Accepted Manuscript

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PII: S0040-4020(19)30508-3

DOI: https://doi.org/10.1016/j.tet.2019.05.001

Reference: TET 30322

To appear in: *Tetrahedron*

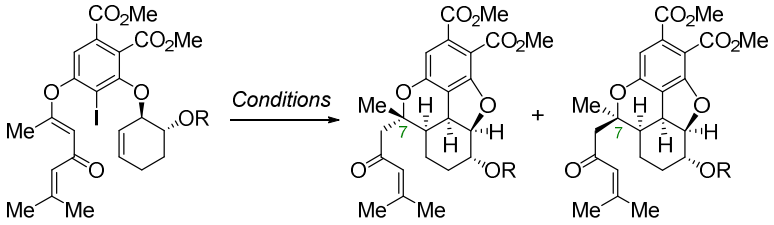
Received Date: 26 March 2019

Revised Date: 29 April 2019

Accepted Date: 1 May 2019

Please cite this article as: am Ende CW, Parker KA, Development of a 5-exo, 6-exo tandem radical cyclization to access bisabosqual A, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.05.001.

Graphical Abstract



Development of a 5-exo, 6-exo tandem radical cyclization to access bisabosqual A

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Abstract:

Substrates were designed to undergo tandem radical cyclizations to afford the *cis*, *cis*-fused hexahydrobenzofurobenzopyran ring system of the bisabosquals. Studies with these revealed that different initiating systems gave different yields and somewhat different diastereomeric ratios. A photocatalytic cyclization was also successful with the bisabosqual substrate.

Keywords. tandem • radical • cyclization • cascade • photoredox • cis fused ring system

Dedicated to Professor Stephen L. Buchwald in tribute to his many clever and practical contributions to synthetic organic chemistry

1. Introduction

Radical cyclization is an effective approach to the construction of *cis*-fused ring systems. The penchant for *cis*-selectivity is a result of geometric constraint and it has been exploited in the construction of *cis*-fused 5,5-,[1] 6,5-[2] and 6,6-[3] ring systems. The utility of this preference was powerfully demonstrated early on by Curran and coworkers who prepared both linear and angular triquinanes by exploiting tandem 5-exo, 5-exo cyclizations.[4]

A 5-exo, 6-exo tandem radical cyclization which affords the *cis, cis*-fused hexahydrobenzofurobenzopyran ring system served as the key step in our total synthesis of (±)-bisabosqual A (**1,** Figure 1).[5] Our cyclization substrate **2** was designed with ester groups as functional equivalents of the required aldehydes. Also, we selected the β-aryloxy α,α'–dienone moiety as the radical trapping sidechain; the vinylogous ester moiety can be introduced cleanly, it is relatively stable, and it was expected to favor the 6-exo closure. While we were confident that the ring junctures at 4,5 and 5,6 in the cyclization product would be *cis*, the stereochemistry to be produced at C-7 was not predictable.

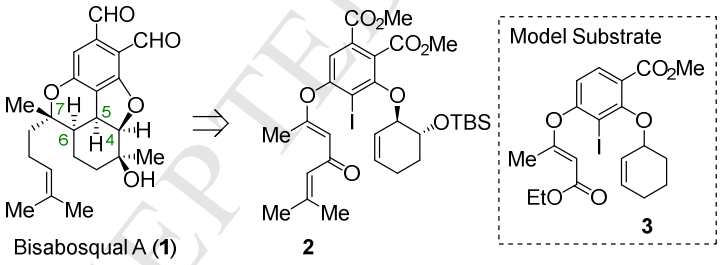


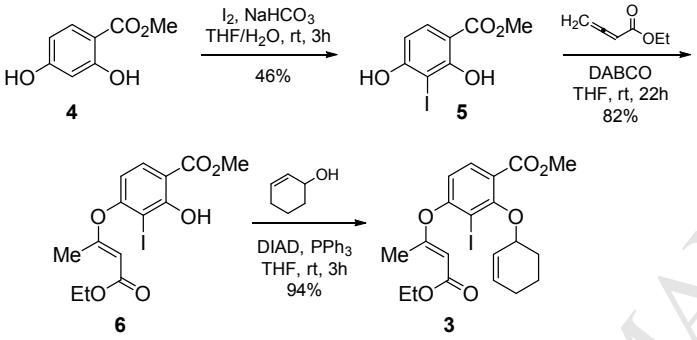
Figure 1. Bisabosqual A and radical cyclization substrates explored.

In order to test the behavior of a vinylogous ester sidechain in the system of interest, we prepared model substrate **3** and examined its behavior in a tandem ring closure. Here we describe the results of those studies and their extension to the cyclization of substrate **2**.

2. Results and Discussion

2.1 Synthesis and Cyclization of Model Substrate 3

The model cyclization substrate **3** was readily assembled in three steps as shown in Scheme 1. Iodination of commercially available ester **4** by the procedure of Kim and coworkers[6] afforded the tetrasubstituted resorcinol **5**. Subsequent DABCO-catalyzed 1,4-addition of compound **5** to ethyl allenecarboxylate proceeded regioselectively to install the vinylogous carbonate side chain.[7] A Mitusunobu reaction completed the sequence, providing cyclization substrate **3** (Scheme 1).



Scheme 1. Assembly of radical cyclization substrate **3**.

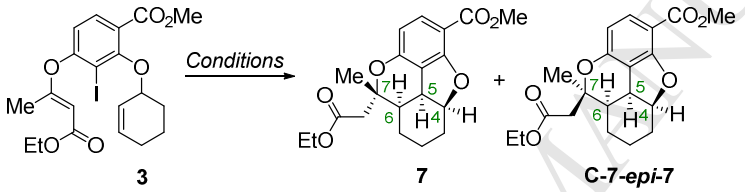
In a preliminary experiment, compound **3** underwent the desired 5-exo, 6-exo radical cyclization upon exposure to *n*-tributyltin hydride and azobisisobutyronitrile (AIBN) at elevated temperature (Table 1, Entry 1). The reaction proceeded with complete selectivity at the C-5 and C-6 carbons (numbering system to correspond to bisabosqual numbering) to produce the *cis, cis*-fused ring system while affording modest selectivity (dr = 3:2, **7**:**C-7-*epi*-7**) at the C-7 quaternary center. The identity of each diastereomer was established by NOE and confirmed by an X-ray crystal structure of the minor isomer (Figure 2 and Supporting Information).

Thus, we were able to access the bisabosqual hexahydrobenzofurobenzopyran ring system via a tandem radical cyclization; however, the yield was low (35%). Furthermore, the use of toxic tin reagents is undesirable. Therefore, we screened alternative conditions for this step. We varied the initiator, the solvent, and the temperature and examined the ^{1}H NMR

spectrum of the crude material obtained in each case. Experiments that gave what appeared to be the most promising product mixtures were scaled up for purification.

Tris(trimethylsilyl)silane, which has relatively low toxicity, has emerged as an alternative to *n*-tributyltin hydride.[8] The stronger bond dissociation (5 kcal/mol) of the Si-H as compared to the Sn-H has been exploited in radical cyclization reactions to reduce the amounts of premature reduction products.[8] When subjected to $(TMS)_3SiH$ and AIBN in toluene at 60, 80 and 120 °C (Table 1, Entries 2-4), substrate **3** afforded the bisabosqual tetracyclic core (**7** + **C-7-*epi*-7**) with no change in diastereoselectivity but with a slight improvement in yield at 80 °C.

Table 1. Radical Cyclizations of Model Substrate **3**.



Entry	Reducing Agent	Initiator	Solvent	Temperature	Time	Yield[a]
1[b]	nBu$_3$SnH	AIBN	Benzene	100 °C	48 h	35%
2[c]	$(TMS)_3SiH$	AIBN	Toluene	60 °C	20 h	37%
3[c]	$(TMS)_3SiH$	AIBN	Toluene	80 °C	20 h	45%
4[c]	$(TMS)_3SiH$	AIBN	Toluene	120 °C	4 h	25%
5[d]	$(TMS)_3SiH$	Et_3B	EtOH	rt	30 m	52%
6[e]	$(TMS)_3SiH$	Et_3B	CH_2Cl_2	rt	30 m	61%
7[f]	$(TMS)_3SiH$	sBu$_3$B	2-MeTHF	rt	30 m	49%

[a]diastereoselecivity = 3:2 (**7:C-7-epi-7**) in all entries. Reaction conditions: [b]nBu$_3$SnH (3 equiv), AIBN (0.2 equiv), conc. 0.025 M, [c]$(TMS)_3SiH$ (2 equiv), AIBN (0.1 equiv), conc. 0.025 M, [d]$(TMS)_3SiH$ (1.2 equiv), Et_3B (5 equiv), conc. 0.025 M, [e]$(TMS)_3SiH$ (1.2 equiv), Et_3B (2 equiv), conc. 0.025 M, [f]$(TMS)_3SiH$ (1.2 equiv), Et_3B (5 equiv), conc. 0.025 M.

The triethylborane/O_2 radical initiating system is noteworthy because it is operative at low temperatures.[9] Again, we tested the approach with a variety of conditions in small scale

reactions and scaled up those with the most promising NMR spectra of crude materials. Indeed, treatment of substrate **3** with the $(TMS)_3SiH$ /Et_3B/O_2 radical reducing system at room temperature resulted in increased yields, shorter reaction times, and milder reaction conditions (Table 1, Entries 5 and 6). While solvent did not seem to play a significant role, dichloromethane provided a slightly higher yield and overall cleaner conversion relative to other solvents explored. Attempts to alter the diastereoselectivity by adding Lewis acids or by decreasing the temperature typically resulted in lower yields with no noticeable effect on C-7 diastereoselectivity (not shown).

In this model cyclization, we also examined sBu_3B/O_2 as the initiating reagent combination. Scaleup of the reaction in 2-methyltetrahydrofuran gave results comparable to those obtained with the Et_3B/O_2 system (Table 1, Entry 7).

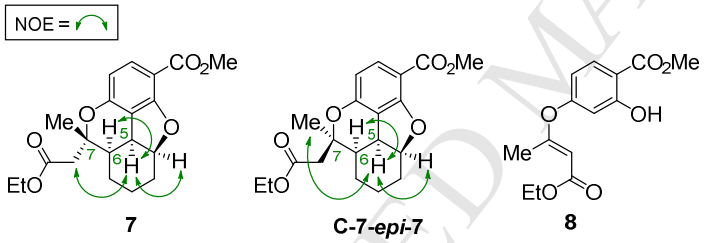
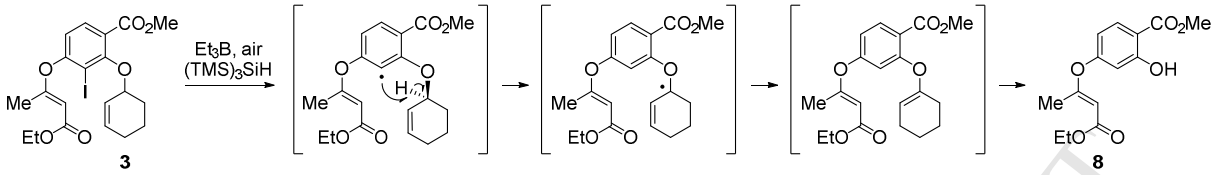


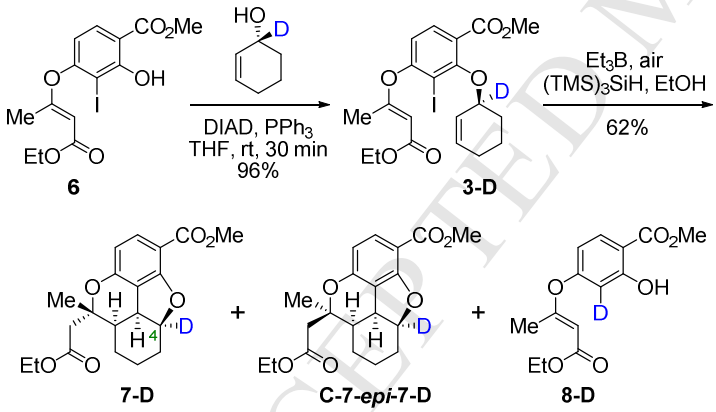
Figure 2. Identification of isomers obtained in the radical cyclization of model system **3** by nuclear Overhauser effects and structure of phenol side product **8**.

A common side product in the radical cyclization of substrate **3** was phenol **8** (Figure 2). We speculated that this side product was a result of a 1,4-hydrogen migration process in which the aryl radical abstracts the allylic hydrogen adjacent to the ether bond (Scheme 2). Typically, there is a strong preference for 1,5-hydrogen atom transfers;[10] however, 1,4-hydrogen abstraction is viable if geometric and steric constraints allow proper orientation to be achieved.[11] In this case, the resulting radical would be stabilized by both the oxygen and the double bond. Quenching of this radical would give an enol ether, expected to hydrolyze in the workup, releasing the phenol (Scheme 2).



Scheme 2. Postulated Mechanism for Formation of Phenol **8**.

To test this premise, we examined the deuterium-labeled substrate **3-D** (see Scheme 3). 1-*d*-Cyclohex-2-ene-1-ol, prepared by Baldwin's procedure,[12] had greater than 90% deuterium incorporation at the desired position as determined by ^{1}H NMR. A subsequent Mitsunobu reaction with phenol **6** generated the deuterium labeled cyclization substrate **3-D**. Subjecting compound **3-D** to the $(TMS)_3SiH/Et_3B/O_2$ radical reducing system afforded the expected deuterium labeled cyclization products in 62% yield; isolated **7-D** appeared to be >90% deuterated at the position numbered 4.



Scheme 3. Deuterated products from substrate **3-D**

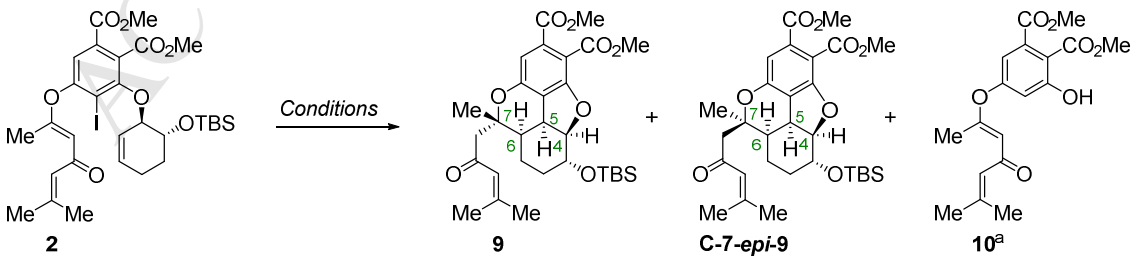
In addition, a 20% yield of the deuterium-labeled phenol **8-D** was obtained. However, the C-3 position of the aromatic ring was only 65% labeled; thus it appears that there must be at least one additional pathway that leads to the reduced and dealkylated phenol structure. In fact, a competing 1,5-hydrogen migration in the aryl radical followed by a fragmentation would give unlabeled **8**.

2.2 Cyclization of Bisabosqual Precursor 2

When applied to the fully elaborated substrate **2**, tandem radical cyclization was generally the major pathway (Table 2). With the $(TMS)_3SiH$/AIBN system (Entry 1), a 51% yield of a 3:2 mixture of tetracyclic diastereomers **9** and **C-7-*epi*-9** was obtained. The $(TMS)_3SiH$ / triethylborane system gave somewhat lower yields and, in methylene chloride (Entry 2), the desired epimer **9** was slightly disfavored. However, when dichloromethane was replaced with a potentially coordinating solvent (acetonitrile), the selectivity at the C-7 center was restored to favor the desired epimer **9** (Table 2, Entry 3).

Postulating that the Lewis acidic triethylborane could be playing a role beyond acting as a radical initiator in the reaction, we next explored the effect of a bulkier trialkylborane as the radical initiator. Replacing triethylborane with *sec*-butylborane had an impressive effect on the reaction, increasing the yield of tetracycle to 72% (Table 2, Entry 4). To our knowledge, this is the first example of the $(TMS)_3SiH/sBu_3B/O_2$ system in radical initiation / reduction. Additional experiments in which the solvent was varied or in which the reaction was performed at elevated temperatures resulted in minor decreases in yield (Table 2, Entries 5-7). However, when the reaction was cooled to -40 °C, a modest improvement in the diastereoselectivity at the C-7 quaternary carbon was observed (dr =5:2, **9**:**C-7-*epi*-9**); unfortunately, this was accompanied by a reduction in yield (Table 2, Entry 8).

Table 2. Tandem radical cyclization of substrate **2**.

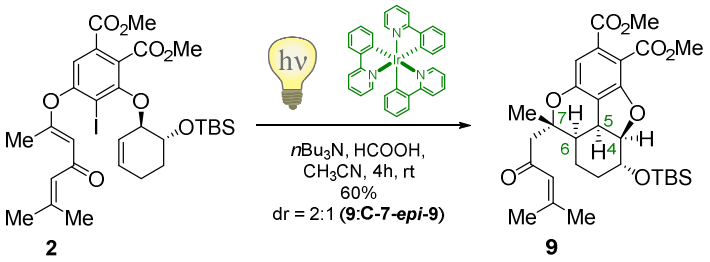


Entry	Reducing Agent	Initiator	Solvent	Temperature	Time	Yield[b]	dr[c]
1[d]	$(TMS)_3SiH$	AIBN	Toluene	70 °C	3 h	51%	3:2
2[e]	$(TMS)_3SiH$	Et_3B	CH_2Cl_2	rt	30 m	31%	2:3
3[e]	$(TMS)_3SiH$	Et_3B	CH_3CN	rt	30 m	39%	3:2
4[f]	$(TMS)_3SiH$	*s*Bu_3B	CH_2Cl_2	rt	30 m	72%	3:2
5[f]	$(TMS)_3SiH$	*s*Bu_3B	Toluene	rt	30 m	60%	3:2
6[f]	$(TMS)_3SiH$	*s*Bu_3B	CH_2Cl_2	40 °C	15 m	58%	3:2
7[f]	$(TMS)_3SiH$	*s*Bu_3B	2-MeTHF	50 °C	15 m	62%	3:2
8[g]	$(TMS)_3SiH$	*s*Bu_3B	CH_2Cl_2	-40 °C	4 h	46%	5:2

[a]Small amounts of the phenolic side product **10** were observed in all reactions (See Experimental Section), [b]Yield is reported as the mixture of diastereomers (**9** and **C-7-*epi*-9**), [c]dr = **9**:**C-7-*epi*-9**, Reaction conditions: [d]$(TMS)_3SiH$ (2 equiv), AIBN (0.1 equiv), conc. 0.025 M, [e]$(TMS)_3SiH$ (1.5 equiv), Et_3B (2 equiv), conc. 0.025 M, [f]$(TMS)_3SiH$ (1.5 equiv), *s*Bu_3B (1 equiv), conc. 0.015 M, [g]$(TMS)_3SiH$ (1.5 equiv), *s*Bu_3B (3 equiv), conc. 0.015 M.

We note that, although it would be beneficial if the cyclization afforded only the desired **9** and not **C-7-*epi*-9**, the formation of the pair does not necessarily result in a major loss of advanced material. As noted in our original report,[5] the epimeric product (**C-7-*epi*-9**) can be equilibrated to a diastereomeric mixture by a retro-Michael / Michael procedure.

Intrigued by the touted benefits of photoredox conversions, we noted Stephenson's photoredox-initiated reductive radical cyclizations of aryl iodides.[13] We subjected our bisabosqual substrate **2** to a slight variation of the recommended reaction conditions (visible light, *fac*-$Ir(ppy)_3$ [5 mol%], *n*Bu_3N, HCO_2H) and obtained 60% yield of a 2:1 mixture of tetracyclic **9** and **C-7-*epi*-9** (Scheme 4).



Scheme 4. Visible light initiated tandem radical cyclization.

The yield and diastereomeric ratio are roughly equivalent to those obtained with more classical approaches. Therefore, the potential advantages of the photoredox approach to this and related cyclizations lie in the benign nature of the reagents, convenience in handling, and opportunities for scaleup, particularly by means of flow systems.[14]

3. Conclusions

Tandem radical cyclization converts readily assembled substrates to tetracyclic hexahydrobenzofurobenzopyrans with ring junction stereochemistry established as completely *cis*, *cis*. The stereochemistry at the fourth new stereocenter is not controlled and is slightly variable. We also identified the origin of a by-product as a 1,4-hydrogen shift to the initially formed aryl radical. In addition, the cascade reaction was readily adapted to a photoredox procedure.

Acknowledgment.

This work was supported by the National Institutes of Health (GM 74776) and by Pfizer Inc. The authors thank Kathleen A. Farley for NMR support, Brian M. Samas and Ivan Samardjiev for X-ray crystal structures, James Bradow for separations, and Martin Pettersson, John M. Humphrey, Christopher J. Helal, Patrick B. Mullins, Thayalan Navaratnam, Michael E. Green, Todd W. Butler, Matthew E. Calder, Anabella Villalobos and Christopher J. O'Donnell for insightful discussions and support.

Notes

[†]Present address: Pfizer Worldwide Research and Development, Eastern Point Road, Groton, Connecticut 06340, United States. The authors declare the following competing financial interest: C.W.A is an employee of Pfizer Inc.

Experimental

General Considerations: Unless otherwise stated, all air and moisture-sensitive reactions were performed in oven-dried glassware under nitrogen and all commercially available chemicals, reagents and solvents were used as received. Triethylborane and tri-*sec*-butylborane were purchased from Sigma-Aldrich as solutions in THF or hexanes. Compounds **2, 9** and **C-7-*epi*-9** were synthesized and characterized previously (see *J. Am. Chem. Soc.* **2013**, 135, 582-585). Reactions were monitored by thin layer chromatography (TLC) performed on Analtech, Inc. silica gel GF 250 μm plates and were visualized with ultraviolet (UV) light (254 nm) and/or $KMnO_4$ staining or by UPLC-MS (Waters Acquity, ESCI (ESI +/-, APCI +/-)). Gas chromatography – mass spectrometry (GC-MS) was performed with an Agilent 5890 GC Oven and an Agilent 5973 Mass Selective Detector. Silica gel flash chromatography was performed with RediSep®Rf normal phase silica flash columns on a CombiFlash Rf system from Teledyne Isco, Inc. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Varian-Inova 400 (400 MHz and 101 MHz, respectively), a Bruker 400 (400 MHz and 101 MHz, respectively), or a Bruker 500 (500 MHz and 126 MHz, respectively) spectrometer. Chemical shifts are reported in ppm relative to $CHCl_3$ (^{1}H, δ = 7.26 and ^{13}C NMR δ = 77.0). The multiplicities are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; spt, septet; m, multiplet; br s, broad singlet. Melting points are uncorrected. Infrared (IR) spectra were recorded with a Thermo-Nicolet Avatar 360 FT-IR. High-resolution mass spectra (HRMS) were acquired on an Agilent model 6220 MS(TOF).

Methyl 2,4-dihydroxy-3-iodobenzoate (5): To a solution of resorcinol **4** (20.0 g, 0.119 mol) in THF (150 mL) and water (150 mL) at 0 °C was added I_2 (30.2 g, 0.119 mol, 1 equiv.) in one

portion followed by $NaHCO_3$ (11.0g, 0.131 mol, 1.1 equiv.) portionwise over a period of 30 minutes. The mixture was allowed to warm to room temperature and stirred at this temperature for 3 hours. The mixture was extracted with Et_2O (2x). The combined organic solution was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by recrystallization from EtOAc/Heptane to afford **5** (16.1 g, 46% yield) as a light pink crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.93 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 5.92 (br. s., 1H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 162.0, 161.0, 131.5, 106.9, 105.7, 76.6, 52.5. FTIR (cm^{-1}) = 3285, 1635, 1434, 1412, 1271, 1017. mp = 141 – 143 °C. HRMS (ESI) calculated for $C_8H_8IO_4$ $[M+H]^+$ 294.9462, found 294.9458.

(*E*)-Methyl 4-(4-ethoxy-4-oxobut-2-en-2-yloxy)-2-hydroxy-3-iodobenzoate (6): To a solution of **5** (2.6 g, 8.8 mmol) in THF (90 mL) were added 4 Å molecular sieves (500 mg) and DABCO (200 mg, 1.8 mmol, 0.2 equiv.) followed by ethyl buta-2,3-dienoate (1.0 g, 8.8 mmol, 1 equiv.) in one portion. The mixture was stirred at room temperature for 22 hours. The mixture was poured into water and the resulting solution was extracted with Et_2O (2x). The combined organic solution was washed with brine (1x), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **6** (2.95 g, 82% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.89 (br. s., 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 6.63 (d, *J* = 8.6 Hz, 1H), 4.82 (s, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.98 (s, 3H), 2.53 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.6, 166.9, 162.8, 159.4, 131.3, 113.4, 109.8, 97.7, 82.2, 59.8, 52.9, 18.1, 14.2. FTIR (cm^{-1}) = 2981, 1712, 1675, 1640, 1437, 1319, 1256, 1204, 1126, 1035. mp = 95 – 96 °C. HRMS (ESI) calculated for $C_{14}H_{16}IO_6$ $[M+H]^+$ 406.9986, found 406.9984.

(*E*)-Methyl 2-(cyclohex-2-enyloxy)-4-(4-ethoxy-4-oxobut-2-en-2-yloxy)-3-iodobenzoate (3): To a solution of compound **6** (1.50 g, 3.69 mmol), 2-cyclohexen-1-ol (0.435 g, 4.43 mmol, 1.2 equiv.) and PPh_3 (1.55 g, 5.90 mmol, 1.6 equiv.) in THF (40 mL) at room temperature was added DIAD (1.19 g, 5.90 mmol, 1.6 equiv.) dropwise over a period of five minutes. After stirring an

additional 19 hours, the reaction mixture was concentrated under reduced pressure. Et_2O was added and the resulting mixture was washed with 0.5 N HCl (1x), saturated $NaHCO_3$ (1x) and brine (1x). The organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was subjected to silica gel flash chromatography (EtOAc/Heptane) to afford **3** (1.67 g, 95% yield) of a white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.00 - 5.93 (m, 1H), 5.86 - 5.79 (m, 1H), 4.76 (s, 1H), 4.60 - 4.54 (m, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.90 (s, 3H), 2.53 (s, 3H), 2.23 - 2.10 (m, 1H), 2.10 - 1.93 (m, 3H), 1.83 - 1.72 (m, 1H), 1.66 - 1.54 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 166.9, 165.9, 159.2, 157.3, 132.9, 132.4, 125.8, 123.5, 117.2, 97.2, 92.6, 79.4, 59.6, 52.4, 28.7, 25.1, 18.7, 18.1, 14.2. FTIR (cm^{-1}) = 2946, 1713, 1640, 1581, 1393, 1281, 1243, 1212, 1127, 1039. mp = 84.5 – 85 °C. HRMS (ESI) calculated for $C_{20}H_{23}INaO_6$ $[M+Na]^+$ 509.0432, found 509.0432.

(±)-(2*S*,2a*R*,2a1*S*,5a*S*)-Methyl 2-(2-ethoxy-2-oxoethyl)-2-methyl-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-*cde*]chromene-7-carboxylate (7): Nitrogen was bubbled through a solution of **3** (102 mg, 0.210 mmol) in CH_2Cl_2 (8 mL) for 5 minutes, followed by addition of Et_3B (0.42 mL, 1M in hexanes, 0.42 mmol, 2 equiv.) and $(TMS)_3SiH$ (78 mg, 0.315 mmol, 1.5 equiv.). Next, air was added via syringe (10 mL) over a period of 15 minutes. The mixture was stirred an additional 30 minutes at room temperature and then concentrated under reduced pressure. The ^{1}H NMR spectrum of the crude material indicated a 3:2 mixture of diastereomers about C-7, favoring **7**. This was subjected to silica gel flash chromatography (EtOAc/Heptane) to afford **7** and **C-7-*epi*-7** (46 mg, 61% yield) as a 3:2 mixture of diastereomers. The isomers were combined with additional material from other cyclization experiments and separated by chiral HPLC (Phenomenex Luna (2) C18 150 x 21.2 mm 5µ, 5 to 95% 0.1% formic acid in water to 0.1% formic acid in methanol, flow = 28 mL/min) to yield separated **7** and **C-7-*epi*-7**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.8, 1.0 Hz, 1H), 6.34 (d, *J* = 8.6 Hz, 1H), 5.20 (dt, *J* = 9.1, 7.6 Hz, 1H), 4.17 - 4.08 (m, 2H), 3.84 (s, 3H), 3.60 (t, *J* = 7.0 Hz, 1H), 2.69 - 2.52 (m, 2H),

2.32 - 2.22 (m, 1H), 2.07 - 1.98 (m, 1H), 1.75 - 1.66 (m, 1H), 1.64 - 1.56 (m, 1H), 1.54 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.09 - 0.91 (m, 2H), 0.84 - 0.71 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 165.5, 160.8, 155.6, 132.0, 110.8, 108.0, 107.5, 87.8, 80.3, 60.6, 51.6, 43.0, 35.9, 33.8, 27.6, 23.4, 21.4, 20.6, 14.1. FTIR (cm^{-1}) = 2943, 1706, 1628, 1609, 1431, 1257, 1188. HRMS (ESI) calculated for $C_{20}H_{25}O_6$ $[M+H]^+$ 361.1645, found 361.1634

(±)-(2*R*,2a*R*,2a1*S*,5a*S*)-Methyl 2-(2-ethoxy-2-oxoethyl)-2-methyl-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-*cde*]chromene-7-carboxylate (C-7-*epi*-7): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.8, 1.0 Hz, 1H), 6.36 (d, *J* = 8.8 Hz, 1H), 5.22 (dt, *J* = 9.0, 7.6 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 3.56 (t, *J* = 7.0 Hz, 1H), 2.87 - 2.74 (m, 2H), 2.38 - 2.31 (m, 1H), 2.09 - 2.01 (m, 1H), 1.77 - 1.71 (m, 1H), 1.64 - 1.57 (m, 1H), 1.45 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.10 - 0.95 (m, 2H), 0.83 - 0.70 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 165.7, 160.7, 155.4, 131.9, 111.2, 108.2, 107.4, 87.8, 80.6, 60.7, 51.7, 42.9, 36.2, 33.5, 27.7, 23.9, 21.8, 20.7, 14.2. FTIR (cm^{-1}) = 2943, 1706, 1628, 1609, 1431, 1257, 1188. HRMS (ESI) calculated for $C_{20}H_{25}O_6$ $[M+H]^+$ 361.1645, found 361.1634. An X-ray structure of **C-7-*epi*-7** was obtained – see attached .cif file for details.

(*E*)-Methyl 4-(4-ethoxy-4-oxobut-2-en-2-yloxy)-2-hydroxybenzoate (8): An analytical sample of phenol **8** was obtained by combining material from several runs and subjecting it to a second flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.93 (s, 1H), 7.85 (d, *J* = 8.6 Hz, 1H), 6.63 (d, *J* = 2.1 Hz, 1H), 6.55 (dd, *J* = 8.7, 2.2 Hz, 1H), 5.04 (s, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 3.95 (s, 3H), 2.45 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 170.0, 167.2, 163.3, 159.4, 131.7, 112.5, 109.8, 109.7, 98.6, 59.7, 52.4, 18.1, 14.3

(±)-Methyl (*E*)-2-((cyclohex-2-en-1-yl-1-*d*)oxy)-4-((4-ethoxy-4-oxobut-2-en-2-yl)oxy)-3-iodobenzoate (3-D): To a solution of **6** (1.02 g, 2.51 mmol), 1-*d*-cyclohex-2-ene-1-ol (348 mg, 3.52 mmol, 1.4 equiv.) and PPh_3 (988 mg, 3.77 mmol, 1.5 equiv.) in THF (10 mL) at room temperature was added DIAD (761 mg, 3.77 mmol, 1.5 equiv.) dropwise over a period of two minutes. After stirring an additional 30 minutes, the reaction mixture was concentrated under

reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **3-D** (1.17 g, 96% yield) of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.6 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 5.97 (dt, *J* = 10.1, 3.5 Hz, 1H), 5.83 – 5.81 (m, 1H), 4.76 (s, 1H), 4.09 (q, *J* = 7.3 Hz, 2H), 3.90 (s, 3H), 2.53 (s, 3H), 2.21 - 2.11 (m, 1H), 2.08 - 1.94 (m, 3H), 1.81 - 1.73 (m, 1H), 1.66 - 1.58 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 167.3, 166.2, 159.5, 157.7, 133.3, 132.7, 126.0, 123.8, 117.5, 97.5, 92.9, 60.0, 52.7, 29.0, 28.9, 25.4, 19.0, 18.4, 14.5. FTIR (cm^{-1}) = 2945, 1712, 1639, 1580, 1432, 1389, 1281, 1242, 1212, 1126. HRMS (ESI) calculated for $C_{20}H_{23}DIO_6$ $[M+H]^+$ 488.0675, found 488.0678.

(±)-Methyl (3a*S*,3a1*S*,9*S*,9a*R*)-9-(2-ethoxy-2-oxoethyl)-9-methyl-2,3,3a,3a1,9,9a-hexahydro-1*H*-benzofuro[4,3,2-cde]chromene-5-carboxylate-3a-*d* (7-D): To a solution of **3-D** (134 mg, 0.275 mmol) and $(TMS)_3SiH$ (82 mg, 0.33 mmol, 1.2 equiv.) in EtOH (10 mL) at room temperature was simultaneously added Et_3B (0.50 mL, 1M in hexanes, 0.50 mmol, 2 equiv.) and air via a syringe (10 mL). The addition procedure took place over a period of 30 minutes. The mixture was stirred an additional 15 minutes at room temperature and then concentrated under reduced pressure. The crude ^{1}H NMR spectrum indicated a 3:2 mixture of diastereomers about C-7, favoring **7-D**. The crude residue was subjected to silica gel flash chromatography (EtOAc/Heptane) to afford a mixture (62 mg, 62% yield) of a 3:2 (**7-D**:**C-7-*epi*-7-D**) mixture of diastereomers as a colorless oil. An additional silica gel chromatography on the mixture of diastereomers (**7-D**:**C-7-*epi*-7-D**) resulted in an analytical sample of **7-D** for characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.7, 0.9 Hz, 1H), 6.37 (d, *J* = 8.6 Hz, 1H), 4.20 - 4.10 (m, 2H), 3.88 (s, 3H), 3.62 (d, *J* = 6.2 Hz, 1H), 2.73 - 2.57 (m, 2H), 2.34 - 2.25 (m, 1H), 2.08 - 2.01 (m, 1H), 1.78 - 1.69 (m, 1H), 1.66 - 1.60 (m, 1H), 1.57 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.11 - 0.94 (m, 2H), 0.89 - 0.75 (m, 1H). ^{13}C NMR: ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 165.7, 160.9, 155.7, 132.1, 110.9, 108.1, 107.6, 99.8, 80.4, 60.7, 51.7, 43.1, 36.0, 33.7, 27.6, 23.5, 21.5,

20.8, 14.2. FTIR (cm^{-1}) = 2945, 1706, 1629, 1609, 1429, 1254, 1188. HRMS (ESI) calculated for $C_{20}H_{24}DO_6$ $[M+H]^+$ 362.1708, found 362.1716.

Methyl (*E*)-4-((4-ethoxy-4-oxobut-2-en-2-yl)oxy)-2-hydroxybenzoate-3-*d* (8-D): A separate reaction run on 2.22 mmol scale was used to isolate **8-D** (125 mg, 20% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 6.57 - 6.53 (m, 1H), 5.04 - 5.03 (m, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 3.95 (s, 3H), 2.45 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 3H. ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 170.0, 167.1, 163.3, 159.3, 131.7, 112.5, 109.8, 109.7, 98.6, 59.7, 52.4, 18.1, 14.3. FTIR (cm^{-1}) = 2956, 1712, 1676, 1639, 1609, 1440, 1334, 1255, 1125. HRMS (ESI) calculated for $C_{14}H_{16}DO_6$ $[M+H]^+$ 282.1082, found 282.1079.

(±)- (2*S*,2a*R*,2a1*S*,5*R*,5a*R*)-Dimethyl 5-(*tert*-butyldimethylsilyloxy)-2-methyl-2-(4-methyl-2-oxopent-3-enyl)-2a,2a1,3,4,5,5a-hexahydro-2*H*-benzofuro[4,3,2-*cde*]chromene-7,8-dicarboxylate (9): To a solution of **2** (99 mg, 0.14 mmol) in MeCN (10 mL) was added tributylamine (269 mg, 1.45 mmol, 10 equiv.), formic acid (66.7 mg, 1.45 mmol, 10 equiv.) and *fac*-Ir(ppy)$_3$ (4.8 mg, 0.0072 mmol, 0.05 equiv.) in a 30 mL vial. The bright yellow solution was degassed by passing nitrogen through the solution for a period of 45 minutes. A household lightbulb (GE Helical 26 W) was placed ~5 cm from the reaction vial (see Figure below) and the mixture was stirred at room temperature until TLC indicated consumption of starting material (4 hours). The mixture was poured over water and extracted with CH_2Cl_2 (4x). The combined organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The ^{1}H NMR of the crude product indicated a 2:1 mixture of diastereomers about C-7, favoring **9**. The crude residue was purified by flash chromatography (EtOAc/Heptane) to afford a mixture of **9** and **C-7-*epi*-9** (49 mg, 60% yield as a 2:1 (**9**:**C-7-*epi*-9**) mixture of diastereomers) as a colorless gum. The spectroscopic data are in full agreement with those previously reported (see *J. Am. Chem. Soc.* **2013**, 135, 582-585).

Dimethyl (*E*)-3-hydroxy-5-((6-methyl-4-oxohepta-2,5-dien-2-yl)oxy)phthalate (10): Phenol **10** (120 mg, 11% yield) was obtained from cyclization of **2** (2.10 g, 3.07 mmol scale) by the

procedure described in *J. Am. Chem. Soc.* **2013**, 135, 582-585. ^{1}H NMR (400MHz, $CDCl_3$) δ 10.89 (s, 1H), 6.72 (d, *J* = 2.3 Hz, 1H), 6.62 (d, *J* = 2.3 Hz, 1H), 5.90 - 5.87 (m, 1H), 5.51 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 2.45 (s, 3H), 2.15 (d, *J* = 1.2 Hz, 3H), 1.85 (d, *J* = 0.8 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 189.8, 169.1, 168.9, 168.5, 163.2, 158.7, 154.9, 137.6, 126.3, 112.3, 111.0, 109.6, 106.9, 53.0, 52.8, 27.7, 20.6, 18.4. LRMS $[M+H]^+$ 349.2. An X-ray structure of **10** was obtained – see attached .cif file for details.

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