Check for updates

EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

Title: 6,7-Benzotropolone Syntheses Based on Ring-Closing Metatheses and Four-Electron Oxidations Table of Contents Title: 6,7-Benzotropolone Syntheses

Authors: Michael Kreibich, Manuel Gemander, David Peter, Dharmendra B. Yadav, Charles B. de Koning, Manuel A. Fernandes, Ivan R. Green, Willem A. L. van Otterlo, and Reinhard Brückner

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202000256

Link to VoR: http://dx.doi.org/10.1002/ejoc.202000256

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.202000256

WILEY-VCH

FULL PAPER

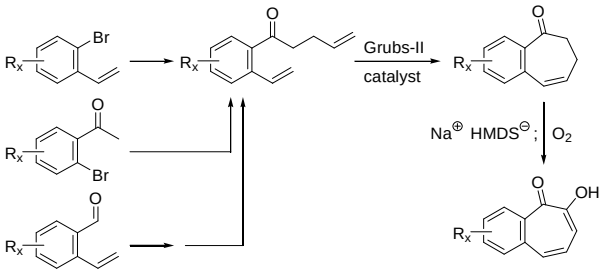
Table of Contents Title:

6,7-Benzotropolone Syntheses Based on Ring-Closing Metatheses and Four-Electron Oxidations

Short Title:

6,7-Benzotropolone Syntheses

Michael Kreibich, Manuel Gemander, David Peter, Dharmendra B. Yadav, Charles B. de Koning, Manuel A. Fernandes, Ivan R. Green, Willem A. L. van Otterlo, Reinhard Brückner



Homoallyl *ortho*-vinylaryl ketones were prepared via several different routes. In the presence of 1-2 mol-% Grubbs-II catalyst, these substrates cyclized to give 6,7-dihydrobenzocyclohepten-5-ones. The enolates derived therefrom by treatment with NaHMDS in THF were oxidized by a stream of molecular oxygen at 0°C. This furnished 6-hydroxybenzocyclohepten-5-ones (“6,7-benzotropolones”).

Accepted Manuscript

This article is protected by copyright. All rights reserved.

WILEY-VCH

FULL PAPER

6,7-Benzotropolone Syntheses Based on Ring-Closing Metatheses and Four-Electron Oxidations

Michael Kreibich,[a] Manuel Gemander,[a] David Peter,[a] Dharmendra B. Yadav,[b] Charles B. de Koning,[b] Manuel A. Fernandes,[b] Ivan R. Green,[c] Willem A. L. van Otterlo,*[b,d] Reinhard Brückner,*[a,e]

Abstract: Four homoallyl *ortho*-vinylaryl ketones (**10a**-**d**) – 1,8-dienes of sorts – were prepared by several approaches. In the presence of 1-2 mol-% Grubbs-II catalyst, they ring-closed to give 6,7-dihydrobenzocycloheptен-5-ones (**11a**-**d**) in 90-96% yield. With SeO_2 the parent compound (**11a**) delivered benzocycloheptен-5-one (**13a**) and/or selenium-containing compounds (**18**-**22**) but no more than traces of 6,7-benzotropolone (**5a**). However, **5a** was accessible from compound **11a** via the sodium enolate and allowing the latter to react with a stream of oxygen (43% yield). The sodium enolates of the substituted 6,7-dihydrobenzocycloheptен-5-ones **11b**-**d** and oxygen underwent analogous 4-electron oxidations. This furnished the substituted 6,7-benzotropolones **11b**-**d**. In contrast, the corresponding lithium enolates were inert towards oxygen. The 6,7-dihydrobenzocycloheptен-5-one **11d** was also accessed differently, namely by a Grubbs-II catalyst-mediated RCM / C=C migration tandem reaction of the allyl *ortho*-allylaryl ketone **73** – another 1,8-diene of sorts (90% yield).

Introduction

Atropine (Figure 1) has been known for almost 200 years.[1] It is the racemate obtained from attempts to extract its (*S*)-enantiomer, the alkaloid (–)-hyosciamine, from *Atropa belladonna* with base.[2] Atropine is composed of two nitrogen-containing heterocycles and an isocyclic periphery which constitutes a trisubstituted cycloheptane. That peripheral ring's relationship to *Atropa belladonna* inspired the trivial names for a number of cycloheptatrienes: "tropylidene[3,]" for cycloheptatriene itself, "tropylium cation[4,5]" for the cycloheptatrienylium cation, "tropone[6]" for cycloheptatrienone, and "tropolone[7]" for 2-hydroxycyclohepatrien-2-one (**1**; Figure 1). Tropone and tropolone can be desribed by resonance forms

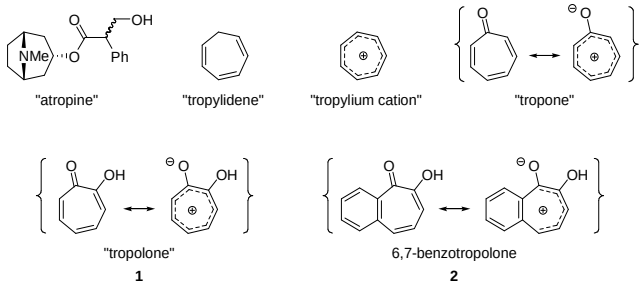
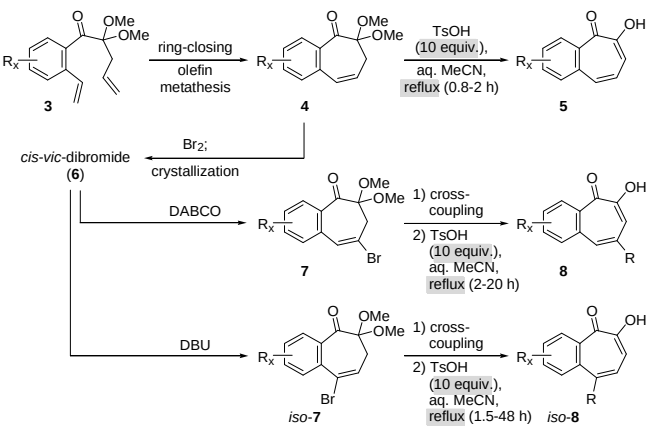


Figure 1: Atropin-based trivial names; tropolone (**1**) and 6,7-benzotropolone (**2**), a donor-substituted cyloheptatrienylium cation and its benz-annulation product, respectively.

which characterize them as donor-substituted cycloheptatrienylium cations. The fusion of a benzene ring to a tropolone core defines two bicyclic compounds, namely "6,7-benzotropolone" (**2**; Figure 1) and "3,4-benzotropolone" (not depicted). The present paper deals with the unsubstituted 6,7-benzotropolone and methoxylated derivatives thereof.



Scheme 1: Top: Our previously established ring-closing olefin metathesis ("RCM") / ketal hydrolysis route to type-**5** 6,7-benzotropolones.[9] Underneath: Regiocomplementary processings of a type-**4** RCM product via the dibromide **7** and the bromoolefins **7** or *iso*-**7** by cross-couplings and hydrolyses giving type-**8** or -*iso*-**8** 6,7-benzotropolones, respectively.[10]

6,7-Benzotropolone (**2**; Figure 1) and substituted 6,7-benzotropolones have been synthesized by at least ten different approaches.[8] The newest strategy is from one of our own the laboratories: (1) Arican developed a ring-closing olefin metathesis ("RCM"; → **4**) / ketal hydrolysis (→ **5**) route[9] whose key steps are sketched in row 1 of Scheme 1. (2) Arican embellished the just mentioned approach by functionalizing the C=C bond formed in the RCM step in 3 extra-steps which preceded the respective

[a] Dr. M. Kreibich, M. Gemander (M. Sc.), Dr. D. Peter, Prof. Dr. R. Brückner
Institut für Organische Chemie, Albert-Ludwigs-Universität
Albertstraße 21, 79104 Freiburg (Germany)
[b] D. B. Yadav (M. Sc.), M. A. Fernandes (M. Sc.), Prof. W. A. L. van Otterlo, Ph. D.
Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, PO Wits, 2050, Johannesburg (South Africa)
[c] Prof. I. R. Green, Ph. D.
Stellenbosch 7602, Western Cape (South Africa)
[d] Prof. W. A. L. van Otterlo, Ph. D.
Stellenbosch 7602, Western Cape (South Africa)
E-mail: wvo@sun.ac.za
Homepage: http://willemvanotterlo.co.za/
[e] Prof. R. Bruckner, Ph. D.
E-mail: reinhard.brueckner@organik.chemie.uni-freiburg.de
Homepage: http://www.brueckner.uni-freiburg.de
The ORCID from the author of this article is available on the WWW under http://orcid.org/0000-0002-9028-8436.
Supporting information for this article is given via a link at the end of the document.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

ketal hydrolysis:[10] by adding Br_2, eliminating HBr, and cross-coupling the resulting bromolefins with organometallic nucleophiles. Gratifyingly, the respective HBr-eliminations could be realized with complementary regioselectivities, delivering either of the bromoolefins **7** and *iso*-**7** selectively.[10] Their cross-couplings and the ensuing enol-releasing ketal hydrolyses provided the corresponding benzotropolones **8** or *iso*-**8** isomerically pure as well.[10]

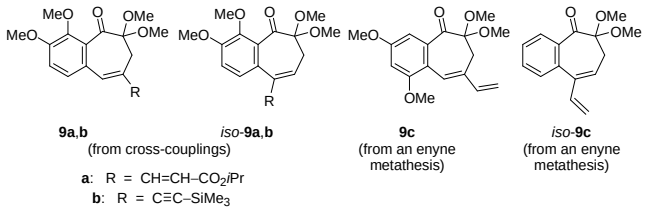
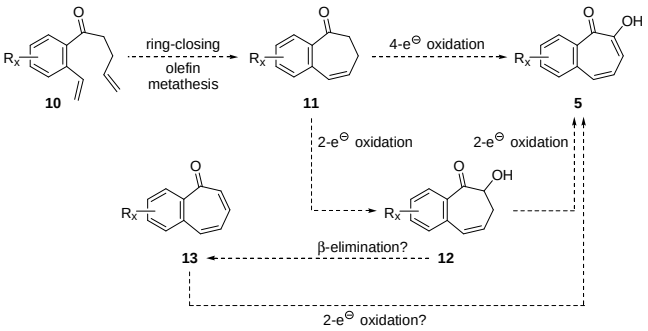


Figure 2: Ketals **9** or *iso*-**9** whose hydrolyses provided no benzotropolones at all (**9a**,[10] **c**[9], *iso*-**9a**,[10] **b**,[10] **c**[9]) or gave a 6,7-benzotropolone with a modified side-chain (**9b**[10]).

The Arican routes of Scheme 1 have a major drawback, though, namely the harsh conditions required for hydrolyzing a type-**4** ketal in the last step: Liberating the enol required refluxing with 10 equiv. of tosic acid and 100 equiv. of water in acetonitrile for 1 h – 2 d.[9,10] These conditions were applicable to certain type-**9** or type-*iso*-**9**-ketals, as well (Figure 2). When their substituent R was Et, Ph, CO_2Me or CO_2Et, such hydrolyses also proceeded well.[9] However, when their substituent R was CH=CH–CO_2*i*Pr (in **9a** or *iso*-**9a**), H_2C=CH (in **9c** or *iso*-**9c**) or C≡C–$SiMe_3$ (in *iso*-**9c**) the substrate vanished under hydrolysis conditions without delivering any benzotropolone.[9,10] The C≡C–$SiMe_3$-containing ketal **9b** was an in-between-case: Its hydrolysis released a benzotropolone as expected but the side-chain R had been converted into C(=O)–CH_3.[10]



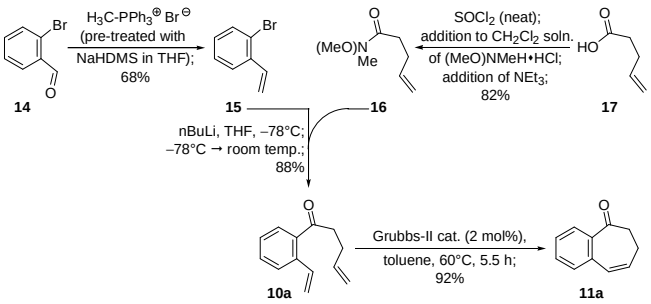
Scheme 2: Can 6,7-benzotropolones **5** be reached via an RCM / oxidation route rather than via the RCM / hydrolysis route of Scheme 1? A 4-e⊖ oxidation **11**→ **5** would be required overall, but two 2-e⊖ oxidations **11**→ **12** and **12**→**5** might be used as an alternative.

Scheme 2 shows how we intended to prepare benzotropolones **5** without the ketal hydrolyses being invoked in the 2-step transformations **4** → **5**, **7** → **8**, and *iso*-**7** → *iso*-**8** of Scheme 1: by depriving the former metathesis substrates **3** of their ketal group. This change meant subjecting ketal-free type-**10** dienes to the RCM reaction. The resulting cycloheptenones **11** would then also be ketal-free. Subsequently, they would have to undergo a 4-electron oxidation for rendering benzotropolones **5** in a single step.

Alternatively, the products **11** of Scheme 2 might be subjected to two 2-electron oxidations for attaining benzotropolones **5** – in two steps: step 1 would lead to a hydroxycycloheptone **12**, step 2 would proceed to a benzotropolone **5**. We wondered whether-step 2 might be disadvantaged vs. a dehydration delivering the benzotropone **13**. While **13** looks like a dead-end at first, it might be re-routable towards **5**. This is because unsubstituted benzotropone (**13**, all R = H) gave unsubstituted benzotropolone (**5**, all R = H) by endoperoxide formation and an ensuing reduction with thiourea.[11] Consequently, benzotropones **13** appeared as conceivable intermediates of our Scheme 2 strategy towards benzotropolones.

A Modified Synthesis of 6,7-Benzotropolone

Our proof-of-principle benzotropolone synthesis by the approach of Scheme 1 delivered the parent compound **5a** and is shown in Scheme 3 and Scheme 5. Scheme 3 advances to the RCM product and Scheme 5 supplements its oxidation.



Scheme 3: Reaching the RCM product **11a**, our synthetic precursor of unsubstituted benzotropolone (**5a**).

Our synthesis began by a salt-free Wittig methylidenation of *ortho*-bromobenzaldehyde (**14**, Scheme 3).[12] The resulting *ortho*-bromostyrene (**15**) was treated sucessively with nBuLi and the Weinreb amide **16**,[13] the latter being obtained via the chloride of pent-4-enoic acid (**17**) by a published[14] procedure. This provided *ortho*-(pent-4-enoyl)styrene (**10a**) in 88% yield. This compound ring-closed in toluene solution at 60°C in the presence of 2 mol% of the 2nd generation Grubbs catalyst[15] ("Grubbs II catalyst"). Yields were 92% on a gram scale or 99% for a 0.4 mmol batch.

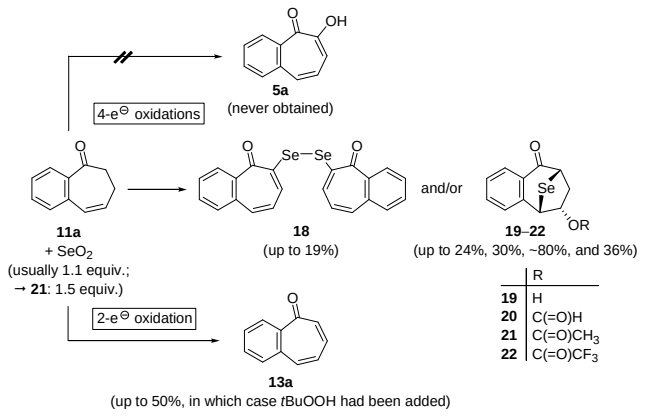
Our RCM product **11a** contained a C_{quat}–C(=O)–CH_2 motif. It should allow for this compound to be subjected to a SeO_2 („Riley"[16]) oxidation. That would establish a C_{quat}–C(=O)–C(=O) moiety,[17] whose enolization would deliver benzotropolone. However, the RCM product **11a** also contained an additional C_{quat}–CH=CH–CH_2 motif. The latter was a second conceivable point of attack of SeO_2, in which case it would react to give either an allyl alcohol or the corresponding enone.

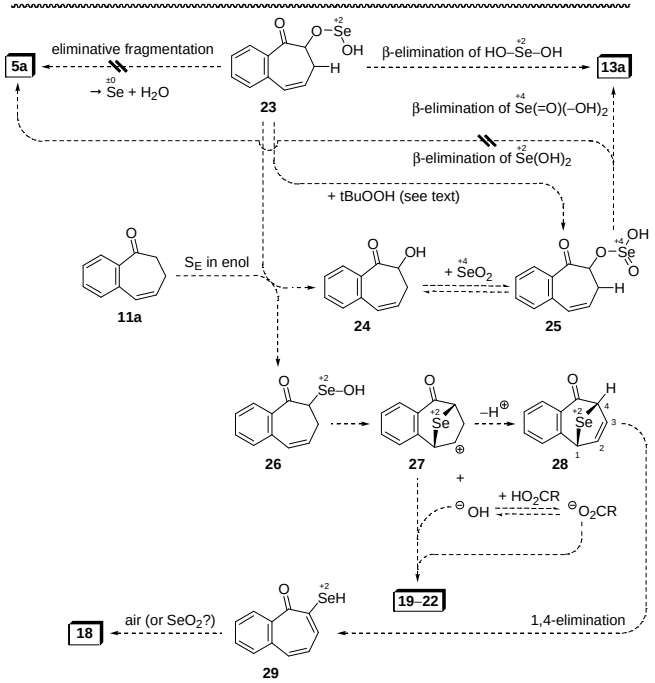
In fact SeO_2 attacked the C_{quat}–C(=O)–CH_2 rather than the C_{quat}–CH=CH–CH_2 motif of compound 11a (Scheme 4, at top). We tried this oxidation in about 30 variations of solvent (hexane, chlorobenzene, toluene, *ortho*-xylene, diethyl ether, DME, THF, aq. dioxane, dichloromethane, acetonitrile, water, formic acid, acetic acid, trifluoroacetic acid, diisopropylamine), temperature (20°C – 155°C), and time (3 h – 6 d). The following products were isolated and identified: the diselenyl bis(benzotropolone) **18** (^{1}H,

Accepted Manuscript

This article is protected by copyright. All rights reserved.

^{13}C, and ^{77}Se NMR, combustion analysis, and HRMS; 19% yield, 70% aq. HOAc, 90°C, 12 h); the selenium-bridged alcohol **19** (^{1}H, ^{13}C, and ^{77}Se NMR; 24% yield, *ortho*-xylene, reflux, 9.5 h) and its carboxylic esters **20**-**22** (^{1}H, ^{13}C, and ^{77}Se NMR; 18-36% yield, in the respective carboxylic acid, reflux or room temp., 2.5 – 4 h); and benzotropone (**13a**, a known compound;[11] 50% yield, chlorobenzene + 2.2 eq. of *t*BuOOH, reflux, 6 h). The amount of benzotropolone (**5a**) never surpassed the 1 percentile rank according to ^{1}H-NMR spectroscopic examinations of the crude product mixtures using an aliquot of 2,4,6-tribromotoluene for calibrating the integrals.





Scheme 4: At top: SeO_2-oxidations of the RCM product **11** (synthesis: Scheme 3); the desired benzotropolone **5a** did not emerge. At bottom: Suggested origin of the product portfolio of the aforementioned oxidations, starting from the α-[(hydroxylselenyl)oxy]ketone **23** which we consider as the first intermediate.

The formation of the oxidation products **13a** and **18**-**22** from the RCM product **11a** is rationalized in the lower parts of Scheme 4. According to Corey and Schaefer[17a] SeO_2 and ketones give an enol ester at first. The latter undergoes a [2,3]-sigmatropic rearrangement (not yet named so at the time[17a]). In the case at hand (Scheme 4) it should form the Se(II) ester **23** of an acyloin. Elimination over a 6-membered cyclic transition state might furnish benzotropone (**13a**) directly. Alternatively, **13a** might result after Se–OH⊕ transfer to the enol tautomer of substrate **11a**. This reaction would deliver the selenenic acid **26** – whose fate is discussed below – and the acyloin **24**. The latter and SeO_2 might form the Se(IV) ester **25**. A β-elimination via a 6-membered cyclic transition state would accomplish a second pathway to benzotropone (**13a**). A different β-elimination of the same Se(IV) ester **25** – via a 5-membered cyclic transition state – would appear as a plausible origin of the desired benzotropolone **5a**, which, however, hardly formed at all.

The selenenic acid **26** is poised for an electrophilic selenylation of its olefinic C=C double bond. It should deliver the carbenium-ion **27** and neither its regioisomer nor the isomeric selenium-ion because **27** should be less ring-strained. If this carbenium-ion is quenched by the co-solvent – water – or the solvent – formic acid, acetic acid or trifluoroacetic acid, respectively – *trans*-selectively[18] and if the resulting (carb)oxonium ion is deprotonated, compounds **19**-**22** result.

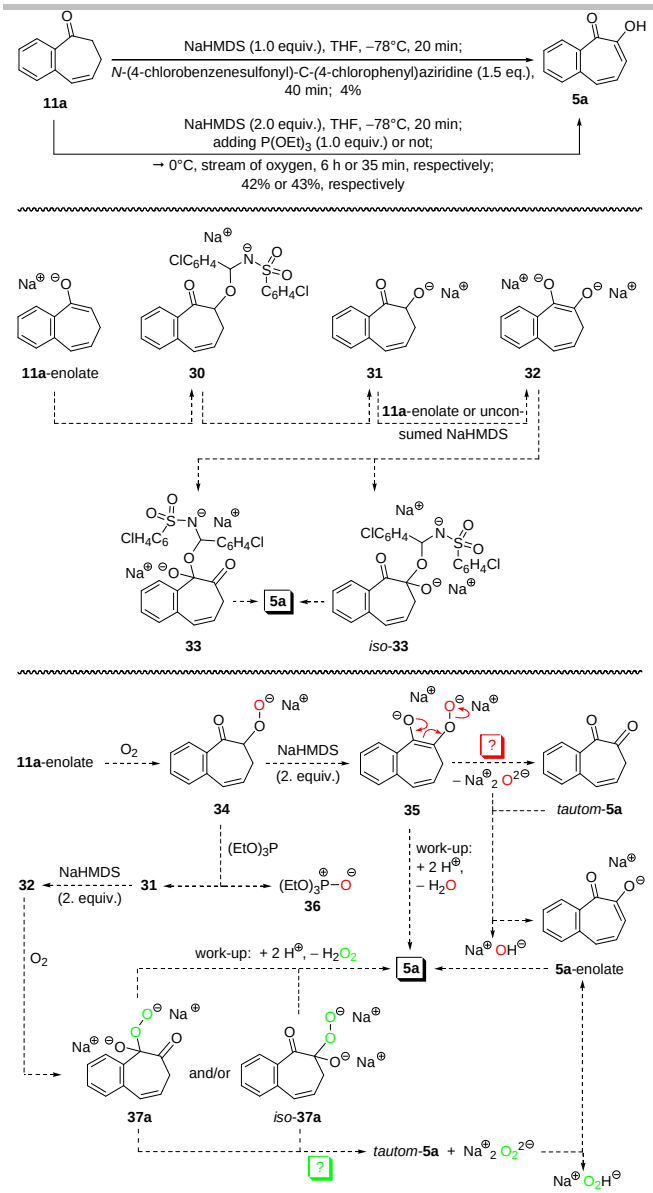
Alternatively, the carbenium-ion **27** of Scheme 4 is capable of being deprotonated and thus also capable of establishing the C=C double bond of the "2,5-dihydroselenophene" **28**. If a 1,4-elimination of H⊕ and RSe⊖ follows, a dieneselenolate and a proton (source) form. They would combined to give the C=C–C=C–Se–H moiety of the dieneselenol **29**. The latter would be (aut)oxidized rapidly, causing a dimerization to compound **18**.

In response to the inability of SeO_2 (Scheme 4) to oxidize the RCM product **11a** to benzotropolone (**5a**) we tried different reagents for accomplishing this oxidation (Scheme 5, at top). Enolate formation with NaHMDS followed by treatment with MoO_5·pyridine·DMPU[19] effected no conversion at all. In contrast, a Davis oxaziridine[20] converted the same sodium enolate completely. Disappointingly, an extractive workup with aq. NaOH (4 M), acidification with concentrated HCl, extraction with CH_2Cl_2, and separation from 4-chlorobenzenesulfonyl *N*-(4-chlorophenyl)amide by flash-chromatography on silica gel[21] provided benzotropolone (**5a**) in just 4% yield.

The center part of Scheme 5 rationalizes this unusual oxidation. If these reactants underwent nothing but the routinely observed α-hydroxylation, the ketone **30** with the ring-opened aziridine as an α-appendage would form first and the acyloin anion **31** thereafter (along with an *N*-sulfonylimine, which is not shown). Normally, the oxidation should have come to an end at this stage. The fact that it proceeded beyond, forces one to consider a deprotonation of **31** by the first-formed **11a**-enolate (unless an inadvertent tiny excess of NaHMDS assumed that role); this would give the acyloin dianion **32**. Either of its two enolate moieties might ring-open some of the extra-amount of the oxaziridine, which we employed. These ring-openings would resemble the ring-opening of the first equivalent of this oxaziridine by the **11a**-enolate. Acccordingly, the ketones **33** and *iso*-**33** should form, each containing the ring-opened aziridine at C-α. These species might resist fragmentation under the reaction conditions but will fragment upon protonation during work-up, thereby liberating, after tautomerism, benzotropolone (**5a**). The 4-electron oxidation **11a** → **5a** would thus be viewed as resulting from two 2-electron oxidations.

Accepted Manuscript

This article is protected by copyright. All rights reserved.



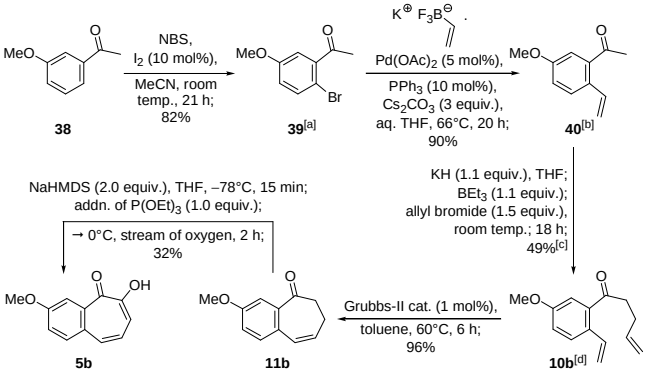
Scheme 5: Oxaziridine- and O_2-oxidations of the RCM product **11** (synthesis: Scheme 3) and conceivable intermediates en route to the resulting benzotropolone **5a**.

The oxidation of the **11a**-enolate to benzotropolone (**5a**) succeeded much better with a stream of oxygen[22] than with the mentioned oxaziridine (Scheme 5, at top). Our best conditions consisted of deprotonating **11a** in a THF solution with 2.0 equiv. of NaHMDS, adding no $P(OEt)_3$ thereafter or 1.0 equiv. thereof,[23] and bubbling pure oxygen through the resulting mixture at 0°C for 6 h. Work-up as described above then furnished benzotropolone (**5a**) as a yellow solid in 43% (42%) yield.[24]

This last-metioned type of oxidation may be unprecedented. We rationalize its course as shown at the bottom of Scheme 5. In the inaugural step or in the two inaugural steps, the **11a**-enolate and O_2 should combine to give the hydroperoxide anion **34**. At this juncture $(EtO)_3P$ may become involved – or not. In the latter case, the hydroperoxide anion **34**, which contains a keto group, must be deprotonated by the second equivalent of NaHMDS. This leads to the enolate-containing hydroperoxide anion **35**. If its O–O bond heterolyzed in spite of expelling fairly unstable Na_2O, the diketo form *tautom*-**5a** of benzotropolone would result. Proton transfer to Na_2O would render the **5a**-enolate and NaOH. However, this enolate would have to stay inert towards the stream of oxygen throughout the rest of the reaction time. This is hard to believe. Accordingly, we prefer to consider the enolate-containing hydroperoxide anion **35** as inert towards O–O bond heterolysis. In this case **35** would await protonation during work-up. This would facilitate the O–O bond heterolysis and thereby render the benzotropolone **5a**. Thus the 4-electron oxidation **11a** → **5a** overall would be a 4-electron oxidation mechanistically speaking.

Conversely, the ketone-containing hydroperoxide anion **34** of Scheme 5 might react not with NaHMDS (cf. above) but with $(EtO)_3P$ – as related hydroperoxide anions presumably do.[23a-c] This would lead to the acyloin anion **31** along with $(EtO)_3P{=}O$ (**36**). The possibility that **31** and the second equivalent of NaHMDS undergo a proton transfer which delivers the acyloin dianion **32** was already mentioned above. Either enolate moiety of this dianion might react with O_2 like the **11a**-enolate supposedly reacts with O_2 (→**35**): by forming a hydroperoxide anion, namely the intermediates **37** or *iso*-**37**. Therein – other than in the hydroperoxide anion **35** discussed before – the O–O bond must not heterolyze for advancing towards benzotropolone (**5a**). This is because the hydroperoxide anions **37** and *iso*-**37** are O,O-hemiketals of sorts. Expelling Na_2O_2 under the reaction conditions or H_2O_2 upon protic work-up would generate a carbonyl group. Tautomerism would then accomplish benzotropolone (**5a**). If this pathway applied, the 4-electron oxidation **11a** → **5a** would comprise two 2-electron oxidations of the substrate and an additional 2-electron redox reaction with $(EtO)_3P$.

Synthesis of a (Methoxybenzo)tropolone



Scheme 6: Preparation of the RCM product **11b** and its oxidation to the benzotropolone **5b**.– [a]Compound **39** was a 91:9 mixture with substrate **38**. [b]Compound **40** was a 91:9 mixture with compound **38**. [c]Taking into account the reisolation of 31% **40**, the yield of **10b** was 71% instead of 49%. [d]Compound **10b** resulted in an 88:12 mixture with allyl-**38** (formula: Experimental Part).

The feasibility of the RCM / 4-electron oxidation route to the unsubstituted benzotropolone **5a** led us to extend our strategy to a number of substituted benzotropolones **5b**-**5d** (Scheme 6-Scheme 9). Striving for the methoxybenzotropolone **5b** the methoxyacetophenone **38** was brominated with NBS following the literature[25] (Scheme 6). This provided 82% of the desired bromide

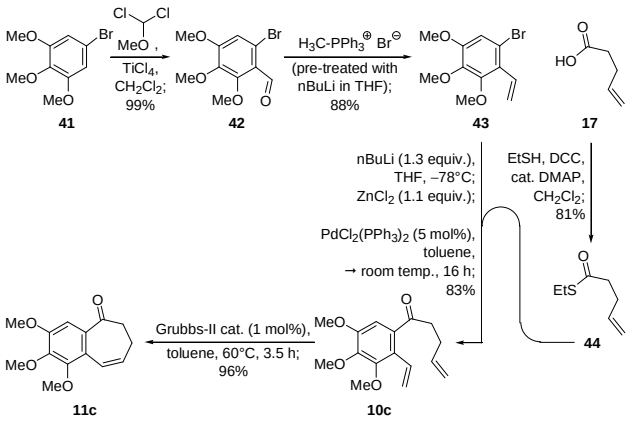
Accepted Manuscript

This article is protected by copyright. All rights reserved.

39. It was subjected to a Suzuki-coupling[26,27] with potassium vinyltrifluoroborate.[28,29] This rendered the styrene **40** in 90% yield. We allylated compound **40** via an ate-complex of its diethylborinate – i. e., using a method of Negishi.[30] Still, the desired monoallylation (→ 49% diene **10b**) competed with inertness (→ 31% re-isolated **40**) and diallylation (→ 9% triene allyl-**10b**; formula: Experimental Part). The diene **10b** was the substrate of a well-working RCM reaction. It delivered compound **11b** in 96% yield. Deprotonation with excess NaHMDS and oxidation with molecular oxygen under the same conditions, which had provided the MeO-free benzotropolone **5a** in 42% yield (Scheme 5, at top), gave the MeO-containing analog **5b** in 30% yield**.**

Synthesis of (Trimethoxybenzo)tropolones

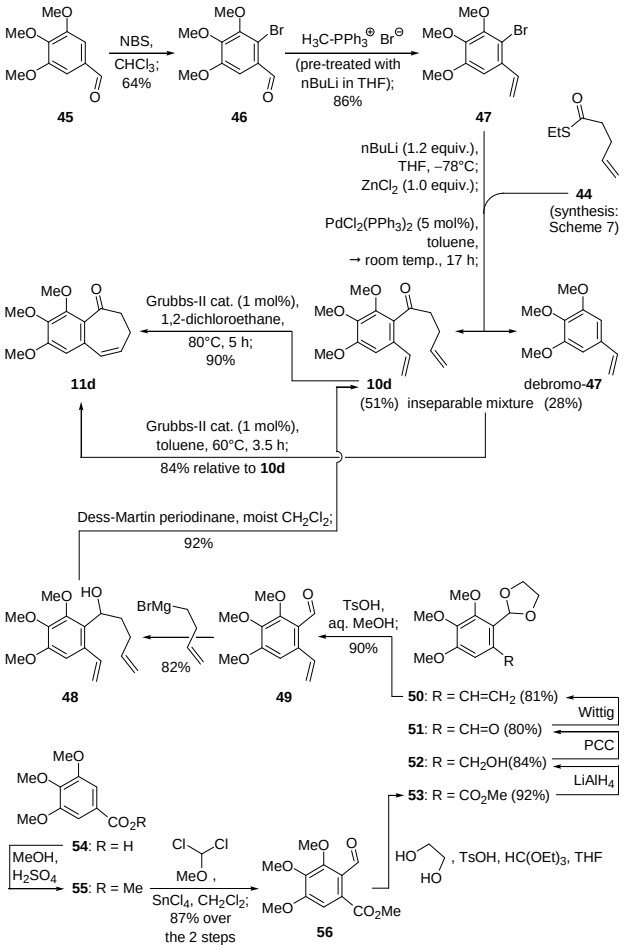
We also synthesized two (trimethoxybenzo)tropolones **5c** and **5d** (Scheme 9). This occurred via the RCM products **11c** (resulting from the sequence of Scheme 7) and **11d** (obtained from either of the two approaches of Scheme 8 or from the appoach of Scheme 11), respectively.



Scheme 7: Preparation of the RCM product **11c**.

The RCM product **11c** was prepared from the commercially available bromotrimethoxybenzene **41** in the 5 steps shown in Scheme 7. The Rieche formulation, with which we started, worked as well as reported,[31] affording the aldehyde **42** in 99% yield. A Wittig methylidenation afforded the corresponding styrene **43** in 88% yield. The C–Br motif of this compound was a place-holder for the C–C(=O)–CH_2–CH_2–CH=CH_2 motif of the desired RCM substrate **10c**. The respective functionalization was attempted via several protocols. It was found that a Fukuyama ketone synthesis[32] worked best. It was accomplished by combining the thioester **44** – prepared from pen-4-enoic acid (**17**), ethanethiol, and DCC – and the arylzinc reagent obtained from the styrene **43** – by successive Br/Li and Li/ZnCl exchanges – under $PdCl_2(PPh_3)_2$ catalysis. The diene **10c** was obtained in 83% yield. 1 mol-% of Grubbs-II catalyst[15] ring-closed this compound and furnished 96% of the RCM product **11c**.

Our least laborious synthesis of the RCM precursor **10d** (Scheme 8, upper part) resembled our synthesis of the isomer **10c** (Scheme 7). Starting from the commercially available trimethoxybenzaldehyde **45**, this synthesis, too, comprised 4 linear steps and 5 steps altogether (Scheme 8). A bromination with NBS in $CHCl_3$ afforded the aldehyde **46** in 64% yield (ref.[33]: 84% in MeCN). A Wittig methylidenation provided the corresponding styrene **47** (86%). The ensuing Fukuyama ketone synthesis delivered the desired diene **10d** in 51% yield. It was isolated as a flash-chromatographically[21] inseparable mixture with a 28% yield of the protonolysis product. The compound is depicted in Scheme 8, namely, debromo-**47** of the arylzinc intermediate. This difference compared to the 83% yield of the diene **10c** of Scheme 7 and the non-occurrence of a protonated aromatic byproduct reflects the greater hindrance of the arylzinc intermediate used in Scheme 8 vs. Scheme 7. When we exposed the 64:36 mixture of the diene **10d** and its contaminant debromo-**47** to 1 mol-% of Grubbs-II catalyst[15] the RCM product **11d** resulted in 84% yield.



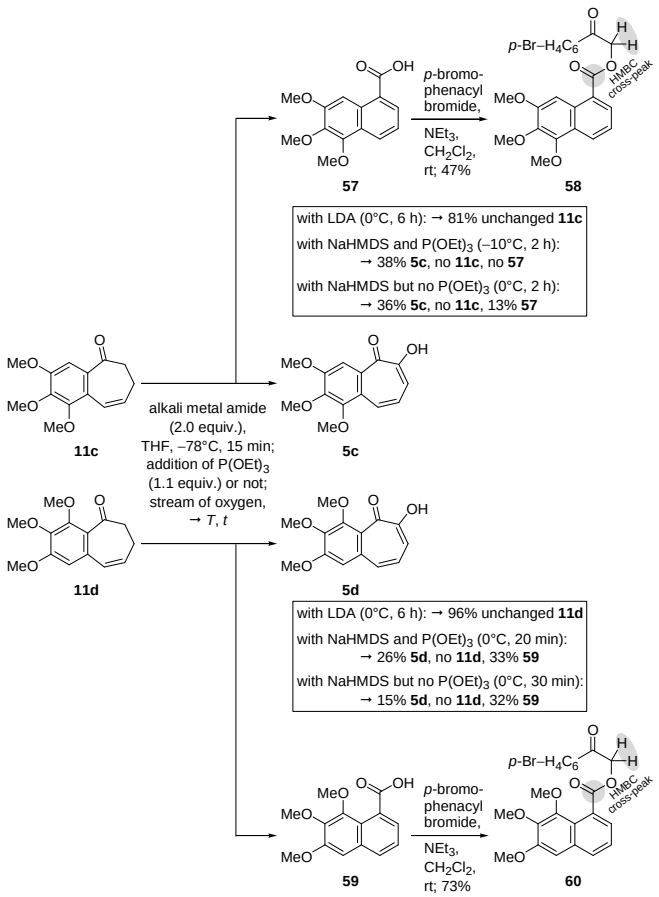
Scheme 8: 4-Step synthesis (at top) and 10-step synthesis (at bottom) of the RCM product **11d** (see second formula line at left).

The same RCM product **11d** was formed in 90% yield, when we ring-closed a pure specimen of the diene **10d**. The latter stemmed from the commercially available trimethoxybenzoic acid **54** and the 9-step sequence depicted in the lower part of Scheme 8. This sequence consists of ① an esterification (→**55**), ② a Rieche formylation (→**56**[34]), ③ acetal formation with ethyleneglycol (→**53**), ④ reduction of the ester moiety with $LiAlH_4$ (→**52**), ⑤ oxidation to the aldehyde with pyridinium chlorochromate[35] (→**51**), ⑥ Wittig olefination (→**50**), ⑦ acetal hydrolysis (→**49**), ⑧ addition of homoallylmagnesium bromide (→**48**), and ⑨ oxidation of the resulting secondary alcohol with the Dess-Martin periodinane[36]

Accepted Manuscript

This article is protected by copyright. All rights reserved.

in moist CH_2Cl_2[37] (→**10d**). The respective overall yield of 29% **10d** was was very similar to the overall yield of the 3-step sequence **45** → **46** → **47** → **10d** (28%; Scheme 8, upper part) + debromo-**47**.



Scheme 9: Reaching the benzotropolones **5c** and **d** by oxidizing the RCM products **11c** and **d**, respectively.

The enolate-forming conditions (exposure to 2 equiv. of NaHMDS in THF at –78°C for 15-20 min) established for the benzotropolone-delivering autoxidations [stream of oxygen, in the absence[22] or presence[23] of $P(OEt)_3$] of the RCM products **11a** (→ **5a**, cf. Scheme 5, line 2) and **11b** (→ **5b**, cf. Scheme 6) let the RCM products **11c** and **d** react similarly (Scheme 9): The RCM product **11c** gave the (trimethoxybenz)tropolone **5c** in 36% and 38% yield, respectively; the isomeric RCM product **11d** gave the corresponding (trimethoxybenz)tropolone **5d** in 15% and 26% yield, respectively. Working up these reactions only after monitoring their progress by TLC indicated complete consumption of the substrate, it became clear, that the better-yielding autoxidation (of **11c**) proceeded more slowly than the less-yielding autoxidation (of **11d**). When we used 2.0 equiv. LDA instead of 2.0 equiv. of NaHMDS, we observed no autoxidations whatsoever. Even when the exposure time to oxygen was 6 h, we re-isolated the RCM substrates **11c** and **d** in yields of 81% and 96%, respectively. Exposure of the RCM substrate **11c** to 2.0 equiv. of KHMDS followed by 3 h of autoxidation destroyed the substrates completely giving 8.6% of the (trimethoxybenz)tropolone **5c** as the only identifiable product.

Only one of the four sodium enolate autoxidations of Scheme 9 delivered the respective (trimethoxybenz)tropolone chemoselectively, namely the *P(OEt)₃-free* autoxidation of the RCM-product **11c** (→ 36% **5c**). The same substrate *in the presence of P(OEt)₃* (→ 38% **5c**) as well as the RCM-product **11d** *no matter whether P(OEt)₃ was present* (→ 26% **5d**) *or absent* (→15% **5d**) delivered rearranged autoxidation products as well: The RCM-product **11c** gave 13% of the trimethoxynaphthoic acid **57** and the RCM-product **11d** 33% and 32% of the trimethoxynaphthoic acid **59**, $P(OEt)_3$ being present or absent, respectively. We confirmed the identity of both acids by preparing and characterizing their *para*-bromophenacyl esters **58** (from **57**) and **60** (from **59**; Scheme 9).

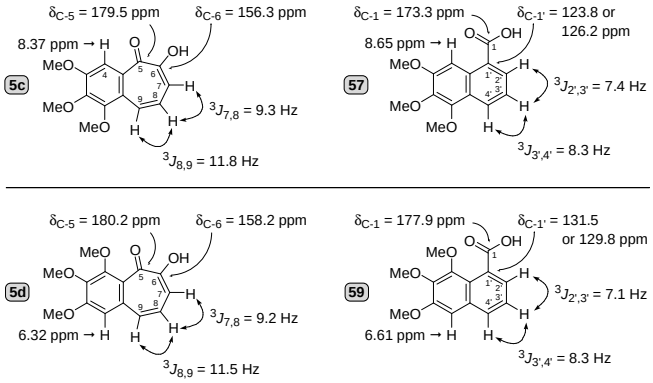


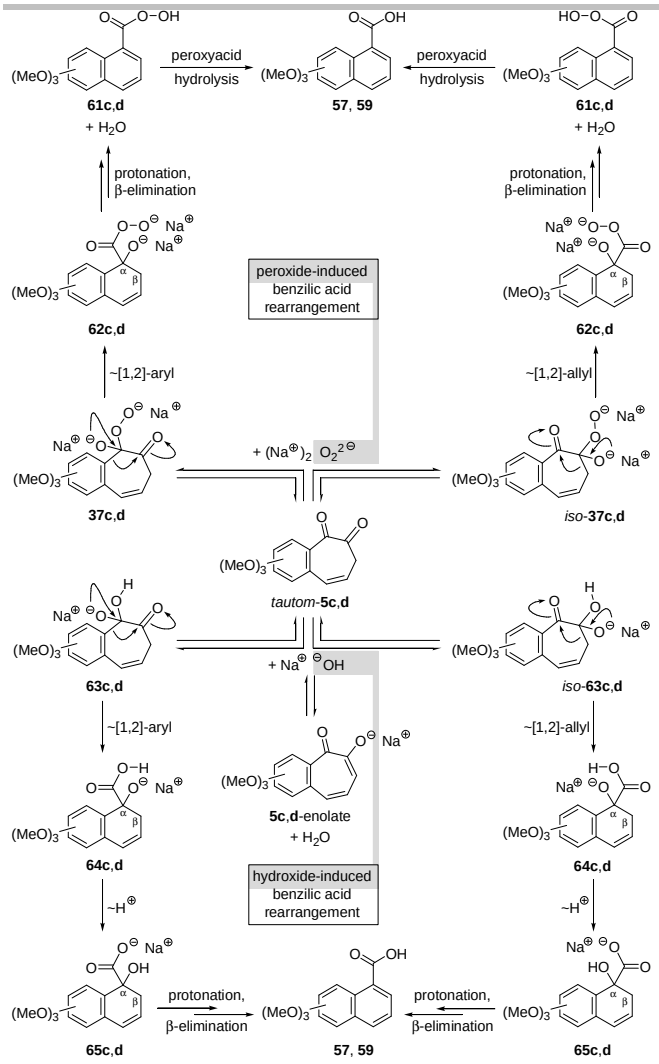
Figure 3: ^1H- (500 MHz) and ^{13}C-NMR (126 MHz) distinctions in C_6D_6 solution between the desired benzotropolones **5c** and **5d** and the naphthoic acids **57** and **59**, respectively, which formed competitively.

In terms of ^{13}C-NMR spectral evidence, formation of the rearrangement products **57** and **59**, in addition to the benzotropolones **5c** and **5d** (Scheme 9) was rather inconspicuous. This was certainly true when comparing the single-most deshielded ^{13}C-nucleus of each compound with one another (Figure 3): The carbonyl-^{13}C of the benzotropolone **5c** resonates at δ = 179.5 ppm and the carboxyl-^{13}C of the naphthalene **57** at δ = 173.3 ppm. Similarly, the carbonyl-^{13}C resonance of the benzotropolone **5d** (δ = 180.2 ppm) is only slightly down-field from the carboxyl-^{13}C resonance of the naphthalene **59** (δ = 177.9 ppm).

The trimethoxynaphthoic acids **57** and **59** are constitutional isomers of the (trimethoxybenz)tropolones **5c** and **5d**, respectively (Scheme 9).This suggests that the former arise via the latter. To our surprise, we failed to induce the respective isomerizations when we (seemingly) re-submitted the pure (trimethoxybenz)tropolone **5c** or its isomer **5d** to the conditions of their formations: ① 45.8 mg (trimethoxybenz)tropolone **5c** and NaHMDS (2.0 equiv.) were combined in THF at –78°C, warmed to 0°C 15-20 min therafter, whereupon a stream of oxygen was passed through the solution for 7 h; extractive workup and purification by flash-chromatography on silica gel[21] led to the recovery of 27.6 mg **5c** (60%) but furnished none of the naphthoic acid **57**. ② Analogously, 60.5 mg (trimethoxybenz)tropolone **5d** and NaHMDS (2.0 equiv.) were combined in THF at –78°C, warmed to 0°C 15-20 min therafter, whereupon a stream of oxygen was passed through the solution for 6 h; extractive workup and purification by flash-chromatography on silica gel[21] afforded 52.4 mg **5d** (86% mg) but gave none of the naphthoic acid **59**.

Accepted Manuscript

This article is protected by copyright. All rights reserved.



Scheme 10: Rationalization of the formation of naphthoic acids **57** and **59** in the course of the oxidations of Scheme 9 (starting from the intermediates *tautom*-**5c**,**d** and/or **5c**,**d**-enolate depicted there) as benzilic acid rearrangements. The lower part of the Scheme represents the classical, i. e., $HO^{\ominus}$-induced mechanism, while the upper part is an $^{\ominus}O–O^{\ominus}$-induced mechanism.

On the other hand, Cook and Somerville reported that "by fusion with 80 per cent potash at 180-185°" **5a** "was almost quantitatively converted into α-naphthoic acid."[38] Differently expressed, a molten 20:80 mixture (w/w) of the benzotropolone **5a** and potash underwent a benzilic acid rearrangement[39] giving 1-naphthoic acid.[40] An oxidation of benzotropylium tetrafluoroborate with 90% Na_2O_2 in THF, possibly not unrelated to our own (aut)oxidations, gave four C_1-substituted naphthalenes (plus other products).[41] Literature autoxidations of the sodium enolates of cholestanone[22d] or benzil[42] went beyond the 1,2-diketone stage due to ensuing benzilic acid rearrangements as well.

Considering these analogies, we do not refrain from rationalizing the formation of our naphthoic acids **57** and **59** during 3 of the 4 autoxidations of Scheme 9 by the diketone monohydrate-anion mechanism[43] of a standard benzilic acid rearrangement (Scheme 10, bottom half). In principle, either substrate might give rise to two "regioisomeric" diketone monohydrate-anions: In **63c**,**d**, the C(–$O^{\ominus}$ $Na^{\oplus}$)(–OH) motif is substituted by *an aryl group* whereas in *iso*-**63c**,**d**, the C(–$O^{\ominus}$ $Na^{\oplus}$)(–OH) motif is substituted by *an allyl group*. As a consequence, the intermediates **63c** and **d** are poised to realize the benzilic acid rearrangement either by a [1,2]-shift of the aryl group – namely if **63c** or **d** rearranges – or by a [1,2]-shift of the allyl group – if *iso*-**63c** or **d** rearranges. Interestingly, both alternatives give rise to the same rearrangement product **64c**,**d**. Proton transfer should give the hydroxycarboxylates **65c**,**d**, whose dehydrations would accomplish the naphthoic acid structures **57** and **59**. If regioisomeric 1,2-diketone monohydrate-anions allow, in principle, [1,2]-shifts of an aryl or a benzyl group, in reality a benzyl group migration is favored.[44] This suggests that in our case (Scheme 10, lower part) allyl group migrations should be faster than aryl group migrations. Accordingly, the diketone monohydrate-anions *iso*-**63c**,**d** would be the rearranging species, not the diketone monohydrate-anions **63c**,**d**.

The upper part of Scheme 10 supplements an unusual benzilic acid rearrangement mechanism as an alternative. It takes into consideration that this kind of rearrangement can also be brought about by alkoxide anions[39] ("ester variant of the benzilic acid rearrangement") and amines[39] ("amide variant of the benzilic acid rearrangement") as well. Why not, accordingly, attribute an analogous role to disodium peroxide? The latter is a plausible side-product of the paralleling autoxidation (cf. mechanism in Scheme 5). Again, either of two "regioisomeric" anion intermediates would be appropriate to rationalize the product structure: the dianions **37c** or **d**, if an aryl group [1,2]-shifts, or the dianions *iso*-**37c** or **d**, if an allyl group [1,2]-shifts. Following the reasoning of the preceding paragraph, **37c**,**d** would appear as less reactive than *iso*-**37c**,**d**.

An RCM / Isomerization Approach to Compound 11d

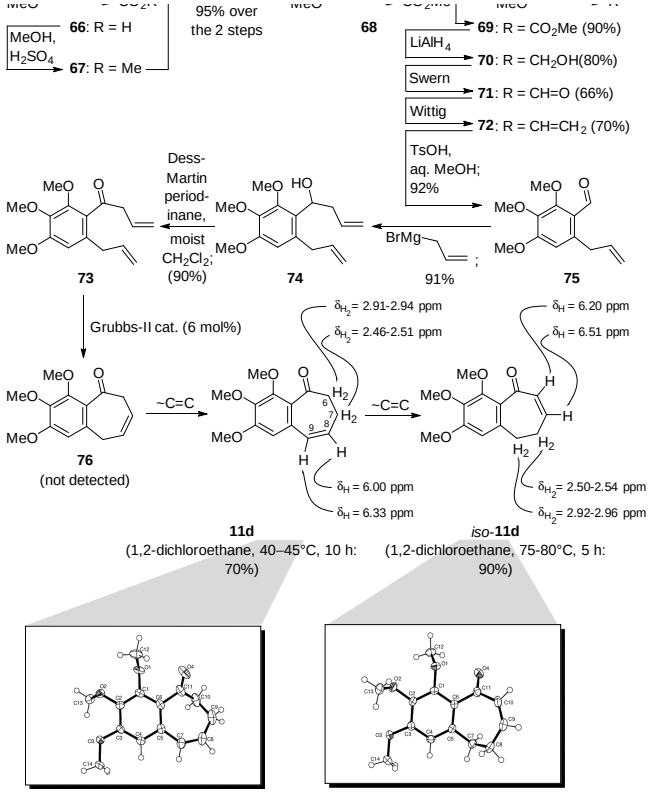
This section describes another synthesis of the RCM-product **11d** (Scheme 11, Table 1). Its required 10 linear steps which is identical with our approach from the lower part of Scheme 8 and 7 steps more than in our approach shown in Scheme 8 at top. The overall yields of the ring-closed product **11d** was 21% by the third route, 28% by the second route, and 24% by the first route.

Our access by Scheme 11 started from the commercially available (trimethoxyphenyl)acetic acid **66**. We applied the same sequence of transformations as in our second approach, changing reagents only in step ⑤ (using a Swern oxidation[45] now and no PCC oxidation as before) and in step ⑧ (adding allylmagnesium bromide to an aromatic aldehyde now as opposed to homoallylmagnesium bromide before). Steps ①-⑨ were routine: ① H_2SO_4-catalyzed esterification (→**67**[46]); ② $SnCl_4$-promoted Rieche formylation[47] (→**68**[46,48]); ③ protection of the formyl group as a dioxolane (→**69**); ④ reduction of the CO_2Me group with $LiAlH_4$ (→**70**); ⑤ Swern oxidation[45] of the resulting CH_2OH group (→**71**); ⑥ Wittig methylidention (→**72**); ⑦ dioxolane hydrolysis (→**75**); ⑧ addition of allylmagnesium bromide to the liberated CH=O group (→**74**); ⑨ water-facilitated[37] Dess-Martin oxidation[36] (→ **73**).

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/ejoc.202000256



Scheme 11: Reaching the RCM product **11d** differently than by the syntheses of Scheme 8 (for details of the crystal structural analyses, cf. ref.[49,50]).

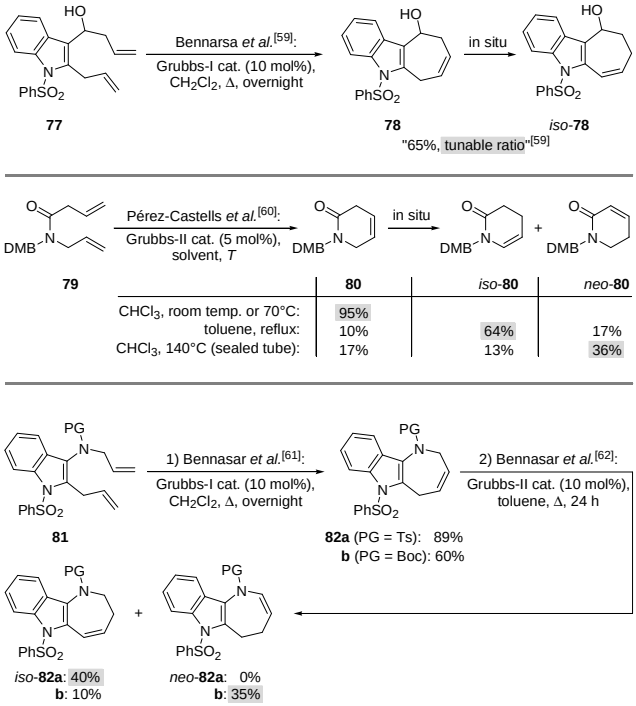
Step ⑩ of our **11d**-synthesis following Scheme 11 was a RCM reaction of the last-mentioned diene **73**. Catalyzed by 6-10 mol-% of the the Grubbs II catalyst,[15] this metathesis turned out to be "special" since it proceeded in tandem with C=C bond migration. In fact, the TLC of the crude reaction mixture showed no discernible trace of the RCM product **76** containing the isolated C=C bond. Accordingly, the migration of the C=C bond must have been considerably faster than its formation. The direction of this bond migration was subject to temperature control. After a reaction at 75-80 °C this allowed for the isolation of *iso*-**11d** in 90% yield and **11d** in 5% yield after separation by flash-chromatography on silica gel[21]. By lowering the temperature to 40-45 °C **11d** and *iso*-**11d** were isolated in 70% and 20% yields, respectively, after flash-chromatography on silica gel.[21] These selectivities were attained under the metathesis conditions illustrated in entries 5 and 4 of Table 1, respectively. They differed from one another as follows: enone *iso*-**11d** formed in 90% yield at 80-85°C in $(ClCH_2)_2$ within 5 h (entry 5) and is thus the thermodynamically favored isomer relative to compounds **11d** and **76**. The styrene **11d** was the major isomer formed at the lower temperature of 40-45°C in CH_2Cl_2 within 10 h (entry 4) or at room temp. in CH_2Cl_2 or $(ClCH_2)_2$ within 1-2 d (entries 1-3). Accordingly, its formation is kinetically favored vs. *iso*-**11d** *and* thermodynamically vs. the initial, yet not observed ring-closure product **76**.

Table 1: Grubbs-II catalyst[15] mediated tandem RCM / isomerization reactions starting from the diene **73** of Scheme 11.[a]

Entry	Solvent	Temp. (°C)	Time (h)	Yields (%)			
				Diene	RCM Products		
				73	**76**	**11d**	*iso*-**11d**
1	CH_2Cl_2	~20	48	20	0	50	5
2	$(ClCH_2)_2$	~20	24	12		60	10
3	CH_2Cl_2	~30	48	15		60	7
4	$(ClCH_2)_2$	40-45	10	5		70	20
5	$(ClCH_2)_2$	75-80	5	0		5	90

[a] Our attempts at cyclizing the diene **73** of Scheme 11 using the Grubbs-I catalyst (5-10 mol-%) failed to give any of the RCM-products **76**, **11d**, and *iso*-**11d** (while allowing to recover **73**) under the following conditions: CH_2Cl_2, ~20 °C, 5 d; $(CH_2Cl)_2$, ~20 °C, 48 h; CH_2Cl_2, 40-45 °C, 48 h; toluene, 80-110 °C, 24 h.

^{1}H-NMR spectroscopy on **11d** and *iso*-**11d** demonstrated that both isolated products contained the CH_2–CH_2–CH=CH moiety (chemical shifts: Scheme 11). This proved that none of them was the originally expected RCM-product **76**. Their identity became clear from single crystal X-ray structure determinations[49,50] (ORTEP plots: Scheme 11): The C=C bond is conjugated with the benzene ring in compound **11d**[51] but with the keto function in compound *iso*-**11d**[52] This was underlined in the ^{13}C-NMR spectra because the *isolated* carbonyl group of **11d** displayed a low-field shift (δ = 202.2 ppm) compared to the *conjugated* carbonyl group of *iso*-**11d** (δ = 194.6 ppm).



Scheme 12: Analogies to the C=C-shifting RCM reaction(s) **73**→**76**→**11d**→*iso*-**11d** of Scheme 11.

C=C bond migrations have been known to accompany olefin metatheses performed in the presence of Grubbs or Schrock catalysts.[53,54,55,56,57,58] Scheme 12 shows three examples which we

Accepted Manuscript

This article is protected by copyright. All rights reserved.

consider pertinent for placing our isomerizing RCMs **73**→→**11d** and **73**→→*iso*-**11d** of Scheme 11: The first line of Scheme 12 shows a(nother) RCM-based cycloheptadiene-annulation to an aromatic nucleus, after whose occurrence (→**78**) some C=C bond migration occurred (→*iso*-**78**).[59] The second line of Scheme 12 shows that the RCM-based formation of a dihydropyridone **80** could be stopped at that stage working in $CHCl_3$ at ≤70°C.[60] The same line also shows how that stage could be left behind for obtaining the C=C-bond shifted isomers *iso*-**80** or *neo*-**80**.[60] Which of these compounds was the mejor product depended on whether the respective RCM was executed at 120°C in toluene or at 140°C in $CHCl_3$ (sealed tube), respectively.[60] The third line of Scheme 12 shows two RCM-based dihydroazepine annulations to an indole-*N*-sulfonamide scaffold.[61] Performed in refluxing dichloromethane, compounds **82a** and **b** resulted,[61] the newly established C=C bond staying where formed.[61] However, according to the transformation depicted at the bottom of Scheme 12, this location of the C=C bond was disfavored when exposure to the Grubbs-II catalyst[15] in refluxing toluene provided an opportunity for the migration.[62] When the dihydroazepine moiety contained an *N*-Ts group, this migration was unidirectional and "clockwise" (→*iso*-**78b**).[62] When the dihydroazepine moiety contained an *N*-Boc group, the C=C bond moved "counter-clockwise" (→*neo*-**78a**) with a 3:1 preference over moving "clockwise" (→*iso*-**78a**).[62] The yields of *our* RCM product isomers (**11d** and *iso*-**11d**, Scheme 11) supercedes the isomerization yields of Scheme 12.

Conclusions

We turned the 4-e$^{\ominus}$ oxidation RCM-route to benzotropolones, as conceived in Scheme 2, into reality. To our delight as much as to our surprise, the crucial oxidation functioned in a single step employing O_2 (1 bar, 0°C); its yield being at best 43% hitherto, there is clearly a need for improvement. In addition, the functional group compatibility of our novel access will have to be studied. Nevertheless, we were able to reach the benzotropolones **5a**-**d** in just 3-5 steps.

Our 10-step syntheses of the RCM-product **11d** totalling a higher overall yield than the far shorter route. This makes it attractive to explore the scope of our not-so-straightforward approach of Scheme 11 to the RCM-*substrate* – or 1,8-diene – **73**: Will it allow to perform tandem RCM/C=C bond migration reactions quite generally for gaining the substrates proper (like **11d**) of our benzotropolone-delievering 4-e$^{\ominus}$ oxidation step? If yes, it would be advantageous to proceed via allylated (e. g. the 1,8-diene **73** and its precursors, Scheme 11) rather than vinylated aromatics (e. g. the 1,8-diene **10d** and its precursors, Scheme 8) as synthetic intermediates. This is because the former are easier to prepare than the latter.

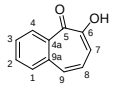
Last but not least the considerable regioselectivities – including regiocomplementarity! – and the yields of the tandem RCM/C=C bond migration reactions of our 1,8-diene **73** are noteworthy. This notion is warranted both from an "absolute", i. e. basic science view-point and relative to tandem processes of the same kind.[53]

Experimental Section

General Working Technique and Analytic Techniques

Organometallic and metal hydride reactions were carried out under an N_2-atmosphere. Reaction flasks were dried in vacuo with a heat gun prior to use. Liquids were added with a syringe through a septum. THF was distilled over potassium, *i*-Pr_2NH over CaH_2 under an N_2-atmosphere prior to use. Other solvents and reagents were purchased and used without further purification. **Flash-chromatography**:[21] Macherey-Nagel silica gel 60® (230-400 mesh). All eluents were distilled prior to use. Chromatography conditions are documented as in, for example, "[*a* × *b* cm, *c*C_6H_{12}:EtOAc = *c*:*d* (v:v), *e* mL] ... Ff-g", which means: a column with a diameter of *a* cm was packed with *b* cm silica high, it was eluted with *c*C_6H_{12} and EtOAc in a *c*:*d* ratio (v:v), fractions of the size of *e* mL were taken, and the product was isolated from fractions f-g. **Nuclear magnetic resonance spectra**: Bruker Avance 500 spectrometer (500 MHz and 125 MHz for ^1H and ^{13}C respectively), Bruker Avance 400 spectrometer (400 MHz and 100 MHz for ^1H and ^{13}C respectively), and Bruker Avance 300 spectrometer (300 MHz and 75 MHz for ^1H and ^{13}C respectively) referenced internally by the ^1H- and ^{13}C NMR signals of the solvent [$CDCl_3$: 7.26 ppm (^1H) and 77.16 ppm (^{13}C); C_6D_6: 7.16 ppm (^1H) and 128.06 ppm (^{13}C); $(CH_3)_4Si$: 0.00 ppm (^1H) and 0.00 ppm (^{13}C)]. ^1H NMR data are reported as follows: chemical shift (δ in ppm), multiplicity (s for singlet; d for doublet; t for triplet; q for quartett, m for multiplet; m_c for symmetrical multiplet; br for broad signal), number of protons (concluded from the integrals), coupling constant(s) (Hz), specific assignment or integral. ^{13}C NMR data are reported in terms of chemical shift and assignment. For AB signals the high-field part was named A and the low-field part B. The atom numbering used for NMR assignments follows the IUPAC nomenclature unless noted otherwise. **High-resolution mass spectra** were obtained on a Finnigan MAT 8200 instrument (EI: 70 eV; CI/NH_3: 110 eV) using an orbitrap analyzer; alternatively, a Kratos MS 9/50, VG 70E MS or VG 70 SEQ mass spectrometer, a WatersAPI Q-TOF Ultima or Waters GCT Premier mass spectrometer were utilized. **Elemental analyses** were obtained on a CHNS analysator Elementar Vario EL. **Melting points** were determined in a Büchi melting point or Reichert hot stage apparatus using open glass capillaries. **IR spectra** were obtained on an FT-IR Perkin Elmer Paragon 1000 spectrometer, a Bruker IFS 25 Fourier Transform spectrometer or on a Bruker Vector 22 Fourier Transform spectrometer in $CHCl_3$ solution or as a film of the substance on a polyethylene-foil (Spectra-Tech Inc.; self-absorption may compete in the regions 2920-2850, 1480-1430, and 740-700 cm^{-1}).

6-Hydroxy-5*H*-benzo[7]annulen-5-one ("Benzotropolone"; 5a[11])



$C_{11}H_8O_2$
172.18 g/mol

NaHMDS (2 M, solution in THF, 0.96 mL, 1.92 mmol, 2.0 equiv.) was added to a solution of **11a** (151 mg, 0.96 mmol, 1.0 equiv.) in THF (9.6 mL) at −78°C within 5 min. The mixture was stirred for 15 min. The temperature was raised to 0°C and $P(OEt)_3$ (0.16 mL, 0.96 mmol, 1 equiv.) was added in one portion. O_2 (moderate gas flow) was passed through the solution for 6 h at 0°C. An aqueous solution of NaOH (4 M, 10 mL) was added and the aqueous solution was washed with CH_2Cl_2 (3 × 10 mL). The aqueous layer was acidified with HCl (conc., pH ≈ 1) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers (after acidification) were dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash-chromatography on silica gel[21] [2 × 15 cm, *c*C_6H_{12}:EtOAc + 5% AcOH, 40:1 to 10:1 (v:v), 20 mL] to render the title compound (F5-21; 69.6 mg, 42%) as yellow solid [mp.79-81°C (ref.[11]: 81°C)].– When then identical substrate **11a** (120 mg) was oxidized *without* $P(OEt)_3$ [THF, −78°C; NaHMDS (2.0 equiv.), 0°C, stream of O_2, 35 min], flash-chromatography on silica gel[21] provided the benzotropolone **5c** in a slighly better yield (56.0 mg, 43%).

^1H NMR (500.22 MHz, $CDCl_3$): δ = 6.96 (dd, $J_{8,9}$ = 11.5 Hz, $J_{8,7}$ = 9.5 Hz, 1H, 8-H), 7.21 (dd, $J_{7,8}$ = 2.1 Hz, $^4J_{7,9}$ = 0.8 Hz, 1H, 7-H), 7.38 (dddd, $J_{9,7}$ = 11.4 Hz, $^4J_{9,7}$ = $^4J_{9,1}$ = $^5J_{9,4}$ = 0.6 Hz, 1H, 9-H), 7.70 (ddd, $J_{3,4}$ = 8.3 Hz, $J_{3,2}$ = 6.6 Hz, $^4J_{3,1}$ = 1.7 Hz, 1H, 3-H), 7.78 (ddd, $J_{2,1}$ = 8.0 Hz, $J_{2,3}$ = 6.6 Hz,

Accepted Manuscript

This article is protected by copyright. All rights reserved.

$^4J_{2,4}$ = 1.4 Hz, 1H, 2-H), 7.81 (dddd, $J_{1,2}$ = 8.0 Hz, $^4J_{1,3}$ = 1.7 Hz, $^4J_{1,9}$ = $^5J_{1,4}$ = 0.5 Hz, 1H, 1-H), 8.66 (s_{br}, 1H, 6-O*H*), 8.92 (dddd, $J_{4,3}$ = 8.3 Hz, $^4J_{4,2}$ = 1.4 Hz, $^5J_{4,1}$ = $^5J_{4,9}$ = 0.6 Hz, 1H, 4-H).

^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 114.39 (C-7)^A, 126.76 (C-8)^A, 129.46 (C-3)^A, 131.21 (C-4)^A, 132.89 (C-2)^A, 132.98 (C-4a)^B, 133.26 (C-9)^A, 134.07 (C-1)^A, 138.36 (C-9a)^B, 157.17 (C-6)^B, 180.88 (C-5)^B; ^{A} the indicated ^{13}C nuclei – they are non-quaternary – were identified in an edHSQC spectrum by their crosspeaks with directly bond protons; ^{B} the indicated ^{13}C nuclei are quaternary and were distinguished in an HMBC spectrum by their crosspeaks due to ^2J, ^3J and/or ^4J couplings to "remote" protons.

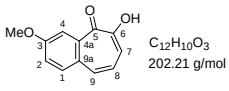
IR (KBr): ν = 3470, 3181, 3035, 1680, 1635, 1610, 1590, 1545, 1530, 1485, 1415, 1350, 1230, 1165, 1120, 1065, 985, 960, 930, 905, 865, 825, 790, 740, 705, 670, 580, 565, 530, 515 cm^{-1}.

HRMS (pos. ESI): $C_{11}H_9O_2^{\oplus}$ ($M+H^{\oplus}$): calculated: 173.05971; found: 173.05984 (Δ = +0.8 ppm).

Elemental analysis:

$C_{11}H_8O_2$ (172.18 g/mol)	calc.	C 76.73	H 4.68
	found	C 76.42	H 4.75

6-Hydroxy-3-methoxy-5*H*-benzo[7]annulen-5-one (5b)



At −78 °C a solution of $NaN(SiMe_3)_2$ in THF (2 M, 0.5 mL, 1 mmol, 2 equiv.) was added dropwise to a solution of the RCM product **11b** (100 mg, 531 µmol) in THF (5.3 mL). The mixture was stirred at −78 °C for 15 min, warmed to 0 °C and stirred at that temperature for 15 min. $P(OEt)_3$ (0.09 mL, 0.09 g, 0.5 mmol, 1 equiv.) was added and a stream of O_2 was passed through the solution for 2 h while continuing to stir at 0 °C. The reaction was quenched by addition of aq. NaOH (4 M, 10 mL). The mixture was extracted with CH_2Cl_2 (20 mL). The aqueous phase was acidified to pH 1 with conc. aq. HCl solution (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification by flash-chromatography on silica gel[21] [1.5 × 15 cm, 7 mL, cyclohexane/EtOAc/AcOH = 100:10:5.5 (F1–12) → 100:20:6 (F13–28), F4–23] afforded **5b** (33 mg, 0.16 mmol, 31%) as a yellow solid (m.p. 90-95°C). It was slightly contaminated with unidentified compounds.

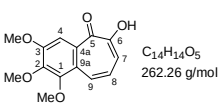
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 4.01 (s, 3H, 3-OCH_3), 6.89 (dd, $J_{8,9}$ = 11.3 Hz, $J_{8,7}$ = 9.5 Hz, 1H, 8-H), 7.27 (dd, $J_{7,8}$ = 9.5 Hz, $J_{7,9}$ = 0.8 Hz, 1H, 7-H), 7.37 (m_C, 1H, 9-H), 7.38 (dd, $J_{2,1}$ = 8.8 Hz, $J_{2,4}$ = 2.9 Hz, 1H, 2-H), 7.75 (d, $J_{1,2}$ = 8.8 Hz, 1H, 1-H), 8.32 (d, $J_{4,2}$ = 2.8 Hz, 1H, 4-H), 8.7 (br. s, 1H, 6-OH) ppm.

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 55.86 (3-OCH_3), 110.35 (C-4), 115.43 (C-7), 123.59 (C-2), 124.65 (C-8), 132.98 (C-4a)*, 133.05 (C-9), 134.99 (C-9a)*, 136.30 (C-1), 156.15 (C-6), 160.74 (C-3), 179.66 (C-5) ppm; **assignment interchangeable*.

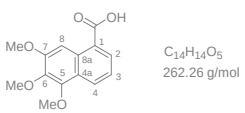
IR ($CHCl_3$): ν = 3277, 3005, 2965, 2940, 1755, 1710, 1635, 1615, 1590, 1565, 1545, 1490, 1440, 1425, 1375, 1280, 1245, 1220, 1180, 1125, 1060, 1035, 1005, 885, 835, 790, 745 cm^{-1}.

HRMS: (pos. APCI): $C_{12}H_{11}O_3^{\oplus}$ ($M+H^{\oplus}$): calculated: 203.0703; found: 203.0700 (Δ = –1.2220 ppm).

6-Hydroxy-1,2,3-trimethoxy-5*H*-benzo[7]annulen-5-one (5c) and 5,6,7-Trimethoxy-1-naphthoic acid (57)



5c



57

(characterization data: *vide infra*)

NaHMDS (2 M, solution in THF, 484 µL, 967 µmol, 2.0 equiv.) was added dropwise to a solution of compound **11c** (120 mg, 483 µmol, 1.0 equiv.) in THF (11 mL) at –78°C. The mixture was stirred for 20 min at the same temperature. Then, the temperature was raised to 0°C and $P(OEt)_3$ (94 µL, 88.0 mg, 532 µmol, 1.1 equiv.) was added in one portion. O_2 (moderate gas flow, 1 atm.) was bubbled through the solution for 2 h at 0°C. The reaction was complete, if the color change from yellow to red. An aqueous solution of NaOH (1 M, 10 mL) was added and the aqueous solution was washed with CH_2Cl_2 (1 × 10 mL). The aqueous layer was acidified with conc. HCl (pH 1) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers (after acidification) were dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by flash-chromatography on silica gel[21] [d = 1.0 cm, h = 14 cm, F = 10 mL; *c*-C_6H_{12}/EtOAc 4:1 (F1-13)] gave the benzotropolone **5c** [F3-7, $R_{f,\ 1:1}$ = 0.73, 47.8 mg, 38%] as a yellow solid (mp. 88-91°C); no 1-naphthoic acid **57** was observed under this reaction conditions.– When the identical oxidation was carried out under the same conditions (**11c**: 120 mg) but *without* $P(OEt)_3$, flash-chromatography on silica gel[21] [d = 1.0 cm, h = 14 cm, F = 10 mL; *c*-C_6H_{12}/EtOAc 4:1 (F1-13) → 0:1 (F14-21)] led to the benzotropolone **5c** (F3-7, 46.2 mg, 36%) as an oil[63] and to the naphthoic acid **57** (F9-20, 16.5 mg, 13%) as a solid [mp. 132-133°C (ref.[64]: 159°C)].

^{1}H NMR (500.10 MHz, C_6D_6): δ = 3.34 (s, 3H, 3-OCH_3), 3.59 (s, 3H, 1-OCH_3), 3.69 (s, 3H, 2-OCH_3), 6.49 (dd, $J_{8,9}$ = 11.8 Hz, $J_{8,7}$ =9.4 Hz, 1H, 8-H), 7.07 (d, $J_{7,8}$ = 9.3 Hz, 1H, 7-H), 7.86 (d, $J_{9,8}$ = 11.8 Hz, 1H, 9-H), 8.37 (s, 1H, 4-H), 9.14 (br. s, 1H, 6-OH) ppm.

NOESY (500.10 MHz/500.10 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{1}H)]: δ = 3.34 (3-OCH_3) ↔ δ = 8.37 (4-H); 3.59 (1-OCH_3) ↔ δ = 7.86 (9-H); 6.49 (8-H) ↔ δ = 7.07 (7-H), 7.86 (9-H); 7.07 (7-H) ↔ δ = 6.49 (8-H); δ = 7.86 (9-H) ↔ δ = 3.59 (1-OCH_3), 6.49 (8-H).

^{13}C NMR (125.75 MHz, C_6D_6): δ = 55.30 (3-OCH_3), 60.56 (2-OCH_3), 61.32 (1-OCH_3), 107.65 (C-4), 114.69 (C-7), 124.43 (C-9), 125.29 (C-8), 129.06 (C-9a), 130.90 (C-4a), 147.00 (C-2), 152.07 (C-1), 155.48 (C-3), 156.63 (C-6), 179.47 (C-5) ppm.

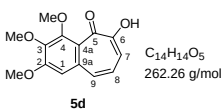
edHSQC ("short-range H,C-COSY", 500.10 MHz/125.75 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{13}C)]: δ = 3.34 ↔ δ = 55.30; 3.59 ↔ δ = 61.32; 3.69 ↔ δ = 60.56; 6.49 ↔ δ = 125.29; 7.07 ↔ δ = 114.69; 7.86 ↔ δ = 124.43; 8.37 ↔ δ = 107.65.

HMBC ("long-range H,C-COSY", 500.10 MHz/125.75 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{13}C)]: δ = 3.34 (3-OCH_3) ↔ δ = 155.48 (C-3); δ = 3.59 (1-OCH_3) ↔ δ = 152.07 (C-1); δ = 3.69 (2-OCH_3) ↔ δ = 147.00 (C-2); δ = 6.49 (8-H) ↔ δ = 129.06 (C-9a), 156.63 (C-6); δ = 7.07 (7-H) ↔ δ = 124.43 (C-9), 156.63 (C-6), 179.48 (C-5); δ = 7.86 (9-H) ↔ δ = 114.69 (C-7), 130.90 (C-4a), 152.07 (C-1); δ = 8.37 (4-H) ↔ δ = 129.06 (C-9a), 130.90 (C-4a), 147.00 (C-2), 155.48 (C-3), 179.48 (C-5).

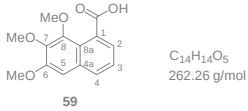
IR (KBr): ν = 3430, 3280, 2955, 2930, 2840, 1635, 1605, 1580, 1540, 1485, 1435, 1415, 1370, 1295, 1250, 1205, 1160, 1100, 1045, 1030, 1005, 925, 865, 810, 785, 735, 660 cm^{-1}.

HRMS: (pos. APCI): calcd. for $C_{14}H_{15}O_5$ $[M+H]^-$ = 263.0914; found 263.0917 (+1.16 ppm).

6-Hydroxy-2,3,4-trimethoxy-5*H*-benzo[7]annulen-5-one (5d) and 6,7,8-Trimethoxy-1-naphthoic acid (59)



5d



59

(characterization data: *vide infra*)

NaHMDS (2 M, solution in THF, 484 µL, 967 µmol, 2.0 equiv.) was added dropwise to a solution of 2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[7]annulen-5-one (**11d**) (120 mg, 483 µmol, 1.0 equiv.) in THF (6 mL) at –78°C. The mixture was stirred for 20 min at the same temperature. Then, the temperature was raised to 0°C and $P(OEt)_3$ (94 µL, 88.0 mg, 532 µmol, 1.1 equiv.) was added in one portion. O_2 (moderate gas flow, 1 atm.) was bubbled through the solution for 20 min at 0°C. The reaction was complete, if the color change from yellow to red. An aqueous solution of NaOH (1 M, 5 mL) was added and the aqueous solution was washed with CH_2Cl_2 (1 × 5 mL). The aqueous layer was acidified with conc. HCl (pH 1) and

Accepted Manuscript

This article is protected by copyright. All rights reserved.

extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers (after acidification) were dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by flash-chromatography on silica gel[21] [d = 1.0 cm, h = 11 cm, F = 10 mL; *c*-C_6H_{12}/EtOAc 3:1 (F1-20)] gave the benzotropolone **5d** (F6-9, $R_{f,\,3:1}$ = 0.24, 42.1 mg, 33%) as a yellow solid (mp. 132-134°C) and the naphtalen-1-carboxylic acid **59** (F11-18, $R_{f,\,3:1}$ = 0.35, 33.1 mg, 26%) as a light brown solid (mp. 138-140°C).– When the identical oxidation was carried out under the same conditions (**11d**: 100 mg) but *without* $P(OEt)_3$ for 30 min instead of for 20 min,flash-chromatography on silica gel[21] led to the benzotropolone **5d** (16.3 mg, 15%) and to the naphthoic acid **59** (34.0 mg, 32%).

^{1}H NMR (500.10 MHz, C_6D_6): δ = 3.21 (s, 3H, 2-OCH_3), 3.72 (s, 3H, 3-OCH_3), 4.06 (s, 3H, 4-OCH_3), 6.20 (dd, $J_{8,9}$ = 11.5 Hz, $J_{8,7}$ =9.2 Hz, 1H, 8-H), 6.32 (s, 1H, 1-H), 6.58 (ddd, $J_{9,8}$ = 11.5 Hz, $^4J_{9,7} \approx {}^4J_{9,1} \approx$ 0.7 Hz, 1H, 9-H), 6.75 (dd, $J_{7,8}$ = 9.2 Hz, $^4J_{7,9} \approx$ 0.8 Hz, 1H, 7-H), 9.00 (br. s, 1H, 6-OH) ppm.

NOESY (500.10 MHz/500.10 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{1}H)]: δ = 3.21 (2-OCH_3) ↔ δ = 6.32 (1-H); 6.32 (1-H) ↔ δ = 3.21 (2-OCH_3), 6.58 (9-H); 6.58 ppm (9-H) ↔ δ = 6.32 ppm (1-H).

^{13}C NMR (125.75 MHz, C_6D_6): δ = 55.12 (2-OCH_3), 60.69 (3-OCH_3), 62.04 (4-OCH_3), 109.64 (C-1), 110.47 (C-7), 124.24 (C-4a), 125.66 (C-8), 130.83 (C-9), 136.31 (C-9a), 145.23 (C-3), 156.52 (C-4)*, 156.57 (C-2)*, 158.16 (C-6), 180.19 (C-5) ppm; **assignment interchangeable*

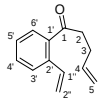
edHSQC ("short-range H,C-COSY", 500.10 MHz/125.75 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{13}C)]: δ = 3.21 ↔ δ = 55.12; δ = 3.72 ↔ δ = 60.69; δ = 4.06 ↔ δ = 62.04; δ = 6.20 ↔ δ = 125.66; δ = 6.32 ↔ δ = 109.64; δ = 6.58 ↔ δ = 130.83; δ = 6.75 ppm ↔ δ = 110.47 ppm.

HMBC ("long-range H,C-COSY", 500.10 MHz/125.75 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{13}C)]: δ = 3.21 (2-OCH_3) ↔ δ = 156.52 or 156.57 (C-2); δ = 3.72 (3-OCH_3) ↔ δ = 145.23 (C-3); δ = 4.06 (4-OCH_3) ↔ δ = 156.52 or 156.57 (C-4); δ = 6.20 (8-H) ↔ δ = 136.31 (C-9a), 158.16 (C-6); δ = 6.32 (1-H) ↔ δ = 124.24 (C-4a), 130.83 (C-9), 145.23 (C-3), 156.52 or 156.57 (C-2 or C-4); δ = 3.59 (1-OCH_3) ↔ δ = 152.07 (C-1); δ = 6.58 (9-H) ↔ δ = 109.64 (C-1), 110.47 (C-7), 124.24 (C-4a); δ = 6.75 ppm (7-H) ↔ δ = 130.83 (C-9), 158.16 (C-6), 180.19 ppm (C-5).

IR (KBr): ν = 3425, 3295, 2925, 1640, 1605, 1585, 1555, 1490, 1450, 1430, 1400, 1365, 1280, 1260, 1230, 1210, 1195, 1150, 1100, 1055, 1040, 985, 975, 865, 790, 750, 675 cm^{-1}.

HRMS (pos. APCI): calcd. for $C_{14}H_{15}O_5$ $[M+H]^-$ = 263.0914; found 263.0916 (+0.6963 ppm).

1-(2-Vinylphenyl)pent-4-en-1-one (10a)



$C_{13}H_{14}O$
186.25 g/mol

*n*BuLi (2.45 M, solution in *n*-hexane; 0.2 mL, 546 μmol, 1.1 equiv.) was added dropwise within 10 min to a solution of **15** (101 mg, 546 μmol, 1.1 equiv.) in THF (1 mL) at −78°C. The mixture was stirred for 30 min at −78°C. The Weinreb amide **16** (71.1 mg, 497 μmol, 1 equiv) was added in one portion and the resulting mixture was stirred for 3 h at −78°C. A saturated aqueous solution of NH_4Cl (2 mL) and H_2O (10 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl (15 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash-chromatography on silica gel[21] [2 × 15 cm, *c*C_6H_{12}:EtOAc 40:1 to 10:1 (v:v), 20 mL] to render the title compound (F 9-13; 57.2 mg, 88%) as colorless oil.

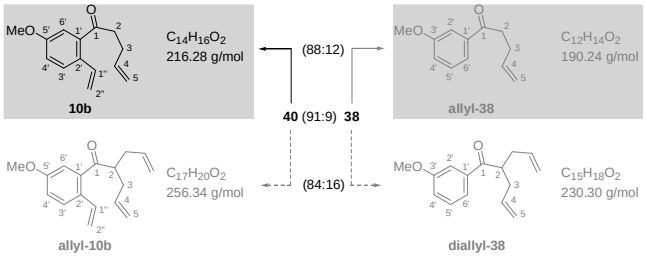
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.43-2.49 (m, 2H, 3'-H_2), 2.98 (t, 2H, $J_{2,3}$ = 7.4 Hz, 2'-H_2), 5.00 (tdd, 1H, $J_{5'\text{-}H(1),4'}$ = 10.2 Hz, J_{gem} = 1.7 Hz, $^4J_{5'\text{-}H(1),3'}$ = 1.3 Hz, 5'-H^1), 5.06 (tdd, 1H, $J_{5'\text{-}H(2),4'}$ = 17.1 Hz, J_{gem} = 1.7 Hz, $^4J_{5'\text{-}H(2),3'}$ = 1.7 Hz, 5'-H^2), 5.33 (dd, 1H, $J_{2''\text{-}(1),1''}$ = 11.0 Hz, J_{gem} = 1.2 Hz, 2''-H^1), 5.63 (dd, 1H, $J_{2''\text{-}H(2),1''}$ = 17.4 Hz, J_{gem} = 1.2 Hz, 2''-H^2), 5.87 (tdd, 1H, $J_{4',5'\text{-}H(2)}$ = 17.0 Hz, $J_{4',5'\text{-}H(1)}$ = 10.4 Hz, $J_{4',3'}$ = 6.6 Hz, 4'-H), 7.09 (dd, 1H, $J_{1'',2''\text{-}H(2)}$ = 17.4 Hz, $J_{1'',2''\text{-}H(1)}$ = 11.0 Hz, 1''-H), 7.32 (ddd, $J_{5,4}$ = $J_{5,6}$ = 7.6 Hz, $^4J_{5,3}$ = 1.3 Hz, 5-H), 7.44 (dddd, $J_{4,3}$ = 7.9 Hz, $J_{4,5}$ = 7.3 Hz, $^4J_{4,6}$ = 1.4 Hz, $^5J_{4,1''}$ = 0.5 Hz, 4-H), 7.55 (ddd, 1H, $J_{6,5}$ = 7.7 Hz, $J_{6,4}$ = 1.4 Hz, $^4J_{6,3}$ = 0.5 Hz, 6-H), 7.56 (ddd, 1H, $J_{3,4}$ = 7.8 Hz, $^4J_{3,5}$ = 1.2 Hz, $^5J_{3,6}$ = 0.6 Hz, 3-H).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 28.47 (C-3')^A, 41.29 (C-2')^A, 115.50 (C-5')^A, 116.77 (C-2'')^A, 127.46 (C-3)^A, 127.53 (C-5)^A, 127.91 (C-6)^A, 131.28 (4-C)^A, 135.65 (C-1'')^A, 137.16 (C-4')^A, 137.42 (C-2)^B, 138.07(C-1)^B, 204.24 (C-1')^B; ^{A} the indicated ^{13}C nuclei – they are non-quaternary – were identified in an edHSQC spectrum by their crosspeaks with directly bond protons; ^{B} the indicated ^{13}C nuclei are quaternary and were distinguished in an HMBC spectrum by their crosspeaks due to ^2J, ^3J and/or ^4J couplings to "remote" protons.

IR (film): ν = 3080, 3065, 3025, 2980, 2920, 1830, 1685, 1640, 1595, 1565, 1480, 1445, 1410, 1350, 1290, 1255, 1240, 1210, 1195, 1115, 1020, 980, 915, 770, 750, 700, 655 cm^{-1}.

HRMS (pos. APCI): $C_{13}H_{14}ONa^{\oplus}$ ($M+Na^{\oplus}$): calculated: 209.0937; found: 209.0937 (Δ = ±0.0 ppm).

1-(5-Methoxy-2-vinylphenyl)pent-4-en-1-one (10b) in an 88:12 Mixture With 1-(3-Methoxyphenyl)pent-4-en-1-one (allyl-38)



At 0 °C a solution of a 91:9 (mol:mol) mixture (870 mg) of compounds **40** (802 mg, 4.55 mmol) and **38** (68 mg, 0.45 mmol) in THF (2 mL) was added dropwise to a suspension of KH (washed, 0.22 g, 5.5 mmol, 1.1 equiv. relative to the combined amounts of **40** and **38**). The mixture was stirred at 0 °C for 5 min and then at room temp. for 2 h. A solution of BEt_3 in THF (1 M, 5.5 mL, 5.5 mmol, 1.1 equiv. relative to the combined amounts of **40** and **38**) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 5 min and at room temp. for 1 h. Allyl bromide (0.65 mL, 0.91 g, 7.5 mmol, 1.5 equiv. relative to the combined amounts of **40** and **38**) was added dropwise and the resulting mixture was stirred at room temp. for 18 h. The reaction was quenched at 0 °C by adding aq. NaOH (15%, 10 mL) and H_2O_2 (15%, 10 mL) and stirring for 1 h at room temp. Et_2O (50 mL) was added and – while stirring at room temp. for 3 h – sat. aq. Na_2SO_3 (200 mL), 5% aq. $FeSO_4$ (100 mL), and solid $FeSO_4$ (approx. 5 g) were added successively. Nevertheless, peroxides could still be detected in the mixture. The phases were separated. The organic phase was washed with a mixture of sat. aq. Na_2SO_3 and 10% aq. $FeSO_4$ (200 mL) until no more peroxide species were detectable. The aqueous phase was extracted with Et_2O (2 × 100 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Purification by flash-chromatography on silica gel[21] [3.5 × 19 cm, 50 mL, cyclohexane/EtOAc = 50:1 (F1–17) → 30:1 (F18–29) → 20:1 (F30–43) → 10:1 (F44–50)] afforded the following isolates: 1) F15–20 = 125 mg of a colorless oil representing a 84:16 mixture (mol:mol) of the bisallylation product 2-allyl-1-(5-methoxy-2-vinylphenyl)pent-4-en-1-one (**allyl-10b**; 107 mg, 9% relative to **40**) and its vinyl-free analog 2-allyl-1-(3-methoxyphenyl)pent-4-en-1-one (**diallyl-38**; 18 mg, 17% relative to **38**); 2) F21–28 = 542 mg of a yellowish oil which was a 88:12 mixture (mol:mol) of the desired monoallylation product **10b** (484 mg, 49% relative to **40**) and its vinyl-free analog 1-(3-methoxyphenyl)pent-4-en-1-one (**allyl-38**; 58 mg, 68% relative to **38**); 3) F33-40 = 246 mg of a yellowish oil which was the pure substrate **40** (31% relative to the original amount of **40**; accordingly, the 49% yield of isolated monoallylation product **10b** was tantamount to 71% b.o.r.s.m.). In contrast, the vinyl-free substrate **38** was not re-isolated.

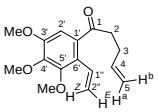
Accepted Manuscript

This article is protected by copyright. All rights reserved.

^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta_{\mathbf{10b}}$ = 2.46 (m_C, 2H, 3-H_2), 2.95 (t, $J_{2,3}$ = 7.1 Hz, 2H, 2-H_2), 3.84 (s, 3H, 5'-OCH_3), 5.01 (ddt, $J_{5\text{-}H^E,4}$ =10.2 Hz, $^2J_{5\text{-}H^E,5\text{-}H^Z}$ = $^4J_{5\text{-}H^E,3}$ = 1.3 Hz, 1H, 5-H^E), 5.06 (ddt, $J_{5\text{-}H^Z,4}$ =17.1 Hz, $^2J_{5\text{-}H^Z,5\text{-}H^E}$ = $^4J_{5\text{-}H^Z,3}$ = 1.6 Hz, 1H, 5-H^Z), 5.23 (dd, $J_{2''\text{-}H^E,1''}$ =11.0 Hz, $^2J_{2''\text{-}H^E,2''\text{-}H^Z}$ = 1.3 Hz, 1H, 2''-H^E), 5.53 (dd, $J_{2''\text{-}H^Z,1''}$ =17.4 Hz, $^2J_{2''\text{-}H^Z,2''\text{-}H^E}$ = 1.2 Hz, 1H, 2''-H^Z), 5.86 (ddt, $J_{4,5\text{-}H^Z}$ = 16.7 Hz, $J_{4,5\text{-}H^E}$ = 10.2 Hz, $J_{4,3}$ = 6.5 Hz, 1H, 4-H), 6.96 (dd, $J_{1'',2''\text{-}H^Z}$ = 17.9 Hz, $J_{1'',2''\text{-}H^E}$ = 10.9 Hz, 1H, 1''-H), 6.98 (dd, $J_{4',3'}$ = 8.6 Hz, $J_{4',6'}$ = 2.7 Hz, 1H, 4'-H), 7.02 (d, $J_{6',4'}$ = 2.6 Hz, 1H, 6'-H), 7.50 (d, $J_{3',4'}$ = 8.6 Hz, 1H, 3'-H) ppm.– $\delta_{\mathbf{allyl\text{-}38}}$ = 2.50 (m_C, 2H, 3-H_2), 3.06 (t, $J_{2,3}$ = 7.2 Hz, 1H, 2-H_2), 3.86 (s, 3H, 3'-OCH_3), 5.01 (ddt, $J_{5\text{-}H^E,4}$ =10.3 Hz, $^2J_{5\text{-}H^E,5\text{-}H^Z}$ = $^4J_{5\text{-}H^E,3}$ = 1.3 Hz, 1H, 5-H^E), 5.09 (ddt, $J_{5\text{-}H^Z,4}$ =17.0 Hz, $^2J_{5\text{-}H^Z,5\text{-}H^E}$ = $^4J_{5\text{-}H^Z,3}$ = 1.6 Hz, 1H, 5-H^Z), 5.90 (ddt, $J_{4,5\text{-}H^Z}$ = 16.9 Hz, $J_{4,5\text{-}H^E}$ = 10.3 Hz, $J_{4,3}$ = 6.6 Hz, 1H, 4-H), 7.11 (ddd, $J_{6',5'}$ = 8.3 Hz, $J_{6',2'}$ = 2.7 Hz, $J_{6',4'}$ = 1.0 Hz, 1H, 6'-H)*, 7.37 (ddd, $J_{5',6'}$ = 8.0 Hz, $J_{5',4'}$ = 7.6 Hz, $J_{5',2'}$ = 0.4 Hz, 1H, 5'-H), 7.49 (dd, $J_{2',6'}$ = 2.6 Hz, $J_{2',4'}$ = 1.5 Hz, 1H, 2'-H), 7.54 (ddd, $J_{4',5'}$ = 7.6 Hz, $J_{4',2'}$ = 1.6 Hz, $J_{4',6'}$ = 1.0 Hz, 1H, 4'-H)* ppm; **assignment interchangeable*.

^{13}C NMR (100.61 MHz, $CDCl_3$): $\delta_{\mathbf{10b}}$ = 28.44 (C-3), 41.52 (C-2), 55.60 (5'-OCH_3), 113.07 (C-6'), 115.12 (C-2''), 115.54 (C-5), 116.69 (C-4'), 128.63 (C-3'), 129.68 (C-2'), 134.81 (C-1''), 137.10 (C-4), 139.46 (C-1'), 158.95 (C-5'), 204.36 (C-1) ppm.– $\delta_{\mathbf{allyl\text{-}38}}$ = 28.32 (C-3), 37.98 (C-2), 55.54 (3'-OCH_3), 112.46 (C-2'), 115.38 (C-5), 119.55 (C-6')*, 120.75 (C-4')*, 129.66 (C-5'), 137.38 (C-4), 138.49 (C-1'), 159.99 (C-3'), 199.33 (C-1) ppm; **assignment interchangeable*.

1-(3,4,5-Trimethoxyphenyl-2-vinyl)pent-4-en-1-one (10c)



$C_{16}H_{20}O_4$
276.33 g/mol

n-BuLi (1.6 M in hexane, 7.15 mL, 11.4 mmol, 1.5 equiv.) was added to a stirred solution of the styrene **43** (2.58 g, 9.53 mmol, 1.25 equiv.) in THF (24 mL) at –78°C. The resulting red solution was stirred at that temperature for 20 min, before a solution of anhydrous $ZnCl_2$ (1.66 g, 12.2 mmol, 1.6 equiv.) in THF (12 mL) was added. The cooling bath was exchanged by an ice bath and the mixture was stirred at 0°C for 1 h. The clear colorless solution was transferred to a solution of $PdCl_2(PPh_3)_2$ (214 mg, 305 µmol, 4 mol-%) and *S*-ethyl pent-4-enethioate (**44**; 1.10 g, 7.63 mmol) in toluene (48 mL) at room temp. . The resulting mixture was stirred at the same temperature for 16 h and filtered over a pad of celite (d = 2 cm, h = 3 cm). The filter residue was washed with EtOAc (50 mL). The solvents were removed in vacuo and the residue was purified by flash-chromatography on silica gel[21] [d = 6.0 cm, h = 14 cm, F = 50 mL; *c*-C_6H_{12}/EtOAc 20:1 (F1-35); *c*-C_6H_{12}/EtOAc 10:1 (F36-57)] to give the target compound (F34-55, $R_{f,\ 4:1}$ = 0.29, 1.75 g, 83%) as a yellow oil.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.34-2.40 (m, 2H, 3-H_2), 2.82 (t, *J* = 7.3 Hz, 2H, 2-H_2), 3.82 (s, 3H, 5'-OCH_3), 3.86 (s, 3H, 3'-OCH_3), 3.90 (s, 3H, 4'-OCH_3), 4.97 (ddt, J_{cis} = 10.1 Hz, J_{gem} = 1.6 Hz, $^4J_{5\text{-}Ha,3}$ = 1.3 Hz, 1H, 5-H^a), 5.02 (ddt, J_{trans} = 17.1 Hz, J_{gem} = 1.7 Hz, $^4J_{5\text{-}Hb,3}$ = 1.7 Hz, 1H, 5-H^b), 5.32 (dd, J_{trans} = 17.7 Hz, J_{gem} = 1.5 Hz, 1H, 2''-H^Z), 5.41 (dd, J_{cis} = 11.3 Hz, J_{gem} = 1.5 Hz, 1H, 2''-H^E), 5.81 (ddt, J_{trans} = 17.0 Hz, J_{cis} = 10.3 Hz, $J_{4,3}$ = 6.6 Hz, 1H, 4-H), 6.66 (s, 1H, 2'-H), 6.88 (dd, J_{trans} = 17.7 Hz, J_{cis} = 11.3 Hz, 1H, 1''-H) ppm.

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 29.01 (C-3), 42.44 (C-2), 56.18 (3'-OCH_3), 60.85 (5'-OCH_3), 61.00 (4'-OCH_3), 106.80 (C-5'), 115.33 (C-5), 120.44 (C-2''), 124.32 (C-6'), 130.94 (C-1''), 136.37 (C-1'),137.11 (C-4), 144.04 (C-4'), 151.67 (C-5'), 152.75 (C-3'), 206.40 (C-1) ppm.

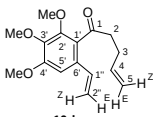
IR (film): ν = 3080, 2975, 2935, 2845, 1690, 1585, 1490, 1455, 1380, 1355, 1330, 113,1115, 1025, 915, 840, 745 cm^{-1}.

HRMS (pos. APCI): calcd. for $C_{16}H_{21}O_4^{\oplus}$ ($M+H^{\oplus}$) = 277.14344; found 277.14283 (Δ = –2.2 ppm).

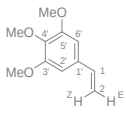
Elemental analysis:

$C_{16}H_{20}O_4$ (276.3 g/mol)	calc. C 69.55	H 7.30
	found C 69.12	H 7.27

1-(2,3,4-Trimethoxy-6-vinylphenyl)pent-4-en-1-one (10d) in a 65:35 Mixture With 3,4,5-Trimethoxystyrene (debromo-47)



$C_{16}H_{20}O_4$
276.33 g/mol
10d



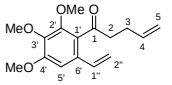
$C_{11}H_{14}O_3$
194.23 g/mol
debromo-**47**

n-BuLi (1.6 M in hexane, 3.25 mL, 5.20 mmol, 1.5 equiv.) was added to a stirred solution of the bromostyrene **47** (1.17 mg, 4.33 mmol, 1.25 equiv.) in THF (11 mL) at –78°C. The resulting yellow solution was stirred at that temperature for 20 min, before a solution of anhydrous $ZnCl_2$ (756 mg, 5.55 mmol, 1.6 equiv.) in THF (6 mL) was added at –78°C. The mixture was allowed to warm up to 0°C and stirred for 1 h. The clear colorless solution was transferred to a mixture of $PdCl_2(PPh_3)_2$ (97 mg, 0.14 mmol, 4 mol-%) and *S*-ethyl pent-4-enethioate (**44**; 500 mg, 3.47 mmol) in toluene (22 mL) at room temp. . The resulting mixture was stirred at the same temperature for 18 h, filtered over a pad of celite, and washed with EtOAc (50 mL). The solvents were removed in vacuo. The residue was purified via flash-chromatography on silica gel[21] (d = 4.0 cm, h = 15 cm, F = 50 mL; *c*-C_6H_{12}/EtOAc 10:1) to give a 64:36-mixture (mol:mol; F8-22, $R_{f,\ 4:1}$ = 0.38, 842 mg) of **10d** (607 mg, 51%) and **debromo-47** (235 mg, 28%) as a yellow oil.

^{1}H NMR (400.13 MHz, $CDCl_3$, NMR-file: 2018: 20181108-4220): $\delta_{\mathbf{10d}}$ = 2.40–2.47 (m, 2H, 3-H_2), 2.85 (t, $J_{2,3}$ = 7.2 Hz, 2H, 2-H), 3.86 (s, 3H, 3'-OCH_3)[i], 3.878 (s, 3H, 2'-OCH_3)[i], 3.90 (s, 3H, 4'-OCH_3)[ii], 4.99 (ddt, J_{cis} = 10.2 Hz, J_{gem} = $^4J_{5\text{-}H^E,3}$ = 1.3 Hz, 1H, 5-H^E), 5.06 (ddt, J_{trans} = 17.1 Hz, J_{gem} = $^4J_{5\text{-}H^Z,3}$ = 1.7 Hz, 1H, 5-H^Z), 5.25 (dd, J_{cis} = 10.9 Hz, J_{gem} = 0.9 Hz, 1H, 2''-H^E), 5.59 (dd, J_{trans} = 17.4 Hz, J_{gem} = 1.0 Hz, 1H, 2''-H^Z), 5.86 (ddt, J_{trans} = 16.6 Hz, J_{cis} = 10.1 Hz, $J_{4,3}$ = 6.4 Hz, 1H, 4-H), 6.58 (dd, J_{trans} = 17.4 Hz, J_{cis} = 11.0 Hz, 1H, 1''-H), 6.83 (s, 1H, 5'-H) ppm.– $\delta_{\mathbf{debromo\text{-}47}}$ = 3.85 (s, 3H, 4'-OCH_3), 3.88 (s, 6H, 3'-OCH_3, 5'-OCH_3), 5.21 (dd, J_{cis} = 10.8 Hz, J_{gem} = 0.8 Hz, 1H, 2-H^E), 5.65 (dd, J_{trans} = 17.6 Hz, J_{gem} = 0.9 Hz, 1H, 2-H^Z), 6.64 (s, 2H, 2'-H, 6'-H), 6.64 (dd, J_{trans} = 17.6 Hz, J_{cis} = 10.7 Hz, 1H, 1-H) ppm.

HRMS (pos. ESI): calcd. for $C_{16}H_{21}O_4$ [$M_{\mathbf{10d}}$+H]$^+$ = 277.14344; found 277.14385 (+1.48 ppm); calcd. for $C_{11}H_{15}O_3$ [$M_{\mathbf{debromo\text{-}47}}$+H]$^+$ = 195.10157; found 195.10116 (–2.10 ppm).

1-(2,3,4-Trimethoxy-6-vinylphenyl)pent-4-en-1-one (10d)



$C_{16}H_{20}O_4$
276.33 g/mol

This reaction was performed in a very similar manner to that described for compound **73** utilizing Dess-Martin periodinane (6.00 g, 14.1 mmol), 48 (1.97 g, 7.07 mmol) in moist DCM (50 mL, saturated with H_2O). A similar work-up afforded a residue which was purified by flash column chromatography on silica gel (10% EtOAc/hexane) to give the diene **10d** (1.80 g, 6.50 mmol, 92%) as a light reddish-colored liquid.

^{1}H NMR (300 MHz; $CDCl_3$): δ = 2.47-2.40 (m, 2H, 3-H), 2.85 (t, *J* = 7.5 Hz, 2H, 2-H), 3.86 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.90 (s, 3H, (OMe), 5.10-4.97 (m, 2H, 5-H), 5.25 (d, *J* = 10.8 Hz, 1H, *cis* 2''-H), 5.59 (d, *J* = 17.2 Hz, 1H, *trans* 2''-H), 5.88 (ddt, $J_{trans\ H\text{-}4\text{-}H\text{-}5}$ = 16.8, $J_{cis\ H\text{-}4\text{-}H\text{-}5}$ = 10.2, $J_{H\text{-}4\text{-}H\text{-}3}$ = 6.5 Hz, 1H, 4-H), 6.58 (dd, $J_{trans\ H\text{-}1''\text{-}H\text{-}2''}$ = 17.2, $J_{cis\ H\text{-}1''\text{-}H\text{-}2''}$ = 10.8 Hz, 1H, 1''-H), 6.83 (s, 1H, 5'-H) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ = 27.8 (C-3), 44.3 (C-2), 56.0 (OMe), 60.9 (OMe), 61.7 (OMe), 104.5 (C-5'), 115.1 (C-5), 116.0 (C-2''), 128.4 (C-1'), 130.6 (C-1''), 133.4 (C-6'), 137.2 (C-4), 141.5 (C-2')*, 150.3 (C-3')*, 154.3 (C-4')*, 205.5 (CO) ppm; *assignments interchangeable.

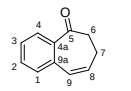
IR (neat): ν = 2937, 1696, 1589, 1558, 1487, 1399, 1320, 1249, 1196 cm^{-1}.

HRMS: calcd for $C_{16}H_{21}O_4$ (M^++H) = 277.1434, found: 277.1436 (Δ = +0.72 ppm).

Accepted Manuscript

This article is protected by copyright. All rights reserved.

6,7-Dihydro-5*H*-benzo[7]annulen-5-one (11a)

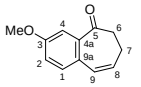


$C_{11}H_{10}O$
158.20 g/mol

A mixture of the 1,8-diene **10a** (1.18 mg, 6.34 mmol, 1.0 equiv.) and Grubbs 2nd generation catalyst[15] (115 mg, 1.8 mol-%) in toluene (31 mL) was stirred at 60°C for 6 h. After cooling to room temp. silica gel was added. The solvent was evaporated and the residue was purified by flash-chromatography on silica gel[21] [6 × 15 cm, *c*C_6H_{12}:EtOAc 80:1 (v:v), 100 mL] to render the title compound (FF18-32; 927 mg, 92%) as a colorless oil.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.49-2.54 (m, 2H, 3-H_2), 2.93-2.97 (m, 2H, 4-H_2), 6.19 (ddd, 1H, $J_{2,1}$ = 11.5 Hz, $J_{2,3}$ = $J_{2,4}$ = 5.7 Hz, 2-H), 6.47 (ttdd, 1H, $J_{1,2}$ = 12.8 Hz, $J_{1,3}$ = $J_{1,2}$ = 2.7 Hz, $J_{1,4'}$ = 1.2 Hz, 1-H), 7.23 (dd, 1H, $J_{4',3'}$ = 7.7 Hz, $J_{4',1}$ = 1.2 Hz, 4'-H), 7.29 (ddd, 1H, $J_{2',1'}$ = $J_{2',3'}$ = 7.6 Hz, $J_{2',4'}$ = 1.3 Hz, 2'-H), 7.47 (ddd, 1H, $J_{3',2'}$ = $J_{3',4'}$ = 7.5 Hz, $J_{3',1'}$ = 1.5 Hz, 3'-H), 7.91 (dddd, 1H, $J_{1',2'}$ = 7.8 Hz, $J_{1',3'}$ = 1.5 Hz, $J_{1',4'}$ = $J_{1',1}$ = 0.5 Hz, 1'-H).
^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 24.41 (C-3)^A, 42.02 (C-4)^A, 127.14 (C-2')^A, 129.62 (C-1')^A, 131.38 (C-1)^A, 131.79 (C-4')^A, 132.52 (C-3')^A, 133.23 (C-2)^A, 135.95 (C-7)^B, 136.80 (C-6)^B, 202.14 (C-5)^B; ^{A} the indicated ^{13}C nuclei – they are non-quaternary – were identified in an edHSQC spectrum by their crosspeaks with directly bond protons; ^{B} the indicated ^{13}C nuclei are quaternary and were distinguished in an HMBC spectrum by their crosspeaks due to ^2J, ^3J and/or ^4J couplings to "remote" protons.
IR (film): ν = 3060, 3025, 2965, 2920, 2885, 2835, 2685, 2440, 2330, 1945, 1840, 1675, 1595, 1480, 1445, 1430, 1345, 1320, 1285, 1270, 1245, 1200, 1175, 1155, 1105, 1080, 1040, 1025, 1010, 960, 910, 870, 820, 785, 740, 725, 700, 665, 575, 550, 535, 505 cm^{-1}.
HRMS (pos. APCI): $C_{11}H_{14}NO^{\oplus}$ ($M+NH_4^{\oplus}$): calculated: 176.10699; found: 176.10706 (Δ = +0.4 ppm).

3-Methoxy-6,7-dihydro-5*H*-benzo[7]annulen-5-one (11b)

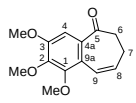


$C_{12}H_{12}O_2$
188.22 g/mol

At room temp. a solution of the Grubbs 2nd generation catalyst[15] (20 mg, 24 µmol, 1.1 mol%) in toluene (4.0 mL) was added dropwise to a solution of an 88:12 (mol:mol) mixture (510 mg) of the 1,8-diene **10b** (455 mg, 2.10 mmol) and the arylpentenone **allyl-38** (55 mg, 0.29 mmol) in toluene (20 mL). The solution was stirred at 60 °C for 6 h and then cooled to room temp. Silica (2 g) was added and the solvent was evaporated under reduced pressure. Purification by flash-chromatography on silica gel[21] [3.5 × 13 cm, 20 mL, cyclohexane/EtOAc = 50:1 (F1–20) → 30:1 (F21–35) → 20:1 (F36–58), F37–52] afforded the title compound **11b** (379 mg, 2.01 mmol, 96%) as a yellowish oil.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.48 (m_C, 2H, 7-H_2), 2.94 (m_C, 2H, 6-H_2), 3.85 (s, 3H, 3-OCH_3), 6.05 (dt, $J_{8,9}$ = 11.1 Hz, $J_{8,7}$ = 5.5 Hz, 1H, 8-H), 6.41 (m_C, 1H, 9-H), 7.01 (dd, $J_{2,1}$ = 8.5 Hz, $J_{2,4}$ = 2.9 Hz, 1H, 2-H), 7.15 (d, $J_{1,2}$ = 8.4 Hz, 1H, 1-H), 7.44 (d, $J_{4,2}$ = 2.9 Hz, 1H, 4-H) ppm.
^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 24.15 (C-7), 42.01 (C-6), 55.58 (3-OCH_3), 113.19 (C-4), 119.47 (C-2), 129.33 (C-9a), 130.64 (C-8), 130.77 (C-9), 133.49 (C-1), 137.74 (C-4a), 158.54 (C-3), 201.81 (C-5) ppm.
IR ($CHCl_3$): ν = 3025, 2005, 2960, 2940, 2910, 2835, 1675, 1605, 1565, 1495, 1465, 1430, 1395, 1345, 1330, 1290, 1250, 1230, 1195, 1185, 1155, 1075, 1035, 875, 855, 835, 560 cm^{-1}.
MS (CI, NH_3): 206 (48%, $M+NH_4^{\oplus}$), 189 (100%, $M+H^{\oplus}$), 188 (26%, $M^{\oplus}$).

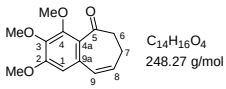
1,2,3-Trimethoxy-6,7-dihydro-5*H*-benzo[7]annulen-5-one (11c)



$C_{14}H_{16}O_4$
248.27 g/mol

The 1,8-diene **10c** (725 mg, 2.62 mmol) was added to a stirred solution of the Grubbs 2nd generation catalyst[15] (22 mg, 26 µmol, 1.0 mol-%) in toluene (26 mL) at room temp. The mixture was heated to 60°C and stirred for 3 h. After letting the mixture cool down to room temp. , the solvents were removed in vacuo. Flash-chromatography on silica gel[21] [d = 3.0 cm, h = 17 cm, F = 20 mL; *c*-C_6H_{12}/*t*-BuOMe 6:1 (F1-24); *c*-C_6H_{12}/ *t*-BuOMe 3:1 (F25-35)] gave the target compound (F15-30, $R_{f,\ 4:1}$ = 0.24, 624 mg, 96%) as yellow solid (mp. 51-54°C).
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.42-2.47 (m, 2H, 7-H_2), 2.89-2.92 (m, 2H, 6-H_2), 3.83 (s, 3H, 1-OCH_3), 3.91 (s, 3H, 3-OCH_3), 3.93 (s, 3H, 2-OCH_3), 6.19 (ddd, J_{cis} = 11.8 Hz, $J_{8,7\text{-}H^a}$ = 5.9 Hz, $J_{8,7\text{-}H^b}$ = 5.9 Hz, 1H, 8-H), 6.84 (dddd, J_{cis} = 11.9 Hz, $^4J_{9,7\text{-}H^a}$ = 1.4 Hz, $^4J_{9,7\text{-}H^b}$ = 1.4 Hz, $^5J_{9,6\text{-}H^a}$ = 0.4 Hz, 1H, 9-H), 7.29 (s, 1H, 4-H) ppm.
^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 23.74 (C-7), 43.15 (C-6), 56.06 (3-OCH_3), 60.96 (2-OCH_3), 61.33 (1-OCH_3), 108.51 (C-4), 123.69 (C-9), 124.42 (C-9a), 131.79 (C-8), 132.91 (C-4a), 146.20 (C-2), 151.58 (C-1), 152.17 (C-3), 201.53 (C-5) ppm.
IR (film): v = 2940, 2840, 1670, 1585, 1490, 1430, 1375, 1340, 1290, 1215, 1130, 1100, 1025, 925, 865, 740 cm^{-1}.
HRMS (pos. ESI, 70 eV): calcd. for $C_{14}H_{17}O_4^{\oplus}$ ($M+H^{\oplus}$) = 249.1121; found 249.1121 (Δ = ± 0.0 ppm).

2,3,4-Trimethoxy-6,7-dihydro-5*H*-benzo[7]annulen-5-one (11d)



$C_{14}H_{16}O_4$
248.27 g/mol

A) Preparation I (From a Mixture of the 1,8-Diene 10d and the Styrene debromo-47):
A 64:36-mixture (845 mg) of the 1,8-diene **10d** (608 mg, 2.20 mmol) and the styrene **debromo-47** (237 mg, 1.23 mmol) was added to a stirred solution of the Grubbs 2nd generation catalyst[15] (19 mg, 23 µmol, 1.0 mol-%) in toluene (22 mL) at room temp. The mixture was heated to 60°C and stirred for 2 h. After letting the mixture cool down to room temp. , the solvents were removed in vacuo. The residue was purified via flash-chromatography on silica gel[21] [d = 4.0 cm, h = 16 cm, F = 20 mL; *c*-C_6H_{12}/EtOAc 20:1 (F1-22); *c*-C_6H_{12}/EtOAc 15:1 (F23-36); *c*-C_6H_{12}/EtOAc 10:1 (F37-89); *c*-C_6H_{12}/EtOAc 7:1 (F90-122); *c*-C_6H_{12}/EtOAc 4:1 (F123-130)] gave the title compound (F70-126, $R_{f,\ 4:1}$ = 0.24, 471 mg, 84% based on the employed amount of substrate **10d**) as a light brown solid (mp. 97-99°C).
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.46-2.51 (m, 2H, 7-H_2), 2.91-2.94 (m, 2H, 6-H_2), 3.88 (s, 6H, 3-OCH_3 and 4-OCH_3), 3.91 (s, 3H, 2-OCH_3), 6.00 (ddd, J_{cis} = 11.2 Hz, $J_{8,7\text{-}H^a}$ = 5.6 Hz, $J_{8,7\text{-}H^b}$ = 5.6 Hz, 1H, 8-H), 6.33 (dddd, J_{cis} = 11.6 Hz, $^4J_{9,7\text{-}H^a}$ = 1.5 Hz, $^4J_{9,7\text{-}H^b}$ = 1.5 Hz, $^5J_{9,6\text{-}H^a}$ = 0.5 Hz, 1H, 9-H), 6.47 (s, 1H, 1-H) ppm
^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 26.08 (C-7), 44.59 (C-6), 56.07 (3-OCH_3)*, 60.96 (4-OCH_3)*, 62.56 (2-OCH_3), 109.49 (C-1), 127.84 (C-4a), 130.42 (C-8), 130.69 (C-9a), 131.74 (C-9), 141.87 (C-3), 151.88 (C-2), 154.67 (C-4), 202.25 (C-5) ppm; *assignment interchangeable.
IR ($CHCl_3$): ν = 2940, 2845, 1690, 1585, 1555, 1490, 1450, 1385, 1335, 1265, 1195, 1130, 1100, 1005, 935, 845, 550 cm^{-1}.
HRMS: (pos. APCI): calcd. for $C_{14}H_{17}O_4$ $[M+H]^+$ = 249.11214; found 249.11181 (-1.32 ppm).

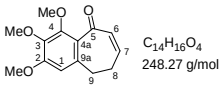
B) Preparation II (From the 1,8-Diene 73):
Grubbs second generation catalyst (0.37 g, 6.0 mol%) was added under Ar to a degassed solution of keto-alkene **10d** (1.80 g, 6.50 mmol) in dry ClCH2CH2Cl (25 mL). The mixture was then heated at reflux (40-45 ºC) for 10 h. The solvent was then removed under reduced pressure and the residue was subjected to column chromatography on silica gel (20% EtOAc/hexane) to afford mainly the cyclized product 11d (1.13 g, 4.55 mmol, 70%) as a light brown solid, along with regioisomer *iso*-**11d** (0.32 g, 1.3 mmol, 20%) as a white solid.
X-ray crystal structure details of compound **11d**:[49] crystallized from EtOAc/hexane, formula: $C_{14}H_{16}O_4$, M = 248.27, color of crystal: colorless,

Accepted Manuscript

This article is protected by copyright. All rights reserved.

needle, crystal size 0.44 × 0.27 × 0.11 mm^3, *a* = 7.5208(4) Å, *b* = 7.5470(4) Å, *c* = 22.1488(13) Å, *β* = 97.455(2)°, *V* = 1246.53(12) Å^3, ρ_{calcd} = 1.323 Mg/m^3, μ = 0.097 mm^{-1}, F(000) = 528, *Z* = 4, *T* = 173(2)K, 8183 reflections collected, 2992 [R_{int} = 0.0479] independent reflections, θ_{max} 27.99° (99.8%), Largest diff. peak and hole 0.264 and -0.220 e.Å^{-3}, *R*1 = 0.0427, *wR*2 = 0.0913, *R*1 = 0.0711, *wR*2 = 0.1031.

2,3,4-Trimethoxy-8,9-dihydro-5*H*-benzo[7]annulene-5-one (*iso*-11d)



Grubbs second generation catalyst[15] (0.27 g, 5.0 mol%) was added under Ar to a degassed solution of diene **73** (1.77 g, 6.40 mmol) in dry $ClCH_2CH_2Cl$ (30 mL). The mixture was heated at 75-80 °C for 5 h. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography on silica gel (20% EtOAc/hexane) to give the cyclised compound *iso*-**11d** (1.43 g, 5.76 mmol, 90%), as a white solid. A minor amount of the regioisomer **11d** was also isolated (0.079 g, 0.32 mmol, 5%).

Mp. 137-139 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50-2.54 (m, 2H, 8-H), 2.96-2.92 (m, 2H, 9-H), 3.85 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.90 (s, 3H, OMe), 6.20 (dt, $J_{H\text{-}6\text{-}H\text{-}7}$ = 12.0, $J_{H\text{-}6\text{-}H\text{-}8}$ = 1.8 Hz, 1H, 6-H), 6.46 (s, 1H, 1-H), 6.51 (dt, $J_{H\text{-}7\text{-}H\text{-}6}$ = 12.0, $J_{H\text{-}7\text{-}H\text{-}8}$ = 4.5 Hz, 1H, 7-H) ppm.

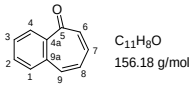
^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.0 (C-8), 34.2 (C-9), 55.9 (OMe), 60.8 (OMe), 62.2 (OMe), 107.2 (C-1), 129.1 (C-4a), 132.6 (C-6), 135.0 (C-9a), 141.2 (C-4)*, 143.8 (C-7), 152.5 (C-3)*, 154.8 (C-2)*, 194.6 (C-5) ppm.

IR (neat): *ν* = 2938, 1644, 1591, 1488, 1449, 1407, 1387, 1361, 1339, 1318, 1280, 1236 cm^{-1}.

HRMS: calcd for $C_{14}H_{17}O_4$ (M^++H) = 249.1126, found: 249.1125 (Δ = −0.40 ppm).

X-ray crystal structure details of compound *iso*-**11d**:[50] crystallized from EtOAc/hexane, formula: $C_{14}H_{16}O_4$, M = 248.27, color of crystal: colorless, needle, crystal size 0.50 × 0.36 × 0.10 mm^3, *a* = 9.9788(7) Å, *b* = 14.5190(10) Å, *c* = 9.0942(6) Å, *β* = 111.999(3)°, *V* = 1221.65(14) Å^3, ρ_{calcd} = 1.350 Mg/m^{-3}, μ = 0.099 mm^{-1}, F(000) = 528, *Z* = 4, *T* = 173(2)K, 8142 reflections collected, 2942 [R_{int} = 0.0455] independent reflections, θ_{max} 28°, 436 refined parameters, Largest diff. peak and hole 0.257 and -0.182 e.Å^{-3}, *R*1 = 0.0401, *wR*2 = 0.0971, *R*1 = 0.0687, *wR*2 = 0.1090.

5*H*-Benzo[7]annulen-5-one (13a[11])



A mixture of **11a** (67.1 mg, 424 mmol, 1.0 equiv.), SeO_2 (51.8 mg, 467 mmol, 1.1 equiv.), and *t*BuOOH (50% in CH_2Cl_2, 0.1 mL, 2.2 equiv.) in chlorobenzene (1.9 mL) was stirred at 115°C for 6 h. After cooling to room temp. the mixture was filtered through a syrring filter (∅ = 2 μm) and washed with Et_2O (2 × 10 mL). The solvent was evaporated and the residue was purified by flash-chromatography on silica gel[21] [2 × 15 cm, *c*C_6H_{12}:EtOAc 40:1 to 10:1 (v:v), 20 mL] to render the title compound (F28-40; 32.9 mg, 50%).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 6.72 (ddd, 1H, $J_{8,9}$ = 11.3 Hz, $J_{8,7}$ = 8.9 Hz, 8-H), 7.39 (dd, 1H, $J_{9,8}$ = 11.3 Hz, $J_{9,7}$ = 0.6 Hz, 9-H), 7.67 (dd, 1H, $J_{7,8}$ = 9.0 Hz, $J_{7,9}$ = 0.8 Hz, 7-H), 7.72-7.79 (m, 3H, 1-H, 2-H and 3-H), 8.68-8.72 (m, 1H, 4-H).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 125.64 (C-8)^A, 130.95 (C-1, C-2, or C-3)^A, 131.57 (C-4)^A, 132.93 (C-2, C-3, or C-1)^A, 133.78 (C-7)^A, 134.03 (C-3, C-1, or C-2)^A, 134.55 (C-4a)^B, 136.52 (C-9a)^B, 137.65 (C-9)^A, 143.17 (C-6)^B, 185.73 (C-5)^B; ^{A} the indicated ^{13}C nuclei – they are non-quaternary – were identified in an edHSQC spectrum by their crosspeaks with directly bond protons; ^{B} the indicated ^{13}C nuclei are quaternary and were distinguished in an HMBC spectrum by their crosspeaks due to ^2J, ^3J and/or ^4J couplings to "remote" protons.

HRMS (pos. APCI): $C_{11}H_9O^{\oplus}$ ($M+H^{\oplus}$): calculated: 157.06479; found: 157.06479 (Δ = ±0.0 ppm).

***ortho*-Bromostyrene (15)**

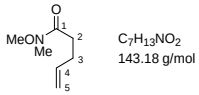
NaHMDS (2 M solution in THF, 17 mL, 34 mmol, 1.7 equiv.) was slowly added to a suspension of $MePh_3P^+Br^-$ (12.2 g, 34.1 mmol, 1.7 equiv.) in THF (72 mL). The mixture was stirred for 3 h at room temp. A solution of 2-bromobenzaldehyde (**14**; 3.70 g, 20.3 mmol) in THF (40 mL) was added dropwise within 30 min. After complete addition the mixture was stirred additional 3.5 h at room temp. A saturated aqueous solution of $NaHCO_3$ (100 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (4 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash-chromatography on silica gel[21] [6.0 × 14 cm, PE (30-50°C), 50 mL] to obtain the title compound (F7-16; 2.48 g, 68%) as a colorless liquid.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 5.36 (dd, 1H, $J_{2'\text{-}H(1),1'}$ = 11.0 Hz, J_{gem} = 1.1 Hz, 2'-H^1), 5.69 (dd, 1H, $J_{2'\text{-}H(2),1'}$ = 17.4 Hz, J_{gem} = 1.1 Hz, 2'-H^2), 7.06 (ddd, 1H, $J_{1',2'\text{-}H(2)}$ = 17.5 Hz, $J_{1',2'\text{-}H(2)}$ = 11.0 Hz, $J_{1',3'}$ = 0.7 Hz, 1'-H), 7.11 (ddd, 1H, $J_{5,6}$ = 7.7 Hz, $J_{5,4}$ = 7.6 Hz, $J_{5,3}$ = 1.9 Hz, 5-H), 7.25-7.29 (m, 1H, 4-H), 7.53-7.55 (m_c, 2H, 3-H and 6-H).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 116.75 (C-2')^A, 123.70 (C-1)^B, 126.91 (C-3)^A, 127.56 (C-4)^A, 129.16 (C-5)^A, 132.98 (C-6)^A, 135.94 (C-1')^A, 137.62 (C-2)^B; ^{A} the indicated ^{13}C nuclei – they are non-quaternary – were identified in an edHSQC spectrum by their crosspeaks with directly bond protons; ^{B} the indicated ^{13}C nuclei are quaternary and were distinguished in an HMBC spectrum by their crosspeaks due to ^2J, ^3J and/or ^4J couplings to "remote" protons.

IR ($CHCl_3$): *ν* = 3090, 3065, 3020, 2980, 2930, 2870, 1915, 1835, 1800, 1625, 1590, 1560, 1565, 1435, 1415, 1275, 1200, 1140, 1120, 1030, 986, 915, 860, 785, 760, 730, 660 cm^{-1}.

***N*-Methoxy-*N*-methylpent-4-enamide (16[14])**



The mixture of pent-4-enoic acid (**17**; 1.0 mL, 10.0 mmol, 1 equiv.) and $SOCl_2$ (1.1 mL, 15.0 mmol, 1.5 equiv.) was stirred at 60°C for 5 h, cooled to 0°C and added dropwise to the solution of *N,O*-dimethylhydroxylamine hydrochloride (1.46 g, 15.0 mmol, 1.5 equiv.) in CH_2Cl_2 (50 mL) in one portion. NEt_3 (4.2 mL, 3.05 g, 30.1 mmol, 3.0 equiv.) was added dropwise within 15 min and stirring was continued at 0°C for 30 min. The temperature was raised to ambient within 2 h and the reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (25 mL). The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl (40 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash-chromatography on silica gel[21] [3.5 × 15 cm, *c*C_6H_{12}:EtOAc 4:1 to 2:1 (v:v), 50 mL] to render the title compound (F9-22; 1.17 g, 82%; ref.[14]: 83%) as a pale brown oil.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.36-2.42 (m, 2H, 3-H_2), 2.50-2.56 (m, 2H, 2-H_2), 3.18 (s, 3H, N-CH_3), 3.69 (s, 3H, O-CH_3), 4.99 (tdd, 1H, $J_{5\text{-}H(1),4}$ = 10.2 Hz, J_{gem} = 1.9 Hz, $^4J_{5\text{-}H(1),3}$ = 1.2 Hz, 5-H^1), 5.07 (tdd, 1H, $J_{5\text{-}H(2),4}$ = 17.1 Hz, J_{gem} = 1.7 Hz, $^4J_{5\text{-}H(2),3}$ =1.6 Hz, 5-H^2), 5.87 (tdd, 1H, $J_{4,5\text{-}H(2)}$ = 16.9 Hz, $J_{4,5\text{-}H(1)}$ = 10.4 Hz, $J_{4,3}$ = 6.6 Hz, 4-H).

Accepted Manuscript

This article is protected by copyright. All rights reserved.

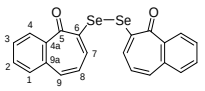
^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 28.62 (C-3)^A, 31.28 (C-2)^A, 32.30 (N-*C*H$_3$)^A, 61.27 (O-CH$_3$)^A, 115.164 (C-5)^A, 137.55 (C-4)^A, 173.90 (C-1)^B; ^{A} the indicated ^{13}C nuclei – they are non-quaternary – were identified in an edHSQC spectrum by their crosspeaks with directly bond protons; ^{B} the indicated ^{13}C nuclei are quaternary and were distinguished in an HMBC spectrum by their crosspeaks due to ^2J, ^3J and/or ^4J couplings to "remote" protons.

IR (film): ν = 3505, 3320, 3080, 5975, 2940, 2820, 2240, 1775, 1665, 1465, 1440, 1420, 1385, 1315, 1175, 1150, 1120, 995, 915, 840, 790, 740 cm^{-1}.

Elemental analysis:

$C_7H_{13}NO_2$ (143.18 g/mol)	calc. C 58.72	H 9.15	N 9.78
	found C 58.47	H 8.96	N 9.80

6,6'-Diselanediylbis(5*H*-benzo[7]annulen-5-one) (18)



A solution of the RCM-product **11a** (440.6 mg, 2.79 mmol, 1 equiv.) and SeO_2 (339.9 mg, 3.06 mmol, 1.1 equiv.) in AcOH:H_2O (v:v, 70:30, 28 mL) was heated at 90°C for 12 h. H_2O (200 mL) was added and the crude product was extracted with EtOAC (3 × 200 mL). The combined organic layers were washed with a saturated aqueous solution of Na_2CO_3 (2 × 100 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash-chromatography on silica gel[21] [4.5 × 1.5 cm, *c*C_6H_{12}:EtOAc (v:v) 40:1 to 1:1, 50 mL] rendering the unchanged RCM-product **11a** (F26-34; 9.8 mg, 2%), the benzotropone **13a** (F48-58; 92.1 mg, 21%), the title compound [**18**; F63-90; 227.8 + (18.9-1.7) mg = 245.0 mg, 19%], the benzotropolone **5a** (F91-98; 1.7 mg, 0.4%), and the tricyclic selenide **19** (F107-120; 116.6 mg, 17%).

^{1}H NMR (500.22 MHz, acetone-[D$_6$]): δ = 6.91 (dd, 1H, $J_{8,9}$ = 11.4 Hz, $J_{8,7}$ = 9.0 Hz, 8-H), 7.60 (dd, 1H, $J_{9,8}$ = 11.4 Hz, $4J_{9,7}$ = 0.6 Hz, 9-H), 7.69 (dd, 1H, $J_{7,Se}$ = 30.1 Hz, $J_{7,8}$ = 8.9 Hz, $^4J_{7,9}$ = 0.7 Hz, 7-H), 7.87 (ddd, 1H, $J_{3,4}$ = 8.2 Hz, $J_{4,2}$ = 6.9 Hz, $^4J_{3,1}$ = 1.4 Hz, 3-H), 7.91 (ddd, 1H, $J_{2,1}$ = 7.8 Hz, $J_{2,3}$ = 7.0 Hz, $^4J_{2,4}$ = 1.6 Hz, 2-H), 7.97 (dd, 1H, $J_{1,2}$ = 7.8 Hz, $^4J_{1,3}$ = 1.6 Hz, 1-H), 8.63 (dd, 1H, $J_{4,3}$ = 8.1 Hz, $^4J_{4,2}$ = 1.7 Hz, 4-H).

^{13}C NMR (125.78 MHz, acetone-[D$_6$]): δ = 126.45 (C-8)^A, 131.71 (C-4)^A, 131.86 (C-3)^A, 134.05 (C-2)^A, 134.46 (C-7)^A, 135.04 (C-4a)^B, 135.25 (C-1)^A, 137.39 (C-9a)^B, 138.49 (C-9)^A, 143.10 (C-6)^B, 185.81 (C-5)^B; ^{A} the indicated ^{13}C nuclei – they are non-quaternary – were identified in an edHSQC spectrum by their crosspeaks with directly bond protons; ^{B} the indicated ^{13}C nuclei are quaternary and were distinguished in an HMBC spectrum by their crosspeaks due to ^2J, ^3J and/or ^4J couplings to "remote" protons.

^{77}Se NMR (95.40 MHz, acetone-[D$_6$]): δ = 408.29 (s, 1Se).

^{77}Se HMBC {"long-range Se,H-COSY spectrum" (95.40/500.22 MHz), acetone-[D$_6$]}: 408.29 (^{77}Se) ↔ 7.69 (7-^{1}H).

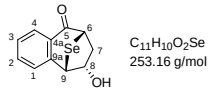
IR (film): ν = 2995, 1770, 1760, 1575, 1550, 1475, 1375, 1310, 1245, 1055, 930, 850, 790 cm^{-1}.

HRMS (pos. APCI): $C_{22}H_{14}NaO_2Se_2^{\oplus}$ (M+Na$^{\oplus}$): calculated: 492.921; found: 492.9212 (Δ = –0.8 ppm!).

Elemental analysis:

$C_{22}H_{14}O_2Se_2$ (468.27 g/mol)	calc. C 56.43	H 3.01	
	found C 55.86	H 3.12	

(6-*rel*-*S*,8-*rel*-*S*,9-*rel*-*S*)-8-Hydroxy-6,9-seleno-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (19)



A mixture of the RCM-product **11a** (32.4 mg, 205 mmol, 1.0 equiv.) and SeO_2 (25.0 mg, 225 mmol, 1.1 equiv.) in *o*-xylene (1.4 mL) was heated under reflux for 9.5 h. After cooling to room temp. the reaction was filtered through a pad of silica gel (2 cm × 1 cm) and rinsed with Et_2O (2 × 10 mL). The solvent was evaporated and the residue was purified by flash-chromatography on silica gel[21] [2 × 15 cm, *c*C_6H_{12}:EtOAc 10:1 to 2:1 (v:v), 20 mL] to render the benzotropone **13a** (F6-11; 13.4 mg, 42%) and the tricyclic selenide **19** (F38-47; 12.6 mg, 24%).

^{1}H NMR (500.32 MHz, $CDCl_3$): δ = AB-Signal (δ_A = 2.08, δ_B = 3.19, J_{AB} = 14.4 Hz, A-part additionally split by $J_{7\text{-H(A)},8}$ = 5.0 Hz, B-part additionally split by $J_{7\text{-H(B)},8}$ = 9.5 Hz, $J_{7\text{-H(B)},6}$ = 7.5 Hz, 7-H$_2$), 4.04 (d, $J_{6,7\text{-H(B)}}$ = 7.5 Hz, 6-H), 4.25 (d, 1H, $J_{9,8}$ = 4.8 Hz, 9-H), 5.20 (ddd, 1H, $J_{8,7\text{-H(B)}}$ = 9.5 Hz, $J_{8,9}$ = $J_{8,7\text{-H(A)}}$ = 4.8 Hz, 8-H), 7.20 (dd, 1H, $J_{1,2}$ = 7.4 Hz, $J_{1,3}$ = 1.3 Hz, 1-H), 7.39 (ddd, 1H, $J_{3,2}$ = $J_{3,4}$ = 7.5 Hz, $J_{3,1}$ = 1.4 Hz, 3-H), 7.44 (ddd, 1H, $J_{2,1}$ = $J_{2,3}$ = 7.4 Hz, $J_{2,4}$ = 1.6 Hz, 2-H), 8.06 (dd, 1H, $J_{4,3}$ = 7.6 Hz, $J_{4,2}$ = 1.6 Hz, 4-H).

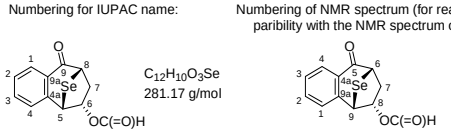
^{13}C NMR (125.81 MHz, $CDCl_3$): δ = 36.17 (C-7)^A, 44.70 (C-6)^A, 47.51 (C-9)^A, 80.39 (C-8)^A, 128.88 (C-1)^{A,*}, 128.92 (C-3)^{A,*}, 129.83 (C-4)^A, 131.01 (C-4a)^B, 132.82 (C-2)^A, 142.97 (C-9a)^B, 194.63 (C-5)^B; * assignment interchangeable; ^{A} the indicated ^{13}C nuclei – they are non-quaternary – were identified in an edHSQC spectrum by their crosspeaks with directly bond protons; ^{B} the indicated ^{13}C nuclei are quaternary and were distinguished in an HMBC spectrum by their crosspeaks due to ^2J, ^3J and/or ^4J couplings to "remote" protons.

^{77}Se NMR (95.42 MHz, $CDCl_3$): δ = 578.09 [dd, 1Se, $^2J_{Se,6\text{-H}}$ = $^2J_{Se,7\text{-H}}$ = 25.4 Hz, Se(CH)$_2$].

^{77}Se HMBC ["long-range Se,H-COSY spectrum" (95.42/500.32 MHz), $CDCl_3$]: 578.09 (^{77}Se) ↔ 2.08 (7-^{1}H^A), 4.04 (6-^{1}H), and 4.25 (9-^{1}H).

HRMS (neg. ESI): $C_{11}H_9O_2Se^{\ominus}$ (M–H$^{\oplus}$): calculated: 252.97732; found: 252.97732 (Δ = ±0.0 pm!).– **HRMS** (pos. ESI): $C_{11}H_{11}O_2Se^{\oplus}$ (M+H$^{\oplus}$): calculated: 254.99188; found: 254.99174 (Δ = –0.5 ppm).

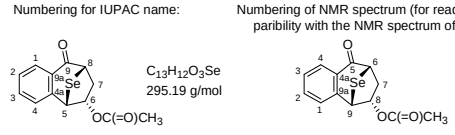
(5-*rel*-*S*,6-*rel*-*S*,8-*rel*-*S*)-9-Oxo-5,8-seleno-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-6-yl Formate (20)



The mixture of the RCM-product **11a** (25.5 mg, 161 µmol, 1.0 equiv.) and SeO_2 (19.7 mg, 177 µmol, 1.1 equiv.) as well as 2,4,6-tribromotoluene (26.5 mg, 80.6 µmol, 0.5 equiv.; not a reactand but a reference compound for ^{1}H-NMR analyses) in formic acid (1.1 mL) was heated under reflux for 3 h. Silica gel was added and the solvent was evaporated. The residue was purified by flash-chromatograpy on silica gel[21] [2 × 15 cm, *c*C_6H_{12}:EtOAc 10:1 to 2:1 (v:v), 20 mL] to render the NMR standard (F1-6; 20.2 mg, 76%) and a mixture (F8-20; 45.6 mg) of what seemed to be mostly the tricyclic title compound **20** (100% yield would have represented 45.3 mg), some contaminant(s) with aromatic/olefinic resonances only (yet no **13a**), and AcOEt.

^{1}H NMR (300.13 MHz, $CDCl_3$; contaminated; all non-aromatic/non-olefinic resonances plus the most notable low-field resonances are listed): δ = 2.39 (dd, J_{gem} = 14.6 Hz, $J_{7,6}$ = 4.7 Hz, 1H, 7-H^1), 3.26 (ddd, J_{gem} = 14.6 Hz, $J_{7,8}$ = 9.8 Hz, $J_{7,6}$ = 7.3 Hz, 1H, 7-H^2), 4.10 (d, $J_{6,7\text{-H(2)}}$ = 7.3 Hz, 1H, 6-H), 4.61 (d, $J_{9,8}$ = 4.9 Hz, 1H, 9-H), 5.93 (dddd, $J_{8,7\text{-H(2)}}$ = 9.8 Hz, $J_{8,7\text{-H(1)}}$ = $J_{8,9}$ = 4.8 Hz, $^4J_{8,CHO}$ = 1.0 Hz, 1H, 8-H), 7.04-7.11 (m, 1H, 1-H), 7.37-7.41 (m, 2H, 2-H and 3-H), 7.88 (d, $^4J_{CHO,8}$ = 0.8 Hz, 1H, C*H*O), 8.04-8.07 (m, 1H, 4-H).

(5-*rel*-*S*,6-*rel*-*S*,8-*rel*-*S*)-9-Oxo-5,8-seleno-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-6-yl Acetate (21)



H_2SO_4 (0.03 mL, 557.5 µmol, 3 equiv.) was added in one portion to a suspension of SeO_2 (30.9 mg, 278.8 µmol, 1.5 equiv.) in H_2O (0.01 mL,

Accepted Manuscript

This article is protected by copyright. All rights reserved.

557.5 μmol, 3 equiv.). The mixture was stirred at room temp. for 20 min. A solution of the RCM-product **11a** (29.4 mg, 185.8 μmol, 1 equiv.) and 2,4,6-tribromotoluene (30.6 mg, 92.9 μmol, 0.5 equiv.; not a reactand but a reference compound for ^{1}H-NMR analyses) in conc. acetic acid (1.9 mL) was added. The resulting mixture was stirred at room temp. for 2.5 h. The mixture was diluted with ice-cold NH_3/H_2O 25:75 (v:v; 10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash-chromatography on silica gel[21] [2 × 15 cm, *c*C_6H_{12}:EtOAc 80:1 to 10:1 (v:v), 20 mL] to render the tricyclic title compound (F24-35; 9.6 mg, 18%) as a yellow oil.

^{1}H NMR (500.22 MHz, acetone-[D]$_6$): δ = 1.81 (s, 3H, 2'-H$_3$), 2.27 (dddd, 1H, J_{gem} = 14.6 Hz, $J_{7\text{-H}(1),8}$ = 4.7 Hz, $J_{7\text{-H}(1),6}$ = 0.8 Hz, $^4J_{7\text{-H}(1),9}$ = 0.5 Hz, 7-H^1), 3.25 (ddd, 1H, J_{gem} = 14.6 Hz, $J_{7\text{-H}(2),8}$ = 9.8 Hz, $J_{7\text{-H}(2),6}$ = 7.3 Hz, 7-H^2), 4.11 (ddd, $J_{6,7\text{-H}(2)}$ = 7.3 Hz, $J_{6,7\text{-H}(1)}$ = 0.9 Hz, $J_{6,9}$ = 0.9 Hz; in addition, the isotopologue containing ^{77}Se gives rise to satellites as 2 ddd due to $^2J_{6,Se}$ = 25.5 Hz; 1H, 6-H), 4.73 (ddd, $J_{9,8}$ = 4.9 Hz, $^5J_{9,6}$ = 0.8 Hz, $^4J_{9,7\text{-H}(2)}$ = 0.4 Hz; in addition, the isotopologue containing ^{77}Se gives rise to satellites as 2 ddd due to $^2J_{9,Se}$ = 27.2 Hz; 1H, 9-H), 5.80 (ddd, 1H, $J_{8,7\text{-H}(2)}$ = 9.8 Hz, $J_{8,7\text{-H}(1)}$ = $J_{8,9}$ = 4.9 Hz, 8-H), 7.17 (dd, 1H, $J_{1,2}$ = 7.5 Hz, $^4J_{1,3}$ = 1.3 Hz, 1-H), 7.41 (ddd, 1H, $J_{3,2}$ = $J_{3,4}$ = 7.5 Hz, $^4J_{3,1}$ = 1.3 Hz, 3-H), 7.48 (ddd, 1H, $J_{2,3}$ = $J_{2,1}$ = 7.5 Hz, $^4J_{2,4}$ = 1.5 Hz, 2-H), 7.96 (dd, 1H, $J_{4,3}$ = 7.6 Hz, $^4J_{4,2}$ = 1.5 Hz , 4-H).

NOESY {500.22 MHz, acetone-[D]$_6$}: crosspeaks for δ_H = 7.17 (1-H) ↔ δ_H = 3.25 (7-H^2), 4.11 (6-H), 4.73 (9-H), and 5.80 (8-H) identify 1-H; crosspeaks for δ_H = 3.25 (7-H^2) ↔ δ_H = 4.11 (6-H), 4.73 (9-H), and 5.80 (8-H) identify 7-H^2; crosspeaks for δ_H = 4.73 (9-H) ↔ δ_H = 5.80 (8-H) and 7.17 (1-H) identify 9-H; crosspeak δ_H = 7.17 (1-H) ↔ δ_H = 7.48 (2-H) identifies 1-H; crosspeaks for δ_H = 7.41 (3-H) ↔ δ_H = 7.48 (2-H) and 7.96 (4-H) identify 3-H; crosspeak for δ_H = 7.48 (2-H) ↔ δ_H = 7.96 (4-H) identifies 2-H.

^{13}C NMR (125.78 MHz, acetone-[D]$_6$): δ = 20.64 (C-2')^A, 34.38 (C-7)^A, 44.96 (C-9)^A, 45.20 (C-6)^A, 81.91 (C-8)^A, 128.94 (C-1)^A, 129.19 (C-3)^A, 129.67 (C-4)^A, 131.62 (C-4a)^B, 133.44 (C-2)^A, 145.05 (C-9a)^B, 170.74 (C-1')^B, 194.61 (C-5)^B; ^{A} the indicated ^{13}C nuclei – they are non-quaternary – were identified in an edHSQC spectrum by their crosspeaks with directly bound protons; ^{B} the indicated ^{13}C nuclei are quaternary and were distinguished in an HMBC spectrum by their crosspeaks due to ^2J, ^3J and/or ^4J couplings to "remote" protons.

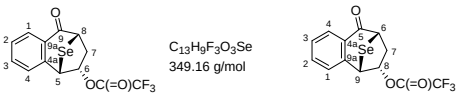
^{77}Se NMR (95.40 MHz, acetone-[D]$_6$): δ = 573.85 (br. dd, $^2J_{Se,6\text{-H}}$ ~ $^2J_{Se,9\text{-H}}$ ~ 26 Hz, Se).

^{77}Se HMBC {"long-range Se,H-COSY spectrum" (95.40/500.22 MHz), acetone-[D]$_6$}: 573.85 (^{77}Se) ↔ δ_H = 2.27 (7-^{1}H^1), 4.11 (6-^{1}H), and 4.73 (9-^{1}H).

HRMS (pos. ESI): $C_{11}H_9OSe^{\oplus}$ ($M-H_3CCO_2^{\ominus}$): calculated: 236.9813; found: 236.9813 (Δ = ±0.0 ppm).

(5-*rel*-*S*,6-*rel*-*S*,8-*rel*-*S*)-9-Oxo-5,8-seleno-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-6-yl Trifluoroacetate (22)

Numbering for IUPAC name: Numbering of NMR spectrum (for ready comparibility with the NMR spectrum of **19**):



$C_{13}H_9F_3O_3Se$
349.16 g/mol

The mixture of the RCM-product **11a** (245.7 mg, 1.55 μmol, 1 equiv.) and SeO_2 (189.6 mg, 1.71 μmol, 1.1 equiv.) in F_3CCO_2H (10 mL) was heated under reflux for 4 h. Silica gel was added and the solvent was evaporated. The residue was purified by flash-chromatograpy on silica gel[21] [3 × 10 cm, *c*C_6H_{12}:EtOAc 80:1 to 20:1 (v:v), 20 mL] to render the tricyclic title compound (F17-23; 197.7 mg 36%) as a slightly orange solid (mp. 89°C). In addition, we identified small amounts of benzotropone (**13a**, 5%), the tricyclic compound **19** (1%), and the diselenide **18** (1%).

^{1}H NMR (500.22 MHz, $CDCl_3$): δ = 2.54 (ddd, 1H, J_{gem} = 14.8 Hz, $J_{7\text{-H}(1),8}$ = 4.4 Hz, $J_{7\text{-H}(1),6}$ = 0.7 Hz, 7-H^1), 3.32 (ddd, 1H, J_{gem} = 14.8 Hz, $J_{7\text{-H}(2),8}$ = 9.9 Hz, $J_{7\text{-H}(2),6}$ = 7.2 Hz, 7-H^2), 4.12 (ddd, $J_{6,7\text{-H}(2)}$ = 7.2 Hz, $J_{6,7\text{-H}(1)}$ = $J_{6,8}$ = 0.8 Hz; in addition, the isotopologue containing ^{77}Se gives rise to satellites as 2 ddd due to $^2J_{6,Se}$ = 25.6 Hz; 1H, 6-H), 4.67 (d, $J_{9,8}$ = 5.1 Hz; in addition, the isotopologue containing ^{77}Se gives rise to satellites as 2 d due to $^2J_{9,Se}$ = 26.8 Hz; 1H 9-H), 5.98 (ddd, 1H, $J_{8,7\text{-H}(2)}$ = 9.8 Hz, $J_{8,9}$ = 4.8 Hz, $J_{8,7\text{-H}(1)}$ = 4.8 Hz, 8-H), 7.01-7.04 (m, 1H, 1-H), 7.37-7.43 (m, 2H, 2-H and 3-H), 8.05-8.08 (m, 1H, 4-H).

^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 33.92 (C-7)^A, 43.43 (the isotopologue containing ^{77}Se causes satellites as d due to $^1J_{C\text{-}9,Se}$ = 53.4 Hz; C-9)^A, 44.12 (the isotopologue containing ^{77}Se causes satellites as d due to $^1J_{C\text{-}6,Se}$ = 44.7 Hz; C-6)^A, 84.25 (C-8)^A, 114.18 (q, 1C, J_{CF_3} = 285.6 Hz, $COCF_3$)^B, 127.67 (C-1)^A, 129.23 (C-2)^{A,*}, 129.97 (C-4)^A, 130.35 (C-4a)^B, 133.11 (C-3)^{A,*}, 141.89 (C-9a)^B, 157.16 (q, 1C, J_{COCF_3} = 42.9 Hz, $COCF_3$)^B, 193.64 (C-5)^B; ^{A} the indicated ^{13}C nuclei – they are non-quaternary – were identified in an edHSQC spectrum by their crosspeaks with directly bond protons; ^{B} the indicated ^{13}C nuclei are quaternary and were distinguished in an HMBC spectrum by their crosspeaks due to ^2J, ^3J and/or ^4J couplings to "remote" protons; * assignment interchangeable.

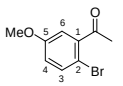
^{77}Se NMR (95.40 MHz, $CDCl_3$): δ = 590.61 (dd, $^2J_{Se,6\text{-H}}$ = $^2J_{Se,9\text{-H}}$ = 26.4 Hz, Se).

^{77}Se HMBC ["long-range Se,H-COSY spectrum" (95.40/500.22 MHz), $CDCl_3$]: 590.61 (^{77}Se) ↔ δ_H = 2.54 (7-^{1}H^1), 4.12 (6-^{1}H), 4.67 (9-^{1}H), and 8.06 (4-^{1}H)

^{19}F NMR (470.68 MHz, $CDCl_3$): δ = −75.11 (CF_3).

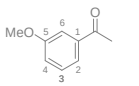
HRMS (pos. APCI): $C_{13}H_{10}F_3O_3Se^{\oplus}$ ($M+H^{\oplus}$): calculated: 350.9742; found: 350.9740 (Δ = –0.6 ppm).

1-(2-Bromo-5-methoxyphenyl)ethanone (39[25]) in a 91:9 Mixture With 1-(3-Methoxyphenyl)ethanone (38)



$C_9H_9BrO_2$
229.07 g/mol

39



$C_9H_{10}O_2$
150.17 g/mol

38

At room temp. 3-methoxyacetophenone (**38**; 30.0 g, 200 mmol) was added dropwise to a solution of NBS (35.6 g, 200 mmol, 1.00 equiv.) and I_2 (4.9 g, 19 mmol, 0.10 equiv.) in MeCN (1000 mL). The mixture was stirred at room temp. in the dark for 21 h. The reaction was quenched by addition of sat. aq. $Na_2S_2O_3$ solution (200 mL) and H_2O (50 mL) and stirring at room temp. for 30 min. The precipitate was filtered off. Brine (200 mL) was added to the filtrate. The phases were separated and the aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phases were concentrated to approx. 200 mL and the residue was taken up in EtOAc (200 mL). The suspension was filtered . The filtrate was washed with a mixture of aq. NaOH (1 M, 100 mL) and brine (50 mL), with aq. NaOH (1 M, 100 mL), and with brine (2 x 100 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification by vacuum distillation ($b.p._{0.2\ mbar}$ = 73-81°C) afforded a yellow oil (39.8 g). It was a 91:9 (mol:mol) mixture of compounds **39** (37.4 g, 82%; ref.[25]: 94%) and **38** (2.4 g, 8%).

^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta_{\mathbf{39}}$ = 2.62 (s, 3H, 2''-H$_3$), 3.80 (s, 3H, 5-OCH$_3$), 6.84 (dd, $J_{4,3}$ = 8.8 Hz, $J_{4,6}$ = 3.1 Hz, 1H, 4-H), 6.97 (d, $J_{6,4}$ = 3.1 Hz, 1H, 6-H), 7.47 (d, $J_{3,4}$ = 8.8 Hz, 1H, 3-H) ppm.– $\delta_{\mathbf{38}}$ = 2.59 (s, 3H, 2'-H$_2$), 3.85 (s, 3H, 3-OCH$_3$), 7.11 (ddd, $J_{4,5}$ = 8.2 Hz, $J_{4,2}$ = 2.7 Hz, $J_{4,6}$ = 1.0 Hz, 1H, 4-H), 7.36 (ddd, $J_{5,4}$ = 8.2 Hz, $J_{5,6}$ = 7.6 Hz, $J_{5,2}$ = 0.4 Hz, 1H, 5-H), 7.48 (dd, $J_{2,4}$ = 2.7 Hz, $J_{2,6}$ = 1.4 Hz, 1H, 2-H), 7.53 (ddd, $J_{6,5}$ = 7.6 Hz, $J_{6,2}$ = 1.6 Hz, $J_{6,4}$ = 1.0 Hz, 1H, 6-H) ppm.

^{13}C NMR (100.61 MHz, $CDCl_3$): $\delta_{\mathbf{39}}$ = 30.35 (C-2''), 55.71 (5-OCH$_3$), 109.20 (C-1), 114.27 (C-6), 117.95 (C-4), 134.64 (C-3), 142.40 (C-2), 158.96 (C-5), 201.26 (C-1') ppm.– $\delta_{\mathbf{38}}$ = 26.75 (C-2'), 55.51 (3-OCH$_3$), 112.50 (C-2), 119.67 (C-4), 121.18 (C-6), 129.62 (C-5), 138.64 (C-1), 159.94 (C-3), 197.95 (C1') ppm.

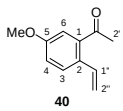
IR ($CHCl_3$): ν = 3390, 3005, 2965, 2940, 2840, 1705, 1700, 1590, 1570, 1470, 1440, 1425, 1420, 1405, 1395, 1355, 1315, 1285, 1240, 1220, 1180, 1095, 1035, 1020, 875, 815 cm^{-1}.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

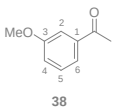
HRMS (pos. APCI): $C_9H_{10}{}^{79}BrO_2^{\oplus}$ (M+H$^{\oplus}$): calculated: 228.9859; found: 228.9855 (Δ = –1.5254 ppm); $C_9H_{10}{}^{81}BrO_2^{\oplus}$ (M+H$^{\oplus}$): calculated: 230.9838; found: 230.9834 (Δ = –1.5254 ppm).

1-(5-Methoxy-2-vinylphenyl)ethanone (40) in a 91:9 Mixture With 1-(3-Methoxyphenyl)ethanone (38)



$C_{11}H_{12}O_2$
176.21 g/mol

40



$C_9H_{10}O_2$
150.17 g/mol

38

At room temp. THF (180 mL) was added to a mixture of potassium vinyltrifluoroborate (4.02 g, 30.0 mmol, 1.50 equiv.), $Pd(OAc)_2$ (0.22 g, 1.0 mmol, 5.0 mol%), and PPh_3 (0.52 g, 2.0 mmol, 10 mol%) under Ar. A degassed solution of Cs_2CO_3 (20 g, 60 mmol, 3.0 equiv.) in H_2O (20 mL) was added. The mixture was stirred at room temp. for 5 min. 4.87 g of a 91:9 (mol:mol) mixture of compounds **39** (4.57 g, 20.0 mmol) and **38** (0.30 g, 2.0 mmol) was added dropwise. The resulting mixture stirred at room temp. for 15 min and then heated to reflux at 90 °C (oil bath temperature) for 20 h. After cooling to room temp. silica (10 g) was added, the mixture was stirred at room temp. for 15 min. and then filtered through a plug of Celite® (10 x 3 cm). The filter cake was washed with EtOAc (2 x 100 mL) and the filtrate was concentrated to approx. 100 mL. H_2O (100 mL) and brine (100 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (100 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification by flash-chromatography on silica gel[21] [5.0 × 15 cm, 50 mL, cyclohexane/EtOAc = 30:1 (F1–20) → 20:1 (F21–39) → 10:1 (F40–59), F32–45] afforded a yellow oil (3.42 g) which was a 91:9 (mol:mol) mixture of compounds **40** (3.15 g, 89%) and **38** (0.27 g, 90%).

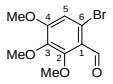
^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta_{\mathbf{40}}$ = 2.55 (s, 3H, 2'-H_3), 3.84 (s, 3H, 5-OCH_3), 5.25 (dd, $J_{2''\text{-}H^Z,1''}$ = 10.9 Hz, $^2J_{2''\text{-}H^Z,2''\text{-}H^E}$ = 1.3 Hz, 1H, 2''-H^Z), 5.54 (dd, $J_{2''\text{-}H^E,1''}$ = 17.4 Hz, $^2J_{2''\text{-}H^E,2''\text{-}H^Z}$ = 1.3 Hz, 1H, 2''-H^E), 6.99 (ddd, $J_{4,3}$ = 8.6 Hz, $J_{4,6\,=\,2.7}$ Hz, $^5J_{4,1''}$ = 0.6 Hz, 1H, 4-H), 7.07 (dddd, $J_{1'',2''\text{-}H^E}$ = 17.4 Hz, $J_{1'',2''\text{-}H^Z}$ = 10.9 Hz, $^4J_{1'',3}$ = $^5J_{1'',4}$ = 0.6 Hz, 1H, 1''-H), 7.09 (d, $J_{6,4}$ = 2.7 Hz, 1H, 6-H), 7.49 (br. d, $J_{3,4}$ = 8.6 Hz, 1H, 3-H) ppm.– The $\delta_{\mathbf{38}}$-values were as specified in conjunction with the preparation of compound **39**.

^{13}C NMR (100.61 MHz, $CDCl_3$): $\delta_{\mathbf{40}}$ = 30.06 (C-2'), 55.57 (5-OCH_3), 113.79 (C-6), 115.15 (C-2''), 117.00 (C-4), 128.78 (C-3), 130.05 (C-2), 135.12 (C-1''), 138.97 (C-1), 158.91 (C-5), 202.16 (C-1'') ppm.– The $\delta_{\mathbf{38}}$-values were as specified in conjunction with the preparation of compound **39**.

IR ($CHCl_3$): ν = 3005, 2965, 2940, 2840, 1685, 1605, 1560, 1490, 1465, 1445, 1415, 1355, 1320 1290, 1270, 1255, 1220, 1180, 1045, 1025, 990, 960, 910, 870, 855, 830, 705 cm^{-1}.

HRMS (pos. APCI): $C_{11}H_{12}O_2Na^{\oplus}$ (M+Na$^{\oplus}$): calculated: 199.0730; found: 199.0731 (Δ = +0.6203 ppm).

6-Bromo-2,3,4-trimethoxybenzaldehyde[31] (42)

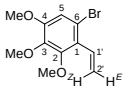


$C_{10}H_{11}BrO_4$
275.10 g/mol

5-Bromo-1,2,3-trimethoxybenzaldehyde (4.94 g, 20.0 mmol) in CH_2Cl_2 (25 mL) was transferred to a stirred solution of $TiCl_4$ (5.25 mL, 9.08 g, 47.9 mmol, 2.4 equiv.) and dichloromethyl methyl ether (3.6 mL, 4.6 g, 40 mmol, 2.0 equiv.) in CH_2Cl_2 (75 mL) at 0°C. After stirring at room temp. for 5 h, 1 M HCl (20 mL) was cautiously added at 0°C. After complete Addition the mixture was stirred 15 min at 0°C. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with an aqueous 8% $NaHCO_3$ solution (60 mL) and brine (60 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash-chromatography on silica gel[21] (d = 4 cm, h = 14 cm, F = 50 mL; *c*-C_6H_{12}/EtOAc 5:1) gave the target compound [F9-16, $R_{f,\,4:1}$ = 0.27, 5.44 g, 99% (ref.[31]: 99%)] as a yellow solid [mp. 39-40°C (ref.[31]: 51-52°C)].

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.87 (s, 3H, 2-OCH_3*), 3.93 (s, 3H, 3-OCH_3*), 3.96 (s, 3H, 1-OCH_3*), 6.96 (s, 1H, 6-H), 10.24 (s, 1H, 4-CHO) ppm; *assignment interchangeable.

6-Bromo-2,3,4-trimethoxystyrene (43)



$C_{11}H_{13}BrO_3$
273.12 g/mol

n-BuLi (1.6 M in hexane, 12.0 mL, 19.2 mmol, 1.06 equiv.) was added to a stirred suspension of methyltriphenylphosphonium bromide (6.83 g, 19.1 mmol, 1.05 equiv.) in THF (50 mL) at 0°C. After stirring for 25 min at the same temperature, a solution of the aldehyde **42** (4.98 g, 18.2 mmol) in THF (23 mL) was added at 0°C. The ice bath was removed. The mixture was stirred vigorously at room temp. for 3 h, before water (50 mL) and EtOAc (50 mL) were added to the reaction mixture at 0°C. The layers were separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were dried over Na_2SO_4 and the solvents removed in vacuo. Flash-chromatography on silica gel[21] (d = 6.5 cm, h = 12 cm, F = 50 mL; *c*-C_6H_{12}/EtOAc 9:1) gave the title compound (F4-12, $R_{f,\,4:1}$ = 0.56, 4.33 g, 88%) as a colorless oil.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 3.82 (s, 3H, 2-OCH_3), 3.85 (s, 3H, 4-OCH_3), 3.86 (s, 3H, 3-OCH_3), 5.48 (dd, J_{cis} = 11.8 Hz, J_{gem} = 2.0 Hz, 1H, 2'-H^E), 5.89 (dd, J_{trans} = 17.8 Hz, J_{gem} = 2.0 Hz, 1H, 2'-H^Z), 6.69 (dd, J_{trans} = 17.8 Hz, J_{cis} = 11.8 Hz, 1H, 1'-H), 6.92 (s, 1H, 5-H) ppm.

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 56.26 (4-OCH_3), 60.58 (2-OCH_3), 61.01 (3-OCH_3), 112.39 (C-5), 117.94 (C-6), 119.91 (C-2'), 124.89 (C-1), 131.89 (C-1'), 142.40 (C-3), 152.90 (C-4), 153.08 (C-2) ppm.

IR ($CHCl_3$): ν = 2995, 2965, 2935, 2835, 1585, 1480, 1450, 1395, 1295, 1240, 1200, 1130, 1080, 1015, 945, 920, 825, 795, 780 cm^{-1}.

HRMS: (pos. APCI): Calcd. for $C_{11}H_{14}{}^{79}BrO_3^{\oplus}$ (M+H$^{\oplus}$) = 273.01208; found 273.01204 (Δ = –0.1 ppm); calcd. for $C_{11}H_{14}{}^{81}BrO_3^{\oplus}$ (M+H$^{\oplus}$) = 275.01004; found 275.00983 (Δ = –0.8 ppm).

Elemental analysis:

$C_{11}H_{13}BrO_3$ (273.12 g/mol)	calc.	C 48.37%	H 4.80%
	found	C 48.44%	H 4.86%

S-Ethyl Pent-4-enethioate (44)

$C_7H_{12}OS$
144.23 g/mol

4-Pentenoic acid (3.20 mL, 3.11 g, 30.2 mmol) was added to a stirred, clear solution of *N*,*N'*-dicyclohexylcarbodiimide (7.48 g, 36.2 mmol, 1.2 equiv.) and 4-dimethylaminopyridine (959 mg, 7.85 mmol, 26 mol-%) in CH_2Cl_2 (200 mL) at room temp. and a white precipitate was formed. After adding ethanethiol (2.30 mL, 1.93 g, 30.2 mmol, 1.0 equiv.) to the resulting suspension at room temp. , the reaction mixture was stirred vigorously at the same temperature for 16 h. Then, the reaction mixture was filtered through a paper filter and the residue was washed with CH_2Cl_2 (2 × 30 mL). The combined organic phases were washed with a saturated aqueous Na_2CO_3 solution (100 mL). The organic phase was dried over Na_2SO_4, silica gel was added to the dry organic phase, and the solvents were removed in vacuo. The residue was purified via flash-chromatography on silica gel[21] (d = 6.5 cm, h = 11 cm, F = 50 mL; *c*-C_6H_{12}/EtOAc 20:1) to give the target compound (F3-8, $R_{f,\,4:1}$ = 0.72, 3.52 g, 81%) as a colorless oil.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.25 (t, $J_{2',1'}$ = 7.4 Hz, 3H, 1'-H_3), 2.38-2.44 (m, 2H, 3-H_2), 2.62-2.65 (m, 2H, 2-H_2), 2.88 (q, $J_{1',2'}$ = 7.4 Hz, 2H, 1'-H_2), 5.01 (ddt, J_{cis} = 10.1 Hz, J_{gem} = 1.6 Hz, $^4J_{5\text{-}Ha,3}$ = 1.3 Hz, 1H, 5-H^a), 5.06 (ddt, J_{trans} = 17.1 Hz, J_{gem} = 1.6 Hz, $^4J_{5\text{-}Hb,3}$ = 1.6 Hz, 1H, 5-H^b), 5.80 (ddt, J_{trans} = 16.9 Hz, J_{cis} = 10.4 Hz, $J_{4,3}$ = 6.6 Hz, 1H, 4-H) ppm.

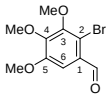
^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 14.84 (C-2'), 23.36 (C-1'), 29.52 (C-3), 43.25 (C-2), 115.82 (C-5), 136.35 (C-4), 198.89 (C-1) ppm.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

IR (film): ν = 2930, 2855, 2640, 2490, 2330, 2120, 1735, 1450, 1360, 1240, 1085, 1045, 915, 790, 650, 515 cm^{-1}.

2-Bromo-3,4,5-trimethoxybenzaldehyde (46)

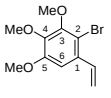


$C_{10}H_{11}BrO_4$
275.10 g/mol

3,4,5-Trimethoxybenzaldehyde (5.91 g, 30.1 mmol) was suspended in $CHCl_3$ (61 mL) and stirred at room temp. . *N*-Bromosuccinimide (6.45 g, 36.2 mmol, 1.2 equiv.) was added in portions. After heating the mixture to reflux for 3 h, it was washed with a saturated aqueous $NaHCO_3$ solution (50 mL), a saturated aqueous Na_2SO_3 solution (30 mL), and H_2O (30 mL). The aqueous phases were extracted with Et_2O (3 × 30 mL) and the combined organic phases were dried over Na_2SO_4. The solvents were removed in vacuo and the residue was purified via flash-chromatography on silica gel[21] [d = 6.5 cm, h = 13 cm, F = 100 mL; *c*-C_6H_{12}/EtOAc 19:1 (F1-13); *c*-C_6H_{12}/EtOAc 9:1 (F14-25)] to obtain the product [F13-21, $R_{f,\ 4:1}$ = 0.30, 5.24 g, 64% (ref.[33] in H_3CCN: 84%)] as a pale yellow solid [mp. 60-62°C (ref.[33]: 58.5-59.5°C).

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.90 (s, 3H, 5-OCH_3*), 3.91 (s, 3H, 3-OCH_3*), 3.98 (s, 3H, 4-OCH_3*), 7.30 (s, 1H, 6-H), 10.29 (s, 1H, 1-CHO) ppm; *assignment interchangeable.

2-Bromo-3,4,5-trimethoxystyrene (47)



$C_{11}H_{13}BrO_3$
273.12 g/mol

n-BuLi (1.6 M in hexane, 13.0 mL, 20.8 mmol, 1.07 equiv.) was added to a stirred suspension of methyltriphenylphosphonium bromide (7.29 g, 20.4 mmol, 1.05 equiv.) in THF (56 mL) at 0°C. After stirring for 30 min at the same temperature, a solution of 2-bromo-3,4,5-trimethoxybenzaldehyde (**46**) (5.00 g, 19.4 mmol) in THF (18 mL) was added via transfer cannula at 0°C. The ice bath was removed and the mixture was stirred vigorously at room temp. for 70 min. To the reaction mixture were slowly added EtOAc (60 mL) and water (60 mL) at 0°C. The layers were separated and the aqueous phase was extracted with EtOAc (3 × 35 mL). The combined organic phases were dried over Na_2SO_4 and the solvents removed in vacuo. Flash-chromatography on silica gel[21] (d = 5.5 cm, h = 12 cm, F = 50 mL; *c*-C_6H_{12}/EtOAc 9:1) gave the target compound (F4-16, $R_{f,\ 4:1}$ = 0.47, 4.52 g, 86%) as a white amorphous solid (mp. 33-34°C).

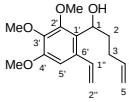
^{1}H NMR (500.22 MHz, $CDCl_3$): δ = 3.889 (s, 3H, 4-OCH_3), 3.891 (s, 6H, 5-OCH_3 and 3-OCH_3), 5.32 (dd, J_{cis} = 11.0 Hz, J_{gem} = 0.9 Hz, 1H, 2'-H^E), 5.61 (dd, J_{trans} = 17.3 Hz, J_{gem} = 1.0 Hz, 1H, 2'-H^Z), 6.89 (s, 1H, 6-H), 7.05 (dd, J_{trans} = 17.4 Hz, J_{cis} = 10.9 Hz, 1H, 1'-H) ppm.

^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 56.22 (4-OCH_3)*, 61.01 (3-OCH_3)*, 61.25 (5-OCH_3), 105.39 (C-6), 110.63 (C-4), 115.95 (C-2'), 133.26 (C-1), 136.00 (C-1'), 143.12 (C-5)**, 150.93 (C-3)**, 152.85 (C-4)** ppm; *,** assignments interchangeable.

IR (film): ν = 2300, 2965, 2935, 2845, 2830, 1585, 1555, 1480, 1430, 1415, 1390, 1330, 1240, 1200, 1165, 1110, 1010, 920, 840, 805 cm^{-1}.

HRMS (pos. APCI): calcd. for $C_{11}H_{14}{}^{79}BrO_3^{\oplus}$ ($M+H^{\oplus}$) = 273.01208; found 273.01202 (Δ = −0.2 ppm) and calcd. for $C_{11}H_{14}{}^{81}BrO_3^{\oplus}$ ($M+H^{\oplus}$) = 275.01004; found 275.00981 (Δ = −0.8 ppm).

1-(2',3',4'-Trimethoxy-6'-vinylphenyl)pent-4-en-1-ol (48)



$C_{16}H_{22}O_4$
278.35 g/mol

4-Bromo-but-1-ene-magnesium bromide was prepared by adding a few drops of 4-bromobut-1-ene to a stirring suspension of Mg turnings (0.414 g, 17.3 mmol) in dry THF (10 mL) under Ar and at 35 °C. Upon reaction initiation the rest of the 4-bromo-but-1-ene (2.33 g, 17.3 mmol), in dry THF (25 mL), was added drop-wise at the same temperature. The reaction mixture was then heated at reflux for 1 h, after which it was allowed to cool to room temp. A solution of aldehyde **49** (1.92 g, 8.62 mmol) in THF (80 mL) was then added drop-wise over 3 min. The reaction mixture was then stirred at 70 °C for 3 h, cooled to rt and quenched into a solution of NH_4Cl (sat., 50 ml), after which the mixture was diluted with EtOAc (150 mL). The bi-phasic mixture was separated, and the aqueous phase extracted with EtOAc (2 × 50 mL). The combined organic extracts were then washed with brine (25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product. This material was purified by column chromatography on silica gel (20% EtOAc/hexane) to afford alcohol **48** (1.97 g, 7.07 mmol, 82%) as a colorless liquid.

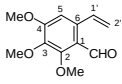
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79-1.74 (m, 1H, 2-H), 2.01-1.94 (m, 1H, 2-H), 2.12-2.04 (m, 1H, 3-H), 2.28-2.22 (m, 1H, 3-H), 3.41 (bs, 1H, 1-OH), 3.84 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.97 (s, 3H, OMe), 5.02-4.94 (m, 2H, 5-H and 1-H), 5.07-5.06 (m, 1H, 5-H), 5.27 (dd, $J_{cis\ H\text{-}2''\text{-}H\text{-}1''}$ = 10.9, $J_{H\text{-}2''\text{-}H\text{-}2''}$ = 1.2 Hz, 1H, *cis* 2''-H), 5.48 (dd, $J_{trans\ H\text{-}2''\text{-}H\text{-}1''}$ = 17.3, $J_{H\text{-}2''\text{-}H\text{-}2''}$ = 1.2 Hz, 1H, *trans* 2''-H), 5.84 (ddt, $J_{trans\ H\text{-}4\text{-}H\text{-}5}$ = 16.9, $J_{cis\ H\text{-}4\text{-}H\text{-}5}$ = 10.2, $J_{H\text{-}4\text{-}H\text{-}3}$ = 6.4 Hz, 1H, 4-H),), 6.73 (s, 1H, 5'-H), 7.03 (dd, $J_{trans\ H\text{-}1''\text{-}H\text{-}2''}$ = 17.3, $J_{cis\ H\text{-}1''\text{-}H\text{-}2''}$ = 10.9 Hz, 1H, 1''-H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.5 (C-3), 37.7 (C-2), 55.9 (OMe), 60.6 (OMe), 61.2 (OMe), 69.7 (C-1), 105.7 (C-5'), 114.7 (C-2''), 116.2 (C-5), 127.1 (C-1'), 132.2 (C-1''), 134.9 (C-4), 138.2 (C-6'), 141.8 (C-2')*, 151.8 (C-3')*, 152.5 (C-4')* ppm; *assignments interchangeable.

IR (neat): ν = 3440, 2936, 1563, 1 487, 1406, 1316, 1237, 1195 cm^{-1}.

HRMS: calcd for $C_{16}H_{22}O_4Na$ (M^++Na) = 301.1410, found: 301.1408 (Δ = −0.66 ppm).

2,3,4-Trimethoxy-6-vinylbenzaldehyde (49)



$C_{12}H_{14}O_4$
222.24 g/mol

This reaction was performed in a very similar manner to that described for compound **75** utilizing **50** (2.55 g, 9.58 mmol), (undried) methanol (50 mL), *p*TSA (monohydrate, 0.37 g, 20 mol%) at room temp. for 30 min. After a similar work-up, the crude product was purified by column chromatography on silica gel (20% EtOAc/hexane) to afford aldehyde **49** (1.92 g, 8.62 mmol, 90%) as a light reddish liquid.

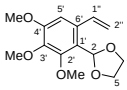
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.89 (s, 3H, OMe), 3.96 (s, 3H, OMe), 3.99 (s, 3H, OMe), 5.37 (dd, $J_{cis\ H\text{-}2'\text{-}\ H\text{-}1'}$ = 10.9, $J_{cis\ H\text{-}2'\text{-}H\text{-}1'}$ = 1.4 Hz, 1H, *cis* H-2'), 5.59 (dd, $J_{trans\ H\text{-}2'\text{-}H\text{-}1'}$ = 17.4, $J_{H\text{-}2'\text{-}H\text{-}2'}$ = 1.4 Hz, 1H, *trans* H-2'), 6.82 (s, 1H, H-5), 7.52 (dd, $J_{trans\ H\text{-}1'\text{-}H\text{-}2'}$ = 17.4, $J_{cis\ H\text{-}1'\text{-}H\text{-}2'}$ = 10.9 Hz, 1H, H-1'), 10.4 (s, 1H, CHO) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.0 (OMe), 61.0 (OMe), 62.3 (OMe), 105.9 (C-5), 116.9 (C-2'), 120.4 (C-6), 135.7 (C-1), 137.1 (C-1'), 141.2 (C-2)*, 157.7 (C-3)*, 157.9 (C-4)*, 190.9 (CHO) ppm; *assignments interchangeable.

IR (neat): ν = 2938, 1677, 1587, 1555, 1493, 1450, 1384, 1300, 1241, 1195 cm^{-1}.

HRMS: calcd for $C_{12}H_{15}O_4$ (M^++H) = 223.0964, found: 223.0965 (Δ = +0.44 ppm).

2-(2',3',4'-Trimethoxy-6'-vinylphenyl)-1,3-dioxolane (50)



$C_{14}H_{18}O_5$
266.29 g/mol

This reaction was performed in a very similar manner to that described for compound **72** utilizing *n*-butyllithium (11.1 mL, 17.8 mmol, 1.6 M solution in hexane), methyltriphenylphosphonium iodide (7.2 g, 18 mmol), dry THF (50 mL). Then **51** (3.18 g, 11.8 mmol) in dry THF (20 mL) was added drop-wise. After a similar work-up, the residue obtained was purified by column

This article is protected by copyright. All rights reserved.

Accepted Manuscript

chromatography on silica gel (20% EtOAc/hexane) to afford the alkene **50** (2.55 g, 9.58 mmol, 81%) as a colorless viscous liquid.

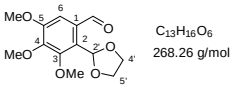
^{1}H NMR (300 MHz; MeOD-d_4): δ = 3.83 (s, 6H, 2 × OMe), 3.88 (s, 3H, OMe), 4.05-3.94 (m, 2H, 4-H*cis* and 5-H*cis*)*, 4.20-4.15 (m, 2H, 4-H*trans* and 5-H*trans*)*, 5.08 (dd, $J_{cis\ H\text{-}2''\ H\text{-}1''}$ = 11.0, $J_{H\text{-}2''\text{-}H\text{-}2''}$ = 1.4 Hz, 1H, *cis* 2''-H), 5.42 (dd, $J_{trans\ H\text{-}2''\text{-}H\text{-}1''}$ = 17.5, $J_{H\text{-}2''\text{-}H\text{-}2''}$ = 1.4 Hz, 1H, *trans* 2''-H), 6.0 (s, 1H, 2-H), 6.83 (s, 1H, 5'-H), 7.11 (dd, $J_{trans\ H\text{-}1''\text{-}H\text{-}2''}$ = 17.5, $J_{cis\ H\text{-}1''\text{-}H\text{-}2''}$ = 11.0 Hz, 1H, 1''-H) ppm; *assignments interchangeable.

^{13}C NMR (75 MHz; MeOD-d_4): δ = 56.4 (OMe), 61.3 OMe), 62.5 (OMe), 66.1 (CH_2CH_2), 100.9 (C-2), 107.4 (C-5''), 115.0 (C-2''), 120.4 (C-1''), 136.3 (C-6''), 136.5 (C-1''), 142.9 (C-2'') ‡, 154.7 (C-3'') ‡, 155.5 (C-4'') ‡ ppm; ‡ assignments interchangeable.

IR (neat): ν = 2936, 1565, 1491, 1454, 1375, 1321, 1240, 1194 cm^{-1}.

HRMS: calcd for $C_{14}H_{19}O_5$ (M^++H) = 267.1227, found: 267.1228 (Δ = +0.37 ppm).

2-(1',3'-Dioxolan-2'-yl)-3,4,5-trimethoxybenzaldehyde (51)



A suspension of sodium acetate (1.82 g, 14.8 mmol) and pyridinium chlorochromate (4.7 g, 22 mmol) in dry CH_2Cl_2 (40 mL) was cooled in an ice bath under an Ar atmosphere and treated with solution of alcohol **52** (4.00 g, 14.8 mmol) in CH_2Cl_2 (10 mL), over a 30 min. period. The reaction was then stirred for 5 h at 0-5 °C, diluted with Et_2O (200 mL) and further stirred at room temp. for 30 min. The solid was collected by filtration (cotton wool plug) and washed with Et_2O (50 mL). The combined filtrate was washed with Na_2CO_3 solution (5%, 50 mL) and brine (sat., 50 mL), after which it was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude aldehyde. This material was subjected to column chromatography on silica gel (30% EtOAc/hexane) to give compound **51** (3.18 g, 11.8 mmol, 80%) as a white solid, mp. 60-62 °C.

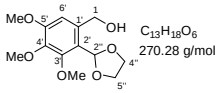
^{1}H NMR (300 MHz; MeOD-d_4): δ = 3.86 (s, 3H, OMe), 3.91 (s, 6H, 2 × OMe), 4.06-3.98 (m, 2H, 4'-H*cis* and 5'-H*cis*)*, 4.25-4.21 (m, 2H, 4'-H*trans* and 5'-H*trans*)*, 6.18 (s, 1H, 2'-H), 7.36 (s, 1H, 6-H), 10.43 (s, 1H, CHO) ppm; *assignments interchangeable.

^{13}C NMR (75 MHz; MeOD-d_4): δ = 56.5 (OMe), 61.2 (OMe), 62.8 (OMe), 66.0 (CH_2CH_2), 100.0 (C-2'), 108.0 (C-6), 125.9 (C-2), 133.4 (C-1), 147.9 (C-3) ‡, 154.5 (C-4) ‡, 155.6 (C-5) ‡, 192.4 (CHO) ppm; ‡ assignments interchangeable.

IR (neat): ν = 2903, 1677, 1585, 1494, 1421, 1376, 1318, 1248, 1998 cm^{-1}.

HRMS: calcd for $C_{13}H_{17}O_6$ (M^++H) = 269.1019, found: 269.1019 (Δ = ±0.0 ppm).

[2'-(1'',3''-Dioxolan-2''-yl)-3',4',5'-trimethoxyphenyl]methanol (52)



This reaction was performed in a very similar manner to that described for compound **70** utilizing lithium aluminium hydride (1.3 g, 35 mmol), **53** (5.28 g, 17.7 mmol) and dry THF (150 mL), 0 °C for 2 h and quenched by successive slowly addition of H_2O (8 mL), NaOH solution (10%, 8 mL) and EtOAc (200 mL). After a similar work-up, concentration under reduced pressure gave the crude alcohol **52** (4.02 g, 14.9 mmol, 84%) as a colorless thick liquid, which was used as such in next step without further purification.

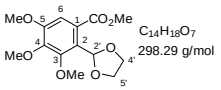
^{1}H NMR (300 MHz; MeOD-d_4): δ = 3.82 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.89 (s, 3H, OMe), 4.01-3.96 (m, 2H, 4''-H*cis* and 5''-H*cis*)*, 4.19-4.15 (m, 2H, 4''-H*trans* and 5''-H*trans*)*, 4.76 (s, 2H, 1-H), 6.09 (s, 1H, 2''-H), 7.06 (s, 1H, 6'-H) ppm; *assignments interchangeable.

^{13}C NMR (75 MHz; MeOD-d_4): δ = 56.4 (OMe), 61.2 (OMe), 61.8 (OMe), 62.5 (C-1), 65.9 (CH_2CH_2), 101.0 (C-2''), 108.6 (C-6'), 119.7 (C-2'), 139.7 (C-1'), 142.0 (C-3'') ‡, 154.8 (C-4'') ‡, 155.4 (C-5') ‡ ppm; ‡ assignments interchangeable.

IR (neat): ν = 3440, 2937, 1599, 1471, 1416, 1340, 1229, 1242, 1194 cm^{-1}.

HRMS: calcd for $C_{13}H_{18}O_6Na$ (M^++Na) 293.0995 found: 293.0994 (Δ = –0.34 ppm).

Methyl 2-(1',3'-Dioxolan-2'-yl)-3,4,5-trimethoxybenzoate (53)



This reaction was performed in a very similar manner to that described for compound **68** utilizing 1,2-ethanediol (4.9 g, 79 mmol), triethyl orthoformate (2.9 g, 20 mmol) and *p*-toluenesulfonic acid monohydrate (0.037 g, 0.20 mmol), **56** (5.0 g, 20 mmol) in THF (75 mL), 40 °C for 5 h. The same work-up and purification by column chromatography on silica gel (30% EtOAc/hexane) afforded compound **53** (5.28 g, 17.7 mmol, 89%) as a white solid, mp. 48-50 °C.

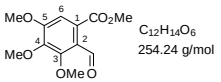
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 6H, 2 × OMe) 3.88 (s, 3H, OMe), 3.92 (s, 3H, OMe), 4.01-3.98 (m, 2H, 4'-H*cis* and 5'-H*cis*)*, 4.01-3.98 (m, 2H, 4'-H*trans* and 5'-H*trans*)*, 6.19 (s, 1H, 2'-H), 6.80 (s, 1H, 6-H) ppm; *assignments interchangeable.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.3 (CO_2Me), 56.1 (OMe), 60.8 (OMe), 61.6 (OMe), 65.5 (CH_2CH_2), 99.5 (C-2'), 107.4 (C-6), 122.2 (C-1), 128.1 (C-2), 153.3 (C-3) ‡, 153.8 (C-4') ‡, 155.0 (C-5') ‡, 169.0 (CO_2Me) ppm; ‡ assignments interchangeable.

IR (neat): ν = 2883, 1736, 1575, 1456, 1415, 1375, 1336, 1224 cm^{-1}.

HRMS: calcd for $C_{14}H_{19}O_7$ (M^++H) = 299.1125, found: 299.1123 (Δ = –0.66 ppm).

Methyl 2-Formyl-3,4,5-trimethoxybenzoate (56) via Methyl 3,4,5-Trimethoxybenzoate (55))



A solution of 3,4,5-trimethoxybenzoic acid (**54**, 5.0 g, 24 mmol) in MeOH (50 mL) and concentrated HCl (35%, 0.5 mL) was stirred at room temp. for 20 h. The solvent was evaporated off under reduced pressure. The residue was then diluted with EtOAc (150 mL), washed with $NaHCO_3$ solution (10%, 50 mL) and brine (25 mL), before being dried over Na_2SO_4 and concentrated under reduced pressure to furnish the crude methyl ester **55** as an off-white solid. This crude methyl ester (5.2 g) was dissolved in dry CH_2Cl_2 (50 mL) and α,α-dichloromethyl methyl ether (5.3 g, 46 mmol) was added under Ar at room temp. This mixture was cooled to –70 °C, and neat $SnCl_4$ (9.0 g, 34 mmol) was added drop-wise. The resulting yellow reaction mixture was warmed slowly to 0 °C, and stirred for 2 h at 0-5 °C. The reaction mixture was quenched in H_2O (100 mL), neutralized with aqueous saturated $NaHCO_3$ solution and solid $NaHCO_3$ and diluted with CH_2Cl_2 (200 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give crude product which was purified by column chromatography on silica gel (30% EtOAc/hexane) to give aldehyde **56** as a white solid (5.28 g, 20.8 mmol, 87% over the 2 steps, ref.[34]), mp. 48-50 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.91 (s, 6H, 2 × OMe), 3.95 (s, 3H, OMe), 3.98 (s, 3H, OMe), 6.95 (s, 1H, 6-H), 10.29 (s, 1H, CHO) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.8 (CO_2Me), 56.3 (OMe), 61.1 (OMe), 62.4 (OMe), 107.8 (C-5), 123.5 (C-1), 128.6 (C-6), 143.9 (C-2)*, 155.2 (C-3)*, 157.0 (C-4)*, 168.2 (CO_2Me), 189.1 (CHO) ppm. **assignment interchangeable*

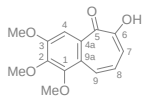
IR (neat): ν = 2947, 1730, 1694, 1584, 1491, 1480, 1333, 1232, 1194 cm^{-1}.

HRMS: calcd for $C_{12}H_{15}O_6$ (M^++H) = 255.0863, found: 255.0864 (Δ = +0.39 ppm).

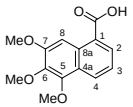
Accepted Manuscript

This article is protected by copyright. All rights reserved.

5,6,7-Trimethoxynaphthalene-1-carboxylic Acid (57) and 6-Hydroxy-1,2,3-trimethoxy-5*H*-benzo[7]annulen-5-one (5c)



5c



57

(characterization data: *vide supra*)

How this compound was obtained is described in the context of making benzotropolone **5c**.

^{1}H NMR (500.10 MHz, C_6D_6): δ = 3.56 (s, 3H, 7-OCH_3), 3.77 (s, 3H, 6-OCH_3), 3.78 (s, 3H, 5-OCH_3), 7.08 (dd, $J_{3,4}$ = 8.3 Hz, $J_{3,2}$ = 7.4 Hz, 1H, 3-H), 8.36 (ddd, $J_{4,3}$ = 8.3 Hz, $J_{4,2}$ = 1.4 Hz, $J_{4,8}$ = 0.7 Hz, 1H, 4-H), 8.44 (dd, $J_{2,3}$ = 7.4 Hz, $J_{2,4}$ = 1.4 Hz, 1H, 2-H), 8.65 (s, 1H, 8-H), 11.8 (br. s, 1H, CO_2H) ppm.

NOESY (500.10 MHz/500.10 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{1}H)]: δ = 3.56 (7-OCH_3) ↔ δ = 8.65 (8-H); 7.08 (3-H) ↔ δ = 8.36 (4-H); 8.36 (4-H) ↔ δ = 7.08 (3-H).

^{13}C NMR (125.75 MHz, C_6D_6): δ = 55.33 (7-OCH_3), 60.73 (6-OCH_3), 61.25 (5-OCH_3), 101.83 (C-8), 122.54 (C-3), 123.81 (C-1)*, 126.17 (C-4a)*, 128.72 (C-4), 130.34 (C-8a), 132.26 (C-2), 141.60 (C-6), 148.56 (C-5), 155.64 (C-7), 173.26 (CO_2H) ppm; **assignment interchangeable*.

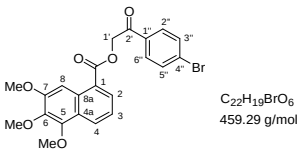
edHSQC ("short-range H,C-COSY", 500.10 MHz/125.75 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{13}C)]: δ = = 3.56 ↔ δ = 55.33; 3.77 ↔ δ = 60.73; 3.78 ↔ δ = 61.25; 7.08 ↔ δ = 122.54; 8.36 ↔ δ = 128.72; 8.44 ↔ δ = 132.26; 8.65 ↔ δ = 101.83.

HMBC ("long-range H,C-COSY", 500.10 MHz/125.75 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{13}C)]: δ = 3.56 (7-OCH_3) ↔ δ = 155.64 (C-7); δ = 3.77 (6-OCH_3) ↔ δ = 141.60 (C-6); δ = 3.78 (5-OCH_3) ↔ δ = 148.56 (C-5); δ = 7.08 (3-H) ↔ δ = 123.81 (C-1 or C-4a), 126.17 (C-4a or C-1); δ = 8.36 (4-H) ↔ δ = 130,34 (C-8a), 132.26 (C-2), 148.56 (C-5); δ = 8.44 (2-H) ↔ δ = 128.72 (C-4), 130.34 (C-8a), 173.26 (CO_2H); δ = 8.65 (8-H) ↔ δ = 123.81 (C-1 or C-4a), 126.17 (C-4a or C-1), 141.60 (C-6), 155.64 (C-7).

IR ($CDCl_3$): ν = 3140, 3070, 3000, 2945, 2840, 2645, 1685, 1590, 1580, 1500, 1480, 1405, 1380, 1335, 1275, 1195, 1140, 1120, 1040, 1015, 960, 915, 850, 820, 750 cm^{-1}.

HRMS: (pos. APCI, 70 eV): calcd. for $C_{14}H_{13}O_5$ [M-H]$^-$ = 261.0768; found 261.0767 (–0.48 ppm).

2-(4-Bromophenyl)-2-oxoethyl 5,6,7-Trimethoxynaphthalene-1-carboxylate (58)



The naphthalenecarboxylic acid **57** (10 mg, 38 µmol) was added to a stirred solution of *p*-bromophenacyl bromide (20 mg, 72 µmol, 1.9 equiv.) and NEt_3 (14 µL, 10 mg, 0.10 mmol, 2.6 equiv.) in CH_2Cl_2 (250 µL) at room temp. . The reaction mixture was stirred at room temp. for 20 min. After addition of H_2O (5 mL) the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude product was purified by flash-chromatography on silica gel[21] (d = 0.5 cm, h = 5 cm, F = 1.5 mL; *c*-C_6H_{12}/EtOAc 5:1). The title compound **58** (F2-7, 8.3 mg, 47%) was obtained as yellow solid (mp. 96–99°C).

^{1}H NMR (500.10 MHz, C_6D_6): δ = 3.67 (s, 3H, 7-OCH_3), 3.79 (s, 3H, 6-OCH_3), 3.81 (s, 3H, 5-OCH_3), 5.00 (s, 2H, 1'-H_2), 7.09 (m_C, 2H, 3''-H, 5''-H), 7.17 (dd, $J_{3,4}$ = 8.3 Hz, $J_{3,2}$ = 7.4 Hz, 1H, 3-H), 7.25 (m_C, 2H, 2''-H, 6''-H), 8.38 (m_C, 1H, 4-H), 8.53 (dd, $J_{2,3}$ = 7.3 Hz, $^4J_{2,4}$ = 1.3 Hz, 1H, 2-H), 8.73 (s, 1H, 8-H) ppm.

NOESY (500.10 MHz/500.10 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{1}H)]: δ = 3.67 (7-OCH_3) ↔ δ = 8.73 (8-H); δ = 5.00 (1'-CH_2) ↔ δ = 7.25 (2''-H, 6''-H); δ = 7.17 ppm (3-H) ↔ δ = 8.38 ppm (4-H).

^{13}C NMR (125.75 MHz, C_6D_6): δ = 55.51 (7-OCH_3), 60.75 (6-OCH_3), 61.26 (5-OCH_3), 66.22 (C-1'), 101.96 (C-8), 122.58 (C-3), 124.87 (C-1)*, 126.10 (C-4a)*, 128.63 (C-4"), 129.39 (C-2'', C-6"), 130.18 (C-8a), 131.21 (C-2), 132.06 (C-3", C-5"), 133.35 (C-1"), 141.69 (C-6), 148.53 (C-5), 155.55 (C-7), 167.28 [1-C(=O)O], 191.04 (C-2) ppm; *assignment interchangeable.

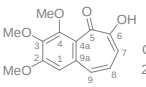
edHSQC ("short-range H,C-COSY", 500.10 MHz/125.75 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{13}C)]: δ = 3.67 ↔ δ = 55.51; δ = 3.79 ↔ δ = 60.75; δ = 3.81 ↔ δ = 61.26; δ = 5.00 ↔ δ = 66.22; δ = 7.09 ↔ δ = 132.06; δ = 7.17 ↔ δ = 122.58; δ = 7.25 ↔ δ = 129.39; δ = = 8.38 ↔ δ = 127.96; δ = 8.53 ↔ δ = 131.21; δ = 8.73 ppm ↔ δ = 101.96 ppm.

HMBC ("long-range H,C-COSY", 500.10 MHz/125.75 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{13}C)]: δ = 3.67 (7-OCH_3) ↔ δ = 155.55 (C-7); δ = 3.79 (6-OCH_3) ↔ δ = 141.69 (C-6); δ = 3.81 (5-OCH_3) ↔ δ = 148.69 (C-6); δ = 5.00 (1'-H) ↔ δ = 133.35 (C-1"), 167.28 [1-C(=O)O], 191.04 (C-2'); δ = 7.09 (3''-H, 5''-H)) ↔ δ = 129.39 (C-2"), 133.35 (C-1"); δ = 7.17 (3-H) ↔ δ = 124.87 (C-1 or C-4a), 126.10 (C-4a or C-1); δ = 7.25 (2''-H, 6''-H) ↔ δ = 128.63 (C-4"), 132.06 (C-3"), 191.04 (C-2'); δ = 8.38 (4-H) ↔ δ = 130.18 (C-8a), 131.21 (C-2), 148.53 (C-5); δ = 8.53 (2-H) ↔ δ = 127.96 (C-4), 130.18 (C-8a), 167.28 [1-C(=O)O]; δ = 8.73 ppm (8-H) ↔ δ = 124.87 (C-1 or C4a), 126.10 (C-4a or C-1), 141.69 (C-6), 155.55 ppm (C-7).

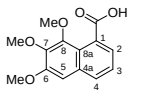
IR (KBr): ν = 3430, 3130, 2990, 2935, 2850, 1910, 1705, 1590, 1500, 1475, 1465, 1425, 1400, 1380, 1330, 1275, 1255, 1235, 1135, 1115, 1070, 1030, 975, 860, 825, 810, 755 cm^{-1}.

HRMS (pos. APCI): calcd. for $C_{22}H_{20}O_6{}^{79}Br$ [M+H]$^+$ = 459.0438; found 459.0436 (-0.4357 ppm); calcd. for $C_{22}H_{20}O_6{}^{81}Br$ [M+H]$^+$ = 461.0417; found 461.0419 (+0.4338 ppm).

6,7,8-Trimethoxynaphthalene-1-carboxylic Acid (59) and 6-Hydroxy-2,3,4-trimethoxy-5*H*-benzo[7]annulen-5-one (5d)



5d



59

(characterization data: *vide supra*)

How this compound was obtained is described in the context of making benzotropolone **5d**.

^{1}H NMR (500.10 MHz, C_6D_6): δ = 3.34 (s, 3H, 6-OCH_3), 3.71 (s, 3H, 7-OCH_3), 4.11 (s, 3H, 8-OCH_3), 6.61 (s, 1H, 5-H), 7.08 (dd, $J_{3,4}$ = 8.2 Hz, $J_{3,2}$ =7.1 Hz, 1H, 3-H), 7.38 (dd, $J_{2,3}$ = 7.1 Hz, $^4J_{2,4}$ =1.1 Hz, 1H, 2-H), 7.44 (dd, $J_{4,3}$ = 8.3 Hz, $^4J_{4,2}$ =1.1 Hz, 1H, 4-H) ppm; a resonance of COO*H* was not observed.

NOESY (500.10 MHz/500.10 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{1}H)]: δ = 3.34 (6-OCH_3) ↔ δ = 6.61 (5-H); δ = 6.61 (5-H) ↔ δ = 3.34 (6-OCH_3), 7.44 (4-H); δ = 7.08 (3-H) ↔ δ = 7.38 (2-H), 7.44 (4-H); δ = 7.38 (3-H) ↔ δ = 7.08 (3-H); δ = 7.44 ppm (4-H) ↔ δ = 6.61 ppm (5-H).

^{13}C NMR (125.75 MHz, C_6D_6): δ = 55.25 (6-OCH_3), 60.53 (7-OCH_3), 61.18 (8-OCH_3), 103.14 (C-5), 121.21 (C-8a), 123.22 (C-2), 124.86 (C-3), 128.29 (C-4), 129.75 (C-4a)*, 131.52 (C-1)*, 142.62 (C-7), 148.33 (C-8), 154.17 (C-6), 177.93 (1-CO_2H) ppm; *assignment interchangeable.

edHSQC ("short-range H,C-COSY", 500.10 MHz/125.75 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{13}C)]: δ = 3.34 ↔ δ = = 55.25; δ = 3.71 ↔ δ = 60.53; δ = = 4.11 ↔ δ = 61.18; δ = 6.61 ↔ δ = 103.14; δ = = 7.08 ↔ δ = 124.86; δ = 7.38 ↔ δ = 123.22; δ = 7.44 ppm ↔ δ = 128.29 ppm.

HMBC ("long-range H,C-COSY", 500.10 MHz/125.75 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{13}C)]: δ = 3.34 (6-OCH_3) ↔ δ = 154.17 (C-6); δ = 3.71 (7-OCH_3) ↔ δ = 142.62 (C-7); δ = 4.11 (8-OCH_3) ↔ δ = 148.33 (C-8); δ = 6.61 (5-H) ↔ δ = 121.21 (C-8a), 128.29 (C-4), 124.62 (C-7), 154.17 (C-6); δ = 7.08 (3-H) ↔ δ = 129.75 (C-1) or (C-4a), 131.52 (C-1) or (C-4a); δ = 7.38 (2-H) ↔ δ = 121.21 (C-8a), 128.29 (C-4), 177.93 (1-CO_2H), δ = 7.44 ppm (4-H) ↔ δ = 103.14 (C-5), 121.21 (C-8a), 123.22 ppm (C-2).

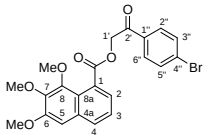
Accepted Manuscript

This article is protected by copyright. All rights reserved.

IR (KBr): ν = 2950, 2925, 2850, 1695, 1620, 1595, 1585, 1500, 1480, 1465, 1425, 1360, 1350, 1290, 1240, 1210, 1200, 1180, 1140, 1115, 1075, 1045, 1010, 835, 800, 775 cm^{-1}.

HRMS (pos. APCI): calcd. for $C_{14}H_{15}O_5$ $[M+H]^-$ = 263.0914; found 263.0916 (+0.6963 ppm).

2-(4-Bromophenyl)-2-oxoethyl 6,7,8-Trimethoxynaphthalene-1-carboxylate (60)



$C_{22}H_{19}BrO_6$
459.29 g/mol

The naphthalenecarboxylic acid(**59** (10 mg, 38 µmol) was added to a stirred solution of *p*-bromophenacyl bromide (20 mg, 72 µmol, 1.9 equiv.) and NEt_3 (14 µL, 10 mg, 0.10 mmol, 2.6 equiv.) in CH_2Cl_2 (250 µL) at room temp. . The reaction mixture was stirred at room temp. for 55 min. After addition of H_2O (5 mL) the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude product was purified by flash-chromatography on silica gel[21] [d = 0.5 cm, h = 5 cm, F = 1.5 mL; *c*-C_6H_{12}/EtOAc 5:1(F1–4) → 4:1 (F5–12)]. The title compound **60** (F3-9, 12.7 mg, 73%) was obtained as yellow solid (mp. 129–128°C).

^{1}H NMR (500.10 MHz, C_6D_6): δ = 3.34 (m_C, 3H, 7-OCH_3), 3.74 (s, 3H, 7-OCH_3), 3.93 (s, 3H, 8-OCH_3), 5.11 (m_C, 2H, 1'-H_2), 6.62 (s, 1H, 5-H), 7.09 (m_C, 2H, 3''-H, 5''-H), 7.12 (m_C, 1H, 3-H), 7.32 (m_C, 2H, 2''-H, 6''-H), 7.45 (dd, $J_{4,3}$ = 8.3 Hz, $^4J_{4,2}$ = 1.1 Hz, 1H, 4-H), 7.84 (m_C, 2-H) ppm.

NOESY (500.10 MHz/500.10 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{1}H)]: δ = 3.34 (6-OCH_3) ↔ δ = 6.62 (5-H); δ = 3.93 (8-OCH_3) ↔ δ = 3.74 (7-OCH_3), 5.11 (1'-H_2); δ = 5.11 (1'-H_2) ↔ δ = 3.93 (8-OCH_3), 7.32 (2''-H, 6''-H); δ = 6.62 (5-H) ↔ δ = 3.34 (6-OCH_3), 7.45 (4-H); δ = 7.12 (3-H) ↔ δ = 7.45 (4-H), 7.84 (2-H); δ = 7.32 (2''-H, 6''-H) ↔ δ = 7.09 (3''-H, 5''-H), 5.11 (1'-H_2); δ = 7.45 (4-H) ↔ δ = 7.12 (3-H), 6.62 ppm (5-H).

^{13}C NMR (125.75 MHz, C_6D_6): δ = 55.25 (6-OCH_3), 60.61 (7-OCH_3), 61.33 (8-OCH_3), 66.53 (C-1'), 103.38 (C-5), 121.35 (C-8a), 124.34 (C-2), 125.13 (C-3), 128.30 (C-4), 128.44 (C-4'')*, 129.52 (C-1')**, 129.58 (C-2'', C-6''), 131.47 (C-4a)*, 131.98 (C-3'', C-5''), 133.62 (C-1'')*, 142.66 (C-7), 148.26 (C-8), 154.02 (C-6), 170.35 ([1-C(=O)O], 191.39 (C-2') ppm; *assignment interchangeable; **assignment interchangeable.

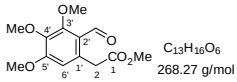
edHSQC ("short-range H,C-COSY", 500.10 MHz/125.75 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{13}C)]: δ = 3.34 ↔ δ = 55.25; δ = 3.74 ↔ δ = 60.61; δ = 3.93 ↔ δ = 61.33; δ = 5.11 ↔ δ = 66.53; δ = 6.62 ↔ δ = 103.38; δ = 7.09 ↔ δ = 131.98; δ = 7.12 ↔ δ = 125.13; δ = 7.32 ↔ δ = 129.58; δ = 7.45 ↔ δ = 128.30; δ = 7.84 ppm ↔ δ = 124.34 ppm.

HMBC ("long-range H,C-COSY", 500.10 MHz/125.75 MHz, C_6D_6): [δ(^{1}H) ↔ δ(^{13}C)]: δ = 3.34 (6-OCH_3) ↔ δ = 154.02 (C-6); δ = 3.74 (7-OCH_3) ↔ δ = 142.66 (C-7); δ = 3.93 (8-OCH_3) ↔ δ = 148.26 (C-8); δ = 5.11 (1'-H_2) ↔ δ = 170.35 [1-C(C=O)O], 191.39 (C-2'); δ = 6.62 (5-H) ↔ δ = 121.35 (C-8a), 128.30 (C-4), 142.66 (C-7), 154.02 (C-6); δ = 7.09 (3''-H, 5''-H) ↔ δ = 133.62 (C-1'' or C-4''), 128.44 (C-4'' or C-1''); δ = 7.12 (3-H) ↔ δ = 129.52 (C-1 or C-4a), 131.47 (C-4a or C-1); δ = 7.32 (2''-H, 6''-H) ↔ δ = 128.44 (C-4'' or C-1''), 131.98 (C-3'', C-5''), 191.39;(C-2'); δ = 7.45 (4-H) ↔ δ = 103.38 (C-5), 121.35 (C-8a), 124.34 (C-2); δ = 7.84 ppm (2-H) ↔ δ = 121.35 (C-8a), 128.30 (C-4), 170.35 ppm [1-C(=O)O].

IR (KBr): ν = 2930, 1745, 1700, 1585, 1500, 1480, 1470, 1425, 1415, 1360, 1355, 1290, 1275, 1235, 1225, 1200, 1185, 1135, 1115, 1070, 1035, 1010, 1000, 975, 945, 840, 805 cm^{-1}.

HRMS (ESI): calcd. for $C_{22}H_{19}O_6{}^{79}BrNa$ $[M+Na]^+$ = 481.0257; found 481.0259 (+0.3260 ppm); calcd. for $C_{22}H_{19}O_6{}^{81}BrNa$ $[M+Na]^+$ = 483.0237; found 483.0238 (+0.3287 ppm).

Methyl (2'-Formyl-3',4',5'-trimethoxyphenyl)acetate (68) via Methyl 3,4,5-Trimethoxybenzoate (67)



$C_{13}H_{16}O_6$
268.27 g/mol

A solution of (3,4,5-trimethoxyphenyl)acetic acid **66** (5.0 g, 22 mmol) in MeOH (50 mL) and concentrated HCl (35%, 0.5 mL) was stirred at room temp. for 24 h. The solvent was evaporated off under reduced pressure. The residue was then diluted with EtOAc (150 mL), washed with $NaHCO_3$ solution (10%, 50 mL) and brine (25 mL), before being dried over Na_2SO_4 and concentrated under reduced pressure to furnish the crude methyl ester **67** as a white solid. The crude methyl ester (5.2 g) was dissolved in dry CH_2Cl_2 (50 mL) and α,α-dichloromethyl methyl ether (5.0 g, 43 mmol) was added under Ar at room temp. This mixture was cooled to –70 °C, and neat $SnCl_4$ (8.4 g, 32 mmol) was added drop-wise. The resulting yellow reaction mixture was warmed slowly to 0 °C, and stirred for 2 h at 0-5 °C. The reaction mixture was quenched in H_2O (100 mL), neutralized with aqueous saturated $NaHCO_3$ solution and solid $NaHCO_3$ and diluted with CH_2Cl_2 (200 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give crude product which was purified by column chromatography on silica gel (30% EtOAc/hexane) to give aldehyde **68** (5.63 g, 21.0 mmol, 95% over two steps) as a white solid, mp. 115-117 °C.

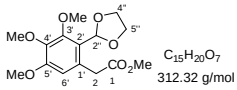
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.72 (s, 3H, OMe), 3.88 (s, 2H, 2-CH_2), 3.93 (s, 6H, 2xOMe), 4.01 (s, 3H, OMe), 6.53 (s, 1H, 6'-H), 10.34 (s, 1H, CHO) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.9 (2-CH_2), 51.9 (CO_2Me) 56.0 (OMe), 60.8 (OMe), 62.3 (OMe), 111.2 (C-6'), 121.2 (C-2'), 132.6 (C-1'), 140.8 (C-3')*, 157.9 (C-4')*, 158.5 (C-5')*, 171.6 (CO_2Me), 190.6 (CHO) ppm; *assignments interchangeable.

IR (neat): ν = 3650, 1736, 1677, 1589, 1498, 1435, 1380, 1317, 1256 cm^{-1}.

HRMS: calcd for $C_{13}H_{17}O_6$ (M^++H) = 269.1025, found: 269.1035 (Δ = +3.72 ppm).

Methyl [2'-(1'',3''-Dioxolan-2''-yl)-3',4',5-trimethoxyphenyl]acetate (69)



$C_{15}H_{20}O_7$
312.32 g/mol

1,2-Ethanediol (5.21 g, 84.0 mmol), triethylorthoformate (3.28 g, 22.0 mmol) and *p*-toluenesulfonic acid monohydrate (0.040 g, 0.21 mmol) was added to a solution of **68** (5.63 g, 21.0 mmol) in THF (75 mL). The reaction mixture was heated at 40 °C for 2 h and was then quenched by pouring into a solution of $NaHCO_3$ (50 mL, 0.25%). The mixture was subsequently extracted with EtOAc (2 × 50 mL) and the combined organic layers were then washed with brine (25 mL) and dried over Na_2SO_4. Concentration under reduced pressure gave a residue which was purified by column chromatography on silica gel (30% EtOAc/hexane) to afford the desired compound **69** (5.90 g, 18.9 mmol, 90%) as a white solid, mp. 42-45 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.67 (s, 3H, OMe), 3.73 (s, 2H, 2-CH_2), 3.83 (s, 3H, OMe), 3.85 (~~m~~ m_c, 3H, OMe) 3.86 (s, 3H,OMe), 4.02-3.92 (m, 2H, 4''-H_{cis} and 5''-H_{cis})*, 4.17-4.08 (m, 2H, 4''-H_{trans} and 5''-H_{trans})*, 6.07 (s, 1H, 2''-H), 6.56 (s, 1H, 6'-H) ppm; * assignments interchangeable.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.6 (CH_2-2), 51.7 (CO_2Me), 55.9 (OMe), 60.7 (OMe), 61.9 (OMe), 64.7 (CH_2CH_2), 99.5 (CH-2''), 112.0 (C-6'), 119.7 (C-1'), 130.3 (C-2'), 140.9 (C-3')*, 153.6 (C-4')*, 153.7 (C-5')*, 172.4 (CO_2Me) ppm; *assignments interchangeable.

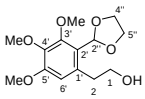
IR (neat): ν = 3628, 2968, 1719, 1599, 1578, 1483, 1458, 1376, 1333, 1240 cm^{-1}.

HRMS: calcd for $C_{15}H_{21}O_7$ (M^++H) = 313.1287, found: 313.1285 (Δ = –0.64 ppm).

Accepted Manuscript

This article is protected by copyright. All rights reserved.

2'-(1'',3''-Dioxolan-2''-yl)-3',4',5'-trimethoxyphenyl]ethanol (70)



$C_{14}H_{20}O_6$
284.31 g/mol

$LiAlH_4$ (1.43 g, 37.8 mmol) was added portion-wise to a solution of ester **69** (5.9 g, 18 mmol) under Ar in dry THF (150 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and quenched by successive addition of H_2O (8 mL), NaOH solution (10%, 8 mL) and EtOAc (200 mL). The quenched reaction mass was warmed to rt, filtered through a celite bed and the resulting granular inorganic precipitate washed with EtOAc (50 mL). The combined organic layers were then washed with brine solution (80 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the alcohol **70** (4.0 g, 14 mmol, 78%) as a colorless thick liquid which was used as such in next step without further purification.

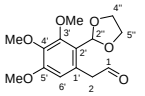
^{1}H NMR (300 MHz; MeOD-d_4): δ = 2.98 (t, *J* = 7.4 Hz, 2H, 2-CH_2), 3.74 (t, *J* = 7.4 Hz, 2H, 1-CH_2), 3.80 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.00-3.95 (m, 2H, 4''-H_{cis} and 5''-H_{cis})*, 4.21-4.15 (m, 2H, 4''-H_{trans} and 5''-H_{trans})*, 6.11 (s, 1H, 2''-H), 6.70 (s, 1H, 6'-H) ppm; *assignments interchangeable.

^{13}C NMR (75 MHz; MeOD-d_4): δ = 37.0 (C-2), 56.4 (OMe), 61.2 (OMe), 62.4 (OMe), 64.6 (C-1), 65.9 (CH_2CH_2), 101.1 (C-2''), 112.2 (C-6'), 121.3 (C-2'), 136.9 (C-1'), 141.7 (C-3')‡, 155.0 (C-4')‡, 155.2 (C-5')‡ ppm; ‡ assignments interchangeable.

IR (neat): ν = 3454, 2933, 1588, 1495, 1459, 1416 cm^{-1}.

HRMS: calcd for $C_{14}H_{20}O_6Na$ (M^++Na) = 307.1157, found: 307.1154 (Δ = –0.98 ppm).

[2'-(1'',3''-Dioxolan-2''-yl)-3',4',5'-trimethoxyphenyl]acetaldehyde (71)



$C_{14}H_{18}O_6$
282.29 g/mol

To a solution of $(COCF_3)_2O$ (4.4 g, 21 mmol) in dry CH_2Cl_2 (50 mL) at -65 °C under Ar was added DMSO (2.7 g, 35 mmol) in dry CH_2Cl_2 (5 mL) drop-wise over 5 min. After being stirred at -65 °C for 15 min, a solution of alcohol **70** (4.0 g, 14 mmol) in dry CH_2Cl_2 (15 mL) was added drop-wise and allowed to stir for 30 min. NEt_3 (7.1 g, 70 mmol) was then added drop-wise and the reaction allowed to stirred for a further 15 min. The reaction mixture was then warmed to room temp. , quenched with H_2O (25 mL) and diluted with CH_2Cl_2 (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic layer was washed sequentially with solutions of HCl (1N, 25 mL), $NaHCO_3$ (10%, 25 mL) and brine (25 mL), after which it was dried over Na_2SO_4. The organic solvent was then concentrated at reduced pressure to give crude product which was purified by column chromatography on silica gel (30% EtOAc/hexane) to give aldehyde **71** (3.02 g, 10.7 mmol, 76%) as a white solid, mp. 50-52 °C.

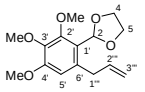
^{1}H NMR (300 MHz; DMSO-d_6): δ = 3.67 (d, *J* = 1.5 Hz, 2H, 2-CH_2), 3.74 (s, 6H, 2 × OMe), 3.81 (s, 3H, OMe), 3.89-3.85 (m, 2H, 4''-H_{cis} and 5''-H_{cis})*, 4.00-3.93 (m, 2H, 4''-H_{trans} and 5''-H_{trans})*, 5.93 (s, 1H, 2''-H), 6.83 (s, 1H, 6-H), 9.43 (bs, 1H, CHO) ppm; *assignments interchangeable.

^{13}C NMR (75 MHz; DMSO-d_6): δ = 46.6 (C-2), 55.8 (OMe), 60.3 (OMe), 61.9 (OMe), 63.9 (CH_2CH_2), 98.4 (C-2''), 112.5 (C-6'), 120.1 (C-2'), 129.6 (C-1'), 140.3 (C-3')‡, 153.1 (C-4')‡, 153.5 (C-5')‡, 199.9 (CHO) ppm; ‡ assignments interchangeable.

IR (neat): ν = 2930, 1601, 1578, 1500, 1461, 1420, 1380, 1333, 1237 cm^{-1}.

HRMS: calcd for $C_{14}H_{19}O_6$ (M^++H) = 283.1181, found: 283.1194 (Δ = + 4.6 ppm).

2-(6'-Allyl-2',3',4'-trimethoxyphenyl)-1,3-dioxolane (72)



$C_{15}H_{20}O_5$
280.32 g/mol

n-Butyllithium (9.9 mL, 15 mmol, 1.6 M solution in hexane) was added drop-wise under Ar at room temp. to a solution of methyltriphenylphosphonium iodide (6.4 g, 16 mmol) in dry THF (40 mL). The resulting yellow-orange solution was stirred at room temp. for 30 min and cooled to 0-5 °C, after which a solution of aldehyde **71** (3.0 g, 10 mmol) in dry THF (20 mL) was added drop-wise under Ar to the resulting ylide solution at 0-5 °C. The reaction mixture was warm to room temp. and stirred for 5 h. The yellow slurry mass was then diluted with Et_2O (150 mL), stirred at room temp. for 10 min. and filtered, after which the filter cake was washed with Et_2O (50 mL). The combined filtrate was concentrated under reduced pressure to give residue which was purified by column chromatography on silica gel (30% EtOAc/hexane) to afford alkene **72** (2.38 g, 8.50 mmol, 85%) as a white solid, mp. 56-58 °C.

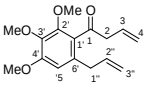
^{1}H NMR (300 MHz; MeOD-d_4): δ = 3.52 (d, *J* = 6.6 Hz, 2H, 1''-H), 3.80 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.99-3.94 (m, 2H, 4''-H_{cis} and 5''-H_{cis})*, 4.17-4.13 (m, 2H, 4''-H_{trans} and 5''-H_{trans})*, 5.04 (ddd, *J* = 16.8, 6.6, 1.6 Hz, 1H, *trans* 3''-H), 5.09 (ddd, *J* = 10.2, 6.6, 1.6 Hz, 1 H, *cis* 3''-H), 5.98 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H, 2''-H), 6.10 (s, 1H, 2-H), 6.63 (s, 1H, 5'-H) ppm; *assignments interchangeable.

^{13}C NMR (75 MHz; MeOD-d_4): δ = 37.8 (C-1''), 56.3 (OMe), 61.2 (OMe), 62.4 (OMe), 65.9 (CH_2CH_2), 101.2 (C-2), 111.2 (C-5'), 115.7 (C-3''), 120.9 (C-1'), 138.3 (C-6'), 139.4 (C-2''), 141.7(C-2')‡, 154.9 (C-3')‡, 155.3 (C-4')‡ ppm; ‡ assignments interchangeable.

IR (neat): ν_{max} (film)/cm^{-1}: 2936, 1580, 1497, 1458, 1427, 1380, 1323, 1235 cm^{-1}.

HRMS: calcd for $C_{15}H_{21}O_5$ (M^++H) = 281.1389, found: 281.1386 (Δ = – 1.1 ppm).

1-(6'-Allyl-2',3',4'-trimethoxyphenyl)-3-buten-1-one (73)



$C_{16}H_{20}O_4$
276.33 g/mol

Dess-Martin periodinane (6.0 g, 14 mmol) was added portion-wise at 0-5 °C over 5 min. to the solution of alcohol **74** (1.98 g, 7.11 mmol) dissolved in moist CH_2Cl_2 (50 mL, saturated with H_2O). The reaction mixture was subsequently stirred at room temp. for 12 h, after which it was quenched into a 1:1 solution of 10% $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer further extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give crude product. This residue was subjected to flash column chromatography on silica gel (10% EtOAc/hexane) to give the desired compound **73** (1.77 g, 6.40 mmol, 90%) as a colorless liquid.

^{1}H NMR (300 MHz; MeOD-d_4): δ = 3.13 (d, *J* = 6.6 Hz, 2H, 1''-H), 3.41 (dt, *J* = 6.9, 1.2 Hz, 2H, 2-H), 3.71 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.76 (s, 3H, OMe), 4.91-4.85 (m, 2H, 4-H and 3''-H), 5.05-4.98 (m, 2H, 4-H and 3''-H), 5.90-5.68 (m, 2H, 3-H and 2''-H), 6.53 (s, 1H, 5'-H) ppm.

^{13}C NMR (75 MHz MeOD-d_4): δ = 38.1 (C-1''), 50.6 (C-2), 56.5 (OMe), 61.2 (OMe), 62.1 (OMe), 110.3 (C-5'), 116.5 (C-3''), 118.8 (C-4), 129.3 (C-1'), 132.2 (C-6'), 134.2 (C-3), 138.3 (C-2''), 141.2 (C-2')*, 151.8 (C-3')*, 156.0 (C-4')*, 206.3 (C=O) ppm; *assignments interchangeable.

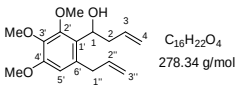
IR (neat): ν = 2938, 1693, 1593, 1570, 1492, 1453, 1397, 1328, 1281, 1243 cm^{-1}.

HRMS: calcd for $C_{16}H_{21}O_4$ (M^++H) = 277.1439, found: 277.1426 (Δ = – 4.7 ppm).

Accepted Manuscript

This article is protected by copyright. All rights reserved.

1-(6'-Allyl-2',3',4'-trimethoxyphenyl)but-3-en-1-ol (74)



Allylmagnesium bromide (15.6 mL, 15.6 mmol, 1 M solution in Et_2O) was added drop-wise at 0-5 °C under Ar to a solution of aldehyde **75** (1.85 g, 7.81 mmol) in dry THF (30 mL). The reaction mixture was then warmed up to rt and stirred for a further 5 h period, after which it was quenched with a saturated solution of NH_4Cl (100 ml) and diluted with EtOAc (150 mL). The biphasic mixture was separated, and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic extracts were then washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give crude product which was purified by flash column chromatography on silica gel (20% EtOAc/hexane) to afford alcohol **74** (1.98 g, 7.11 mmol, 91%) as a colorless liquid.

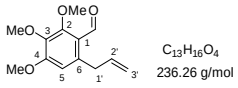
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 1H, 1-OH), 2.49-2.41 (m, 1H, 2-H), 2.70-2.60 (m, 1H, 2-H), 3.37-3.34 (m, 2H, 1''-H), 3.83 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.01 (s, 3H. OMe), 4.83 (dd, *J* = 8.7, 5.4 Hz, 1H, 3-H), 5.14-5.0 (m, 4H, 4-H and 3''-H), 5.97-5.79 (m, 2H, 1-H and 2''-H), 6.46 (s, 1H, 5'-H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.7 (C-1''), 43.1 (C-2), 55.8 (OMe), 60.6 (OMe), 61.2 (OMe), 70.4 (C-1), 108.8 (C-5'), 116.1 (C-3''), 116.9 (C-4), 127.1 (C-1'), 132.3 (C-2''), 135.5 (C-3), 136.9 (C-6'), 140.5 (C-2')*, 152.3 (C-3')*, 152.4 (C-4')* ppm; *assignments interchangeable.

IR (neat): ν = 3445, 2937, 1597, 1492, 1452, 1405, 1324, 1237 cm^{-1}.

HRMS: calcd for $C_{16}H_{22}O_4Na$ (M^+ + Na) = 301.1415, found: 301.1399 (Δ = – 5.3 ppm).

6-Allyl-2,3,4-trimethoxybenzaldehyde (75)



To a solution of acetal **72** (2.38 g, 8.50 mmol) in (undried) MeOH (50 mL) was added *p*-toluenesulfonic acid monohydrate (0.32 g, 20 mol%) at room temp., and the reaction mixture was stirred at room temp. for 3 h. The solvent was removed in vacuo and the residue was taken up in EtOAc (100 mL), before being washed sequentially with saturated Na_2CO_3 solution (25 mL) and brine (25 mL) The organic phase was then dried over Na_2SO_4 and concentrated under reduced pressure to give crude product which was purified by column chromatography on silica gel (20% EtOAc/hexane) to afforded aldehyde **75** (1.85 g, 7.82 mmol, 92%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (d, *J* = 6.6 Hz, 2H, 1'-H), 3.87 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.98 (s, 3H, OMe), 5.08-5.03 (m, 2H, 3'-H), 6.05-5.92 (m, 1H, 2'-H), 6.56 (s, 1H, 5-H), 10.39 (s, 1H, CHO) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.9 (C-1'), 56.0 (OMe), 60.9 (OMe), 62.3 (OMe), 109.3 (C-5), 115.9 (C-3'), 120.8 (C-1), 136.8 (C-6), 139.7 (C-2'), 139.9 (C-2)*, 157.9 (C-3)*, 158.4 (C-4)*, 190.8 (CHO) ppm; *assignments interchangeable.

IR (neat): ν = 2938, 2851, 1678, 1588, 1561, 1496, 1451, 1416, 1382, 1320, 1277, 1251 cm^{-1}.

HRMS: calcd for $C_{13}H_{17}O_4$ (M^+ + H) = 237.1126, found: 237.1116 (Δ = – 4.2 ppm).

Acknowledgements

The authors thank the *Deutsche Forschungsgemeinschaft* for financial support of this work (grant BR 881-8/1) and Ms L. Loots (SU) for updating of cystal cif files and modification of ORTEP plots.

Keywords: isomerization • ring-closing metathesis • oxidations • oxygen • non-benzenoid aromatics • tropolone

1 a) R. Brandes, *J. Prakt. Chem.* **1820**, *28*, 9-31.– b) R. Brandes, *Ann. Pharm.* **1832**, *1*, 68-87.

2 W. Schneider, *Arch. Pharm.* **1951**, *284*, 306-318.

3 A. Ladenburg, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2403-2406.

4 W. v. E. Doering, L. H. Knox, *J. Am. Chem. Soc.* **1954**, *76*, 3203-3206.

5 a) Doering's finding[4] that Merling's "bromotropylidene"[5b] equals the *salt* tropylium bromide let him explain[4] the stability of the latter by Hückel's half-forgotten rule.[5c]– b) G. Merling, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 3108-3126.– c) E. Hückel, *Z. Phys.* **1931**, *70*, 204-286.

6 H. J. Dauben Jr., H. J. Ringold, *J. Am. Chem. Soc.* **1951**, *73*, 876-876.

7 M. J. S. Dewar, *Nature* **1945**, *155*, 50-51.

8 For recent literature compilations, see the references cited in refs.[9,10].

9 D. Arican, R. Brückner, *Org. Lett.* **2013**, *15*, 2582-2585

10 D. Arican, S. Braukmüller, R. Brückner, *Chem. Eur. J.* **2017**, *23*, 4537-4541.

11 M. Güney, A. Dastan, M. Balci, *Helv. Chim. Acta* **2005**, *88*, 830-838.

12 The methylidenation **14**→**15** by the same ylid, prepared from the phosphonium salt and NaH in THF in situ, was described by S. J. Cho, N. H. Jensen, T. Kurome, S. Kadari, M. L. Manzano, J. E. Malberg, B. Caldarone, B. L. Roth, A. P. Kozikowski, *J. Med. Chem.* **2009**, *52*, 1885-1902 (90% ≤ yield ≤ 99%).

13 Related acylations: a) Of *ortho*-bromostyrene (**15**): M. C. de la Torre, A. M. Deometrio, E. A. Álvaro, I. García, M. A. Sierra, *Org. Lett.* **2006**, *8*, 593-594.– b) Of *meta*-bromo-α-methylstyrene: N. Fukushima, N. Ieda, K. Sasakura, T. Nagano, K. Hanaoka, T. Suzuki, N. Miyata, H. Nakagawa, *Chem. Commun.* **2014**, *50*, 587-589 (page S3 of Supporting Information).

14 R. Bénéteau, C. F. Despiau, J.-C. Rouaud, A. Boussonnière, V. Silvestre, J. Lebreton, F. Dénès, *Chem. Eur. J.* **2015**, *21*, 11378-11386 (page 7 of Supporting Information; 83% yield).

15 [1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-(phenylmethylene)(tricyclohexylphosphane)ruthenium: M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, 1, 953-956.

16 Name-giving findings: H. L. Riley, J. F. Morley, N. A. C. Friend, *J. Chem. Soc.* **1932**, 1875-1883.

17 Illustrative examples: a) E. J. Corey, J. P. Schaefer, *J. Am. Chem. Soc.* **1960**, *82*, 917-929.– b) I. Strakova, A. Strakovs, M. Petrova, *Chem. Heterocycl Compd*. **2005**, *41*, 1507-1510.– c) G. K. Pathe, N. Ahmed, *RSC Adv.* **2015**, *5*, 59114-59119.– d) X. Li, D. Xue, C. Wang, S. Gao, *Angew. Chem.* **2016**, *128*, 10096-10100; *Angew. Chem. Int. Ed.* **2016**, *55*, 9942-9946.

18 We assigned a *trans*-orientation to the C^8–O vs. C^9–Se bonds in the tricycles **19**-**22** because we assigned a *trans*-orientation to the 8–H vs. 9–H bonds. We did the latter considering that the resonances of 8–H and 9–H in the alcohol **19** displayed no cross-peak in the NOESY spectrum (500.32 MHz, $CDCl_3$); moreover, the coupling constant $^3J_{8–H,9–H}$ was the same – ca. 5 Hz – in this alcohol *and* its esters **20**-**22**.

19 J. C. Anderson, S. C. Smith, *Synlett* **1990**, 107-108.

20 a) F. A. Davis, R. Jenkins, Jr., S. G. Yocklovich, *Tetrahedron Lett.* **1978**, *19*, 5171-5174.– b) F. A. Davis, L. C. Vishwakarma, J. G. Billmers, J. Finn, *J. Org. Chem.* **1984**, *49*, 3241-3243.

This article is protected by copyright. All rights reserved.

Accepted Manuscript

21 C. W. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923-2925.

22 Triplet oxygen oxidizes certain α,α-unsubstituted cycloalkanones to *vic*-diketones at room temp. in the presence of stoichiometric amounts of KOtBu dissolved in tBuOH, as two groups described from 1960: a) D. Arigoni, D. H. R. Barton, E. J. Corey, O. Jeger, L. Caglioti, S. Dev, P. G. Ferrini, E. R. Glazier, A. Melera, S. K. Pradhan, K. Schaffner, S. Sternhell, J. F. Templeton, S. Tobinaga, *Experientia* **1960**, *16*, 41-49 [limonin and two related di-fused cyclohexanones "dissolved in tBuOH containing KOtBu [were] rapidly autoxidised with uptake of one mole of oxygen" and gave the (enol tautomers of the) di-fused cyclohexane-1,2-diones (yields not specified)].– b) J. B. Davis, B. C. L. Weedon, *Proc. Chem. Soc.* **1960**, 182-183 [under the conditions of ref.[22a] the bis(cyclohex-2-en-1-one) canthaxanthin gave ca. 40% astacene, which is the [bis(enol tautomer) of the corresponding bis(cyclohex-3-en-1,2-dione)].– c) Full paper to ref.[22a]: D. H. R. Barton, S. K. Pradhan, S. Sternhell, J. F. Templeton, *J. Chem. Soc.* **1961**, 255-275 (the two autoxidations described succeeded with 94% and 60% yield).– d) E. J. Bailey, D. H. R. Barton, J. Elks, J. F. Templeton, *J. Chem. Soc.* **1962**, 1578-1591 [the steroid cyclohexanones cholestanone, lanosterone, and hecogenin provided the enol(s) of the corresponding cyclohexane-1,2-diones in yields of ~90%, 48%, and ≥15%, respectively].– e) Ref.[22a-d] concerned cyclohexanone→cyclohexanedione oxidations, exclusively. This chemoselectivity is not self-evident because D. V. Rao, F. A. Stuber, H. Ulrich, *J. Org. Chem.* **1979**, *44*, 456-458 showed when oxidizing at –20°C in DME/tBuOH: Unsubstituted cyclohexanone gave 60% cyclohexane-1,2-dione and 10% adipic acid; unsubstituted cycloheptanone delivered the aldol adduct of non-oxidized substrate to cycloheptane-1,2-dione (and a furan in the sequel); cyclooctanone gave the hemiacetal of the aldol adduct of cyclooctane-1,2-dione (and a spirobutenolide thereafter).

23 Triplet oxygen oxidizes ketones to α-hydroxyketones under conditions related to the further-going oxidations of ref.[22a-d]: a) J. N. Gardner, F. E. Carlon, O. Gnoj, *J. Org. Chem.* **1968**, *33*, 3294-3297 [NaOtBu, $P(OEt)_3$ (stoichiom.), DMF, –25°C]; the phosphite was shown to reduce the initially formed α-hydroperoxyketone. Variants of this oxidation employ $P(OEt)_3$ as well (e. g. ref.[23b,c]) or not (e. g. ref.[23d]).– b) E. g. Y.-F. Liang, N. Jiao, *Angew. Chem.* **2014**, *126*, 558-562; *Angew. Chem. Int. Ed.* **2014**, *53*, 548-552 [Cs_2CO_3 (cat.), $P(OEt)_3$ (2.0 equiv.), DMSO, room temp.].– c) E. g. S.-B. D. Sim, M. Wang, Y. Zhao, *ACS Catal*. **2015**, *5*, 3609-3612 [phase transfer catalyst, $P(OEt)_3$ (stoichiom.), 50% NaOH, toluene].– d) M. B. Chaudhari, Y. Sutar, S. Malpathak, A. Hazra, B. Ganaprakasam, *Org. Lett.* **2017**, *19*, 3628-3631 [air instead of molecular oxygen, KOtBu (stoichiom.) or LiOtBu (stoichiom.), DMSO, room temp. ; the authors sugest that the initially formed α-hydroperoxyketone and non-oxidized enolate "comproportionate" for forming the ultimately obtained α-hydroxyketone].

24 Mp. 79-81°C (ref.[11]: mp. 81°C).

25 P. K. Pramanick, Z.-L. Hou, B. Yao, *Tetrahedron* **2017**, *73*, 7105-7114

26 a) Original report for couplings of alkenyldialkylboranes giving 1,3-dienes and 1-en-3-ynes: N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20,* 3437-3440.– b) Original report for couplings of alkenyldialkylboranes giving styrenes: N. Miyaura, A. Suzuki, *J. Chem. Soc., Chem. Commun.* **1979**, 866-867 (5. Juni 1979).– c) Pertinent review: N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457-2483.

27 a) Short communication about Suzuki couplings of potassium vinyltrifluoroborate with aryldiazonium salts: S. Darses, G. Michaud, J.-P. Genêt, *Tetrahedron Lett*. **1998**, *39*, 5045-5048.– b) Full paper: S. Darses, G. Michaud, J.-P. Genêt, *Eur. J. Org. Chem.* **1999**, 1875-1883.– c) Short communication about Suzuki couplings of potassium alkenyltrifluoroborates with aryl halides, aryl triflates, and *trans*-2-bromostyrene: G. A. Molander, M. R. Rivero, "Suzuki Cross-Coupling Reactions of Potassium Alkenyltrifluoroborates", *Org. Lett.* **2002**, *4*, 107-109.– d) Full paper: G. A. Molander, C. R. Bernardi, *J. Org. Chem.* **2002**, *67*, 8424-8429.– e) Pertinent review: G. A. Molander, B. Canturk, *Angew. Chem.* **2009**, *121*, 9404-9425; *Angew. Chem. Int. Ed.* **2009**, 48, 9240-9261.

28 a) First synthesis (from a vinylboronic ester[29]), first Suzuki coupling with an aryldiazonium salt, and first Suzuki couplings of potassium aryltrifluoroborates with aryldiazonium salts: S. Darses, J.-P. Genêt, J.-L. Brayer, J.-P. Demoute, *Tetrahedron Lett.* **1997**, *38*, 4393-4396 (footnote 7).– b) Review: G. A. Molander, D. J. Cooper, *e-EROS (Encyclopedia of Reagents for Organic Synthesis)*, **2006**, 1-6.

29 Preceding syntheses of potassium aryltetrafluoroborates (from arylboronic acids): E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin, M. R. Schrimpf, *J. Org. Chem.* **1995**, *60*, 3020-3027.

30 Method: E.-i. Negishi, M. J. Idacavage, F. DiPasquale, A. Silveira, Jr., *Tetrahedron Lett.* **1979**, 845-848.

31 W.-R. Yang, Y.-S. Choi, J.-H. Jeong, *Org. Biomol. Chem.* **2017**, *15*, 3074-3083.

32 a) Original report: H. Tokuyama, S. Yokoshima, T. Yamashita, T. Fukuyama, *Tetrahedron Lett.* **1998**, *39*, 3189-3192.– b) Pertinent review: T. Fukuyama, H. Tokuyama, *Aldrichim. Acta* **2004**, *37*, 87-96..

33 M. A. Schmidt, E. M. Simmons, C. S. Wei, H. Park, M. D. Eastgate, *J. Org. Chem.* **2018**, *83*, 3928-3940.

34 S. Dhanasekaran, V. Bisai, R. A. Unhale, A. Suneja, V. K. Singh, *Org. Lett.* **2014**, *16*, 6068-6081 (page 6 of SI).

35 E. J. Corey, W. Suggs, *Tetrahedron Lett.* **1975**, *16*, 2647-2650.

36 Method: D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.

37 Accelerating effect of water in Dess-Martin periodinane[36] oxidations: S. D. Meyer, S. L. Schreiber, *J. Org. Chem.* **1994**, *59*, 7549-7552.

38 J. W. Cook, A. R. Somerville, *Nature* **1949**, *163*, 410-410.

39 Review: G. B. Gill, "Benzil-Benzilic Acid Rearrangements" in: *Carbon-Carbon σ-Bond Formation* (G. Pattenden, Ed.), *Comprehensive Organic Synthesis* (B. M. Trost, I. Fleming, Eds.), Pergamon Press, Oxford, New York, Seoul, Tokyo, **1991**, Vol. 3, 821-839.

40 Tropolone and strong alkali undergo a similar rearrangement giving benzoic acid (no yield was given): W. v. E. Doering, D. B. Denney, *J. Am. Chem. Soc.* **1955**, *77*, 4619-4622.

41 The oxidation products were one benzotropylidene (0.5%), two benzotropones (13%, 3%), 1-naphthaldehyde (2%), 1-naphthoic acid (5%), 2-naphthaldehyde (3%), 2-naphthoic acid (13%), and naphthalene (0.9%) but no benzotropolone: M. Pomerantz, G.-S. Swei, *Tetrahedron Lett.* **1982,** *23,* 3027-3030.

42 Autoxidation followed by an aniline-induced variant of the benzilic acid rearrangement delivered a benzilic acid anilide which then fragmented: X. Wang, R.-X. Chen, Z.-F. Wei, C.n-Y. Zhang, H.-Y. Tu, A.-D. Zhang, *J. Org. Chem.* **2016**, *81*, 238-249 (Scheme 5).

43 Calculational study of this mechanism for a protic environment: S. Yamabe, N. Tsuchida, S. Yamazaki, *J. Org. Chem.* **2006**, *71*, 1777-1783.

44 The benzilic acid rearrangement or its alkoxide-induced variant of two 1-aryl-2-benzylethane-1,2-diones entails the 1,2-shift of the benzyl, not of the aryl substituent. This was shown by ^{14}C- and ^{13}C-labelling experiments, respectively: a) C. J. Collins, O. K. Neville, *J. Am. Chem. Soc.* **1951**, *73*, 2471-2473.– b) C. S. Marques, N. M. M. Moura, A. J. Burke, O. R. Furtado, *Tetrahedron Lett.* **2007**, *48*, 7957-7960.

45 Method: K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651-1660.

46 For proceeding from the acid **66** via its methyl ester **67** to the aldehydoester **68** (Scheme 11), we applied protocols for converting the acid *homo*-**66** into the methyl ester *homo*-**67** and for formylating the latter to give the aldehydoester *homo*-**68**; these compounds differed from **66**, **67**, and **68** by containing $–CH_2–CH_2–C=O$ instead of $–CH_2–C=O$ moieties. a) Short communication: F.-D. Boyer, I. Hanna, Org. Lett. **2007**, *9*, 715-718.– b) Full paper: F.-D. Boyer, I. Hanna, *Eur. J. Org. Chem*. **2008**, *73*, 4938-4948.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

47 Method: A. Rieche, H. Gross, E. Höft, *Chem. Ber.* **1960**, *93*, 88-94.

48 The paper F.-D. Boyer, X. Le Goff, I. Hanna, *J. Org. Chem*. **2008**, *73*, 5163-5166 describes using, in addition to the aldehydoester *homo*-**68**,[46] the aldehydoester **46** itself. The only specification of. ref.[48] about the origin of compound **46** is referring to ref.[46]; there, however, there is no mentioning of compound **46**.

49 The crystallographic data of RCM-product **11d** are contained in CCDC 862376. They can be obtained free of charge from the *Cambridge Crystallographic Data Centre* via the link www.ccdc.cam.ac.uk/data_request/cif.

50 The crystallographic data of RCM-product *iso*-**11d** are contained in CCDC 862377. They can be obtained free of charge from the *Cambridge Crystallographic Data Centre* via the link www.ccdc.cam.ac.uk/data_request/cif.

51 In the solid state,[49] the absolute value of the dihedral angle between the C^7=C^8 bond and the C^5=C^6 bond of the benzene ring, both of compound **11d**, is 11.9°.

52 In the solid state,[50] the absolute value of the dihedral angle between the C^9=C^{10} bond and the C^{11}=O^4 bond, both of compound *iso*-**11d**, is 157.2°.

53 Ring-closing metatheses or cross-metatheses *followed* by C=C bond migration are covered on pp. 3842-3848 and 3850-3851, respectively, of the following review, while C=C bond migrations *preceding* ring-closing metatheses or cross-metatheses are covered on pp. 3848-3850 and 3851-3851, respectively: B. Alcaide, P. Almendros, A. Luna, *Chem. Rev*. **2009**, *109*, 3817-3858.

54 The first examples of C=C bond migrations preceding Ru-catalyzed cross-metatheses, of which we are aware, were by B. Marciniec, Z. Foltynowicz, M. Lewandowski, *J. Mol. Catal*. **1994**, *90*, 125-133.

55 a) The first observation of a (partial) C=C bond migration preceding a Ru-catalyzed ring-closing metathesis, of which we are aware, was by A. Fürstner, O. R. Thiel, L. Ackermann, H.-J. Schanz, S. P. Nolan, *J. Org. Chem.* **2000**, *65*, 2204-2207. The first C=C bond migrations (going to completion) after Ru-catalyzed ring-closing metatheses, were due to Snapper *et al*.[55b] and Schmidt.[55c]– b) A. E. Sutton, B. A. Seigal, D. F. Finnegan, M. L. Snapper, *J. Am. Chem. Soc.* **2002**, *124*, 13390-13391.– c) B. Schmidt, *Eur J. Org. Chem.* **2003**, 816-819.– d) The C=C bond migrations, which followed the metatheses of refs.[55b,c] in situ, were of a type previously studied in non-metathesis substrates by C. Cadot, P. I. Dalko, J. Cossy, *Tetrahedron Lett.* **2002**, *43*, 1839-1841; corrigendum: *Tetrahedron Lett.* **2002**, *43*, 5205-5205.

56 The first examples of C=C bond migrations preceding Mo-catalyzed cross-metatheses, of which we are aware, were by E. Thorn-Csányi, J. Dehmel, H.-D. Luginsland, J. U. Zilles, *J. Mol. Catal. A: Chemical* **1997**, *115*, 29-35.

57 The first (complete) C=C bond migration preceding a Mo-catalyzed ring-closing metathesis, of which we are aware, was by D. Joe, L. E. Overman, *Tetrahedron Lett.* **1997**, *38*, 8635-8638.

58 Earlier examples from our laboratories in which an initially unexpected RCM/isomerization tandem was synthetically useful, see: (a) E. M. Coyanis, J.-L. Panayides, M. A. Fernandes, C. B. de Koning, W. A. L. van Otterlo, *J. Organometallic Chem.*, **2006**, *691*, 5222-5239. (b) W. A. L. van Otterlo, E. M. Coyanis, J.-L. Panayides, C. B. de Koning, M. A. Fernandes, *Synlett*, **2005**, 501-505.

59 M.-L. Bennasar, E. Zulaica, S. Tummers, *Tetrahedron Lett.* **2004**, *45*, 6283-6285.

60 Á. Mallagaray, G. Domínguez, A. Gradillas, J. Pérez-Castells, *Org. Lett.* **2008**, *10*, 597-600.

61 M.-L. Bennasar, E. Zulaica, D. Solé, S. Alonso, *Tetrahedron* **2007**, *63*, 861-865.

62 M.-L. Bennasar, E. Zulaica, D. Solé, T. Roca, D. García-Díaz, S. Alonso, *J. Org. Chem*. **2009**, *74*, 8359-8368.

63 A m.p. of 91-92°C was reported for the benzotropolone **5c** by D. Caunt, W. D. Crow, R. D. Haworth, *J. Chem. Soc.* **1951**, 1313-1318.

64 R. D. Haworth, B. P. Moore, P. L. Pauson, *J. Chem. Soc.* **1949**, 3271-3278.

Accepted Manuscript

This article is protected by copyright. All rights reserved.