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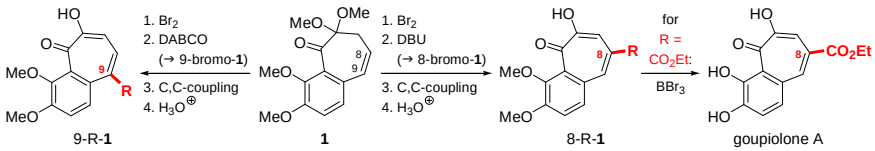

Carbofunctionalizing a C=C bond regioselectively: Adding Br_2 to the RCM product **1** and eliminating HBr gave 8-bromo-**1** using DBU and 9-bromo-**1** using DABCO. Both compounds underwent Sonogashira, Suzuki, Negishi, and Heck couplings and formed esters with CO in ROH. Hydrolysis of the ketal group liberated the enol moiety of benzotropolones type 8- or 9-R-**1**. One of them was bis(demethylated) providing goupiolone A in fewer steps (9) than hitherto (19).

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Nonbenzenoid Aromatic Compounds

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Regioselective Bromination of Benzocycloheptadienones for the Synthesis of Substituted 3,4-Benzotropolones Including Goupiolone A**

Deniz Arican,[†,‡] Stefan Braukmüller,[†] and Reinhard Brückner[†,]*

Abstract**: Type-**18** or -**23** benzocycloheptadienones are readily prepared by ring-closing olefin metatheses. Adding Br_2 to **23** and eliminating HBr gave the bromoolefin **28** using DBU or its isomer* iso-28** using DABCO, both with near-perfect regiocontrol. Both **28** and* iso-***28** underwent Sonogashira, Suzuki, Negishi, and Heck couplings as well as Pd-catalyzed alkoxycarbonylations. Hydrolysis of the resulting α-ketoketals and enolization of the liberated α-diketones delivered a portfolio of hitherto unknown 3,4-benzotropolones. The 8-ethoxycarbonylated dimethyl-3,4-benzotropolone **50** obtained by this route was demethylated to give goupiolone A (**52**). This synthesis encompasses 9 steps from **22**, i. e., half as many as the only previous synthesis (19 steps). A variant of our route afforded the 1,8-dibromide **54**. Coupling with excess phenylboronic acid and ketal hydrolysis provided the diphenylated benzotropolone **56** and suggests a strategy, by which the natural bispulvinone aurantricholone (**7**) might be reached.*

2-Hydroxycyclohepta-2,4,6-trienon-1-one (= tropolone) was the first isocyclic non-benzenoid aromatic compound recognized.[1] Tropolones may tautomerize to give "transposed" tropolones,[2] which may be separable by crystallization.[3] In contrast, 3,4-benzotropolones (**1**, Fig. 1) do not tautomerize (→ less stable[4] 6,7-benzotropolones). At least 36 3,4-benzotropolones including one bis(3,4-benzotropolone)[5] were identified in nature. Without exception their substitution patterns equal **2**. In the laboratory, such benzotropolones result from oxidizing mixtures of catechols (→ benzene moiety) and pyrogallols (→ tropolone moiety). The method was first reported i 1869 [2 × pyrogallol → purpurogallin (**3**)[6]] and, varying the oxidan has remained the most frequently used approach till now.[7,8] Recent ly, it provided the 3,4-benzotropolones **4**[7b] – the first "small mole cule" inhibitor of a toll-like receptor heterodimer[7b] and hence a lea for the chemotherapy of acne[9] or sepsis[10] – and **5**,[7a] namely thea flavin.[11]

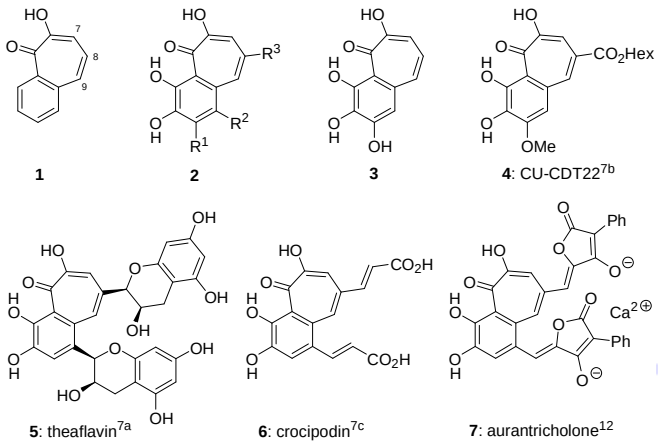

Figure 1. 3,4-Benzotropolone (**1**), 3,4-benzotropolones **2** from nature or, in the case of purpurogallin (**3**), from the oxidation of catechol/ pyrogallol mixtures. Selected *C*-functionalized synthetic (**4**) and naturally occurring 3,4-benzotropolones (**5**-**7**).

It appears as if not each benzotropolone of the substitution pat tern **2** is accessible by co-oxidizing catechol/pyrogallol mixtures c oxidizing pyrogallols alone. Crocipodin (**6**) is a reported excep tion.[7c] Aurantricholone (**7**)[12] might be another one.[13] Such limita tions invite to extend existing methodology – as en route to **6**[7c] – c to contribute novel methodology – like our metathesis route to ben zotropolones **10**.[14] It is outlined in Scheme 1. It perceives **10** as th enol of an α-diketone and reaches the latter by hydrolyzing the re spective monoketal **9**. Representing cycloalkenes as well, com pounds like **9** can be made by ring-closing type-**8** dienes in the pres ence of the 2nd generation Grubbs catalyst[15] ("Grubbs II catalyst").

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Supporting information (Experimental procedures, characterization data, copies of NMR spectra, and crystallographic details) for this article is available on the WWW under http://www.angewandte.org.

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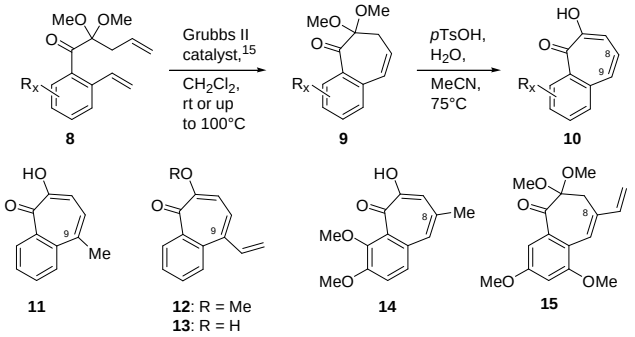
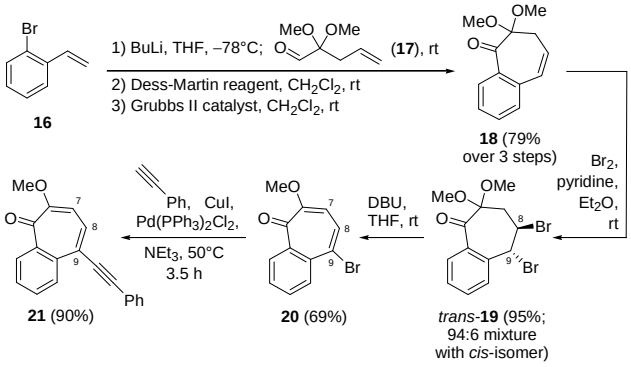


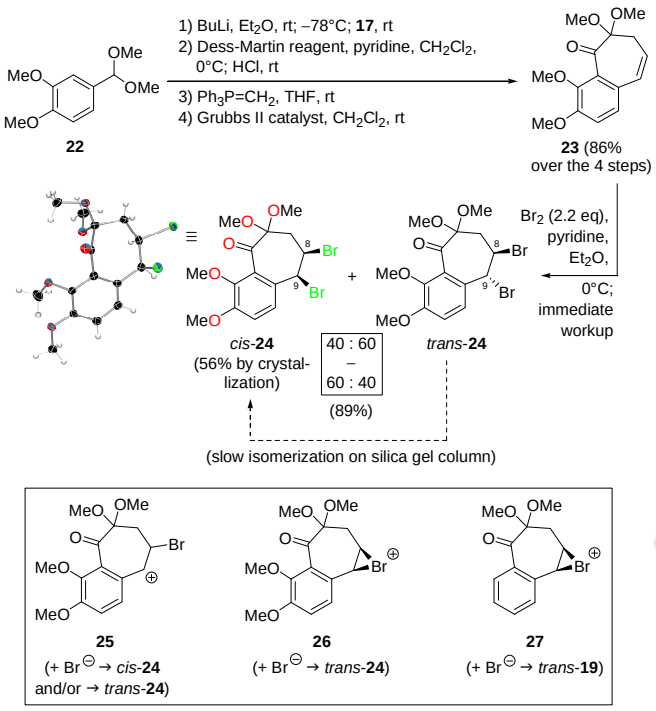
Scheme 1. Existing ring-closing metathesis route to 3,4-benzotropolones **10**.[14] *C*-Functionalizations realized by this strategy (**11**,[14] **14**[14]) or by analogous enyne metatheses (**13**,[14] **15**[16]).

Most benzotropolones **10** prepared as sketched in the preceding paragraph[14] were unsubstituted at C-8 and C-9 (Scheme 1). However, subjecting the α-methylstyrene analog of diene **8**, R_x = H, to the same transformations gave the 9-methylated benzotropolone **11**.[14] Likewise, diene **8**, R_x = 2 × OMe, with a methallyl rather than allyl group furnished the 8-methylated benzotropolone **14**.[14] Replacing, alternatively, one vinyl group of type-**8** dienes by an ethynyl group allowed ring-closures by enyne metatheses. This led to the 9-vinylated benzotropolone **12**[14] (yet not to the *O*-unprotected parent compound **13**) as well as to the 8-vinylated ketal **15**[16] (but no closer to an 8-vinylated benzotropolone). *Here* we disclose – exemplarily – how manipulating the unsubstituted C^8=C^9 bond of the previously described[14] ring-closure products **18** (Scheme 2) and **23** (Scheme 3) leads to a manifold of 9- (Scheme 5) and 8- functionalized 3,4-benzotropolones (Scheme 6).



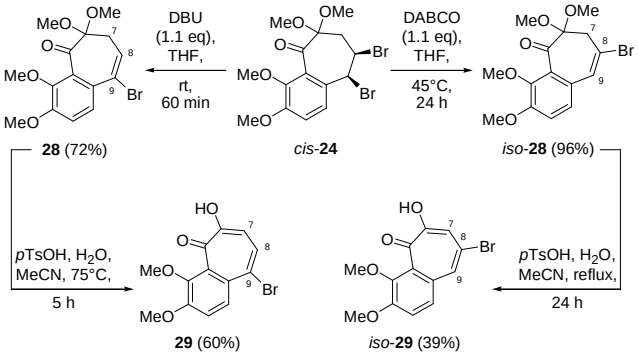
Scheme 2. Synthesis of benzocycloheptadienone **18**,[14] functionalization with Br_2, and a proof-of-principle C,C-coupling.

The benzocycloheptadienone **18** was made from *ortho*-bromostyrene (**16**) in 3 steps[14] (Scheme 2). It picked up elemental bromine in 95% yield with a 94:6 *trans*:*cis*-selectivity[17]. The product mixture and 5 equiv. of DBU underwent β-eliminations both of HBr and MeOH. The benzotropolone methyl ether **20** resulted in 69% yield, the bromine substituent residing at C-9.[18] It Sonogashira-coupled phenylacetylene in triethylamine. This gave 90% of the corresponding benzotropolone ether **21**.



Scheme 3. Synthesis of benzocycloheptadienone **23**[14] and its reaction with elemental bromine. ORTEP plot of the crystal structure of dibromide *cis*-**24** at 115 K.[19]– For the role of the precursors **25**/**26** of dibromides *cis*- and *trans*-**24** and **27** of the precursor **27** of dibromide *trans*-**19** see footnote[20].

The mentioned benzocycloheptadienone **23** was prepared fror the substituted benzaldehyde acetal **22** in 4 steps[14] (Scheme 3) Adding bromine to the C^8=C^9 bond of **23** furnished mixtures (up t 89% yield) of similar amounts of the dibromide diastereomers *cis* **24** ($^3J_{H–CBr–CBr–H}$ = 1.9 Hz) and *trans*-**24** ($^3J_{H–CBr–CBr–H}$ = 4.8 Hz) Working up such mixtures by crystallization from cyclohex ane/AcOEt (5:1) allowed to isolate pure *cis*-**24** [56% yield from **23** m.p. 158-159°C (dec.)]. Its 3D structure was established by singl crystal X-ray analysis[19] (Scheme 3).[20,21] The isomeric dibromid *trans*-**24** was enriched by subjecting mixtures of *cis*- and *trans*-**24** t flash-chromatography on silica gel.[22] However, we could not su pass *trans*-contents of 85:15. This was because on silica *trans*-**2** tended to isomerize giving *cis*-**24** anew.



Scheme 4. Regioselective dehydrobromination of dibromide *cis*-**24** furnishing the bromoolefin isomers **28** and *iso*-**28**. Hydrolyses to the corresponding bromobenzotropolones.

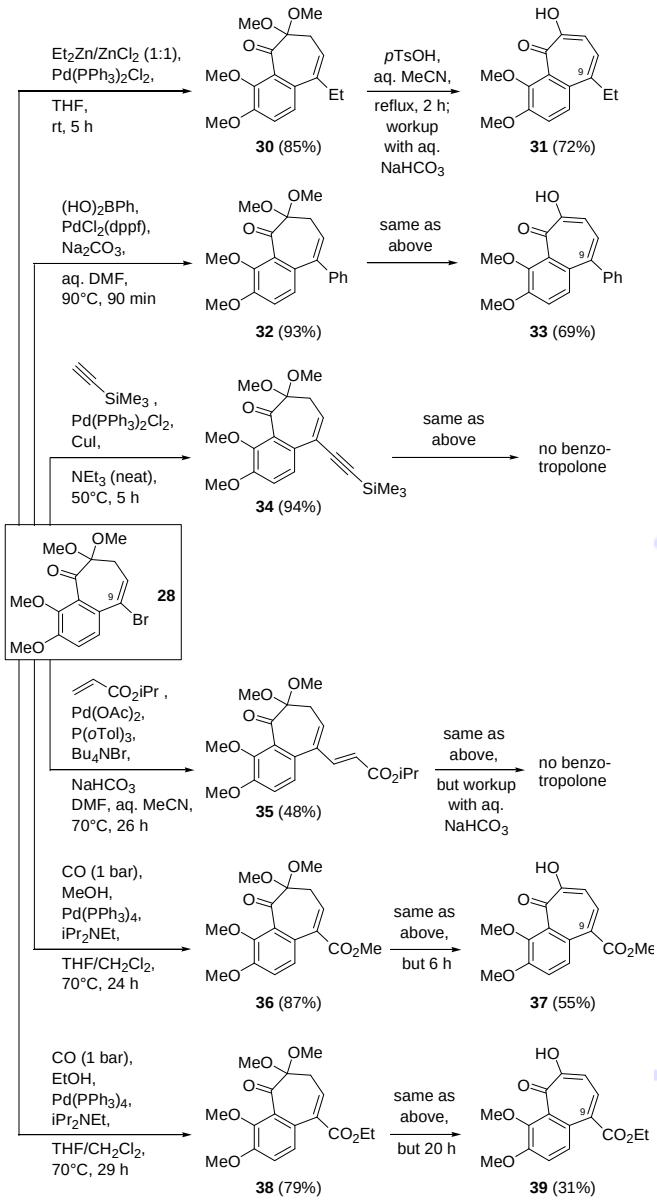
We found that the dibromide *cis*-**24** could be dehydrobrominated in the two conceivable directions with perfect regiocontrol (Scheme 4). Treatment of a THF solution of *cis*-**24** with DBU at ambient

temperature for 2 h furnished a single bromoolefin **28** in 72% yield. It contained the motive C_{quat}–$^{7}CH_2$–^{8}CH=^{9}CBr–C_{quat} in the cycloheptadienone ring as shown ^{1}H-NMR spectroscopically. [23] In contrast, treatment of a THF solution of dibromide *cis*-**24** with DABCO at 45°C for 24 h furnished the bromoolefin *iso*-**28** in 96% yield. Its ^{1}H-NMR spectrum revealed the presence of a C_{quat}–$^{7}CH_2$–^{8}CBr=^{9}CH–C_{quat} unit in the cycloheptadienone ring.[24]

Unpurified mixtures (~1:1) of dibromides *cis*- and *trans*-**24** delivered the bromoolefins **28** or *iso*-**28** as single regioisomers, too, when dehydrobrominated with DBU or DABCO, respectively. The respective yields were 65% and 81% and hence 7% and 15% lower than when to the dehydrobrominating the pure dibromide *cis*-**24**. Because of the higher overall yields, employing **24** as an isomeric mixture was preferable.

Acid-catalyzed hydrolyses of the α-ketoketal moieties of bromoolefins **28** or *iso*-**28** in hot aqueous acetonitrile gave the 9-bromobenzotropolone **29** in 60% yield and the 8-bromobenzotropolone *iso*-**29** in 39% yield (Scheme 4). We did not attempt to cross-couple these compounds although the Sonogashira coupling of Scheme 2 suggests some feasibility. However, the free OH groups of the benzotropolones **29** and *iso*-**29** might interfere with the intended Negishi or Suzuki couplings due to their acidity. We circumvented such problems by cross-coupling the preceding bromoolefins **28** (details: Scheme 5) and *iso*-**28** (details: Scheme 6). Most coupling products delivered the corresponding benzotropolone when hydrolyzed under the previously employed conditions.[14]

The bromoolefin **28** allowed to engage its C^9–Br bond in representative couplings of the Negishi (Scheme 5; → 85% **30**), Suzuki (→ 93% **32**), Sonogashira (→ 94% **34**), and Heck types (→ 48% **35**). The *C*-nucleophiles incorporated during these reactions were ethylzinc chloride, phenylboronic acid, (trimethylsilyl)ethyne, and isopropyl acrylate, respectively. In another coupling, pioneered by Tsuji, cat. $Pd(PPh_3)_4$ allowed to alkoxycarbonylate the bromoolefin **28** adding methanol or ethanol as a co-solvent and an atmosphere of CO. The latter was supplied at atmospheric pressure.[25] This afforded the methyl ester **36** in 87% yield and the ethyl ester **38** in 79% yield. The Negishi coupling, Suzuki, Sonogashira coupling, and alkoxycarbonylation products hydrolyzed under our standard conditions (*p*TsOH, aq. MeCN, prolonged heating). This provided the respective 9-substituted benzotropolones **31**, **33**, **37**, and **39** in 31-72% yield. The enyne moiety formed in the Sonogashira coupling and the dienoic ester moiety formed in the Heck coupling did not stand up to these hydrolysis conditions. By consequence, the respective compounds (**34**, **35**) degraded without rendering benzotropolones.



Scheme 5. Exemplary C,C-couplings with the 9-brominated precursor **28** of 9-*C*-functionalized benzotropolones..

The bromoolefin *iso*-**28** underwent identical cross-couplings at C 8 (Scheme 6) as its isomer **28** underwent at C-9 (Scheme 5). I. e *iso*-**28** Negishi-coupled with ethylzinc chloride at room temp. (– 86% **40**), Suzuki-coupled with phenylboronic acid at 90°C (→ 82% **42**), Sonogashira-coupled with (trimethylsilyl)ethyne at 50°C (– 67% **44**) and Heck-coupled with excess isopropyl acrylate at 70°C (→ 83% **46**). Moreover, the bromoolefin *iso*-**28** was methoxy carbonylated by CO at 1 bar and methanol. This furnished th methyl ester **47** in 75% yield. Analogously, *iso*-**28** was ethoxy-carbonylated by CO and ethanol. This rendered the ethyl ester **49** in 84% yield. 5 of the 6 coupling products of Scheme could be hydrolyzed in yields ranging from 49 to 90%. The Sonogashira coupling product **44** was amenable to such a hydrolysis, too. However, its enyne motive was hydrated concomitantly. Accordingly, the resulting benzotropolone **45** displays an acetyl group at C-8 instead of 2-(trimethylsilyl)ethyn-1-yl. The Heck-coupling product **46** did not tolerate hydrolysis conditions and therefore rendered no benzotropolone.

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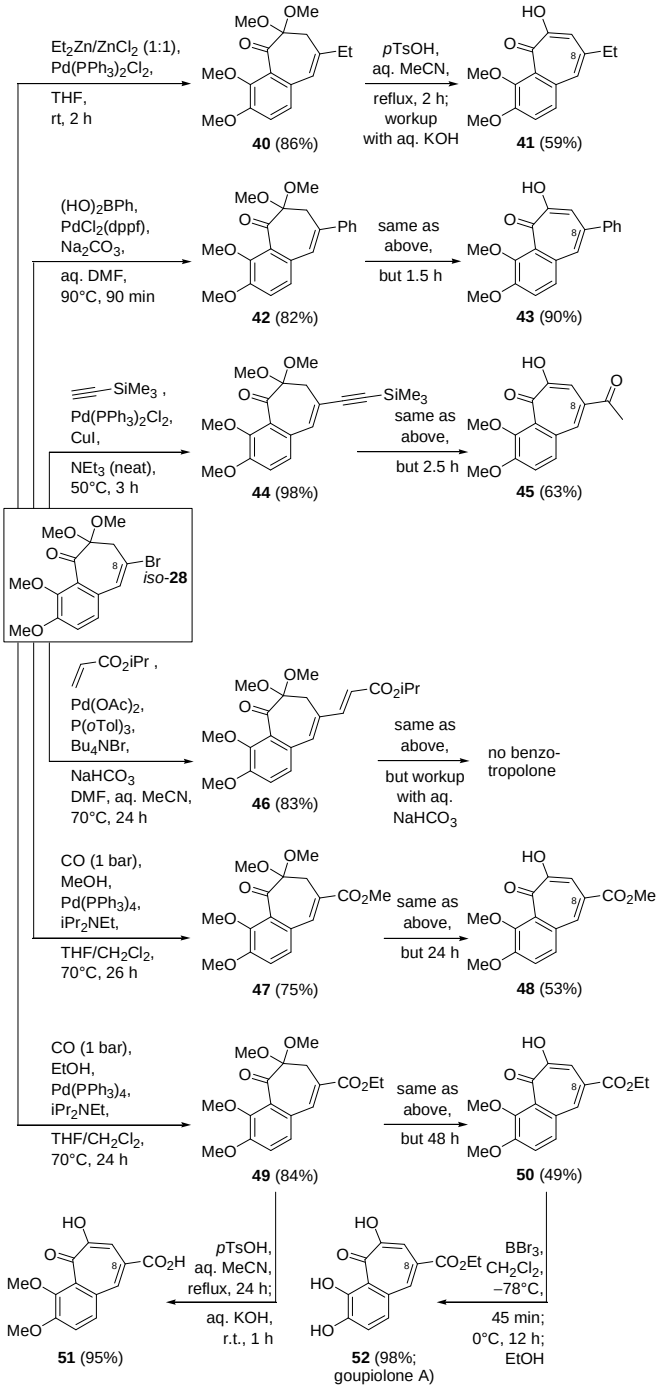
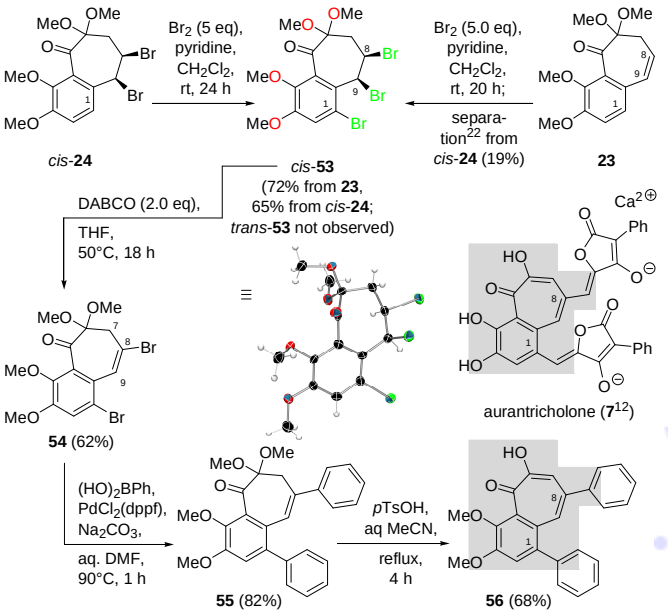


Scheme 6. Illustrative C,C-couplings with the 8-brominated precursor *iso*-**28** of 8-*C*-functionalized benzotropolones.

Hydrolyzing the CO_2Et-containing product **49** in acidic aqueous acetonitrile at reflux temperature for 48 h led to the CO_2Et-containing benzotropolone **50** in 49% yield (Scheme 6). The ester moiety survived the ensuing cleavage of the methoxy groups with BBr_3, too. It delivered 98% of the CO_2Et-containing catechol **52**. This compound equals synthetic goupiolone A. In the current study, it emerges from a 9-step synthesis. It establishes the substituted tropolone moiety in a straightforward manner. The only previous synthesis of goupiolone A (**52**) required 19 steps.[26]



Scheme 7. Model study for a total synthesis of the benzotropolone natural product aurantricholone (**7**[12]) by the bromination/cross-coupling strategy of this work: synthesis of dibromide **54** via tribromide *cis*-**53**, one-pot bis(Suzuki coupling), and hydrolysis/tautomerism to the benzotropolone **56**.

In an extension of our strategy we treated the benzocycloheptadi enone **23** with 5 equiv. of bromine in CH_2Cl_2 rather than with 2. equiv. of bromine in diethyl ether as before (Scheme 3). Now the di bromide *cis*-**24** resulted to some extent (19%) but the tribromide **5** predominantly (72%; Scheme 7). X-ray crystallography reveale that **53** was *cis*-configured.[27] This compound originates from sub strate **23** by a *cis*-addition/*para*-substitution sequence. Indeed, bro mine and the pure dibromide *cis*-**24** reacted to give the same tribro mide *cis*-**53** in 65% yield. DABCO dehydrobrominated this tribrom ide with the same regioselectivity, with which it dehydrobrominate the dibromide *cis*-**24**. In the case at hand (Scheme 7), the bromoar ene/bromoolefin **54** formed as the sole product (62% yield).[28]

At 90°C the bromoarene/bromoolefin **54** and phenylboronic aci Suzuki-coupled under $PdCl_2$(dppf)-catalysis within one hour both a the C^1–Br and the C^8–Br bond (Scheme 7).[29] The bis(couplin product) **55** resulted in 82% yield. Its α-ketoketal moiety could b hydrolyzed as usually (*p*TsOH, aq. MeCN). This provided 68% o the diphenylated benzotropolone **56**. The bicyclic cores of the latte compound, of crocipodin (**6**;[6] Scheme 1), and of aurantricholon (**7**[12]) exhibit identical *O*- and *C*-functionalization sites. With regar to aurantricholone (**7**) this hints at how a total synthesis might b approached – provided one knew a coupling partner for introducin unprotected 4-methylidene-2-phenyltetronic acid groups. Efforts to wards developing such a reagent and the respective cross-couplin conditions are underway in our laboratory.

The benzotropolone syntheses presented here should be readily extendable. The benzene moiety in our key intermediate **23** need not be methoxylated as proved by the bromination **18**→**20** in the entire absence of methoxy groups (Scheme 2). In fact this benzene moiety might tolerate a variety of other substituents. Moreover, compounds like the bromoarene/bromoolefin **54**[29] or analogous iodoarene/bro moolefins look like precursors of bis(carbofunctionalized) benzo tropolones.

Experimental Section

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Keywords: bromination • C,C coupling • dehydrobromination • natural products • nonbenzenoid aromatics • ring-closing olefin metathesis •

Full experimental details are given in the Supporting Information.

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[17] The configurational assignments of dibromides *trans*-**19** *vs. cis*-**19** were based on ^{1}H-NMR comparisons with dibromides *trans*-**24** and *cis*-**24**; the configuration of dibromide *cis*-**24** was clear from the X-ray analysis (Scheme 3). For example, the coupling constant $^3J_{8,9}$ differed characteristically in *trans*-**19** (4.6 Hz) and *trans*-**24** (4.5 Hz) from the 1.9 Hz measured for both *cis*-**19** and *cis*-**24**.
[18] ^{1}H NMR$_{\mathbf{20}}$, tropolone moiety ($CDCl_3$, 400 MHz): δ_{OMe} = 3.85 (d, $^5J_{OMe,7}$ = 0.4 Hz), $\delta_{7\text{-H}}$ = 6.20 (dq, $^3J_{7,8}$ = 9.8 Hz, $^5J_{7,OMe}$ = 0.4 Hz), $\delta_{8\text{-H}}$ = 7.39 ppm (d, $^3J_{8,7}$ = 9.8 Hz).
[19] The crystallographic data of dibromide *cis*-**24** are contained in CCDC 1505660. They can be obtained free of charge from the *Cambridge Crystallographic Data Centre* via the link www.ccdc.cam.ac.uk/data_request/cif.
[20] The intermediacy of bromonium-ion **27** (Scheme 3) in the bromination of benzocycloheptadienone **18** explains why dibromide *trans*-**19** results with a 94:6 preference (Scheme 2). The *cis*-addition of bromine to benzocycloheptadienone **23** implies the intermediacy of carbenium-ion **25** (Scheme 3). It remains unknown whether the latter forms directly from the reactants or indirectly from a *trans*→*cis* isomerization of initially formed dibromide *trans*-**24**. Carbenium-ion **25** looks stabilized by the +M effect of one methoxy group.
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[23] The respective ^{1}H-NMR resonances ($CDCl_3$, 400 MHz) were: $\delta_{7\text{-H}}$ = 2.59 (d, $^3J_{7,8}$ = 7.7 Hz), $\delta_{8\text{-H}}$ = 6.26 ppm (t, $^3J_{8,7}$ = 7.7 Hz).
[24] Pertinent ^{1}H-NMR resonances ($CDCl_3$, 400 MHz) were: $\delta_{7\text{-H}}$ = 3.15 (d, $^4J_{7,9}$ = 1.4 Hz), $\delta_{9\text{-H}}$ = 6.26 ppm (t, $^4J_{9,7}$ = 1.4 Hz).
[25] Pd-catalyzed ester formations under related conditions are known, e.g., in the presence of the diphosphanes Xantphos (J. R. Mantinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder, S. L. Buchwald, *J. Org,. Chem.* **2008**, *73*, 7102-7107) or BINAP (W. Yang, W. Han, W. Zhang, L. Shan, J. Sun, *Synlett* **2011**, 2253-2255).
[26] N. Fukui, K. Ohmori, K. Suzuki, *Helv. Chim. Acta* **2012**, *95*, 2194 2202.
[27] The crystallographic data of tribromide *cis*-**53** are contained in CCDC 1505661. They can be obtained free of charge from the *Cambridge Crystallographic Data Centre* via the link www.ccdc.cam.ac.uk/data_request/cif.
[28] Pertinent ^{1}H-NMR resonances ($CDCl_3$, 400 MHz): $\delta_{7\text{-H}}$ = 3.16 (d, $^4J_{7,9}$ = 0.5 Hz), $\delta_{9\text{-H}}$ = 7.08 ppm (t, $^4J_{9,7}$ = 0.5 Hz).
[29] Interestingly, the bromoarene/bromoolefin **54** revealed a potential for being amenable to *differential* sequential biscouplings: It picked up a C^1-substituted propargyl alcohol selectively at C^8–Br (76% yield).