrogallol. By subjecting the *ortho*-bromostyrenes **8b**[27]–**d** to Br/Li-exchange reactions, adding aldehyde **7a**, and oxidizing the resulting carbinols without prior purification by the Dess-Martin reagent[25] rendered the benzannulated dienones **10b–d** in 39%, 59%, and 54% yield, respectively. Dienone **10b** needed 3 mol % Grubbs II catalyst and 90 °C (9 h) for an effective ring closure to the benzocycloheptadienedione monoketal **10b** (93% yield). Acidic hydrolysis completed the unprecedented benzotropolone **5b** in 32% yield from styrene **8b**. In the presence of 2 mol % Grubbs II catalyst[26] the dienones **10c** and **d** ring-closed at 110 °C (3 h) and 100 °C (90 min), whereupon the respective hydrolyses provided the known[28] benzotropolone **5c** (45% overall yield) and the hitherto unknown benzotropolone **5d** (52% overall yield). In the latter the RCM had established a trisubstituted C=C bond.

Scheme 5. Accessing Benzotropolone **5e** Upon *Ortho*-Lithiation of the Benzaldehyde Dimethyl Acetal **9a**[a]



[a] Prepared from $Ph_3MeP^{\oplus}$ $Br^{\ominus}$ and sodium hexamethyldisilazide. [b] From **9a**.

The sequence in Scheme 5 shows a modified entry into our benzotropolone synthesis. It warrants consideration when proceeding similarly to Scheme 3 or 4 would require an *ortho*-bromostyrene substrate, which is neither commercially available nor readily synthesized. In the first step benzaldehyde dimethyl acetal **9a**[29] and *n*-BuLi gave an *ortho*-lithioacetal, which was added to the aldehyde **7b**. The resulting benzylic alcohol **13e** was oxidized with the Dess-Martin reagent[25] in the presence of pyridine.[30] Hydrochloric acid selectively cleaved the benzylic acetal of the crude product, furnishing ketoaldehyde **14e** (71% yield from **9a**). **14e** was dimethylenated under "salt-free" Wittig conditions, providing 78% of the benzannulated dienone **10e**. This substrate required the harshest RCM conditions of the present study: Within 7 h at 100 °C, 5 mol % of the Grubbs II catalyst[26] led to the bicyclic monoketal **10e** in 91% yield. Hydrolysis afforded the benzotropolone **5e** (49% overall yield for the five steps).

The benzaldehyde dimethyl acetals **9a**[29] and **b**[29] were the starting materials for the benzotropolone syntheses in Scheme 6. Following the course of our proof-of-principle sequence **9a** → **10e** (Scheme 5) we advanced to the

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(24) Recent Br/Li exchanges in *ortho*-bromostyrenes with ensuing hydroxyalkylations: (a) Snyder, S. A.; Sherwood, T. C.; Ross, A. G. *Angew. Chem., Int. Ed.* **2010**, *49*, 5146–5150. (b) Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753–1765. (c) Kim, J.; Li, H. B.; Rosenthal, A. S.; Sang, D.; Shapiro, T. A.; Bachi, M. D.; Posner, G. H. *Tetrahedron* **2006**, *62*, 4120–4127. (d) Tietze, L. F.; Stewart, S. G.; Polomska, M. E.; Modi, A.; Zeeck, A. *Chem.—Eur. J.* **2004**, *10*, 5233–5242.

(25) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

(26) [1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-(phenylmethylene)(tricyclohexylphosphane)ruthenium.

(27) **8b** had been obtained from 2-bromo-3,5-dimethoxybenzaldehyde: Broering, T. J.; Morrow, G. W. *Synth. Commun.* **1999**, *29*, 1135–1142. However, we made **8b** differently (see Supporting Information).

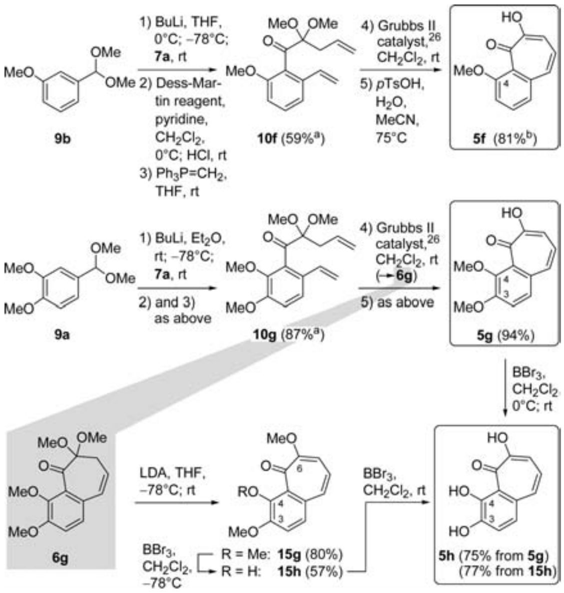
(28) **5c** was synthesized in 3 steps and 7% total yield by: Barltrop, J. A.; Johnson, A. J.; Meakins, G. D. *J. Chem. Soc.* **1951**, 181–185.

(29) Obtained by acetalization of the corresponding aldehyde as described by: Napolitano, E.; Giannone, E.; Fiaschi, R.; Marsili, A. *J. Org. Chem.* **1983**, *48*, 3653–3657.

(30) When the base was absent the benzylic acetal hydrolyzed partially. Thereupon the OH and CH=O groups combined forming a lactol, which was inert to the oxidant. The same kind of lactolization thwarted our attempts of *ortho*-lithiating benzaldehydes rather than benzaldehydedimethyl acetals by Comins in situ protection/*ortho*-lithiation strategy (Comins, D. L. *Synlett* **1992**, 615–625).

(31) The dimethylenation of ketoaldehyde **14g** giving dienone **10g** afforded a 92% yield only under "salt-free" conditions. The ylide resulting from $MePh_3P^{\oplus}$ $Br^{\ominus}$ and *n*-BuLi gave **10g** in 45% yield at best.

Scheme 6. Benzotropolone Syntheses Based on the *ortho*-Lithioacetal Approach of Scheme 5 (a Non-Hydrolytic Ketoketal Cleavage of **6g**→**15g** Is Included)[a]

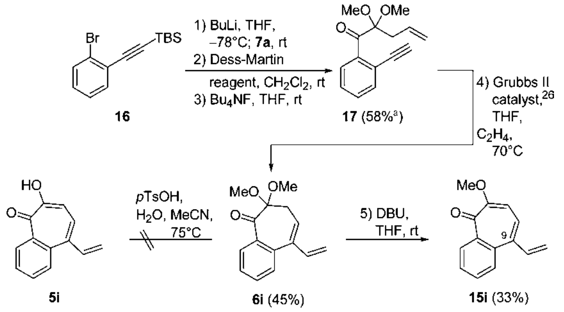


[a] Over the three steps. [b] Over the two steps.

benzannulated dienones **10f** and **g** uneventfully.[31] Ring closure by metathesis and ketal hydrolysis delivered 4-methoxybenzotropolone (**5f**) and 3,4-dimethoxybenzotropolone (**5g**), respectively. Both compounds had not been described. Optimizing their syntheses paid off by overall yields of 48% (**5f**) and 81% (**5g**). Bis(demethylation) of **5g** gave 75% of 3,4-dihydroxybenzotropolone (**5h**). 50 years ago the latter compound was synthesized by the mentioned[14] co-oxidation of a catechol (in this case: the catechol) and a pyrogallol (in this case: the pyrogallol)[32] in a single step with a 47−50% yield. Remarkably, the latter is less than the total yield of our six-step sequence: 61%. This underscores the efficiency of our strategy.[33]

A bypass for the ketal cleavage **6g**→**5g** (Scheme 6, middle), which we had performed at 75 °C under equally acidic conditions as the analogous cleavages **6a**−**f** →**5a**−**f** (Schemes 3−6), deserves mentioning. An LDA-induced *β*-elimination of methanol from the benzocycloheptadienedione monoketal **6g** provided 80% of 3,4-dimethoxybenzotropolone methyl ether (**15g**; Scheme 6, bottom). The latter was mono(demethylated) with BBr_3 at −78 °C at 4-O (→**15h**).[34] **15h** was di(demethylated) at rt giving 3,4-dihydroxybenzotropolone (**5h**) in 77% yield.

Scheme 7. Synthesis of the Benzotropolone Methyl Ether **15i** via a Ring-Closing Enyne Metathesis[a]



[a] Over the 3 steps.

Finally we tested our benzotropolone strategy replacing the ring-closing diene metathesis by a ring-closing enyne metathesis (Scheme 7). The requisite substrate **17** was obtained in a manner similar to that for the dienes **10a**−**d** by our *ortho*-lithiostyrene route (Schemes 3 and 4), namely by adding the lithioarene derived from (*ortho*-bromophenyl)-acetylene **16**[35] to the aldehyde **7a**. After oxidation and deprotection we obtained the enyne **17** in 58% yield over three steps. Ring-closing metathesis in the presence of 5 mol % of the Grubbs II catalyst[26] delivered the vinyl-substituted benzocycloheptadienedione monoketal **6i** in 45% yield. Attempted ketal cleavage with *p*TsOH led to decomposition rather than to the benzotropolone **5i**. However, a DBU-induced *β*-elimination of methanol delivered 9-vinyl-3,4-benzotropolone methyl ether (**15i**) in 33% yield.

The fact that benzoid aromatics can emerge from ring-closing metatheses may not be obvious but is well-known.[36] In the present study, it was established for the first time that a nonbenzenoid aromatic such as a tropolone can emerge from a ring-closing metathesis. This allowed access to the 3,4-benzotropolones **5a**−**h** in 4−6 steps with 22−81% overall yield and the 3,4-benzotropolone methyl ethers **15g**−**i** in 5 steps with 8.6−69% overall yield.

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Supporting Information Available. Experimental procedures, characterization data, copies of NMR spectra, and efficiency comparisons with previous syntheses of benzotropolones **5a**−**h** (if existing). This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) Horner, L.; Dürckheimer, W.; Weber, K.-H.; Dölling, K. *Chem. Ber*. **1964**, *97*, 312–324.

(33) Of course, this efficiency is more valuable when applied to the generation of benzotropolones off the co-oxidation manifold.

(34) The triflate derived from phenol **15h** suggests the possibility of preparing 4-modified benzotropolones in the sequel of Pd-catalyzed cross-coupling reactions.

(35) Compound **16** was prepared in 2 steps from 2-bromobenzaldehyde in 89% overall yield (see Supporting Information).

(36) van Otterlo, W. A. L.; de Koning, C. B. *Chem. Rev*. **2009**, *109*, 3743–3782.

The authors declare no competing financial interest.