ORGANIC LETTERS

2013
Vol. 15, No. 11
2582–2585

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

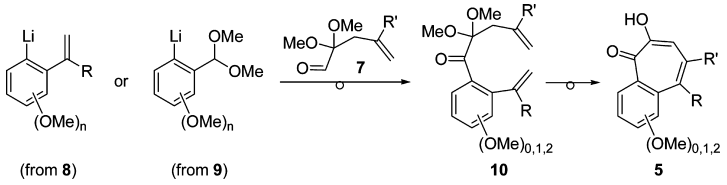
Deniz Arican and Reinhard Brückner*

Institut für Organische Chemie, Albert-Ludwigs-Universität, Albertstraße 21, 79104 Freiburg im Breisgau, Germany

reinhard.brueckner@organik.chemie.uni-freiburg.de

Received February 27, 2013; Revised Manuscript Received May 3, 2013

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]

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]

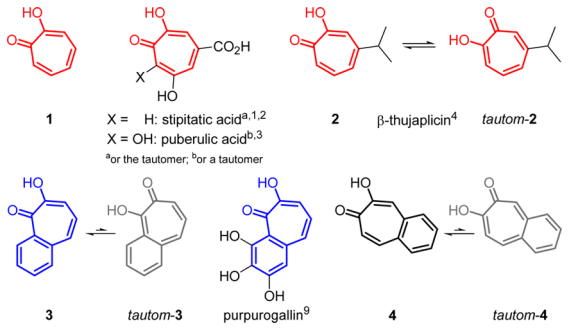


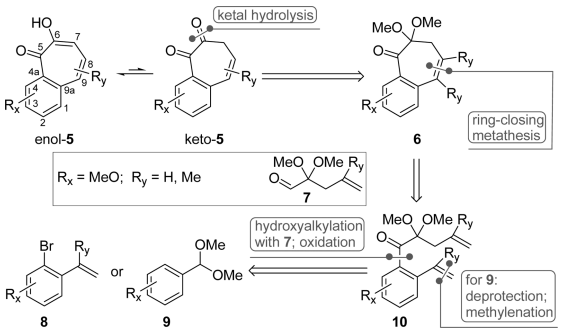
Figure 1. Tropolones (red), 3,4-benzotropolones (blue), and 6,7- (*tautom*-**3**), 4,5- (**4**), and 5,6-benzotropolone (*tautom*-**4**).

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

(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
Published on Web 05/13/2013

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**.

(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.

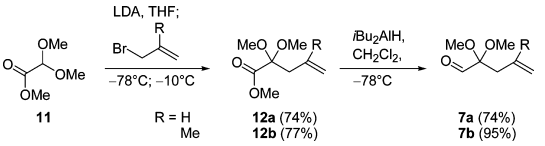
(16) (a) Synthesis of **3**: Cook, J. W.; Somerville, A. R. *Nature* **1949**, *163*, 410–410. (b) Recent example: Daştan, A.; Güney, M.; Balci, M. *Helv. Chim. Acta* **2005**, *88*, 830–838.

(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.

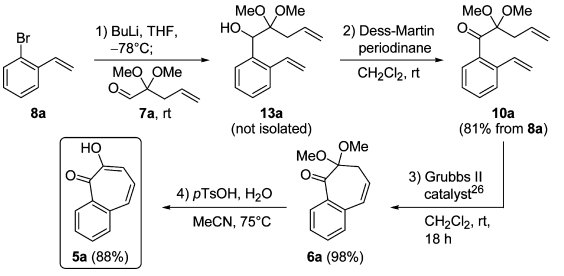
Scheme 2. Syntheses of 2,2-Dimethoxypent-4-enals **7a** and **b**



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 *i*Bu_2AlH[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

(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.

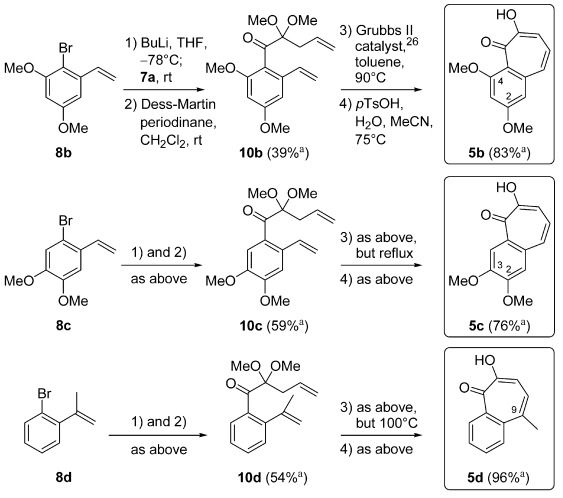
(21) (a) Cameron, A. G.; Hewson, A. T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2979–2983. (b) Griesbaum, K.; Meister, M. *Chem. Ber.* **1987**, *120*, 1573–1580.

(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]

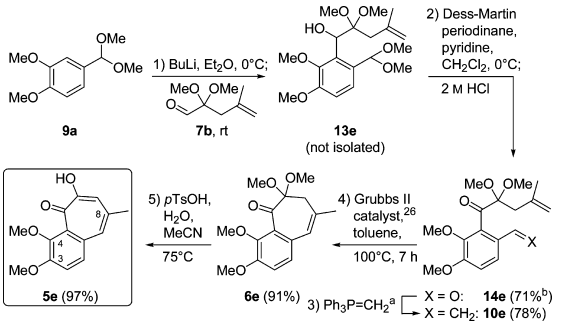
Scheme 4. Synthesis of 3,4-Benzotropolones **5b**–**d**: Embellishing the *ortho*-Lithiostyrene Approach of Scheme *3*,[a]



[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

(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).

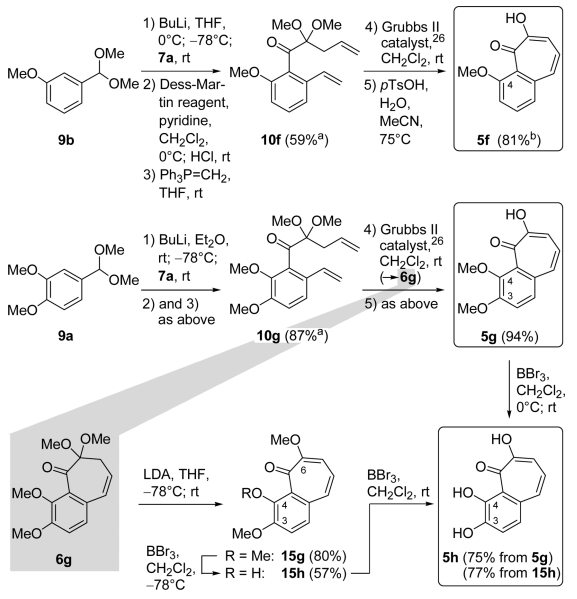
(28) **5c** was synthesized in 3 steps and 7% total yield by: Barltrop, J. A.; Johnson, A. J.; Meakins, G. D. *J. Chem. Soc.* **1951**, 181–185.

(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]

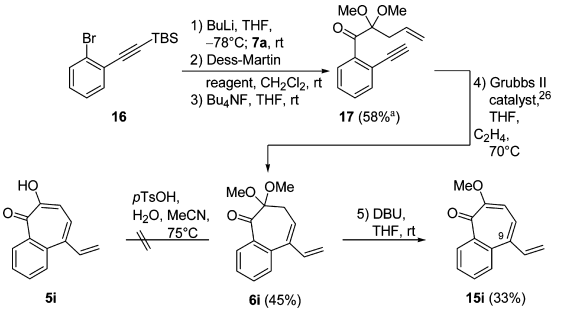


[a] Over the three steps. [b] Over the two steps.

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

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



[a] Over the 3 steps.

4-O (→**15h**).[34] **15h** was di(demethylated) at rt giving 3,4-dihydroxybenzotropolone (**5h**) in 77% yield.

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.

Acknowledgment. The authors thank Clara Heimburger (Institut für Organische Chemie, Albert-Ludwigs-Universität Freiburg) for technical assistance, Dr. Manfred Keller (Institut für Organische Chemie, Albert-Ludwigs-Universität Freiburg) for NMR experiments, and the IRTG 1038 (Deutsche Forschungsgemeinschaft) for financial support.

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.

The authors declare no competing financial interest.

(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.