

SYNTHESIS OF SESQUITERPENE-TROPOLONES

BY

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DISSERTATION

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## ABSTRACT

A modular synthetic platform for the synthesis of the multi-bioactive sesquiterpene-tropolone natural products has been developed in an effort to provide general synthetic access to this class of compounds and related structures. In this work, the convergence of the sesquiterpene and tropolone fragments is enabled by a hetero-Diels–Alder reaction between a tropolone *ortho*-quinone methide and derivatives of  $\alpha$ -humulene. Concise and scalable syntheses of both fragments are described, as well as alternative approaches to key intermediates. During the development of the tropolone synthesis, an unprecedented photochemical fragmentation was discovered. Two natural products, epolone B and deoxypycnidione have been synthesized employing this strategy, as well as two diastereomers of pycnidione. In these studies, a correction to the originally reported structure of epolone B is suggested based upon X-ray crystallographic data. The synthetic compounds were found to be cytotoxic to A459 and HCT116 cell lines. Current efforts are focused on synthesizing pycnidione in its correct relative stereochemical configuration. Future directions include application of these fragments in hetero-Diels–Alder reactions to synthesize related sesquiterpene-tropolones, other tropolone containing natural products, and bistropolone congeners for biological evaluation.

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*To Mariah, Caleb, and my parents*

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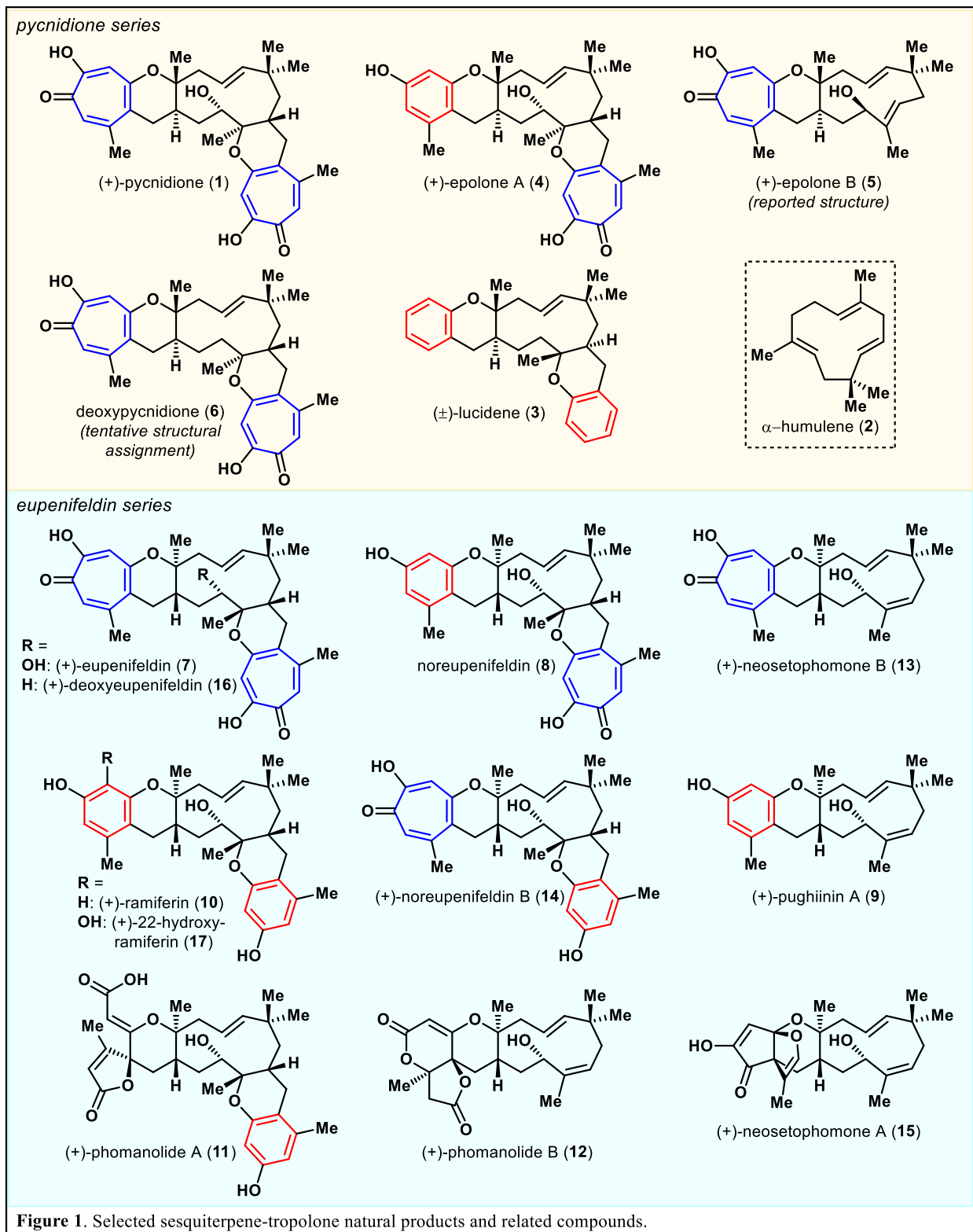
## CHAPTER 1: INTRODUCTION TO THE SESQUITERPENE-TROPOLONES

### 1.1. Isolation and Characterization of the Pycnidione Series

Cultures of a *Phoma* sp. (MF 4726) recovered from soil on Kosrae Island, Federated States of Micronesia, in 1993 were discovered to produce the first sesquiterpene-tropolone natural product, pycnidione (**1**) (104 mg/L of culture broth) (Figure 1).<sup>1</sup> This novel structure comprises a macrocyclic alcohol appended to two identical dihydropyran-fused tropolones. The 11-membered ring core is derived from  $\alpha$ -humulene (**2**), such that the *E*-configuration of the trisubstituted olefins in the latter are conserved as *trans*-fusions at the ring junctures in the former, and the disubstituted olefin is present in both. This core resembles that present in the natural product lucidene (**3**). The structure of pycnidione was unambiguously proven by X-ray crystallography and its absolute stereochemical configuration was determined by circular dichroism.

The isolation of pycnidione was reported for a second time in 1998 from a culture of OS-F69284 along with two new sesquiterpene-tropolones, epolones A (**4**) and B (**5**) (6.0, 0.5, and 1.5 mg/L, respectively) (Figure 1).<sup>2</sup> The core of epolone A was determined to be identical to that of pycnidione, though epolone A bears a phenol in place of one tropolone. While epolone B was determined to contain the tropolone lacked by epolone A, the second dihydropyran-fused tropolone was absent in place of an olefin. Furthermore, the stereochemical configuration of the dihydropyran fusion was reported as identical to that of pycnidione and epolone B, but the configuration of the alcohol was the opposite. Spectroscopic data for pycnidione were consistent with those measured following the initial isolation, however, the full structures of epolones A and B were proposed with evidence from spectroscopic data alone.





Several reports disclosing isolations of pycnidione from various fungal strains emerged over the following years. In 2000 and 2005, pycnidione was isolated from another *Phoma* sp.

(H4-77) derived from marine sponge *H. panicea* (6.2 mg/L).<sup>3,4</sup> In 2002, it was isolated as the major component of a mixture of metabolites from the fungus *K. pughii* (BCC 2878) (62.5 mg/L).<sup>5</sup> Subsequent isolations from *T. rogersii* (92031201) (9.3 µg/L) and *Gloeotinia* sp. (FKI-3416) (34 mg/L) fueled the first in-depth biological studies 19 years after pycnidione's discovery.<sup>6,7</sup> Finally, pycnidione, epolone A, and epolone B, were isolated in submilligram quantities from *N. samarorum* (RKDO834) in 2014 and 2016.<sup>8,9</sup> A new structure suspected to be deoxypycnidione (**6**) was also isolated from this culture, although its characterization could not be completed due to the poor purity of the isolated material. High resolution mass spectrometry and <sup>1</sup>H NMR data were cited in the proposition of this structure.

## 1.2. Isolation and Characterization of the Eupenifeldin Series

Four months after the first isolation of pycnidione, a second sesquiterpene-tropolone, eupenifeldin (**7**), was isolated from a culture broth produced by *Eupenicillium brefeldianum* (ATCC74184) (47.4 mg/L) (Figure 1).<sup>10</sup> Eupenifeldin was characterized thoroughly by spectroscopic methods, though unambiguous structural proof was obtained by X-ray crystallography. The isolate was optically active, but the absolute stereochemical configuration was not determined in this initial report. Pycnidione and eupenifeldin share a diastereomeric relationship. While the ring fusions between the macrocycle and dihydropyran linkages are both *trans* in pycnidione, one is *cis* and one is *trans* in eupenifeldin. Moreover, the *trans* fusion in the latter is inverted relative to the configuration of the secondary alcohol.

In 2007, the fungus *Diaporthe* sp. was reported to produce pycnidione in a yield of 12.5 mg/L.<sup>11</sup> However, careful examination of the spectroscopic data clearly reveals that the isolated compound was eupenifeldin and not pycnidione. Noreupenifeldin (**8**), a new sesquiterpene-tropolone, was isolated with eupenifeldin from an ascomycete fungus (F-150626) in 2008 (10.5

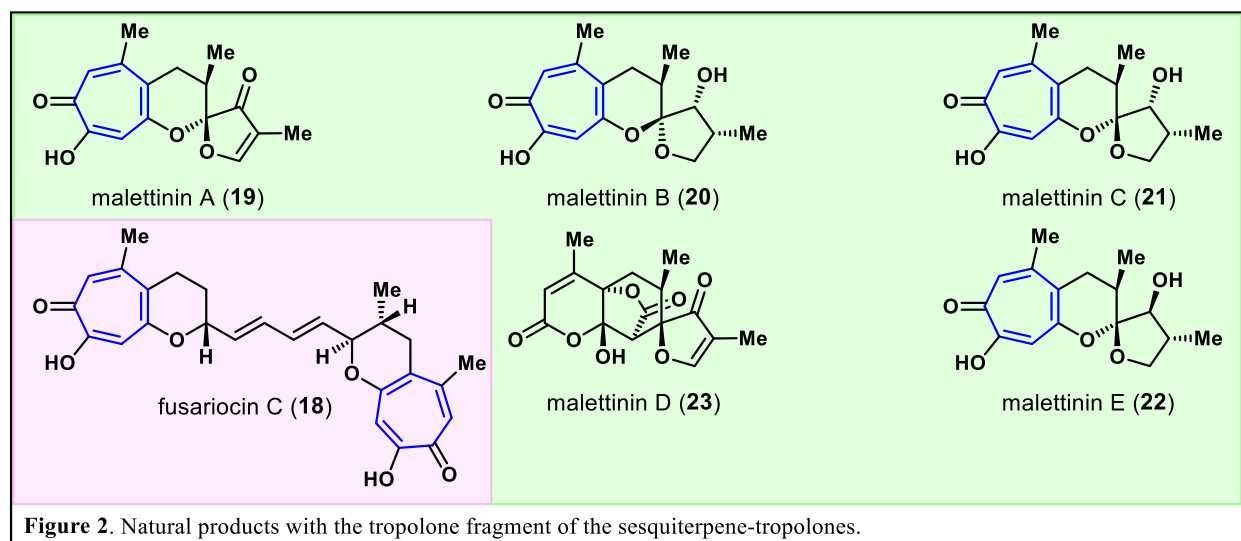
and 57.6 mg/L, respectively).<sup>12</sup> This monotropolone is analogous to epolone A in that a phenol replaces one tropolone, but its macrocyclic core is identical to that of eupenifeldin. A monophenol analogous to both noreupenifeldin and epolone B, pughiinin A (**9**), was isolated with pycnidione in 2002 (0.56 mg/L), and the corresponding bisphenol, ramiferin (**10**), was isolated with eupenifeldin and pughiinin A in 2008 from *K. ramifera* (BCC 7585) (0.54, 25.7, and 1.1 mg/L, respectively).<sup>5,13</sup> The former report is anomalous because in no other case was a natural product from the eupenifeldin series isolated with one from the pycnidione series. While the structure of pughiinin A was verified by X-ray crystallography, the spectroscopic data for pycnidione were omitted and claimed to be identical to those published.

Recently, eupenifeldin was isolated with novel sesquiterpene-tropolones and derivatives. In 2015, phomanolides A (**11**) and B (**12**) were reported from a *Phoma* sp. (KP896486) (25.9 and 2.1, respectively, and 2.5 g/L for eupenifeldin).<sup>14</sup> The phomanolides appear to be oxidative rearrangement products of the corresponding monotropolones, which had hitherto never been identified, and phomanoxide is the bisepoxide of the core of the eupenifeldin series. Indeed, these monotropolones neosetophomone B (**13**) and noreupenifeldin B (**14**) were isolated from *Neosetophoma* sp. (MSX50044) in 2019 (10.07 and 1.920 mg/L, respectively) along with another apparent oxidative rearrangement product neosetophomone A (**15**), deoxyeupenifeldin (**16**), eupenifeldin, and 22-hydroxyramiferin (**17**) (0.704, 1.17, 53.03, and 0.89 mg/L, respectively).<sup>15</sup> Neosetophomone B is the *Z*-olefin isomer of the enantiomer of the reported structure of epolone B and its structure was confirmed by X-ray crystallography. Deoxyeupenifeldin, unlike deoxypycnidione, was properly purified and fully characterized lending credence to existence of deoxypycnidione. Noreupenifeldin B is a constitutional isomer of noreupenifeldin wherein the positions of the phenol and tropolone are exchanged, and it is the

only known sesquiterpene-tropolone to bear this skeletal structure. Likewise, the catechol motif in 22-hydroxyramiferin is also new to this family of natural products.

### 1.3. Isolation and Characterization of Fusariocin C and the Malettinins

The particular dihydropyran-fused tropolone structure present in the sesquiterpene-tropolones is also found in five additional natural products with notable, albeit less ornate, architectures (Figure 2). Fusariocin C (**18**) resembles the sesquiterpene-tropolones such that it is a bistropolone, though the core is derived from a linear nonadiene rather than  $\alpha$ -humulene.<sup>16</sup> This natural product was isolated from *Fasarium moniliforme* (A-130) and its structure was reported in 1981. Characterization of this unprecedented tropolone structure proved to be difficult by chemical and spectroscopic methods, but was made possible by X-ray analysis of crystals grown in pyridine.



Malettinin A (**19**) was first isolated from a *Mycelia sterilia* in 2003, well after this specific tropolone motif had been identified in several other fungal metabolites.<sup>17a</sup> Its structure was determined by spectroscopic methods and verified by X-ray crystallographic analysis of its methanol adduct. In this compound, as well as malettinins B (**20**), C (**21**), and E (**22**), the tropolone forms a spiroketal with furanone-derived structures of varying oxidation states and

stereochemical configurations. Two years after the identification of malettinin A, it was isolated again from the same fungus with malettinins B, C, and D (**23**).<sup>17b</sup> Malettinins B and C share an anomeric relationship, while malettinin D is a novel structure that features a pyranone in place of the tropolone and a bicyclic lactone in place of the dihydropyran. Finally, malettinin E was isolated from *Cladosporium* sp. (KF501) along with malettinins A–C, and it is an epimer of malettinin C.<sup>17c</sup>

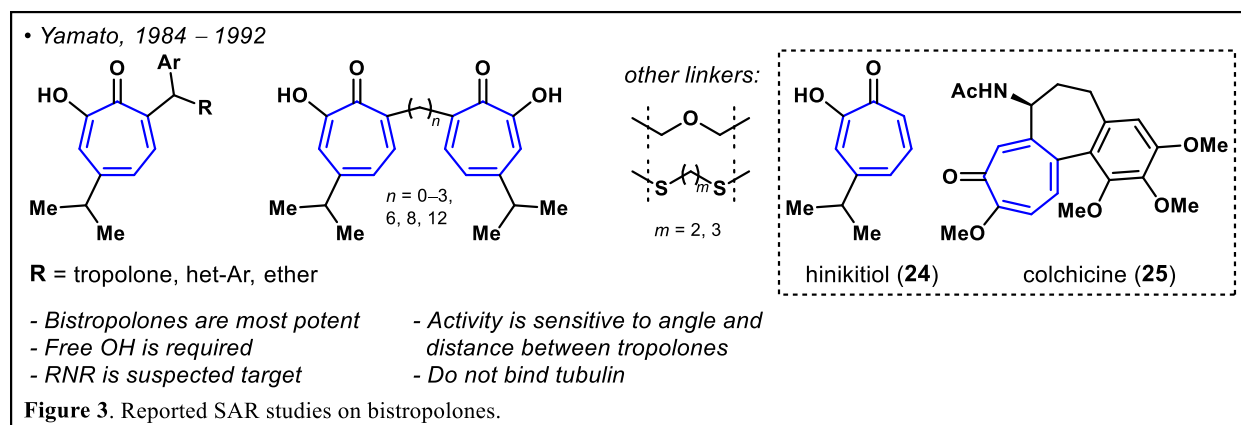
#### 1.4. Biological Activity of the Sesquiterpene-Tropolones

The sesquiterpene-tropolones possess a rich profile of biological activity that suggest potential applications in oncology, infectious disease, hematology, rheumatology, metabolism, and personal care.<sup>1–15</sup> While the available data encourage directed investigations to elucidate the mechanisms of action, biological targets, and structure-activity relationships (SAR) inhumed in this class of natural products, there remains a relative dearth of insight on these fronts. The contemporary understanding of their pharmacology is inconclusive and implications of structure on activity is inferred. However, the continued discovery of new sesquiterpene-tropolones and the pervasiveness of the most active members have inspired some keen observations regarding their activity *in vitro*. The ensuing subsections catalog the available data and summarize the efforts to discern the specific effects of the sesquiterpene-tropolones on biological systems. Table 1 contains all known *in vitro* biological activity data for the sesquiterpene-tropolones and -phenols.

Generally, the most potent activity of the sesquiterpene-tropolones is exhibited by bistropolones pycnidione and eupenifeldin, with particular cytotoxicity toward cancer cells.<sup>2,5–10,12–15</sup> The lowest IC<sub>50</sub> reported for pycnidione is 2.6 nM in DMS273 lung cancer cells and that of eupenifeldin is 3.6 nM in HCT-VM46 colon carcinoma cells.<sup>7,10</sup> It can be inferred from the

data in Table 1 that the bistropolone is required for enhanced activity, as monotropolones or sesquiterpene-phenols are markedly less potent than bistropolone analogues. Likewise, it is imperative to activity that the tropolone bears its native  $\alpha$ -hydroxyenone motif; methylation of the tropolone has been shown in two cases to render even the bistropolones inactive.<sup>2,7</sup> Aside from the knowledge that unprotected bistropolones possess the greatest activity, the SAR of the sesquiterpene-tropolones is poorly understood.

However, the bistropolone moiety has garnered attention as a scaffold that may be significant in drug development outside of the context of the sesquiterpene-tropolones. Nearly a decade before the discovery of pycnidione, the Yamato group published a series of papers that was dedicated to the exploration of the activity of bistropolones derived from hinokitiol (**24**) and analogues in KB cells (*in vitro*) and a P388 leukemia mouse model (*in vivo*) (Figure 3).<sup>18</sup> Generally, their studies corroborated that the bistropolone structure enhances activity relative to the monotropolones by a factor of about 200, and the unprotected tropolone moiety was required for activity (presumably due to the potential for metal chelation). Additional notable findings were that bistropolones are more active than pseudobistropolones (cyclic structures bearing an  $\alpha$ -hydroxyenone motif) in nearly all cases and activity has a dependence on the relative orientation of the tropolones and the length of the linker between them.



Unlike tropolone natural product and drug colchicine (**25**), the mechanism of action of the tropolone subjects in this study was found to be independent of tubulin binding. However, it was suggested that chelation to a metalloenzyme, such as ribonucleotide reductase (RNR), is a more likely mechanism of action. This enzyme, which contains two non-heme iron ions, is responsible for the conversion of RNA to DNA and is thus a viable target for inducing cell death. This hypothesis was tested *via* the monitoring of intracellular deoxyribonucleoside triphosphate pool (dNTP) imbalance caused by downregulation of RNR induced by the bistropolones. Indeed, a complete correlation between dNTP pool imbalance and cytotoxicity was observed, providing evidence that RNR may be the target for the bistropolones in these cell lines. Furthermore, the authors showed with another analogue that breaking of double strands of DNA followed dNTP imbalance.

The SAR studies conducted by the Yamato group were thorough and productive, in that they generated a large volume of bistropolone congeners and their biological evaluation resulted in the proposal of a biomolecular target. However, while the linker between the bistropolones was varied in length and structure, all tropolone subunits were linked at the same position, which inherently limits the diversity of structures that can be synthesized and studied. Granted, these studies were conducted before the isolation of pycnidione; now the knowledge of bistropolone natural products with significantly greater potency may serve as inspiration in the development of cytotoxic bistropolone analogues.

Relative to the frequency of reported sesquiterpene-tropolone isolations and biological activity evaluations, there are a few investigations into their mechanism of action in cancer cells. The Chung group evaluated the effects of pycnidione in A549 lung cancer cells and found that it inhibited cell proliferation with a GI<sub>50</sub> of 9.3 nM *via* G<sub>1</sub> phase arrest.<sup>6</sup> Treating the cells with

pycnidione induced downregulation of cyclin D1 and cyclin E expression, which control cell cycle progression, and the inhibition of the expression of survivin, a member of the inhibitor of apoptosis protein (IAP) family. The generation of reactive oxygen species (ROS) triggers mitochondrial collapse, then activation of caspase-8 and -3 ultimately results in apoptosis. This vital study is a significant contribution toward understanding the mechanism of action of pycnidione in cancer cells, however, a biomolecular target was not identified.

Houck and co-workers reported that pycnidione, epolone A, epolone B, and related compounds increase erythropoietin (EPO) production under normoxic conditions in Hep-3B cells.<sup>2</sup> EPO is a hormone that regulates proliferation of erythroid cells and is produced in response to hypoxia. Under normoxic conditions, the oxygen-labile  $\alpha$ -subunit of heterodimeric hypoxia-inducible factor (HIF-1 $\alpha$ ) is oxidized by iron-containing HIF-specific prolyl-4-hydroxylases (PHDs) and subsequently degraded. However, under hypoxic conditions, HIF-1 $\alpha$  is not hydroxylated, accumulates, and translocates to the nucleus where it binds to hypoxia-responsive elements (HREs) to increase production of EPO and other hypoxic survival factors. While experimental evidence supports that inhibition of PHDs by chelation to iron may be a cause for nuclear accumulation of HIF-1 $\alpha$ , the sesquiterpene-tropolones were not included in experiments that support this hypothesis. However, a later unrelated study indicates that hinokitiol stabilizes HIF-1 $\alpha$  *via* chelation of iron in PHDs.<sup>19</sup>

**Table 1.** Biological activities of sesquiterpene-tropolones.

Cytotoxicity				
Compound	Cell Line	Measurement	Value ( $\mu$ M)	reference
pycnidione	A549	GI <sub>50</sub>	0.0093	6
	BC	IC <sub>50</sub>	3.6	5
	KB	IC <sub>50</sub>	2.9	



**Table 1.** (cont.) Biological activities of sesquiterpene-tropolones.

<b>Cytotoxicity</b>				
<i>Compound</i>	<i>Cell Line</i>	<i>Measurement</i>	<i>Value (<math>\mu</math>M)</i>	<i>reference</i>
pyncnidione	KB	IC <sub>50</sub>	0.3	4
	Jurkat	IC <sub>50</sub>	0.51	7
	Jurkat	IC <sub>50</sub>	0.100 (11 $\mu$ g/mL bleomycin)	
	HBC-4	IC <sub>50</sub>	0.0141	
	BSY-1	IC <sub>50</sub>	0.0132	
	HBC-5	IC <sub>50</sub>	0.0047	
	MCF-7	IC <sub>50</sub>	0.0195	
	MDA-MB-231	IC <sub>50</sub>	0.0347	
	U251	IC <sub>50</sub>	0.0166	
	SF-268	IC <sub>50</sub>	0.0112	
	SF-295	IC <sub>50</sub>	0.0135	
	SF-539	IC <sub>50</sub>	0.0105	
	SNB-75	IC <sub>50</sub>	0.0126	
	SNB-78	IC <sub>50</sub>	0.0209	
	HCC2998	IC <sub>50</sub>	0.0078	
	KM-12	IC <sub>50</sub>	0.0074	
	HT-29	IC <sub>50</sub>	0.0062	
	HCT-15	IC <sub>50</sub>	0.0079	
	HCT-116	IC <sub>50</sub>	0.0035	
	NCI-H23	IC <sub>50</sub>	0.0102	
	NCI-H226	IC <sub>50</sub>	0.0117	
	NCI-H522	IC <sub>50</sub>	0.0081	
	NCI-H460	IC <sub>50</sub>	0.0042	
	A549	IC <sub>50</sub>	0.0047	
	<b>DMS273</b>	<b>IC<sub>50</sub></b>	<b>0.0026</b>	
	DMS114	IC <sub>50</sub>	0.0100	
	LOX-IMVI	IC <sub>50</sub>	0.0214	
	OVCAR-3	IC <sub>50</sub>	0.0126	
	OVCAR-4	IC <sub>50</sub>	0.0117	
	OVCAR-5	IC <sub>50</sub>	0.0224	
	OVCAR-8	IC <sub>50</sub>	0.0263	
SK-OV-3	IC <sub>50</sub>	0.0135		
RXF-631L	IC <sub>50</sub>	0.0437		
ACHN	IC <sub>50</sub>	0.0151		
St-4	IC <sub>50</sub>	0.0115		
MKN1	IC <sub>50</sub>	0.0158		

**Table 1.** (cont.) Biological activities of sesquiterpene-tropolones.

<b>Cytotoxicity</b>				
<i>Compound</i>	<i>Cell Line</i>	<i>Measurement</i>	<i>Value (<math>\mu</math>M)</i>	<i>reference</i>
pyncnidione	MKN7	IC <sub>50</sub>	0.0049	7
	MKN28	IC <sub>50</sub>	0.0051	
	MKN45	IC <sub>50</sub>	0.0055	
	MKN74	IC <sub>50</sub>	0.0078	
	DU-145	IC <sub>50</sub>	0.0209	
	PC-3	IC <sub>50</sub>	0.0257	
	HeKa	MIC	116.6	8
	HeKa	IC <sub>50</sub>	27.3	
	BJ	MIC	116.6	
	BJ	IC <sub>50</sub>	20.0	
epolone A	HeKa	MIC	61.5	8
	HeKa	IC <sub>50</sub>	23.7	
	BJ	MIC	58.3	
	BJ	IC <sub>50</sub>	25.5	
epolone B	HeKa	MIC	>333	8
	HeKa	IC <sub>50</sub>	130.0	
	BJ	MIC	>333	
	BJ	IC <sub>50</sub>	>333	
eupenifeldin	HCT-116	IC <sub>50</sub>	0.0091	10a
	<b>HCT-VM46</b>	<b>IC<sub>50</sub></b>	<b>0.0036</b>	
	CYP3A4	IC <sub>50</sub>	465	11
	BC	IC <sub>50</sub>	0.7	13
	KB	IC <sub>50</sub>	0.7	
	NCI-H187	IC <sub>50</sub>	2	
	Vero	IC <sub>50</sub>	1.3	
	SH-SY5Y	IC <sub>50</sub>	0.08	14
	U251	IC <sub>50</sub>	0.1	
	H4	IC <sub>50</sub>	0.13	
	HeLa	IC <sub>50</sub>	0.0082	
	A549	IC <sub>50</sub>	0.0306	
	T24	IC <sub>50</sub>	0.0125	
	HCT116	IC <sub>50</sub>	0.0312	
	MDA-MB-231	IC <sub>50</sub>	2.83	15
	OVCAR-3	IC <sub>50</sub>	0.33	
	OVCAR-8	IC <sub>50</sub>	0.02	
	MSTO-211H	IC <sub>50</sub>	0.08	
	LCC	IC <sub>50</sub>	0.01	
	A549	IC <sub>50</sub>	1.33	

**Table 1.** (cont.) Biological activities of sesquiterpene-tropolones.

<b>Cytotoxicity</b>				
<i>Compound</i>	<i>Cell Line</i>	<i>Measurement</i>	<i>Value (<math>\mu</math>M)</i>	<i>reference</i>
noreupenifeldin B	MDA-MB-231	IC <sub>50</sub>	7.06	15
	OVCAR-3	IC <sub>50</sub>	2.41	
	OVCAR-8	IC <sub>50</sub>	0.46	
	MSTO-211H	IC <sub>50</sub>	0.44	
	LCC	IC <sub>50</sub>	0.29	
	A549	IC <sub>50</sub>	-	
deoxyeupenifeldin	MDA-MB-231	IC <sub>50</sub>	6.02	15
	OVCAR-3	IC <sub>50</sub>	0.43	
	OVCAR-8	IC <sub>50</sub>	0.07	
	MSTO-211H	IC <sub>50</sub>	0.13	
	LCC	IC <sub>50</sub>	0.27	
	A549	IC <sub>50</sub>	-	
neosetophomone B	MDA-MB-231	IC <sub>50</sub>	11.2	15
	OVCAR-3	IC <sub>50</sub>	3.8	
	OVCAR-8	IC <sub>50</sub>	1.08	
	MSTO-211H	IC <sub>50</sub>	0.28	
	LCC	IC <sub>50</sub>	0.12	
	A549	IC <sub>50</sub>	-	
ramiferin	BC	IC <sub>50</sub>	9.1	13
	KB	IC <sub>50</sub>	12.6	
	NCI-H187	IC <sub>50</sub>	13	
	Vero		9.7	
22-hydroxyramiferin	MDA-MB-231	IC <sub>50</sub>	13.5	15
	OVCAR-3	IC <sub>50</sub>	7.76	
	OVCAR-8	IC <sub>50</sub>	0.89	
	MSTO-211H	IC <sub>50</sub>	0.72	
	LCC	IC <sub>50</sub>	-	
	A549	IC <sub>50</sub>	-	
pughiinin A	BC	IC <sub>50</sub>	-	5
	KB	IC <sub>50</sub>	-	
phomanolide A	SH-SY5Y	IC <sub>50</sub>	81.1	14
	HeLa	IC <sub>50</sub>	14.3	
neosetophomone A	MDA-MB-231	IC <sub>50</sub>	14.9	15
	OVCAR-3	IC <sub>50</sub>	10.6	
	OVCAR-8	IC <sub>50</sub>	2.38	
	MSTO-211H	IC <sub>50</sub>	0.82	
	LCC	IC <sub>50</sub>	-	

**Table 1.** (cont.) Biological activities of sesquiterpene-tropolones.

<b>Cytotoxicity</b>				
<i>Compound</i>	<i>Cell Line</i>	<i>Measurement</i>	<i>Value (<math>\mu\text{M}</math>)</i>	<i>reference</i>
neosetophomone A	A549	IC <sub>50</sub>	1.24	15
<b>Stromelysin Inhibition</b>				
<i>Compound</i>	<i>Protein</i>	<i>Measurement</i>	<i>Value (<math>\mu\text{M}</math>)</i>	<i>reference</i>
pycnidione	3H- $\beta$ casein	IC <sub>50</sub>	31	1
<b>EPO Induction</b>				
<i>Compound</i>	<i>Cell Line</i>	<i>Measurement</i>	<i>Value (<math>\mu\text{M}</math>)</i>	<i>reference</i>
pycnidione	Hep-B3	TIR <sub>5x</sub>	1.6	2
	Hep-B3	TIR <sub>max</sub>	4.3	
epolone A	Hep-B3	TIR <sub>5x</sub>	1	2
	Hep-B3	TIR <sub>max</sub>	4.3	
epolone B	Hep-B3	TIR <sub>5x</sub>	1.6	2
	Hep-B3	TIR <sub>max</sub>	6.5	
<b>Antimalarial</b>				
<i>Compound</i>	<i>Strain</i>	<i>Measurement</i>	<i>Value (<math>\mu\text{M}</math>)</i>	<i>reference</i>
pycnidione	<i>P. falciparum</i> FCR3F86	IC <sub>50</sub>	0.5	3
	<i>P. falciparum</i> W2	IC <sub>50</sub>	0.4	
	<i>P. falciparum</i> D6	IC <sub>50</sub>	0.7	
	<i>P. falciparum</i> K1	IC <sub>50</sub>	0.51	5
	<i>P. falciparum</i> FCR3F86	IC <sub>50</sub>	0.15	4
	<i>P. falciparum</i> W2	IC <sub>50</sub>	0.2	
	<i>P. falciparum</i> D6	IC <sub>50</sub>	0.4	
eupenifeldin	<i>P. falciparum</i> K1	IC <sub>50</sub>	0.07	13
ramiferin	<i>P. falciparum</i> K1	IC <sub>50</sub>	6.3	13
pughiinin A	<i>P. falciparum</i> K1	IC <sub>50</sub>	6.7	5
<b>Anthelmintic</b>				
<i>Compound</i>	<i>Parasite</i>	<i>Measurement</i>	<i>Value (<math>\mu\text{M}</math>)</i>	<i>reference</i>
pycnidione	<i>H. contortus</i>	EC <sub>90</sub>	151	12
eupenifeldin	<i>H. contortus</i>	EC <sub>90</sub>	91	12
noreupenifeldin	<i>H. contortus</i>	EC <sub>90</sub>	-	12
<b>Antifungal</b>				
<i>Compound</i>	<i>Strain</i>	<i>Measurement</i>	<i>Value (<math>\mu\text{M}</math>)</i>	<i>reference</i>
pycnidione	<i>C. albicans</i>	MIC	14.6	8
	<i>C. albicans</i>	IC <sub>50</sub>	9.1	
	<i>M. furfur</i>	MIC	14.6	9
	<i>M. furfur</i>	IC <sub>50</sub>	10.9	
epolone A	<i>C. albicans</i>	MIC	>123	8

**Table 1.** (cont.) Biological activities of sesquiterpene-tropolones.

<b>Antifungal</b>				
<i>Compound</i>	<i>Strain</i>	<i>Measurement</i>	<i>Value (μM)</i>	<i>reference</i>
epolone A	<i>C. albicans</i>	IC <sub>50</sub>	>123	8
	<i>M. furfur</i>	MIC	122.9	9
	<i>M. furfur</i>	IC <sub>50</sub>	92.2	
epolone B	<i>C. albicans</i>	MIC	166.4	8
	<i>C. albicans</i>	IC <sub>50</sub>	111.8	
	<i>M. furfur</i>	MIC	83.2	9
	<i>M. furfur</i>	I IC <sub>50</sub>	62.4	
eupenifeldin	<i>C. albicans</i>	IC <sub>50</sub>	5.3	13
ramiferin	<i>C. albicans</i>	IC <sub>50</sub>	>100	13
<b>Antibacterial</b>				
<i>Compound</i>	<i>Strain</i>	<i>Measurement</i>	<i>Value (μM)</i>	<i>reference</i>
pyncnidione	MRSA	MIC	29.2	8
	MRSA	IC <sub>50</sub>	21.9	
	<i>S. warneri</i>	MIC	116.6	
	<i>S. warneri</i>	IC <sub>50</sub>	21.9	
	VRE	MIC	116.6	
	VRE	IC <sub>50</sub>	83.8	
	<i>P. vularis</i>	MIC	116.6	
	<i>P. vularis</i>	IC <sub>50</sub>	54.7	
	<i>P. aeruginosa</i>	MIC	>233	
	<i>P. aeruginosa</i>	IC <sub>50</sub>	>233	
epolone A	MRSA	MIC	122.9	8
	MRSA	IC <sub>50</sub>	92.2	
	<i>S. warneri</i>	MIC	122.9	
	<i>S. warneri</i>	IC <sub>50</sub>	63.4	
	VRE	MIC	>117	
	VRE	IC <sub>50</sub>	84.5	
	<i>P. vularis</i>	MIC	>117	
	<i>P. vularis</i>	IC <sub>50</sub>	>117	
	<i>P. aeruginosa</i>	MIC	>246	
	<i>P. aeruginosa</i>	IC <sub>50</sub>	>246	
epolone B	MRSA	MIC	166.4	8
	MRSA	IC <sub>50</sub>	124.8	
	<i>S. warneri</i>	MIC	-	
	<i>S. warneri</i>	IC <sub>50</sub>	-	
	VRE	MIC	>166	
	VRE	IC <sub>50</sub>	135.2	
	<i>P. vularis</i>	MIC	>166	

**Table 1.** (cont.) Biological activities of sesquiterpene-tropolones.

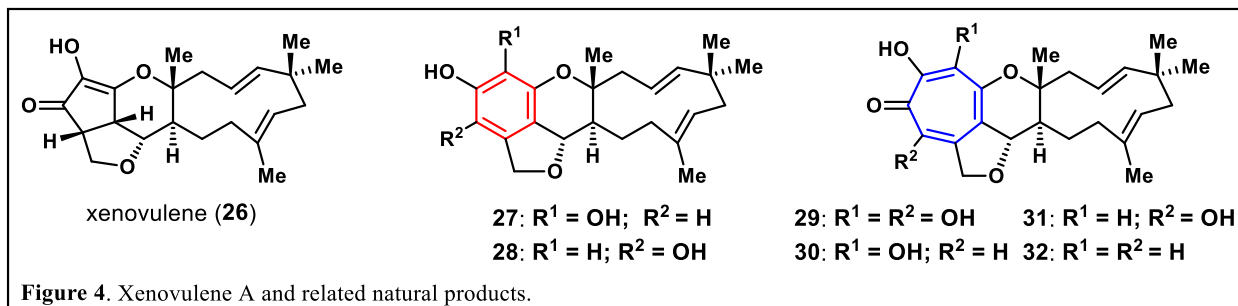
Antibacterial				
Compound	Strain	Measurement	Value ( $\mu\text{M}$ )	reference
epolone B	<i>P. vulgaris</i>	IC <sub>50</sub>	>166	8
	<i>P. aeruginosa</i>	MIC	>333	
	<i>P. aeruginosa</i>	IC <sub>50</sub>	>333	
eupenifeldin	<i>M. tuberculosis</i> H37Ra	MIC	>80	13
ramiferin	<i>M. tuberculosis</i> H37Ra	MIC	12.7	13

## 1.5. Biosyntheses Related to the Sesquiterpene-Tropolones

### 1.5.1. Biosynthesis of the Xenovulenes

Xenovulene A (**26**) is a meroterpenoid isolated from *Acremonium strictum* and is notable for its inhibition of the benzodiazepine, flunitrazepam, to the GABA-benzodiazepine receptor with an IC<sub>50</sub> of 40 nM (Figure 4).<sup>20</sup> This compound is structurally homologous to the sesquiterpene-tropolones in that it bears an  $\alpha$ -humulene-derived core bound to a furocyclopentenone *via* a dihydropyran. Later, closely related structures containing highly oxygenated catechols or tropolones (**27** – **32**) in place of the furocyclopentenone were isolated from cultures of the same fungus.<sup>21</sup> The biosynthesis of these natural products has been studied thoroughly and the conclusions drawn may have implications on the biosynthesis of the sesquiterpene-tropolones.

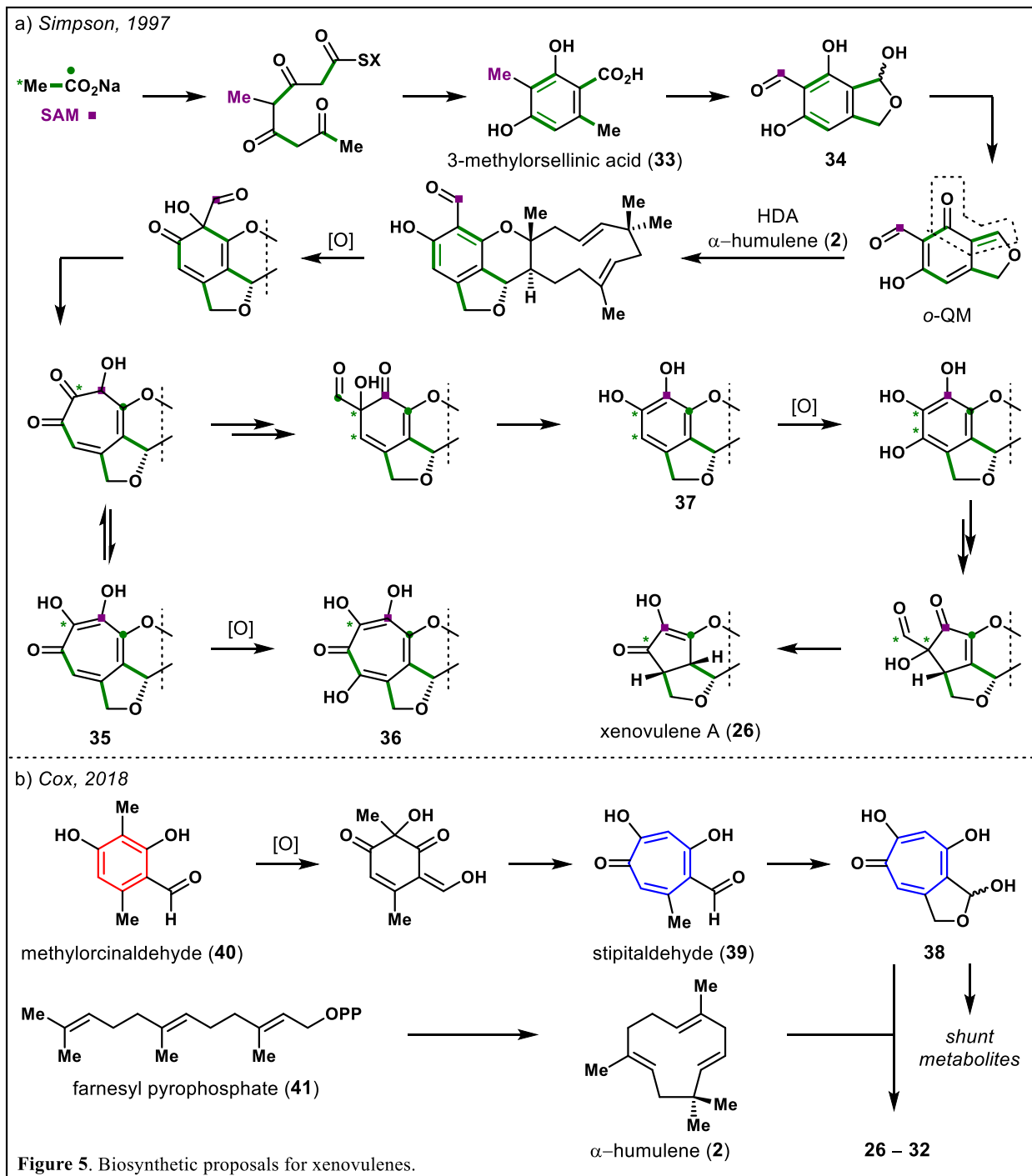
Isotopic labeling studies performed by the Simpson group in 1997 suggest that the furocyclopentenone moiety is a result of a ring expansion–ring contraction mechanism (Figure 5a).<sup>21</sup> Polyketide derived 3-methylorsellinic acid (**33**), a known intermediate in the synthesis of tropolone stipitatic acid, is proposed to be converted to lactol **34**, which is cleaved to reveal an *ortho*-quinone methide (*o*-QM) that undergoes an inverse electron demand hetero-Diels–Alder (HDA) cycloaddition with  $\alpha$ -humulene. Oxidative ring expansion and subsequent oxidation generates tropolones **35** and **36**. Alternatively, ring expansion followed by ring contraction and



hydrolysis would generate phenol **37**, then another oxidative ring contraction would generate the furocyclopentenone of xenovulene A. This proposal was recently revised by Cox and co-workers who, through gene knockout studies, propose that oxidative ring expansion to the tropolone occurs prior to the HDA cycloaddition, as tropolone shunt metabolites derived from lactol **38** were observed in various experiments (Figure 5b).<sup>22</sup> This proposal builds upon the known biosynthesis of key intermediates stipitaldehyde (**39**) and  $\alpha$ -humulene from methylorcinaldehyde (**40**) and farnesyl pyrophosphate (**41**), respectfully. Moreover, the proposal that the xenovulenes are biosynthesized from lactol **38** provides an explanation for the formation of previously unidentified tropolones **31** and **32**, while the previous biosynthetic proposal does not. However, the work by Cox and co-workers is otherwise in full-agreement with the labeling studies performed by Simpson and co-workers.

### 1.5.2. Biosynthesis of the Sesquiterpene-Tropolones

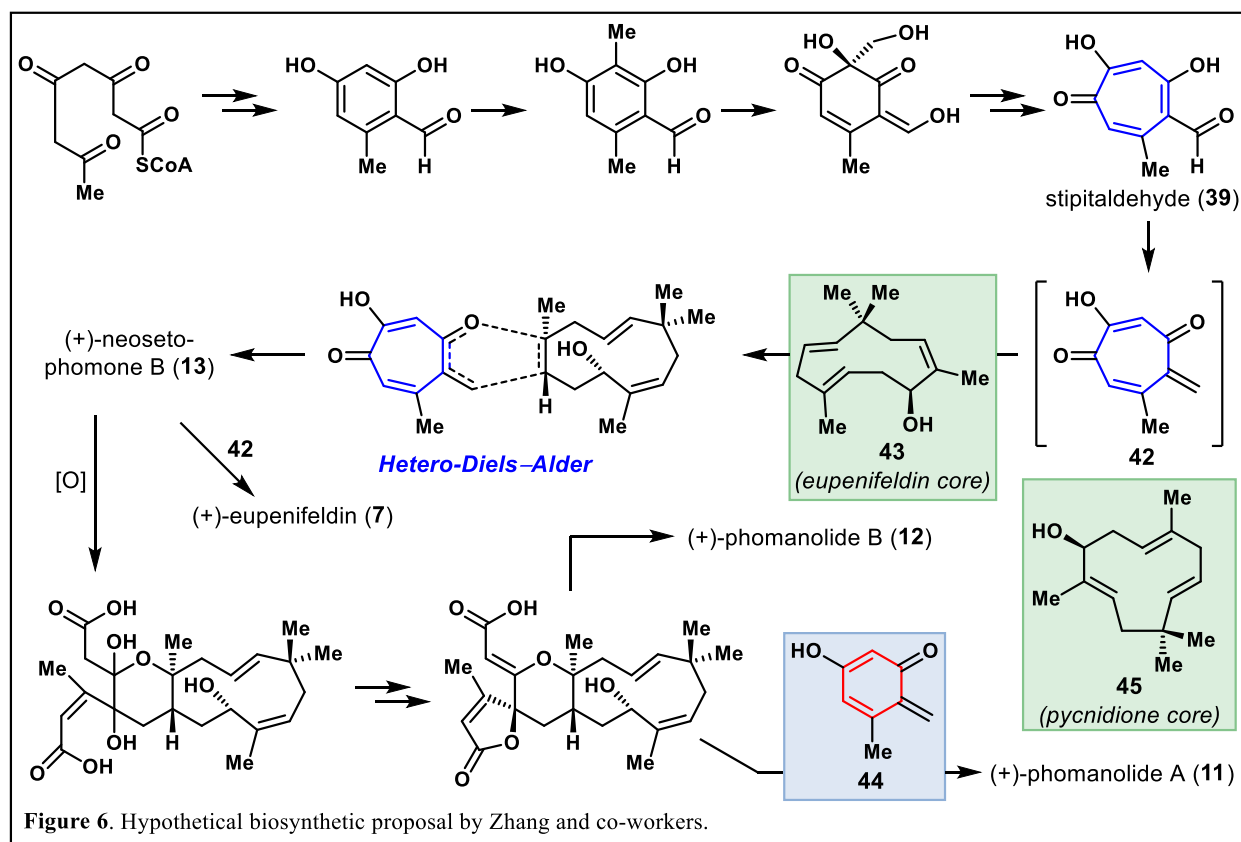
Despite the rigorous studies that have generated valid biosynthetic proposals for the xenovulene natural products, the biogenesis of pycnidione, eupenifeldin, and related sesquiterpene-tropolones remains a matter of speculation. The only published suggestion for the biosynthesis of these natural products comes from Zhang and co-workers in their 2015 report of the isolation of eupenifeldin.<sup>14</sup> Analogous to Cox's proposal for the biosynthesis of xenovulene A, they propose that stipitaldehyde is reduced and dehydrated to form a tropolone *o*-QM (**42**) that undergoes sequential HDA cycloadditions with an olefin isomer of hydroxy- $\alpha$ -humulene



(43) (Figure 6).<sup>22</sup> The phomanolides first described in that report were suspected to result from oxidative rearrangements of the tropolones, and in the case of phomanolide A (11), a HDA cycloaddition with phenol  $\alpha$ -QM 44. However, the authors do not comment on the reason for proposing that the oxidation of the macrocycle or formation of the tropolone formation occurs



before the cycloaddition. The existence of sesquiterpene-tropolone-phenols, such as epolone A, or sesquiterpene-phenols, such as ramiferin indicates that cycloaddition may be occurring prior to the expansion of the phenol to the tropolone, or the formation of a reactive *o*-QM occurs.<sup>2,13</sup> Likewise, the existence of deoxygenated sesquiterpene-tropolones such as deoxypycnidione and deoxyeupenifeldin implies that macrocycle oxidation may be occurring after the cycloaddition.<sup>8,15</sup> Moreover, while various oxidation products of  $\alpha$ -humulene are known natural products, hydroxyhumulenes **45** and **43** (corresponding to pycnidione and eupenifeldin, respectively) are not reported to have been isolated. Regardless, all sesquiterpene-tropolones that have been fully characterized are optically active, indicating that their syntheses are likely enzymatic in nature.



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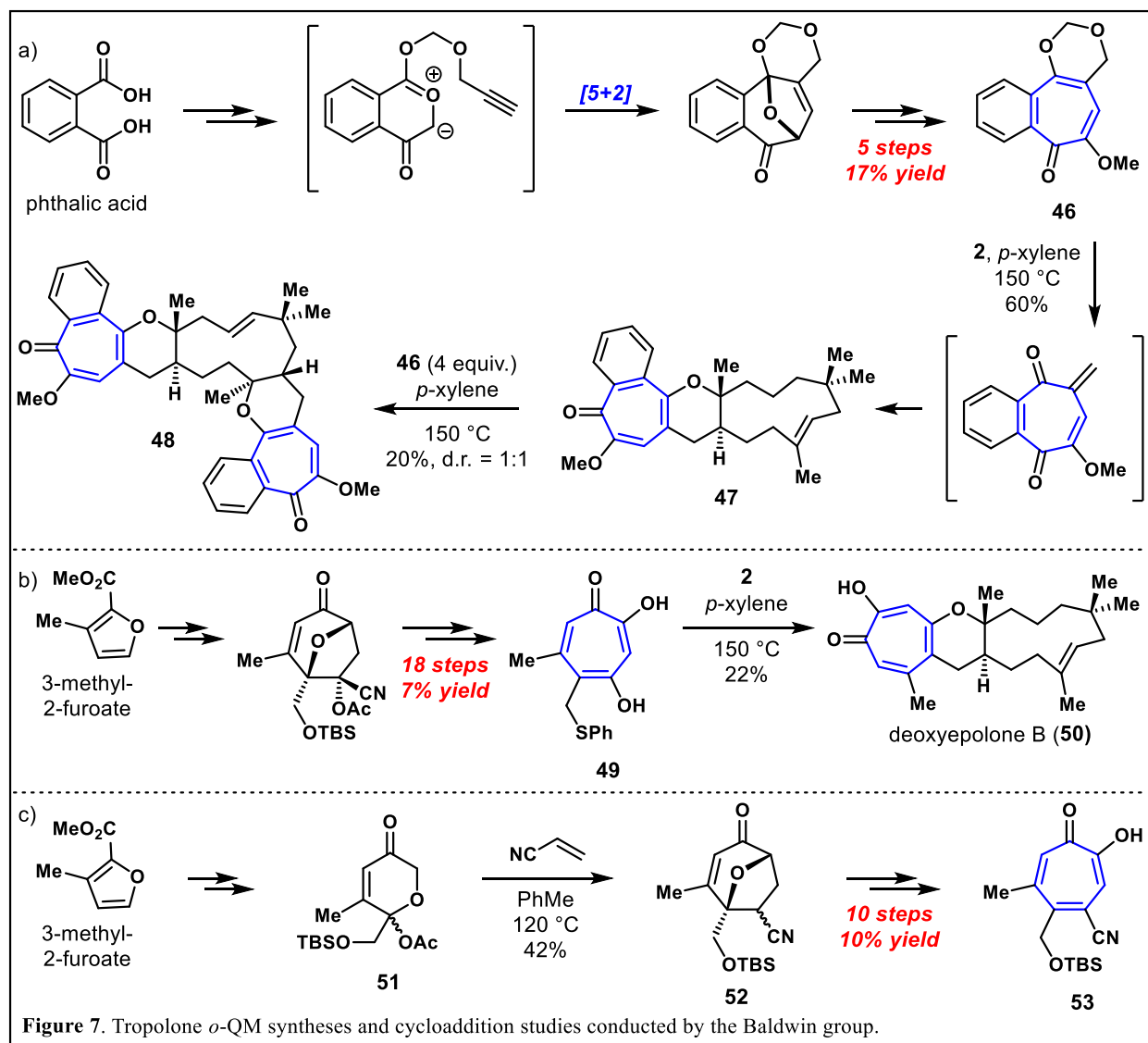
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## CHAPTER 2: PREVIOUS SYNTHETIC APPROACHES TO SESQUITERPENE-TROPOLONES AND FRAGMENTS

In the decades since the discovery of pycnidione (**1**), isolation chemists and chemical biologists have recognized the potential for the sesquiterpene-tropolone framework to serve as inspiration for lead compounds in medicinal chemistry. There have been multiple calls in the literature to synthetic chemists for their development of synthetic routes to this class of compounds in order to enable directed SAR studies.<sup>1,2</sup> However, no completed syntheses of any sesquiterpene-tropolone natural product have been reported. This is in part due to the challenges associated with the facile union and concise construction of the individual tropolone and macrocycle building blocks. Arguably, the most straightforward strategy toward this end would emulate the biosyntheses proposed by Simpson, Cox, and Che wherein an *o*-QM is generated and reacts with an olefin on the  $\alpha$ -humulene (**2**) derived core.<sup>3-5</sup>

### 2.1. *ortho*-Quinone Methide Approach by Baldwin

In the late 1990s and the early 2000s, the Baldwin group devised an efficacious biomimetic approach toward the sesquiterpene-tropolone scaffold that involved the generation of *o*-QMs and their subsequent reactions with  $\alpha$ -humulene (Figure 7a).<sup>6-11</sup> The first publication in this series reported the synthesis of a 1,3-dioxane- and benzene-fused tropolone (**46**) synthesized in five steps and 17% yield from phthalic acid *via* an oxidopyrylium [5+2] cycloaddition.<sup>6</sup> Tropolone **46** thermolytically cleaves to an *o*-QM in a retro-HDA reaction then undergoes a HDA cycloaddition with the most reactive olefin in  $\alpha$ -humulene to give cycloadduct **47**, reminiscent of epolone B (**5**). Under similar conditions, a second HDA reaction between **47** and excess **46** constructs a bistropolone framework (**48**) that resembles pycnidione, albeit less productively than the first cycloaddition. This work is foundational because it demonstrates that



both trisubstituted olefins in  $\alpha$ -humulene participate in HDA reactions with tropolone *o*-QMs. Likewise, it establishes that relative reactivities of the olefins in HDA cycloadditions are consistent with other reactions of  $\alpha$ -humulene olefins with electrophiles. The enhanced reactivity of one trisubstituted olefin over the other is due to the hyperconjugative donation of electron density from adjacent C–C bonds.<sup>12</sup> However, the major drawbacks to this initial work are that the benzene-fused tropolone is not present in any sesquiterpene-tropolone and is thus not applicable in natural product synthesis, and the Baldwin group did not show that the



hydroxyhumulenes **43** and **45** required for the synthesis of many compounds in this class were active in these cycloadditions.

The Baldwin group later reported the synthesis and subsequent cycloaddition of a tropolone *o*-QM with the same structure as the tropolone in the sesquiterpene-tropolones (Figure 7b).<sup>8</sup> The precursor was also synthesized employing an oxidopyrylium [5+2] cycloaddition, though several downstream functional group manipulations were required in order to reveal the final tropolone structure. In total, the tropolone *o*-QM precursor **49** could be accessed in a minimum of 18 steps and 7% yield from 3-methyl-2-furoate. Despite this synthetic overhead, compound **49** successfully undergoes thermolytic elimination of thiophenol to generate the desired tropolone *o*-QM which reacts with  $\alpha$ -humulene to give deoxyepolone B (**50**) with the expected selectivity in 22% yield. As before, this demonstration is significant because it shows that the specific tropolone *o*-QM required for a straightforward synthesis of the sesquiterpene-tropolones reacts with  $\alpha$ -humulene in the predictable fashion. However, the inefficiency of the synthesis and lack of experimental procedures create a formidable bottleneck for the reproduction of this work for applications in natural product synthesis, especially in the likely event that ample quantities of tropolone are needed for scale-up and reaction screening. Moreover, the second cycloaddition toward the pycnidione scaffold was not demonstrated or discussed in this case.

One additional paper was published by the Baldwin group on the synthesis of tropolones of this type, though the final product could not be converted to an *o*-QM.<sup>9</sup> Starting from compound **51**, which was an intermediate in the previously discussed tropolone synthesis, oxidopyrylium [5+2] cycloaddition with acrylonitrile rather than 2-acetoxyacrylonitrile generates intermediate **52** that was carried forward to cyanotropolone **53** in a total of ten steps and 10%

yield (Figure 7c). While this work advances the knowledge of tropolone synthesis, it does not provide a more expedient route to the sesquiterpene-tropolones.

In addition to their work on the generation and reactions of tropolone *o*-QMs, the Baldwin group also synthesized a phenol *o*-QM that is applicable in the synthesis of compounds such as epolone A (**4**) or ramiferin (**10**). Orcinol was formylated under Vilsmeier–Haack conditions, then acetylation of both phenols and a reductive transesterification generated phenol **54** in 23% yield over three steps (Figure 8a).<sup>10,11</sup> This intermediate productively served as a precursor to *o*-QM **55** via thermolytic elimination of acetic acid. The facile nature of this synthesis allowed for a broader study of the reactivity of this intermediate with several electron rich olefins. Most importantly, the cycloaddition with  $\alpha$ -humulene occurred in the expected fashion in 53% yield, and the subsequent hydrolysis of produced a pugiinin A (**9**)-type structure **56** in 82% yield. Finally, the Baldwin group showed that *o*-hydroxybenzyl alcohol (**57**) reacts to form an *o*-QM that undergoes two cycloadditions with  $\alpha$ -humulene to generate the natural

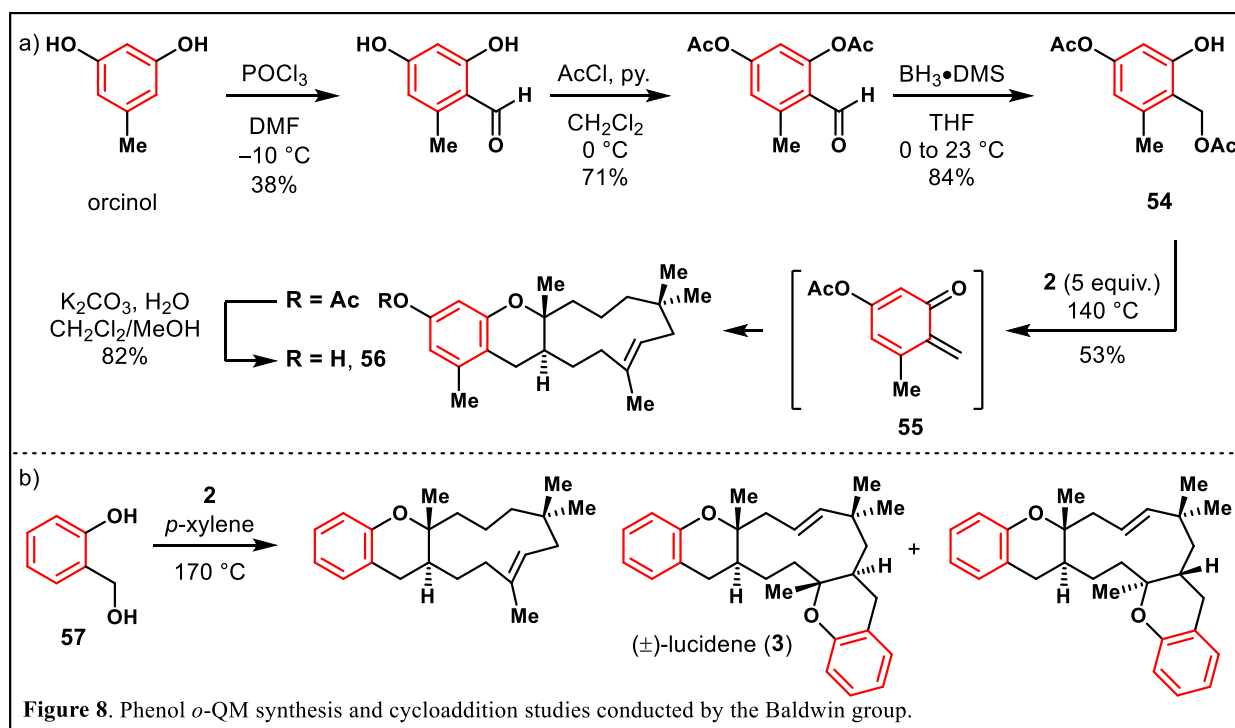


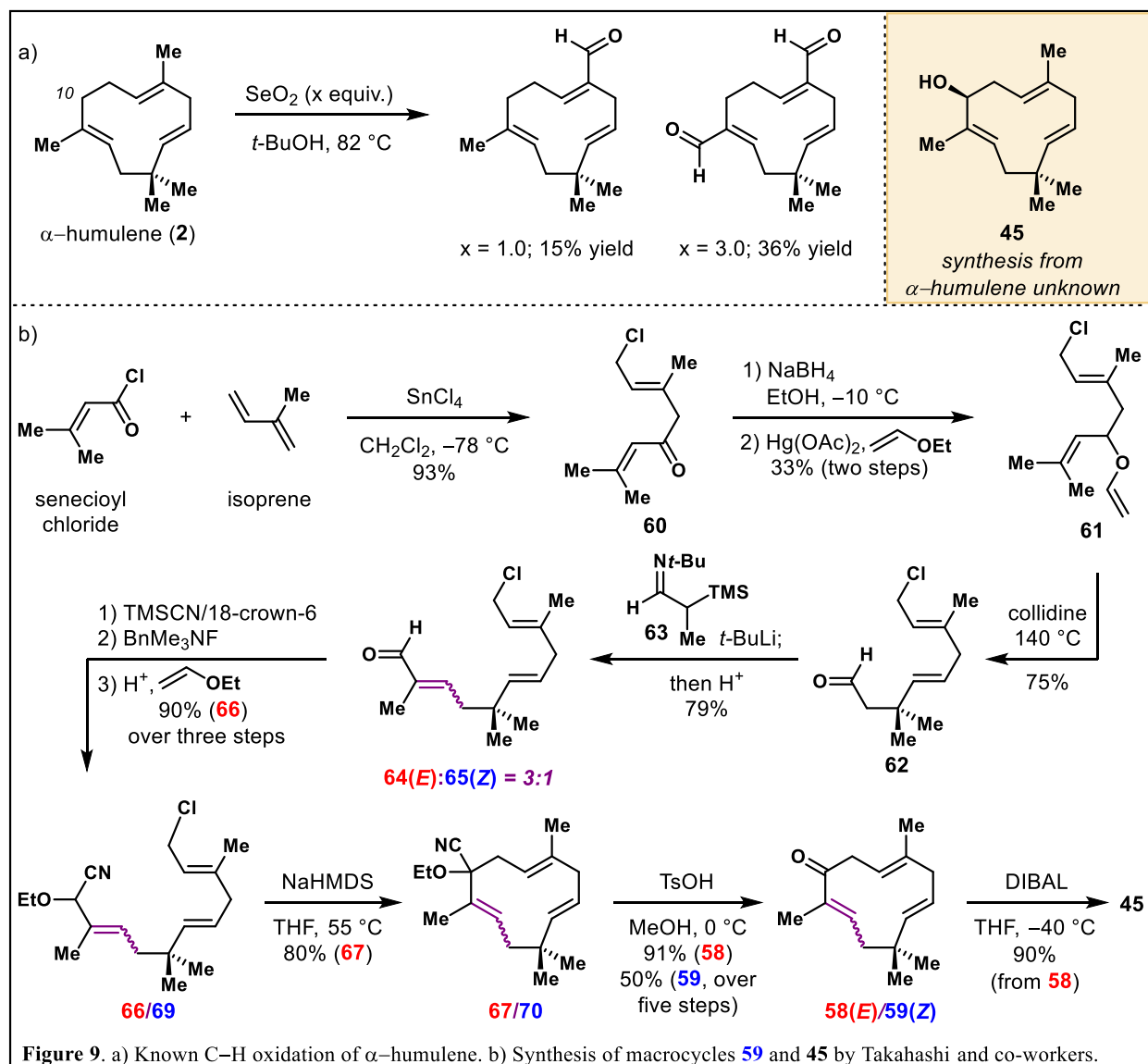
Figure 8. Phenol *o*-QM synthesis and cycloaddition studies conducted by the Baldwin group.

product ( $\pm$ )-lucidene (**3**), its stereoisomer, and the corresponding monocycloadduct with varying yields and product ratios depending on the reaction conditions (Figure 8b).<sup>7,11</sup> In contrast to their work on the tropolone syntheses, the concision of the synthetic route toward phenol **54** developed by the Baldwin group certainly allows for its application in natural product synthesis. However, to the best of our knowledge, this series of reports are the only published work that make any progress directed toward the total synthesis of the sesquiterpene-tropolones.

## 2.2. Synthesis of 10-hydroxy- $\alpha$ -humulene by Takahashi

Rendering 10-hydroxy- $\alpha$ -humulene **45** for application in the synthesis of pycnidione appears at first glance to be accomplishable by selective allylic oxidation of  $\alpha$ -humulene at the C-10 position to either the ketone or alcohol. However, it is known that exocyclic methyl groups are the primary targets for C-H oxidation by selenium dioxide (Figure 9a).<sup>13</sup> It is likely that the C-10 position is among the less active positions for such a reaction in this compound, as no syntheses of compound **45** have been reported by direct oxidation of  $\alpha$ -humulene. The only reported synthesis of an  $\alpha$ -humulene derivative bearing C-10 oxidation was reported by Takahashi in 1983, ten years before the isolation of pycnidione and eupenifeldin (**7**).<sup>14</sup> Serendipitously, their synthesis naturally produces isomeric ketones **58** and **59**, which are the oxidized cores of pycnidione and eupenifeldin, respectively. The syntheses of these two macrocycles are shown in full in Figure 9b.

The addition of isoprene to seneciyl chloride promoted by stannic chloride gives enone **60** in 93% yield as a single olefin isomer. Reduction with sodium borohydride followed by vinyl ether formation using mercury acetate and ethyl vinyl ether proceeded in 43% yield over two steps to give **61**. A Claisen rearrangement at 140 °C in collidine then produced aldehyde **62** in 75% yield. Lithiation of imine **63**, addition to **62**, then combined acidic hydrolysis and Peterson



olefination gives enals **64** and **65** in an *E:Z* ratio of 3:1 and 79% yield. Conversion of **64** to the protected cyanohydrin **66** was achieved in 90% yield by the addition of trimethylsilylcyanide, desilylation with benzyltetramethylammonium fluoride, and protection as the ethoxyethyl ether. Slow addition of this intermediate to a sodium hexamethyldisilazide (NaHMDS) solution triggered an intramolecular cyclization to give 11-membered ring **67** in 80% yield. Collapse of the cyanohydrin afforded (*E,E,E*)-ketone **58** in 91% yield, which could be reduced to **45** in 90% yield with diisobutylaluminum hydride. Enal **68** was subjected to the same sequence of reactions to produce cyanohydrin **70** via **69** in 50% yield, though deprotection to (*E, E, Z*)-ketone **59**

occurred with partial isomerization to **58**. The authors noted that **59** is less stable than **58** under basic conditions.

Takahashi and co-workers' recognition of the importance of  $\alpha$ -humulene derivatives with unconventional oxidation patterns and their successful synthetic endeavors predate the need for these compounds by at least a decade. As a result, the chemistry that was once state of the art is now antiquated relative to modern synthetic techniques, especially those used for the synthesis of macrocycles.  $\alpha$ -Humulene itself has been the subject of several synthetic studies as recently as 2002.<sup>14,15</sup> The key cyclization step converting **67** to **58** is quite efficient, however the surrounding transformations are laborious, requiring superfluous manipulations that introduce short carbon segments to construct the linear precursor. Furthermore, the synthesis of **45** is racemic, while enantiopure material would be desired for the biological studies of compounds to be synthesized from this intermediate. Finally, as with the work on the tropolone by the Baldwin group, the lack to detailed procedures discourages reproduction for further synthetic studies.

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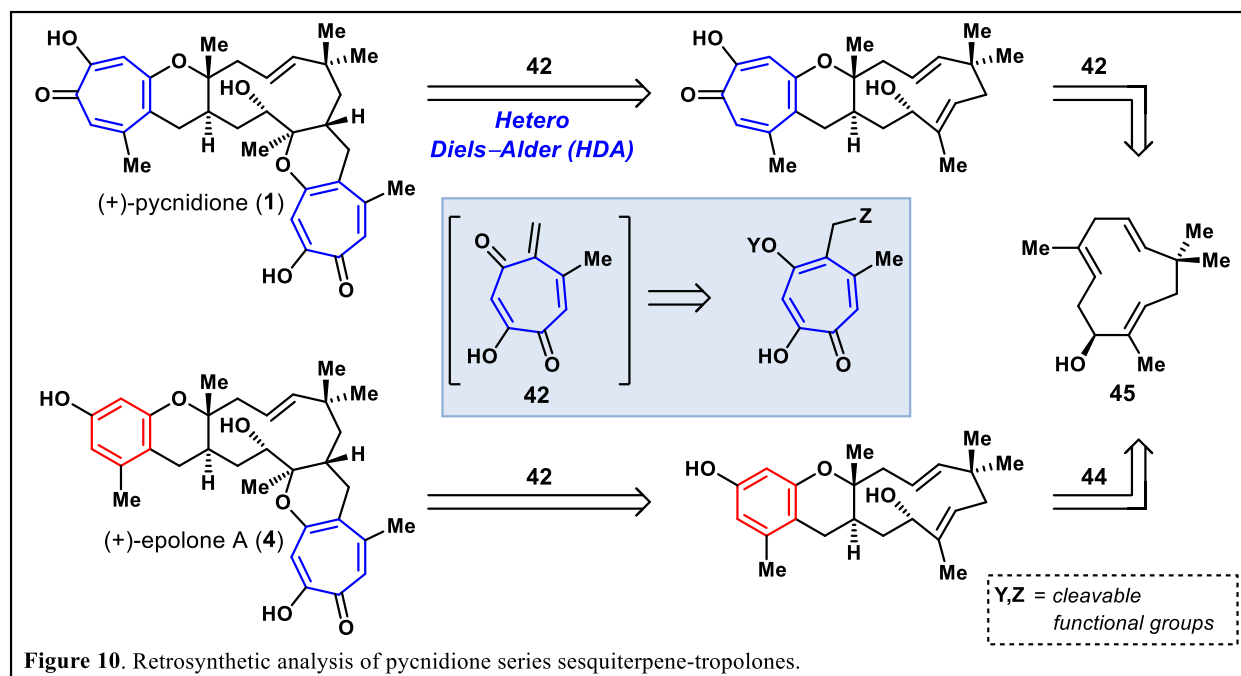
## CHAPTER 3: SYNTHESIS OF SESQUITERPENE-TROPOLONES

Reports of the isolation and biological activity of the sesquiterpene-tropolone natural products are prevalent in the literature. However, studies to elucidate a mechanism of action are relatively sparse and deliberate SAR studies are absent. The shortcomings in the latter categories are undoubtedly a result of the lack of a robust synthetic route that could generate ample quantities of material and analogues. At the outset of the Sarlah group, we recognized this gap in knowledge as an opportunity to impact the field of organic synthesis by providing a solution to an unsolved problem, and ideally, make new discoveries *en route* to our target molecules. Additionally, we aimed to move an underexplored class of potent bioactive compounds into the scope of medicinal chemistry. Finally, and perhaps most honestly, we found the structures of the sesquiterpene-tropolones fascinating and believed their synthesis would prove to be a satisfying challenge.

### 3.1. Retrosynthetic Analysis

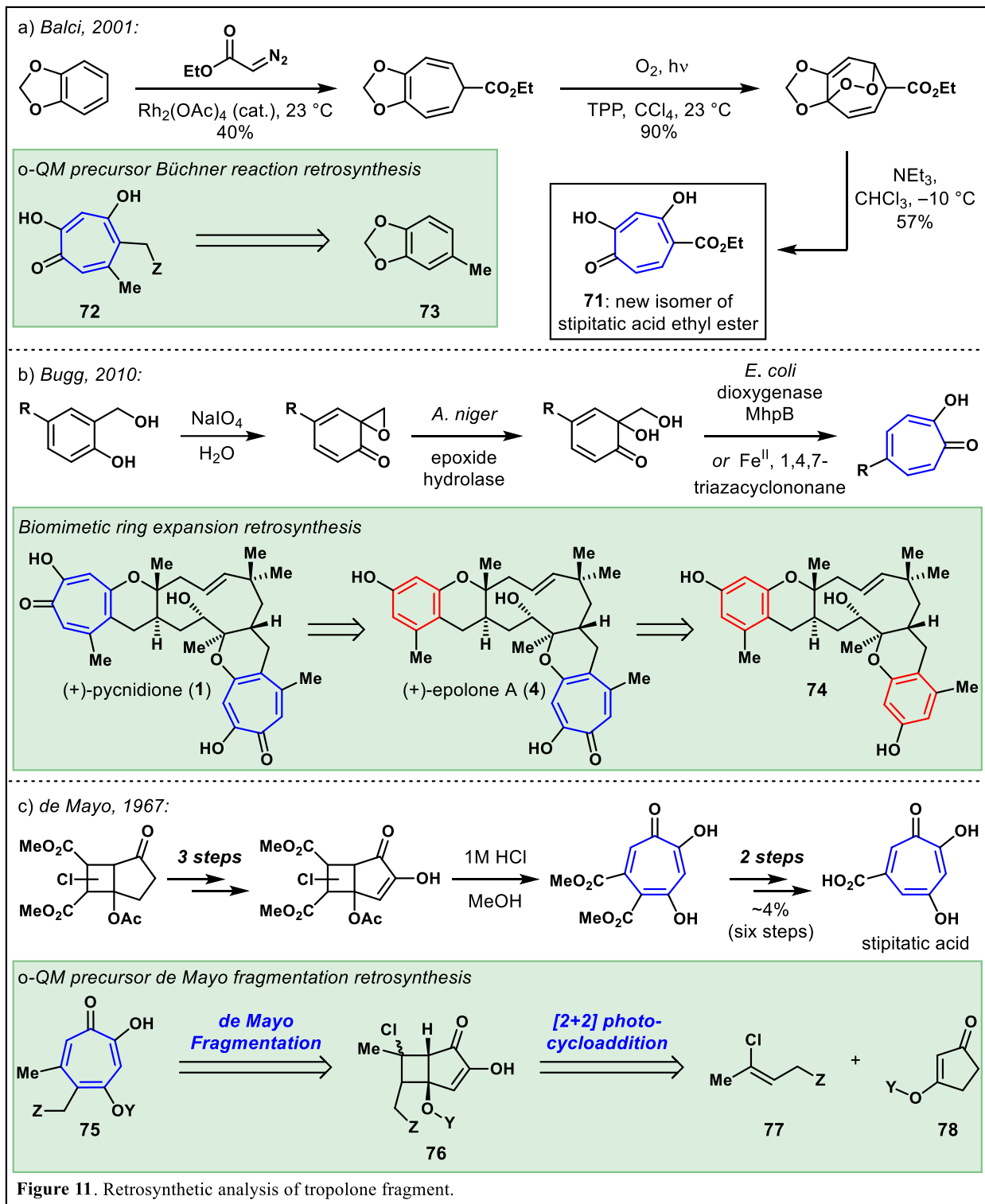
When considering our synthesis of the sesquiterpene-tropolones, we concurred with Baldwin group that a convergent and biomimetic approach would be the most efficient.<sup>1</sup> Thus, the key disconnections in our retrosynthetic analysis of the pycnidione series were sequential HDA cycloaddition reactions between tropolone or phenol *o*-QM intermediates (**42** or **44**) and the macrocyclic alcohol (**45**) derived from  $\alpha$ -humulene (**2**) (Figure 10). Since *o*-QMs are unstable species, appropriate precursors would be key intermediates. As discussed in the previous chapter (Figure 8), the Baldwin group already developed a synthesis of phenol *o*-QM precursor **54**.<sup>2</sup> This synthesis proved to be reproducible and scalable in our laboratory, so we saw no need to make modifications to their work. On the other hand, we required a novel synthesis of a tropolone *o*-QM precursor that could produce gram quantities of the intermediate in short





order. Likewise, a new synthesis of macrocycle **45** would be required. This would also need to be brief, scalable, and enantioselective. The stereogenic center at the secondary alcohol is the only element of chirality in either of these fragments, and would thus dictate the enantioselectivity of the entire synthesis.

We envisioned three different syntheses for the tropolone. The first was inspired by a 2001 report from the Balci group employing a Büchner reaction, singlet oxygen HDA, and Kornblum–DeLaMare fragmentation to synthesize new isomers of stipitatic acid, including **71** (Figure 11a).<sup>3</sup> With this strategy, we could trace *o*-QM precursor **72** back to benzodioxole **73**. In the second approach, we aimed to trigger a biomimetic ring expansion from a phenol-derived spiroepoxydienone to a tropolone, following the precedent reported by the Bugg group in 2010 (Figure 11b).<sup>4</sup> This could be accomplished chemically or chemoenzymatically. With this particular route, we could produce the sesquiterpene-tropolone framework directly from sesquiterpene-phenols; pycnidione or epolone A could be produced from compound **174**. Our third and final approach would reveal the tropolone *o*-QM precursor in a tandem de

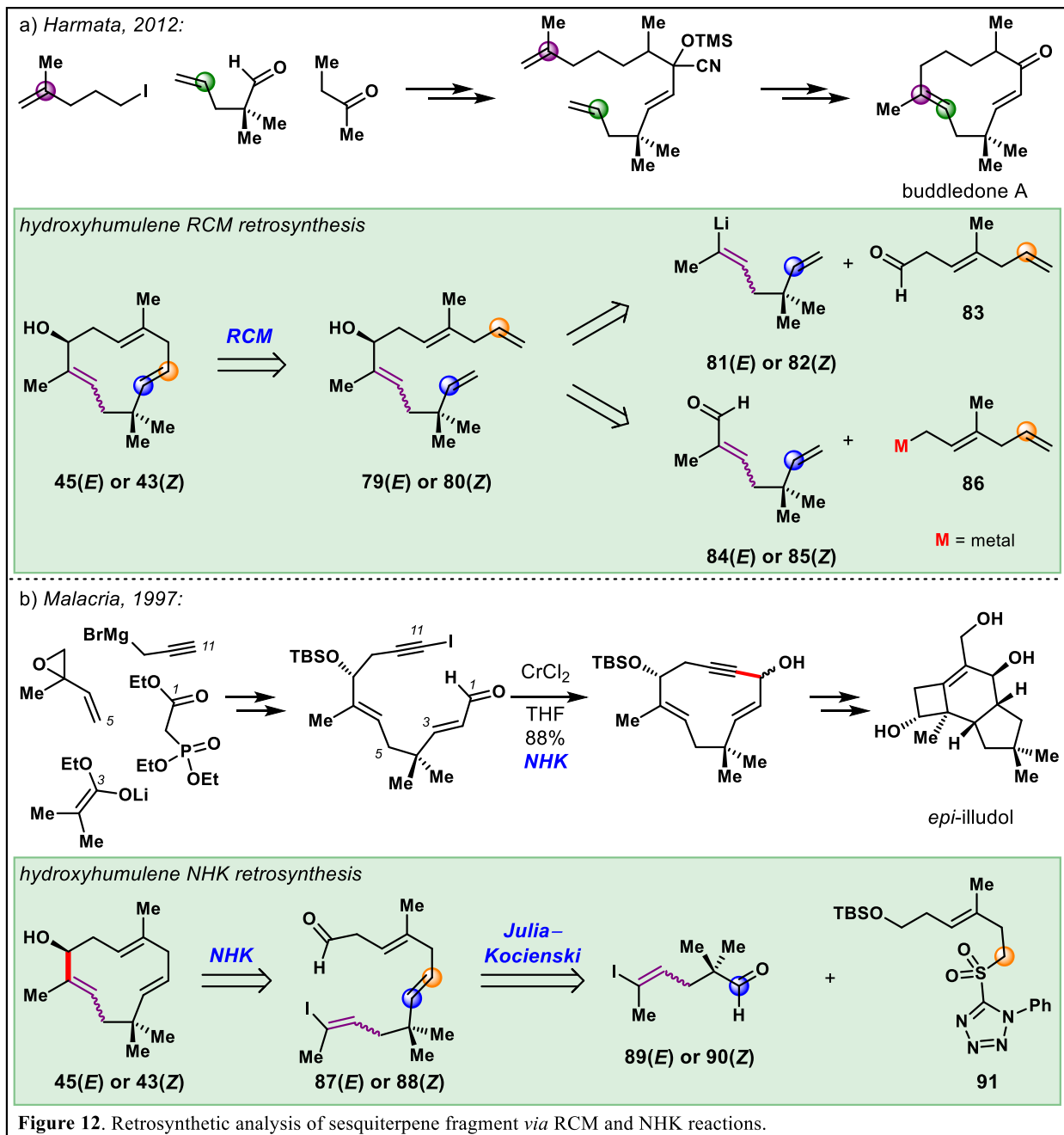


Mayo fragmentation and chloride elimination.<sup>5,6</sup> This was preceded by the de Mayo group themselves in a synthesis of stipitatic acid and other related structures (Figure 11c). Mapping this synthesis onto our own system, we traced **75** back to hydroxyenone **76**, which bears two

additional degrees of unsaturation packaged into its chlorinated bicyclic structure. This could be generated from the oxidative adjustment of the [2+2] photocycladduct of vinylchloride **77** and enone **78**.

Macrocycles **45** and **43** contain three olefins that provide seemingly endless retrosynthetic disconnections drawing on olefin formation and functionalization technologies. Likewise, the secondary allylic/homoallylic alcohol offers the opportunity for the vinylation or allylation of an aldehyde. While our synthetic toolbox was full when approaching the construction and manipulation of these functional groups, the true challenge would be the formation of the 11-membered ring. With a strain energy of 11.3 kcal/mol, saturated 11-membered rings are among the most strained medium-sized rings. However, the previous syntheses of  $\alpha$ -humulene encouraged that this problem would not be insurmountable. Moreover, we saw the potential for innovation in the area of strained cyclic olefins with the aid of modern synthetic methodologies.

We found the most straightforward approach to the synthesis of macrocycle to be ring-closing olefin metathesis (RCM) (Figure 12a). We were encouraged to find that the 11-membered macrocyclic sesquiterpene buddledone A was synthesized by the Harmata group using this strategy.<sup>6</sup> By disconnecting **45** or **43** at the disubstituted olefin, we traced the macrocycle to tetraene **79** or **80**. We envisioned that **79** or **80** could be easily generated from the addition of vinylolithium **81** or **82** into aldehyde **83**. Notably, this route benefits from the convergence of two nearly equally sized fragments, and the aldehyde fragment would be useful in both macrocycle syntheses. Alternatively, alcohol **79** or **80** could be formed in the allylation of aldehyde **84** or **85** with allyl nucleophile **86**. Next, we anticipated that reversing the disubstituted olefin and allylic alcohol formation steps would create new possibilities for macrocycle



formation. We identified that a Nozaki–Hiyama–Kishi (NHK) reaction permits disconnecting **45** or **43** at the allylic alcohol, leaving vinyl halide/aldehydes **87** or **88** (Figure 12b).<sup>7</sup> These two intermediates could be derived from aldehydes **89** or **90** and sulfonyl tetrazole **91** via a Julia–Kocienski olefination. Again, this approach would be expected to enable synthesis of **45** or **43** from similar fragments. Validation for this proposal was found in an alkynyl NHK reaction that

formed an 11-membered ring in the total synthesis of the sesquiterpene *epi*-illudol performed by the Malacria group.

Drawing inspiration from McMurry's  $\alpha$ -humulene synthesis employing his named carbonyl-carbonyl coupling, we imagined **45** being formed from the same reaction with ketoaldehyde **92** or bisaldehyde **93** (Figure 13).<sup>9</sup> In either case, these linear intermediates could be disconnected to a vinyl lithium (**94** or **95**) and aldehyde (**96** or **97**) in the same fashion as the proposed RCM strategy. It is worth noting that neither of these routes would construct the olefin targeted in McMurry's work, but they enabled use of intermediate fragments and reaction methodologies similar to those in other routes that we were pursuing concurrently, allowing us to rapidly synthesize key intermediates.

Our final strategy for the synthesis of **45** was inspired by the synthesis of (-)-humulene oxide II (**98**) from (-)-caryophyllene oxide (**99**) by the Shenvi group using their catalytic hydrogen atom transfer (HAT) mediated olefin isomerization (Figure 14).<sup>10</sup> After tracing macrocycle **45** back to epoxide **100**, by analogy, the latter could be formed from protected allylic alcohol **101**. This could then be generated directly from commercially available (-)-caryophyllene oxide *via* allylic oxidation. While  $\alpha$ -humulene has several oxidizable allylic positions, the chances of effecting the desired allylic oxidation on the single olefin of (-)-caryophyllene oxide were much greater. This route, if successful, would be superior to all other proposed routes toward **45** because the chiral pool starting material inherently renders our synthesis enantioselective. Moreover, it would be concise and presumably scalable, as Shenvi and co-workers already demonstrated this isomerization is high yielding on gram scale.

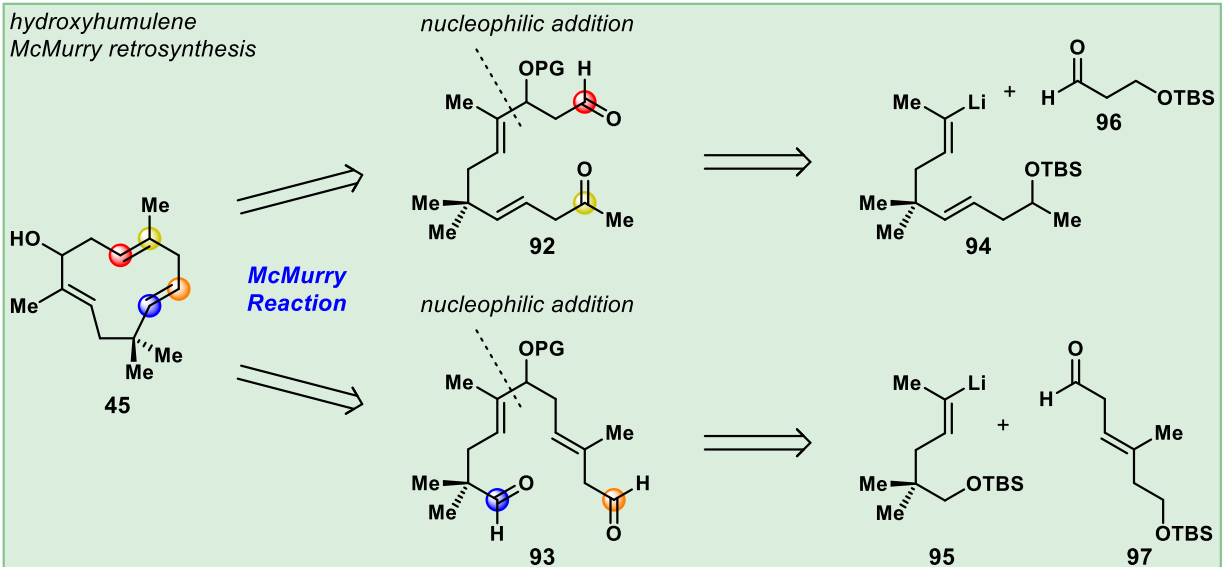
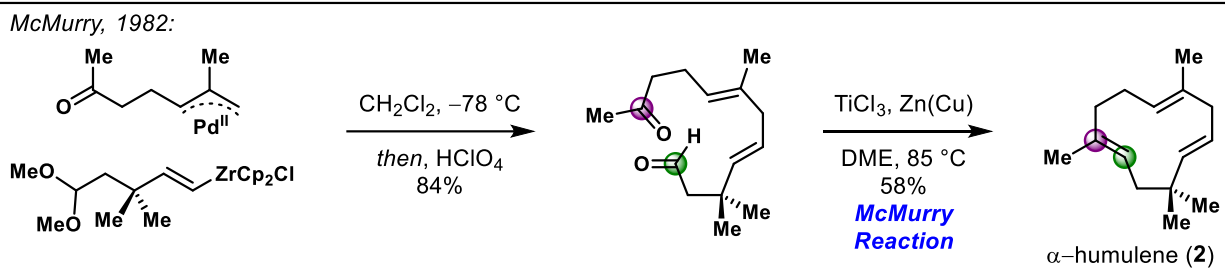


Figure 13. Retrosynthetic analysis of sesquiterpene fragment via the McMurry reaction.

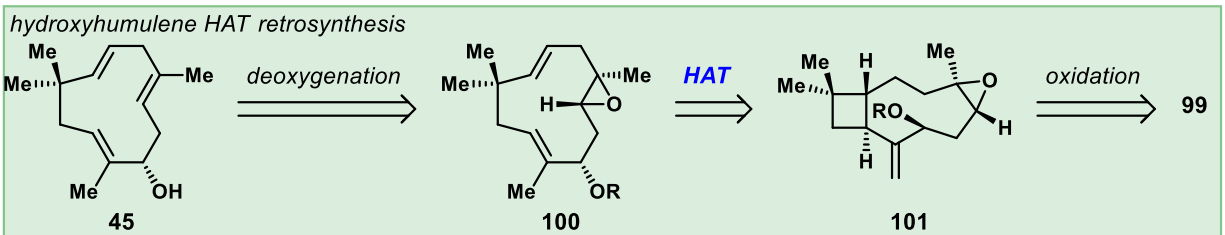
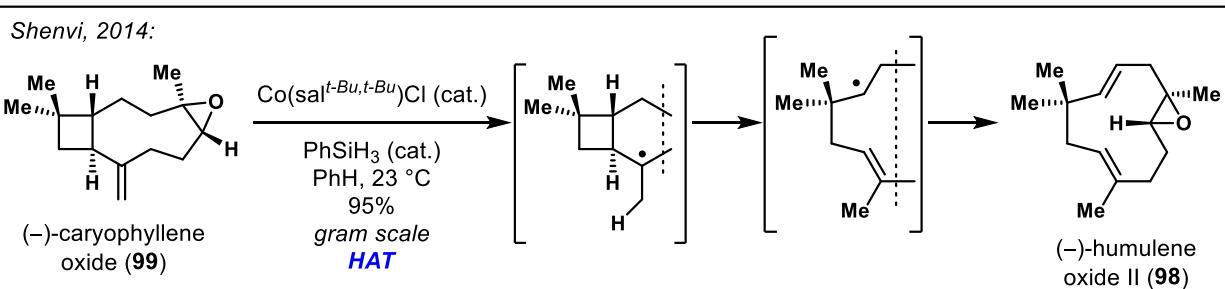


Figure 14. Retrosynthetic analysis of sesquiterpene fragment via HAT.

## 3.2. Synthesis of Tropolone Fragment

### 3.2.1. Büchner Reaction Strategy

The first strategy we devised in pursuit of the tropolone *o*-QM precursor was inspired by the Balci group's work on the synthesis of isomers of stipitatic acid and other tropolones.<sup>3</sup> Compound **71** (Figure 11a) closely resembles the substitution pattern required for *o*-QM precursor that we desired. The only necessary adjustments would be the introduction of a methyl group and reduction of the ester to an alcohol.

We started our synthesis with the preparation of known methyl benzodioxole **73** from the corresponding catechol (**102**) (Figure 15). This was accomplished *via* acetalization with dichloromethane and cesium carbonate in refluxing acetonitrile, giving the product in 63% yield.<sup>12</sup> Next, we performed the Büchner ring expansion in a manner similar to that reported by the Balci group, the only difference being that we performed the reaction on a solution of the benzodioxole rather than running the reaction neat. Nonetheless, the ring expansion proceeded as expected to give a 67% yield of cycloheptatriene ester **103** when ethyl diazoacetate was added to the solution of **73** and rhodium acetate dimer over an hour, which minimized the formation of fumarate or maleate side products. With this ester in hand, our next key task was to perform the singlet oxygen HDA to generate an endo peroxide. To increase our chances of success, we aimed to perform this reaction on four different substrates. First, we used ester **103** with no modifications. Second, we could reduce the ester with lithium aluminum hydride to the corresponding primary alcohol (**104**) in quantitative yield. This alcohol could then be protected as the TBS ether (**105**) in 77% yield or as the acetate (**106**) in 73% yield. (Note that reproduction of Balci's work was successful in our hands, even when employing the desmethyl analogues of **104**, **105**, and **106**.)

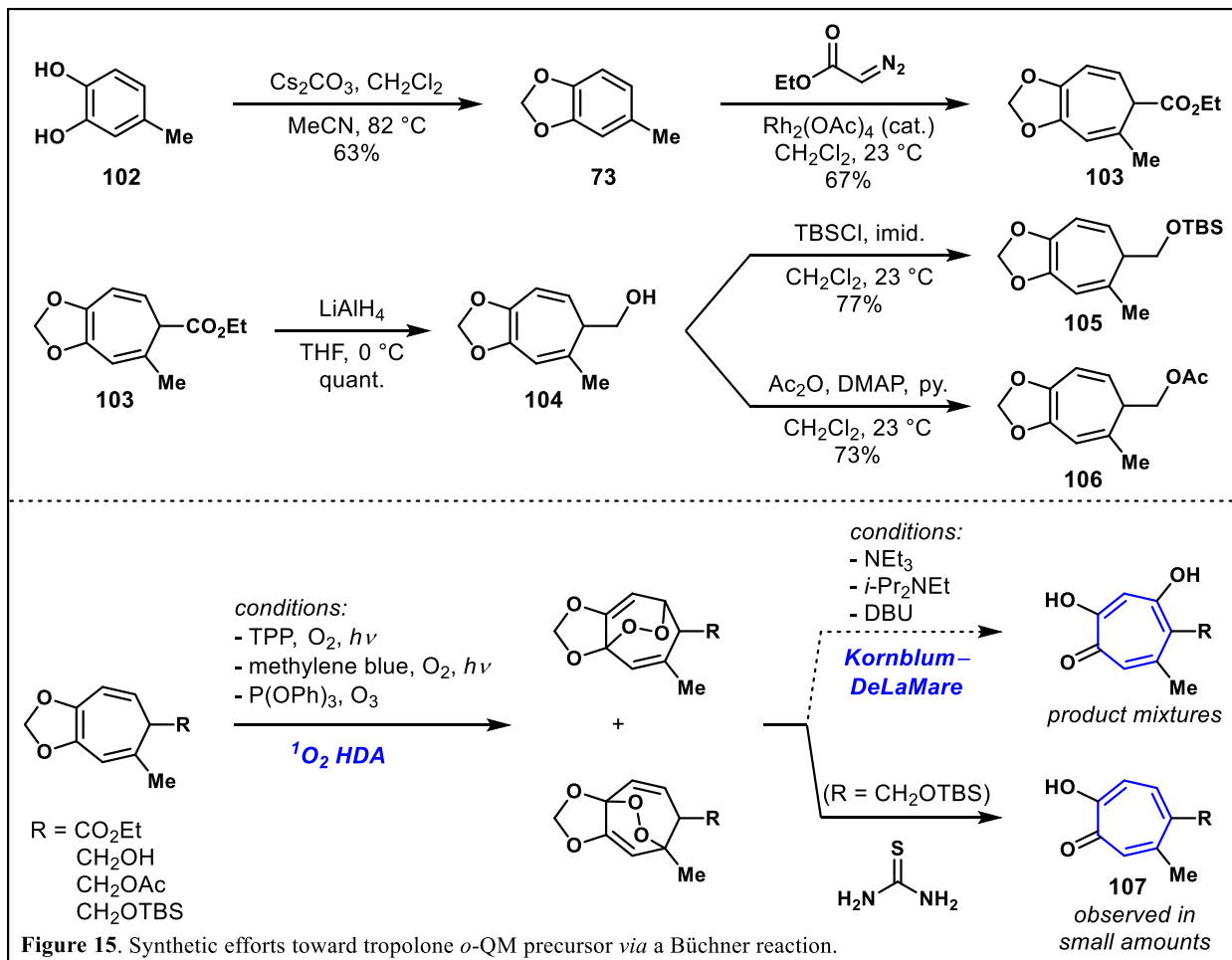


Figure 15. Synthetic efforts toward tropolone *o*-QM precursor via a Büchner reaction.

While the cycloheptatriene in Balci's synthesis of **71** is symmetrical, the symmetry of the four cycloheptatrienes in our synthesis was broken by the presence of the methyl group. Thus, we could expect two endoperoxide products whereas the Balci synthesis only produced one. This is indeed what we observed, though due to the sensitivity of endoperoxides, the two products could not be separated and were taken forward crude. The HDA could be performed by generating singlet oxygen through photochemical conditions with oxygen and a photosensitizer such as tetraphenylporphyrin or methylene blue. Alternatively, the stoichiometric equivalents of singlet oxygen generated could be controlled through the decomposition of triphenylphosphite ozonide. In either case, only one of the endoperoxide intermediates would be capable of undergoing the base-induced Kornblum-DeLaMare fragmentation, while the other would be



unreactive due to the lack of protons germinal to an endoperoxide oxygen. Unfortunately, in very few cases were distinct products observed from the conditions tried, typically employing amine bases such as triethylamine, Hunig's base, or 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU). When the mixture of endoperoxides derived from TBS ether **105** was subjected to reductive cleavage conditions with thiourea, compound **107** appears to have been the major product of the mixture. This could arise from dehydration of the reduced forms of either endoperoxide to establish aromaticity in the tropolone product. After continued failure to control the reactivity, in addition to poor selectivity of the singlet oxygen HDA, we opted to pursue other routes toward the tropolone.

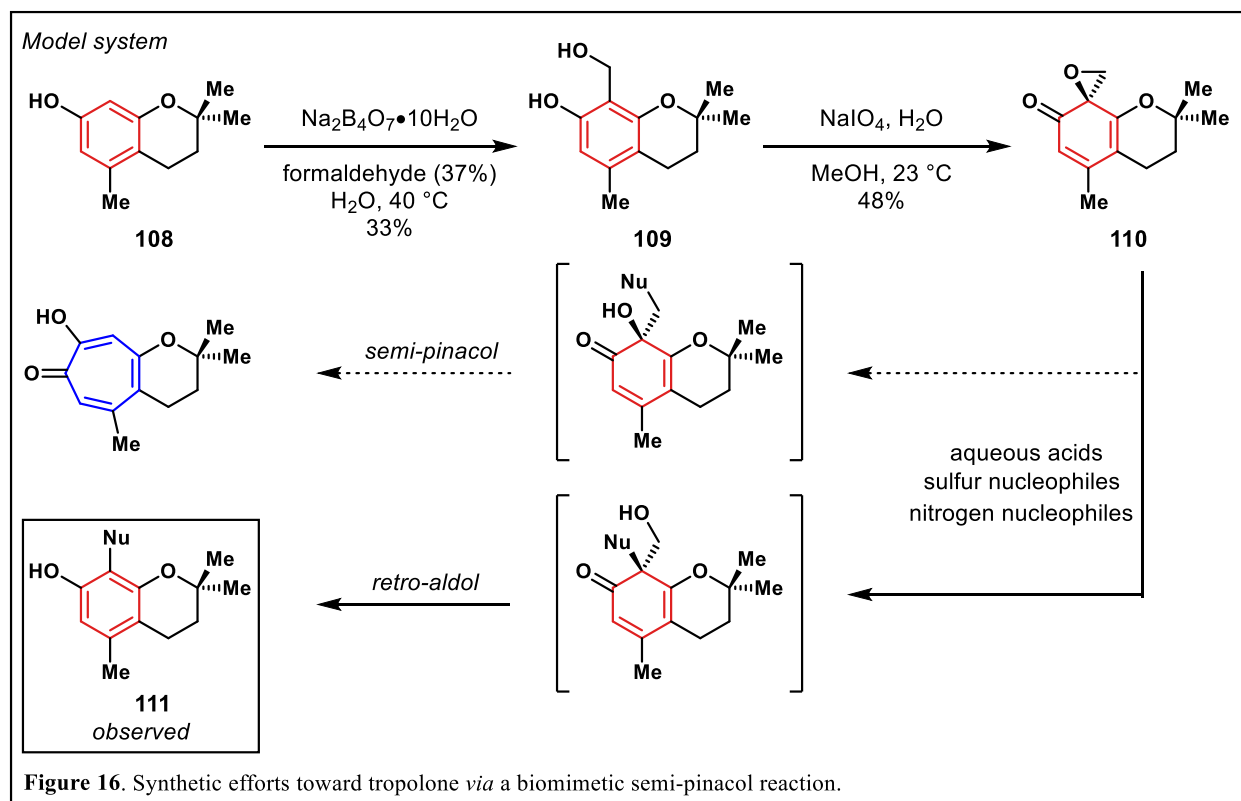
In retrospect, knowing what we now understand about the difficulties associated with the handling of tropolones, there may have been additional opportunities left in this route. At the time we were unaware of the extent to which unprotected tropolones are difficult to purify by column chromatography with silica gel due to their tendency to streak in most solvent systems. Until relatively recently, we did not appreciate how protection of the free tropolone solves this purification problem. Starting with a dimethyl catechol rather than a benzodioxole could potentially give a methylated tropolone after the Kornblum-DeLaMare fragmentation. In fact, we began to pursue this as a substrate during some of our final efforts with this route. Additionally, we now know that these systems have a tendency to undergo retro-aldol reactions, as we saw products resulting from this deleterious pathway during the de Mayo fragmentation studies. While we may not have been able to identify those products at the time, this may have been a cause for the failure of this route when employing free alcohol substrate **104**.

### 3.2.2. Biomimetic Semi-Pinacol Reaction Strategy

Our second approach to the tropolone fragment was a biomimetic semi-pinacol reaction that would generate the seven-membered ring from a six-membered ring derived from a phenol. While this was primarily inspired by the Bugg group's chemoenzymatic synthesis of tropolones from spiroepoxydienones, we believed might it possible to trigger this ring expansion using standard reactions for opening epoxides.<sup>4</sup> We quickly learned that we were not the first group to pursue this idea, as the Reiss group also attempted to synthesize tropolones from these types of intermediates using various nucleophiles in a paper published in 1984.<sup>12</sup> While their efforts were unsuccessful, we devoted a portion of our time to the recapitulation of their strategies on our specific system and attempting conditions that were not covered by their group.

Since the Baldwin group already developed the synthesis and application of the phenol *o*-QM relevant to the sesquiterpene-tropolones such as epolone A (Figure 16), our goal was to convert phenols to tropolones after the cycloaddition to the humulene core.<sup>2</sup> We elected to use a model system that resembles the sesquiterpene-phenol in order to simplify the analysis of our reactions. Known phenol **108** served this purpose well, especially since it is easily prepared on decagram scales by simply treating readily available orcinol and isoprene with phosphoric acid.<sup>13</sup> 2-Naphthol was also studied and gave the same results as **108**, however we preferred **108** due to its similarity to the true substrate. Thus, we treated phenol **108** with aqueous formaldehyde and borax, forming benzylic alcohol **109** in 33% yield. This intermediate underwent intramolecular nucleophilic dearomatization in the presence of sodium periodate to produce spiroepoxydienone **110** in 48% yield.

At this stage we screened various nucleophiles in an attempt to open the epoxide at the terminal position. We anticipated that doing so might lead to a spontaneous semi-pinacol



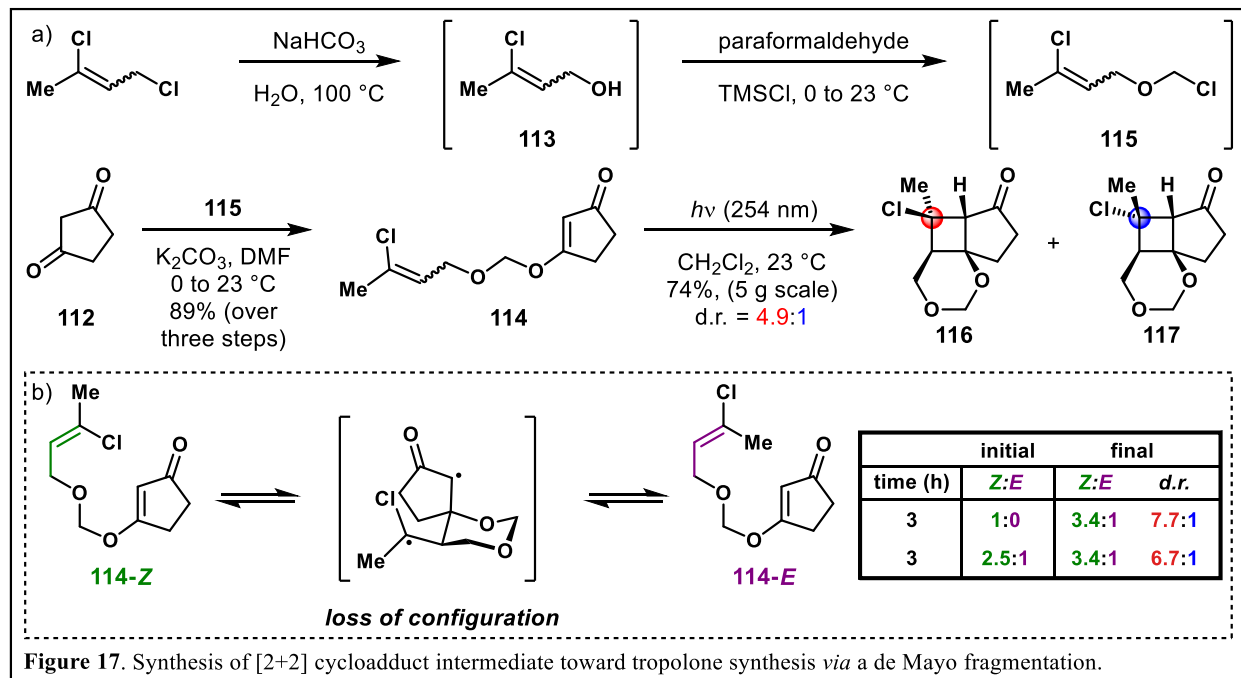
**Figure 16.** Synthetic efforts toward tropolone *via* a biomimetic semi-pinacol reaction.

rearrangement, swiftly delivering the tropolone. However, this was not the case for any of the conditions screened. In short, aqueous acids (oxygen nucleophiles), sulfur nucleophiles, and nitrogen nucleophiles all failed to deliver a tropolone product. When distinct products were formed and could be characterized, we found that they bore the structure of generic compound **111**. This would arise by nucleophile addition to the internal position followed by a retro-aldol reaction to reproduce the phenol. This unfortunate result was not surprising, as it is the primary mode of reactivity observed in the study by the Reiss group.<sup>12</sup> In fact, the last sentence of the Results section of this paper reads, “Although it is attractive as a possible biosynthetic pathway, it would appear unlikely that the ring expansion of an oxapiro[2.5]-5,7-dien-4-one to a tropolone can be effected by nucleophilic processes such as those described here.”

### 3.2.3. De Mayo Fragmentation Strategy

Our only successful pursuit of the tropolone was modeled after work by the de Mayo group wherein the seven membered ring is produced by the fragmentation of a cyclopentenone-olefin [2+2] photocycloaddition product. This route will be covered in more extensive detail than the other routes due to its success and interesting discoveries during its development. Our synthesis commenced with attempts to add derivatives of 1,3-cyclopentane diketone (**112**) and derivatives of 3-chloro-but-2-en-1-ol (**113**, mixture of *E*- and *Z*- isomers, synthesized from the corresponding dichloride) (Figure 17a). (For model studies, crotyl alcohol was used in place of **113**.) Judging by the mixtures of products obtained, it quickly became clear that the use of a tethering group would increase the productivity of our desired reaction. After failed attempts to construct a silyl tether, and failed [2+2] photocycloaddition with a carbonate tether, we opted to utilize a methylene tether. The synthesis of the tethered enone (**114**) proved to be straightforward and scalable. Treating vinyl chloride **113** with paraformaldehyde in chlorotrimethylsilane (TMSCl) solvent generates chloromethyl ether **115**, which was concentrated and used directly in the next reaction with no further purification.<sup>14</sup> This was then added to a suspension of diketone **112** and potassium carbonate in dimethylformamide (DMF) to form **114** as a mixture of olefin isomers in 89% yield.

Next we began our study of the intramolecular [2+2] photocycloaddition of **114** (again, validating the strategy first with the analogous crotyl ether). Fortunately, an initial screen of conditions showed that irradiation of a dichloromethane solution of **114** in a quartz vessel with 254 nm light produced the highest yield and greatest purity of cycloadduct **116** and its diastereomer **117**. Standard conditions employ a ~1-L quartz vessel containing five grams of **114**, 0.04 M in dichloromethane, irradiated by six CFL bulbs for 30 hours, which produces **116**



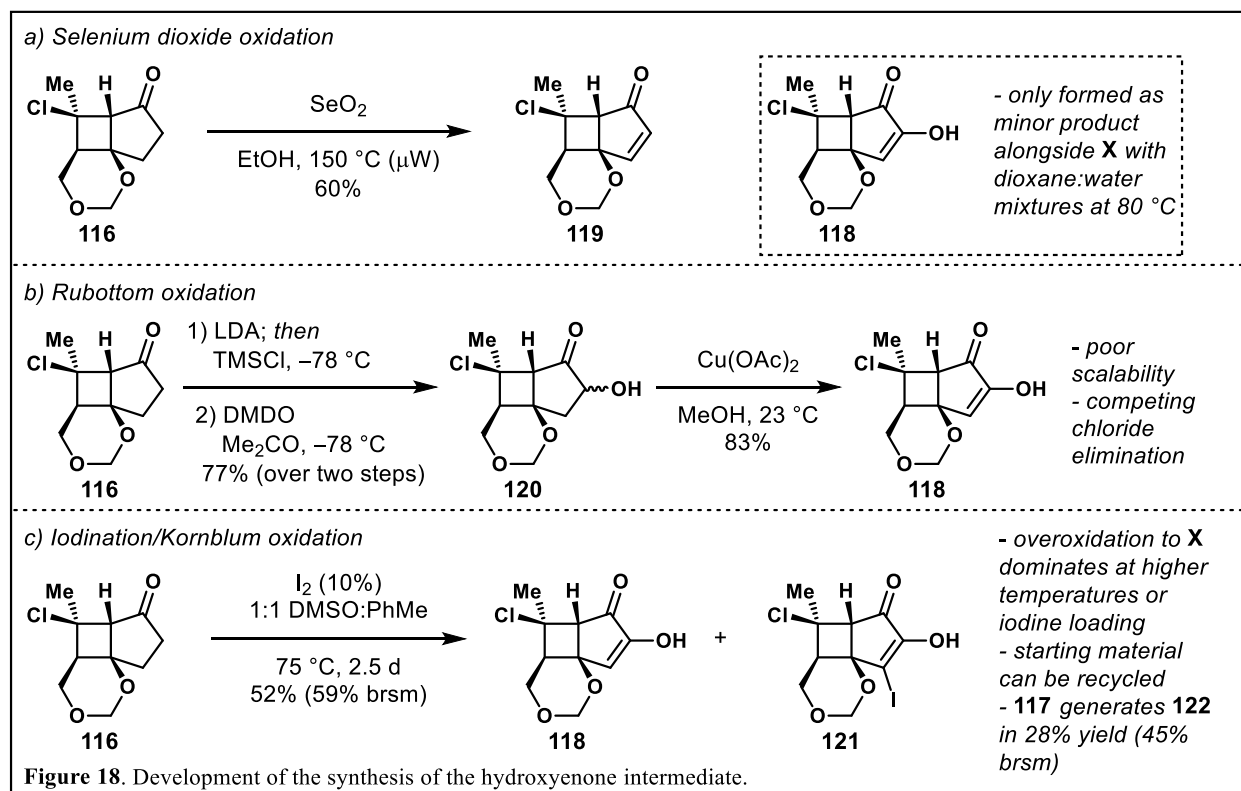
and **117** in a 4.9:1 ratio and 74% total yield. The reaction must be run in a quartz vessel to achieve reasonable reaction rates, and concentrations above 0.04 M cause the reaction to become impractically sluggish. The products can be separated by column chromatography, however, a more practical procedure is to take up the concentrated crude reaction mixture in diethyl ether and filter the suspension. This gives most of **116** generated in the reaction in excellent purity, and the supernatant may be saved for further separation of the isomers later. Both diastereomers can be taken forward in the synthesis and give approximately the same results, but they are separated at this stage to facilitate purification in later steps. The discussion of the development of the synthetic route will refer to major product **116**, though all reactions are successful on **117** as well. The major drawback to this step is the limitation on scale imposed by the size of the vessel. This would be an excellent opportunity for the development of conditions using a photochemical flow reactor.

A final note about the [2+2] photocycloaddition is regarding an observation that provides some mechanistic insight. We found that the ratio of **116** to **117** produced is typically consistent,

and it is independent of the ratio of olefin isomers of **114** employed in the reaction (Figure 17b). To explore this further, we studied the relative quantities of products and starting materials as the reaction progressed on a 50 milligram scale. Whether pure **114-Z** or a 2.5:1 mixture of **114-Z** to **114-E** was employed, after three hours, the ratio between **114-Z** and **114-E** was 3.4:1. The ratio between the products was 7.7:1 or 6.7:1, which, while not identical, do not correspond to the initial ratio of olefin isomers. Compounds **116** and **117** do not interconvert under UV irradiation, but do undergo decomposition at extended reaction times. The loss of olefin configuration and independent diastereoselectivity of product formation indicates that the [2+2] cycloaddition is likely proceeding over a stepwise mechanism such as that shown in Figure 17b. It is possible that a diradical intermediate is initially formed following the closure of the 1,3-dioxane ring. The tertiary radical may freely rotate, then after equilibration, collapse to the product or fragment to the starting material. While we found this interesting, we did not attempt to control the selectivity because either diastereomer can be taken forward to the same tropolone product.

The oxidation of **116** initially proved to be surprisingly difficult. We first attempted direct  $\alpha$ -oxygenation with selenium dioxide to give hydroxyenone **118**, however a mixture of several products were obtained (Figure 18a). After further exploration, the formation of **118** could be achieved alongside enone **119** using dioxane and water mixtures as solvent and heating to 80 °C, though we desired a reaction that could selectively form **118**. However, **119** could be formed selectively in 60% yield by heating a solution of **116** and selenium dioxide in ethanol to 150 °C in a microwave. Compound **119** could also be generated by dehydrogenation using Mukaiyama's method with *N-tert*-butylbenzenesulfinimidoyl chloride in 75% yield.<sup>15</sup>

An improved synthesis of **118** was developed employing a Rubottom oxidation (Figure 18b). Formation of the silyl enol ether with lithium diisopropylamide (LDA) and trimethylsilyl



chloride (TMSCl), then treatment with dimethyldioxirane (DMDO) generated a mixture of alcohols (**120**). No other oxidants tried, such as *m*-CPBA or Davis oxaziridine successfully delivered the oxygenated product. After passing the mixture through a silica plug, the material was treated with copper(II) acetate, which gives hydroxyenone **118**. While this initially provided enough material for exploration of the subsequent tropolone formation, it was not sustainable for the purposes of scale-up for multiple reasons. First, there is a competing chloride elimination reaction that produces the exocyclic olefin in the presence of strong bases. The use of more sterically hindered lithium hexamethyldisilazide (LHMDS) suppresses this side reaction, but did not completely prevent it. Second, DMDO must be prepared immediately before use and has a limited shelf-life. When employing the standard procedure published in *Organic Syntheses*, we could not produce enough DMDO in a single pass to run the Rubottom oxidation on large scales.<sup>16</sup> Finally, we could generate DMDO *in situ*, which enabled reactions of larger scales, but

gave inconsistent yields. The result of these drawbacks was that **118** was delivered in unreliable quantities and purities. Thus, we continued our search for another oxidation.

The next successful oxidation of **116** to **118** uses a catalytic quantities of iodine in the presence of dimethyl sulfoxide (DMSO) and heat (Figure 18c).<sup>17,18</sup> Effectively, it is an  $\alpha$ -iodination of the ketone enabled by keto-enol tautomerization followed by a Kornblum oxidation. The two equivalents of hydroiodic acid generated in this process are oxidized back to iodine by the excess of DMSO to complete the catalytic cycle. After screening several conditions and iodine sources, we found that the reaction produced the greatest quantities of **118** by heating a solution of **116** in 1:1 DMSO:toluene between 70 and 75 °C with 10 mol% iodine for about two and a half days. We found that higher temperatures or greater quantities of iodine causes the product to quickly oxidize to the  $\beta$ -iodohydroxyenone **121**. Thus, we decided to decrease the conversion of both **118** to **121** and **116** to **118**, then recover **116** for resubjection to the reaction conditions. In total, **116** yields **118** in 52% yield, or 59% based on recovered starting material (brsm) and **117** yields **122** in 28% yield, or 45% brsm. While this step is not without flaws, it is currently the most reliable synthesis of **118** and has been run on up to a 15 gram scale.

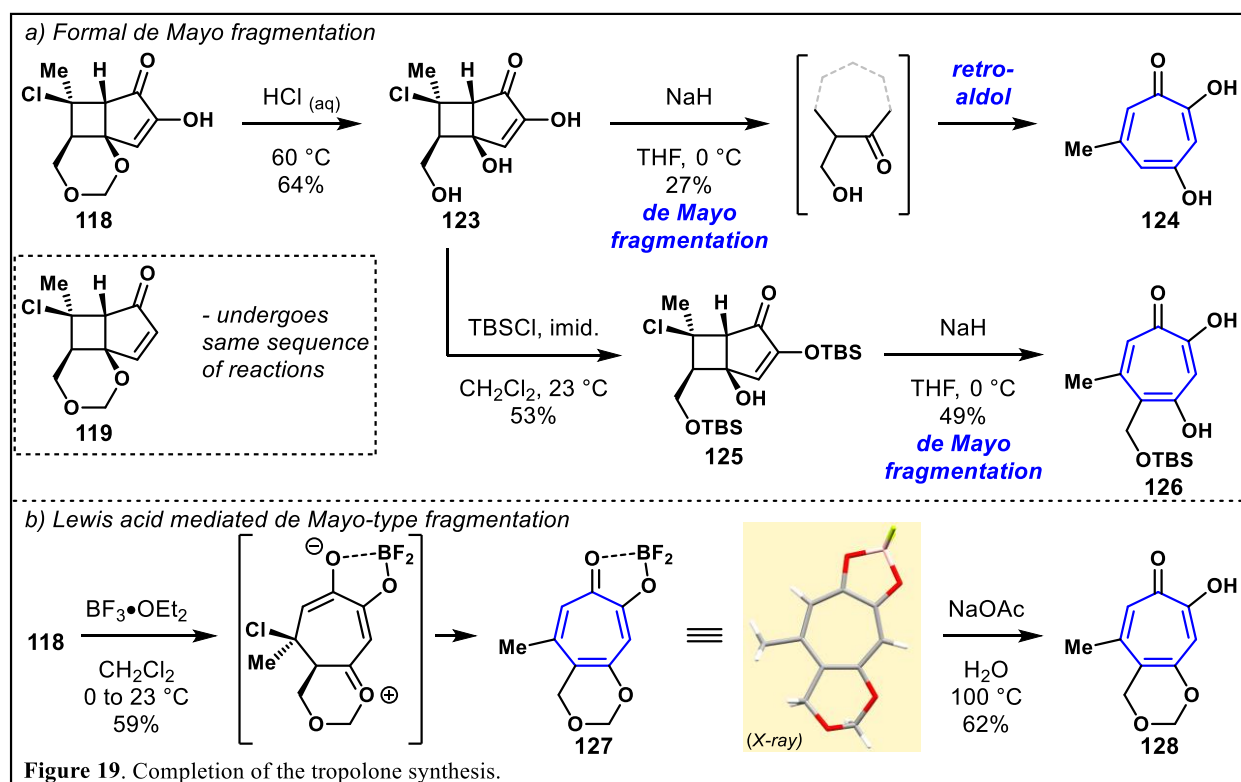
With all functionality needed for the tropolone now packaged into the tricyclic structure, we aimed to induce a de Mayo fragmentation (Figure 19a). Our first strategy was toward a formal de Mayo fragmentation in which an alkoxide is generated and collapses to cleave the cyclobutane ring. To this end, we treated **118** with 1M HCl at 60 °C to deprotect the acetal to give compound **123**. We anticipated that this may undergo spontaneous fragmentation but the tertiary alcohol was stable under acidic and neutral conditions. Notably, this same reactivity was observed for enone **119**, but when an analogous deprotection was conducted on ketone **116**, decomposition occurred. We then treated **118** with excess sodium hydride to produce an



unexpected tropolone (**124**), evidently formed *via* a retro-aldol reaction following de Mayo fragmentation. Since the methylene hydroxy functionality would be needed in order to form an *o*-QM, we elected to protect **123** as the bis-TBS ether **125** (the hydroxyenone was protected preferentially over the primary alcohol) in order to prevent the occurrence of the undesired retro-aldol. This was successful, as treatment of **125** with excess sodium hydride gave tropolone **126**, wherein the TBS protecting group on the tropolone was cleaved.

We were at first encouraged by the short synthesis of the tropolone, as this validated the strategy employing the de Mayo fragmentation. However, we anticipated that a silanolate would be a suboptimal leaving group for *o*-QM formation. Additionally, we discovered at this stage that purification of the unprotected tropolones is quite challenging using standard silica gel chromatography. Concurrently with the development of the synthesis of **126**, we also envisioned a Lewis acid mediated de Mayo-type fragmentation of **118** that may allow for retention of the 1,3-dioxane ring. We were curious to learn if this group could serve as an *o*-QM trigger as it did for tropolone **46** prepared by the Baldwin group (Figure 7).<sup>19</sup> Moreover, this type of Lewis acid mediated fragmentation has been studied by the Bach group, wherein the oxocarbenium generated after fragmentation induced by boron trifluoride diethyletherate was trapped by allyl- or hydrosilanes.<sup>20</sup> We believed that in the absence of a nucleophile, the oxocarbenium would be deprotonated at the  $\alpha$ -position, perhaps by an eliminated chloride anion, to form an enol ether, restore the 1,3-dioxane structure, and bring the seven-membered ring into full conjugation.

Fortuitously, treating **118** with excess boron trifluoride diethyletherate induced the de Mayo fragmentation as desired (Figure 19b). Following purification, spectroscopic data indicated that a tropolone was formed, but an O–H was puzzlingly absent as indicated by IR spectroscopy. To obtain unambiguous proof of the structure, the tropolone was readily crystallized from

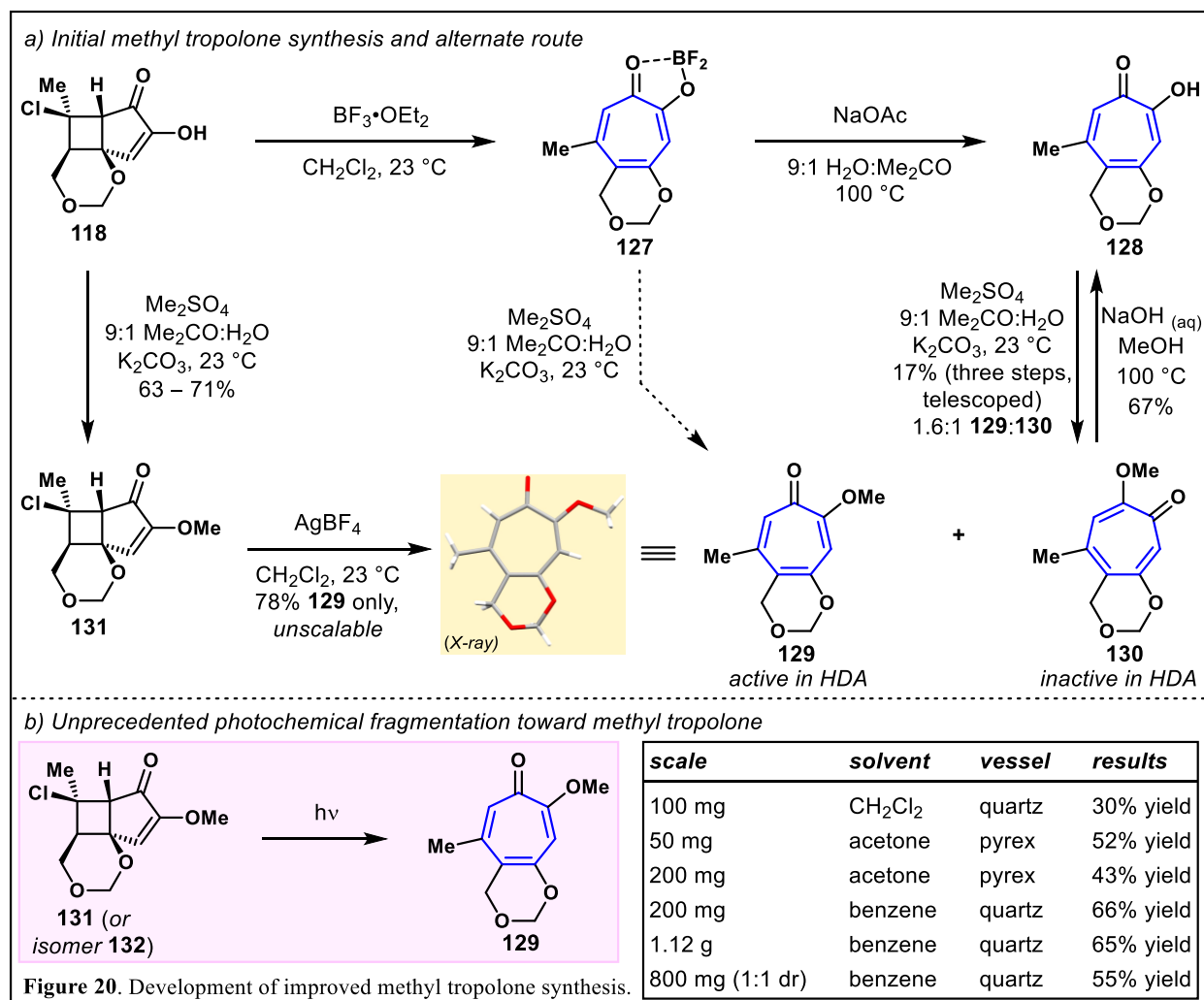


acetone and analyzed by single crystal X-ray diffraction. This revealed that the tropolone was actually tropolone difluoroborate **127**. While the retention of boron difluoride was unexpected after basic work-up, it was not entirely surprising, as these complexes are known.<sup>21</sup> Compound **127** was remarkably stable to ambient conditions and was easily purified by silica gel chromatography or recrystallization. Moreover, decomplexation from boron could be achieved in high yield under a variety of mild conditions. The best condition for **127** being acetolysis in refluxing aqueous sodium acetate to give **128** in 62% yield. Additionally, hydroxyenone **122** could also be converted to **127** in the same manner. The major drawback to this step is that the reaction yield was variable, typically inversely correlated to reaction scale, due to decomposition and the formation of bistropolone chelates to boron. The yields were typically between 30% and 60%, which was sufficient for early studies of the *o*-QM cycloaddition.

The success of the de Mayo fragmentation strategy can be attributed to a number of its features. First, it allows for the introduction and embellishment of the functional groups prior to

the reveal of the tropolone, minimizing the difficulties associated with handling tropolones. More specifically, two degrees of unsaturation are packaged into the chlorocyclobutane moiety, which allow for introduction of the final degree of unsaturation *via* the selective  $\alpha$ -oxygenation of a secondary position over a tertiary position. Such a process may have been more difficult at the tropolone stage as both  $\alpha$ -positions on a tropone would be similarly reactive. Second, the stability of the tropolone-boron complex **127** and facile decomplexation greatly improved the practicality of the route. Finally, the methylene acetal serves three different purposes: a tether in the [2+2] photocycloaddition, a protecting group in the de Mayo fragmentation, and an *o*-QM trigger in the HDA.

For reasons that will be explained in detail in section 3.4, we also required methylated tropolone **129** for our cycloaddition studies. Our initial approach toward synthesizing **129** was by methylation of the unprotected tropolone **128** with dimethyl sulfate and potassium carbonate (Figure 20a). However, methylation was unselective, and tropolone **130** was formed as a minor product. The position of the methyl group for each product was initially determined by 2D NOE  $^1\text{H}$  NMR experiments and later by X-ray crystallographic analysis of the major product. As could be expected from its structure, we later discovered that **130** is incapable of undergoing a retro-HDA reaction to form an *o*-QM and was thus useless in our synthesis. Fortunately, it could be hydrolyzed with refluxing aqueous NaOH in methanol to return **128**. This recycling process eventually became unsustainable for the quantities of tropolone that needed to be generated, so we began the development of a higher yielding synthesis of **129**. Direct methylation of tropolone-boron chelate **127** produced mixtures of **128**, **129**, **130**, and starting material, so this strategy was immediately abandoned. Backing up one step further, we realized that installation of the methyl group at the hydroxyenone stage could allow for the selective formation of **129**



rather than mixtures with **130**, assuming the de Mayo fragmentation could still be achieved. Thus, hydroxyenone **118** was methylated under the same conditions employed for the tropolone to generate **131** in as high as a 71% yield. Treatment of **131** with Lewis acids failed to induce the fragmentation, so we began to explore more unconventional strategies.

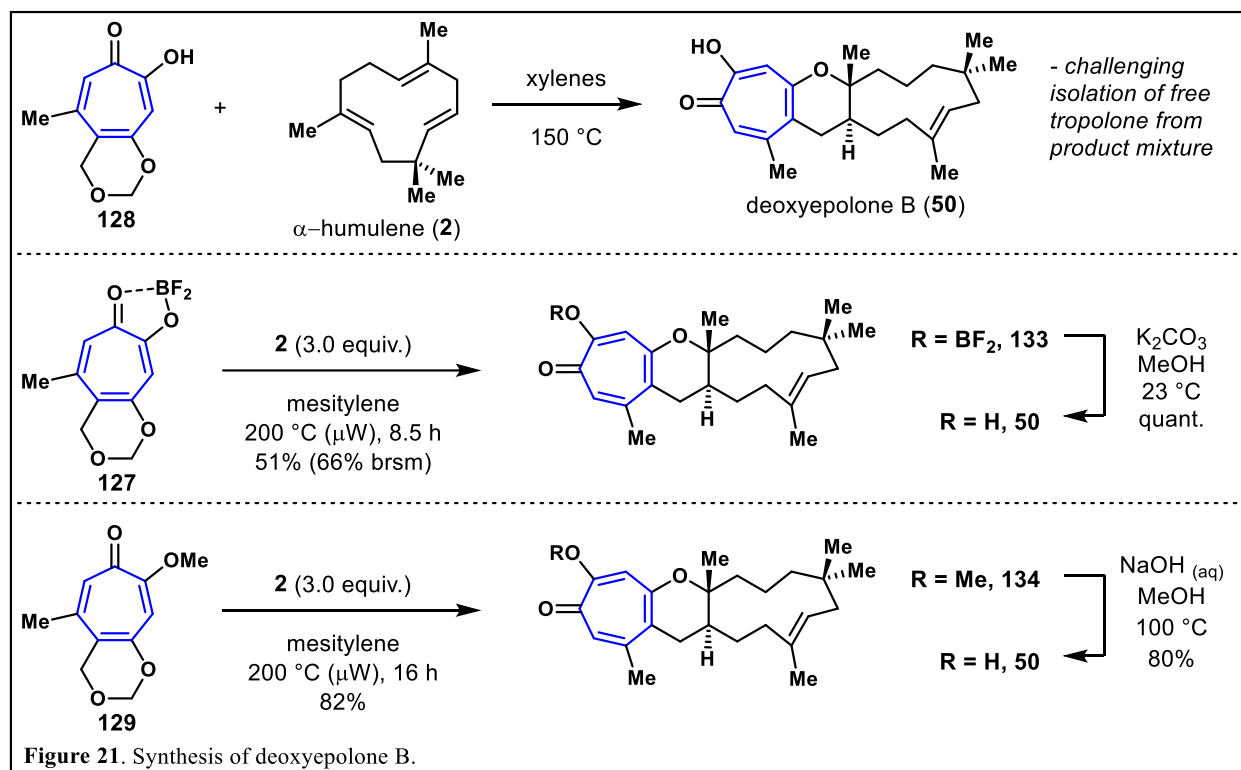
Since one of the final steps in the de Mayo-type fragmentation is the elimination of the chloride, we became curious if it would be possible to initiate the fragmentation by chloride abstraction to generate a tertiary carbocation that could lead to cleavage of the cyclobutane. To achieve this, we screened silver salts and found that silver tetrafluoroborate produced **129** as the only tropolone product in 78% yield. Our excitement about this new and improved synthesis was

quickly quelled by the finding that the fragmentation is impractically slow on scales as high as 200 mg. The cost of the quantity of silver salt required to achieve a reasonable reaction rate was not worth reward of the shorter route.

In continuing to explore ways to manipulate the functionality available in compound **131**, we noticed its vinylcyclobutane moiety and considered the possibility of a radical cyclobutane fragmentation. The pyrolytic rearrangements of vinylcyclobutanes are known to proceed through radical intermediates, but if pyrolysis of **131** could generate **129**, uncontrolled *o*-QM formation would also be likely occur.<sup>22</sup> (We performed an experiment to test this fragmentation and subsequent cycloaddition with **131** and an olefin and did not observe any HDA products.) Alternatively, since the vinylcyclobutane in **131** is part of the hydroxyenone chromophore, we considered the possibility that UV irradiation would induce cyclobutane fragmentation (Figure 20b). To the best of our knowledge, this type of photochemical fragmentation is unprecedented. Indeed, irradiation of a dichloromethane solution of **131** in a quartz vessel produced **129** in 30% yield. This yield could be increased to 52% with acetone as the solvent, but with diminishing returns with an increase in scale. By changing the solvent to benzene, the reaction could be run on gram scale with a consistent yield of about 65%. As before, mixtures of **131** and diastereomer **132** underwent the same reactivity, but in a slightly reduced yield. Notably, photosensitizer additives had no effect and the reaction could not be thermally induced.

#### 3.2.4. Synthesis of Deoxyepolone B

Finally, we were prepared to attempt the synthesis of deoxyepolone B (**50**), which would advance our studies to the state of the art for the sesquiterpene-tropolone syntheses at the time and validate our *o*-QM HDA strategy (Figure 21). Our first attempted cycloaddition was between unprotected tropolone **128** and  $\alpha$ -humulene in xylenes at 150 °C. While it appeared that the



reaction was successful judging by  $^1\text{H}$  NMR analysis of the crude mixture, isolation of the product was complicated by the difficulties associated with purifying tropolones with silica gel chromatography. To bypass these issues, we then attempted the cycloaddition with the boron difluoride tropolone complex **127**, which successfully delivered deoxyepolone B as its boron difluoride complex (**133**). We eventually found that microwave irradiation increases the reaction rate. At 200 °C, **133** could be obtained after 8.5 hours in 51% yield (or 66% based on recovered tropolone). In this case, decomplexation of the tropolone from boron was accomplished best by methanolysis with methanol and potassium carbonate. On the other hand, the cycloaddition between  $\alpha$ -humulene and methyl tropolone **128** proceeded in 82% yield under similar conditions to give methyl deoxyepolone B (**134**). Generally, **128** provides superior yields in HDA reactions compared to **127**. In all cycloaddition reactions performed, a crystal of butylated hydroxytoluene (BHT) is added to the reaction to suppress the propagation of radicals generated under the forcing conditions. Likewise, we ran our early cycloadditions in silylated microwave vials

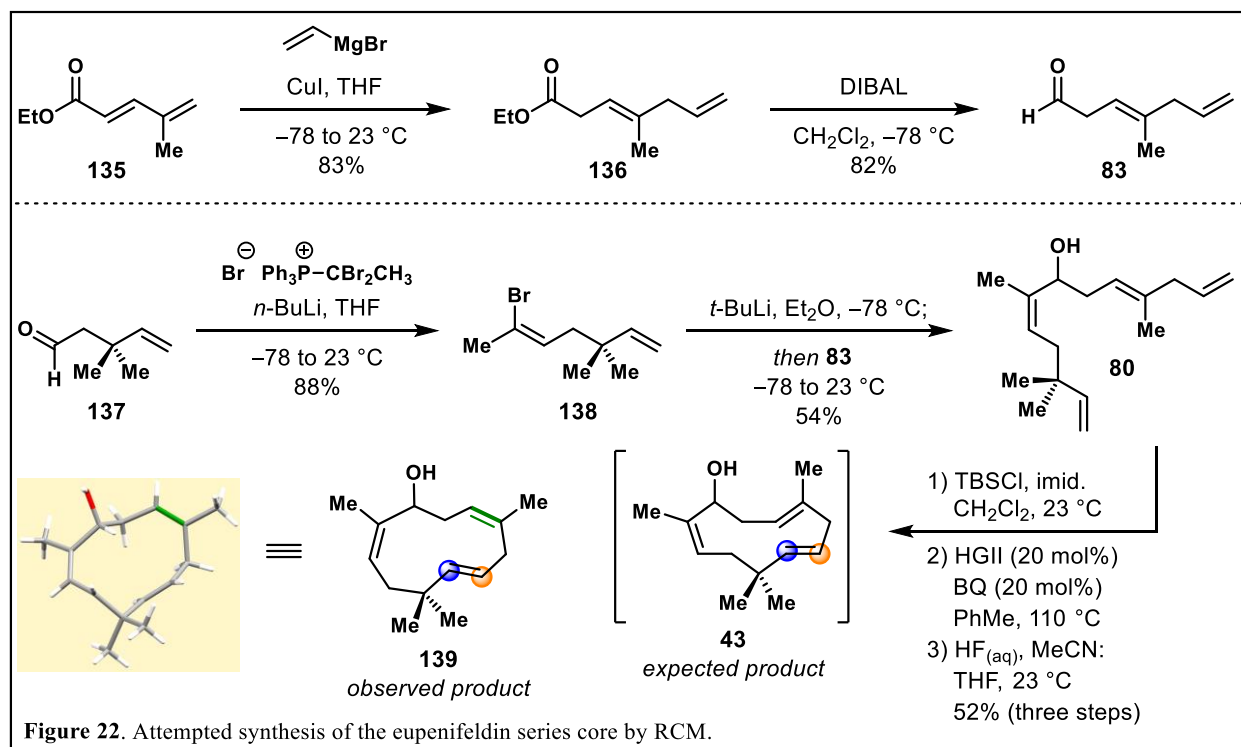
prepared by refluxing hexamethyldisilazane (HMDS) in the glassware for several hours. We took this extra measure to prevent interference of the reaction by the acidity of the glass at high temperatures, though we found later that identical results were obtained with untreated glassware.

In conclusion, we have developed concise and scalable syntheses of tropolone *o*-QM precursors then demonstrated their reactivities in the retro-HDA and HDA sequence to construct the sesquiterpene-tropolone framework. Though these studies we were able to trigger cyclobutane fragmentations in four different ways, one of which, to the best of our knowledge, is unprecedented. We are initiating the development of this photochemical cyclobutane fragmentation into a reaction methodology. What still remained to be tested was the first cycloaddition with the macrocyclic alcohol **43** or **45**, or derivatives, and the second cycloaddition to access the more biologically relevant bistropolones. The approaches taken to overcome these challenges will be addressed in section 3.4.

### **3.3. Synthesis of 10-Hydroxy- $\alpha$ -Humulene**

#### *3.3.1. Ring Closing Metathesis Strategies*

Our first endeavor in the synthesis of the macrocyclic fragment of the sesquiterpene-tropolones employed a RCM strategy to synthesize compound **43**, which is the core of the eupenifeldin series (Figure 22). We began with the synthesis of known unsaturated ester **135** via a Wittig reaction between a stabilized phosphonium ylide and methacrolein.<sup>23</sup> Conjugate addition of a vinylcuprate generated from vinyl magnesium bromide and copper(I) iodide yielded ester **136** in 83% yield. To complete the synthesis of this fragment, **136** was reduced by the slow addition of an equivalent of DIBAL to give aldehyde **83** in 82% yield. Synthesis of the second fragment of the macrocycle started with another careful reduction of a commercially available



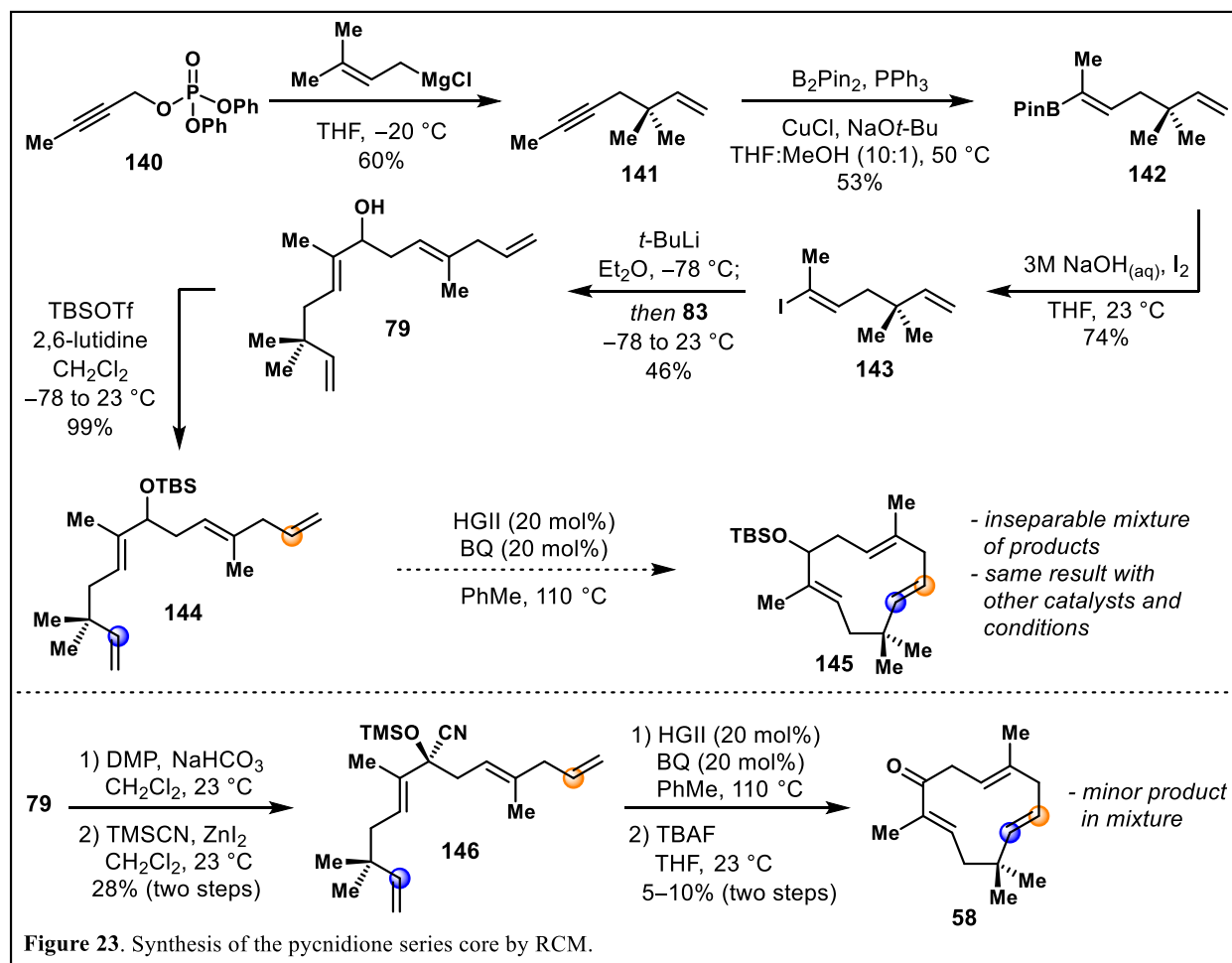
ethyl ester to aldehyde **137**, which is a known compound.<sup>24</sup> A Wittig reaction employing Smithers' dibromoethylphosphonium salt, wherein lithium halogen exchange with *n*-butyllithium forms the ylide rather than deprotonation, produced *Z*-vinyl iodide **138** in 88% yield.<sup>25</sup> Treating **138** with *tert*-butyllithium, then trapping the vinyl lithium species with aldehyde **83** gave allylic alcohol **80** in 54% yield. The RCM precursor was then produced by protection of the alcohol with a TBS group in 98% yield.

The RCM conditions that delivered buddledone were the first that we attempted to form the macrocycle.<sup>6</sup> We were delighted to find that Hoveyda–Grubbs second generation catalyst (HGII) and benzoquinone (BQ), both 20 mol%, in refluxing toluene successfully delivered a macrocyclic product in 88% yield. To verify that the olefin formed possessed the desired configuration, we deprotected the TBS group with hydrofluoric acid in 61% yield and attempted to crystallize the compound. The resulting alcohol spontaneously formed needles when concentrated, and we were able to confirm its structure by X-ray crystallographic analysis. At



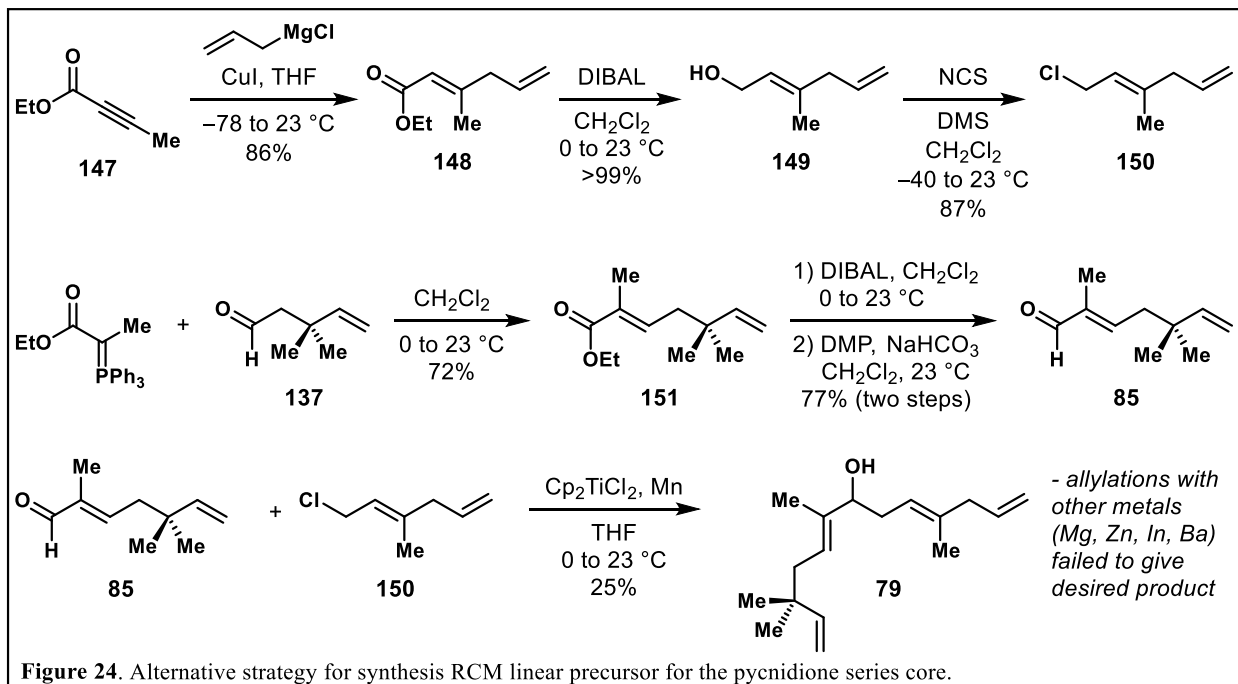
first glance, we saw that the desired configuration was present for the new olefin, then realized that another olefin in the molecule had isomerized from an *E*- to *Z*-configuration, confirming the identity of the compound to be **139**. Unfortunately, this macrocyclic framework is not present in any known sesquiterpene-tropolone, so this compound was not useful in our total synthesis. A screen of conditions that included different solvents, temperatures and catalysts (Grubbs I and II) produced only this undesired product. However, encouraged by the fact that macrocycle formation is possible by RCM, we then turned our efforts toward the all *E*-configured triene that constitutes the pycnidione series core.

We experimented with two separate routes toward macrocycle **45** using the RCM strategy. The favored route bears resemblance to the attempted synthesis of **43** (Figure 23). We were able to continue to use aldehyde **83** in this case, since the only the vinyl lithium fragment differed from the first synthesis. Addition of prenylmagnesium chloride to 2-butynyldiphenyl phosphate (**140**) selectively gave the  $\gamma$ -addition product, **141**, in 60% yield.<sup>26</sup> Copper catalyzed hydroboration of the enyne delivered vinyl pinacolato boronic ester **142** in 53% yield.<sup>27</sup> Stereoretentive *ipso*-iodination then delivered *E*-vinyl iodide **143** in 74% yield.<sup>28</sup> Employing conditions identical to those that formed **80**, allylic alcohol **79** was formed in 46% yield, then TBS protection gave silyl ether **144** in 99% yield. Our first pass at RCM delivered only inseparable product mixtures that did not vary significantly upon changing the reaction conditions, and desired product **145** was not observed. After continued failure to tame the reaction, we again looked to Harmata's synthesis of buddledone and elected to attempt closure of a TMS cyanohydrin, which we anticipated would favor ring closure over oligimerization pathways due to the Thorpe–Ingold effect. Oxidation of alcohol **79** to the corresponding ketone with Dess–Martin periodinane (DMP), then treatment with trimethylsilyl cyanide and catalytic



zinc(II) iodide delivered TMS cyanohydrin **146** in 28% yield over two steps. Our standard RCM conditions with HGII, then deprotection with tetrabutylammonium fluoride (TBAF) gave a ketone that appeared to match the  $^1\text{H}$  NMR spectroscopic data reported by Takahashi in 1983. However, the desired product was only a minor component of a product mixture and could only be isolated, with much difficulty, in 5-10% yield.

We had decided at this point that our time and energy would be better directed toward a different key step for macrocycle formation. However, before moving on, one additional route toward allylic alcohol **79** was pursued and is worth mentioning (Figure 24). This route began with the addition of an allylcuprate generated from allylmagnesium chloride and copper(I) iodide to ethyl 2-butynoate (**147**) to generate  $\alpha,\beta$ -unsaturated ester **148** in 86% yield. Reduction to



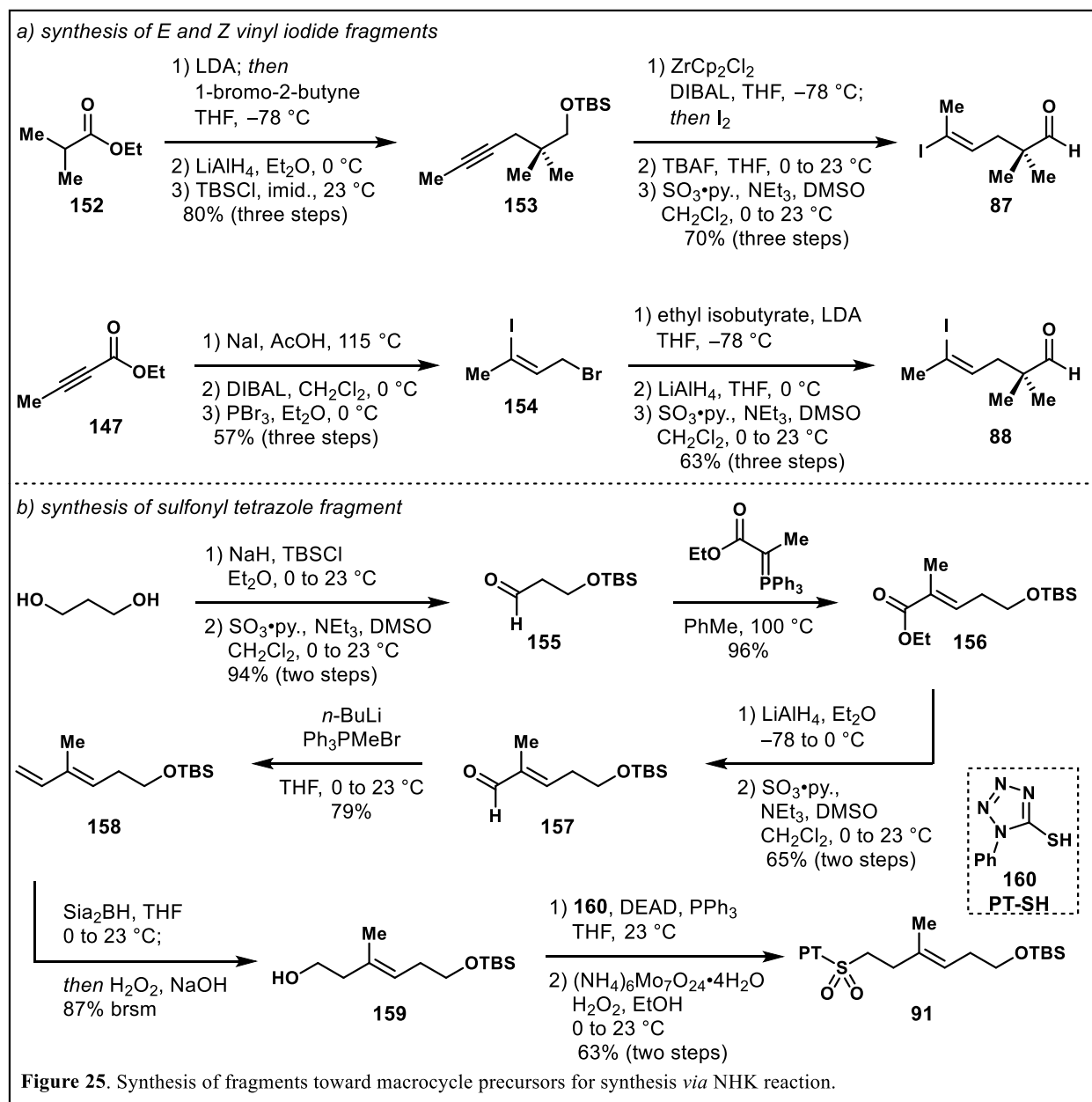
alcohol **149** was achieved with excess DIBAL in quantitative yield. Treatment of the tertiary alcohol with *N*-chlorosuccinimide (NCS) and dimethyl sulfide (DMS) then delivered allylic chloride **150** in 87% yield. Synthesis of the second fragment again began with aldehyde **137**. A Wittig reaction with a stabilized phosphonium ylide gave ester **151** in 72% yield. This ester could not be converted directly to the aldehyde with a single equivalent of DIBAL, so it was instead reduced entirely, then oxidized to aldehyde **85** in a 77% yield over two steps. Finally, we attempted several conditions for the metalation of **150** and subsequent addition into **85**, including the formation of allyl magnesium, zinc, indium, titanium, and barium species. Only the addition of the allyl titanium intermediate, formed from an intermediate titanium(III) species generated by the reduction of titanocene dichloride with manganese, was successful at delivering product **79**, and only in 25% yield.

### 3.3.2. Nozaki-Hiyama-Kishi Reaction Strategies

As with our strategy employing RCM in the synthesis of the macrocycles **45** and **43**, we envisioned that the synthesis of a linear NHK precursor would be modular such that both

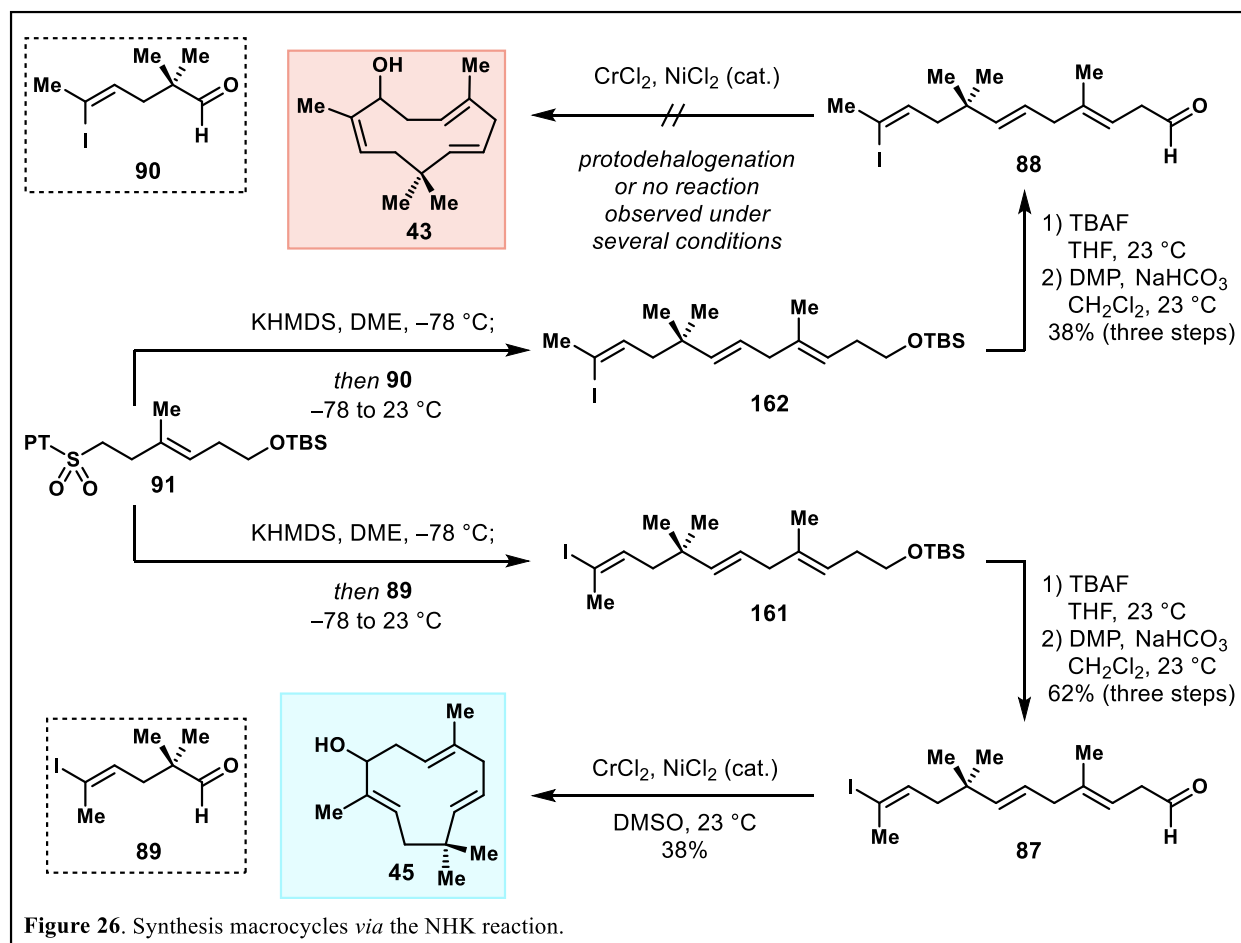
macrocycles could be formed in the combination of one of two olefin isomer fragments with a single fragment applicable in both syntheses. We anticipated that a Julia–Kocienski olefination could unite these components, so we began our efforts with the synthesis of two isomeric vinyl iodides, **87** and **88** (Figure 25a). The former was synthesized by first alkylating the lithium enolate of ethyl isobutyrate (**152**) with 1-bromo-2-butyne. This product was then reduced with lithium aluminum hydride, then protected as the TBS ether to give **153** in 80% yield over three steps. Hydrozirconation with Schwartz’s reagent generated *in situ* from zirconocene dichloride and DIBAL, then trapping with iodine gave the corresponding *E*-vinyl iodide. Deprotection of the TBS group with TBAF followed by a Parikh–Doering oxidation gave aldehyde **87** in 70% yield over three steps. The *Z*-vinyl iodide was synthesized by refluxing **147** in acetic acid with sodium iodide. Reduction of this ester to the alcohol with DIBAL, then bromination with phosphorus tribromide delivered allylic bromide **154** with a *Z*-vinyl iodide in 57% yield over three steps. The same alkylation reaction with **152** was performed with **154**, then lithium aluminum hydride reduction and another Parikh–Doering oxidation gave aldehyde **88** in 63% yield over three steps.

Next, we turned to the synthesis of sulfone **91** to be used in the Julia–Kocienski olefination (Figure 25b). First, we performed a mono-TBS protection of 1,3-propanediol, then a Parikh–Doering oxidation gave aldehyde **155** in 94% yield over two steps. A Wittig reaction with a stabilized ylide delivered **156** in 96% yield. Reduction of the ester and Parikh–Doering oxidation gave the corresponding aldehyde **157** in 65% yield over two steps. Another Wittig reaction installed a methylene group to give conjugated diene **158** in 79% yield. An incomplete but selective hydroboration of the terminal olefin with disiamylborane followed by oxidation with hydrogen peroxide formed homoallylic alcohol **159** in 87% yield based on recovered



starting material. A Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol (**160**, **PT-SH**), then oxidation with ammonium heptamolybdate finally gave sulfone **91** in 63% yield over two steps.

With these three fragments in hand, we pursued the divergent syntheses of both macrocycles **45** and **43** (bottom and top sequences in Figure 26, respectively). Treating sulfone **91** with potassium hexamethyldisilazide (KHMDs) then **89** or **90** delivered trienes **161** or **162**. Deprotection of the silyl ether with TBAF, then oxidation to the corresponding aldehydes with



DMP gave NHK precursors **87** or **88** in 62% or 38% yield over three steps. To our delight, NHK conditions employing superstoichiometric chromonium(II) chloride and catalytic nickel(II) chloride in DMSO delivered macrocycle **45** in 38% yield. However, these same conditions as well as others only delivered protodehalogenation or no reaction in attempts to convert **88** to macrocycle **43**. Even when NHK reactions with both precursors were performed in parallel, these results were obtained. Regardless, this route was the first to generate quantities of macrocycle **45** for early cycloaddition studies toward the pycnidione series of sesquiterpenetropolones. At this time, we were aware that future studies would require larger quantities of **45** to be generated, so the low yield of the NHK reaction and issues with scalability owing to the requirement of dilute reaction conditions led us to continue our search for a higher yielding and shorter route.

### 3.3.3. McMurry Reaction Strategies

After having attempted multiple macrocyclization strategies, we accumulated several intermediates that could be combined using familiar chemistry to build linear precursors to the macrocycle. Inspired by McMurry's synthesis of  $\alpha$ -humulene, we identified ways we could use intermediates we already had on hand to synthesize two dicarbonyl compounds that could potentially undergo a McMurry coupling to give **45**.<sup>9</sup> Our first strategy utilized a Julia–Kocienski olefination much like that we performed in the NHK route (Figure 27). We started with the sodium borohydride reduction of methyl acetoacetate to the alcohol, then TBS protection to give silyl ether **163** in 62% yield over two steps. Reduction of the ester to the alcohol, then a Mitsunobu reaction with **160** produced thioether **164** in 68% yield over two steps. Oxidation to the sulfonyl tetrazole with *m*-CPBA produced known sulfonyl tetrazole **165** in 74% yield.<sup>30</sup> The Julia–Kocienski olefination of **165** with aldehyde **89** proceeded to give vinyl iodide **166** in 74% yield. Lithiation with *tert*-butyllithium and trapping with aldehyde **96**, followed by protection as the tetrahydropyranyl (THP) acetal formed bis-TBS ether **167** in 48% yield over two steps. Orthogonal deprotection of the TBS ethers with TBAF followed by DMP oxidation of both alcohols revealed the required unstable ketoaldehyde **168** in 46% yield over two steps. Several McMurry coupling conditions using low valent titanium generated in various ways were attempted, but only reduction of titanium tetrachloride with zinc metal was successful for the closure of macrocycle **45**. The yield of this reaction never exceeded 10% and the acetal protecting group was cleaved during the reaction. This route left much to be desired due to the need for orthogonal protecting groups that could also tolerate the McMurry coupling conditions, which are rather harsh. Our options for improving this route were limited, but we continued to explore alternative McMurry coupling strategies.

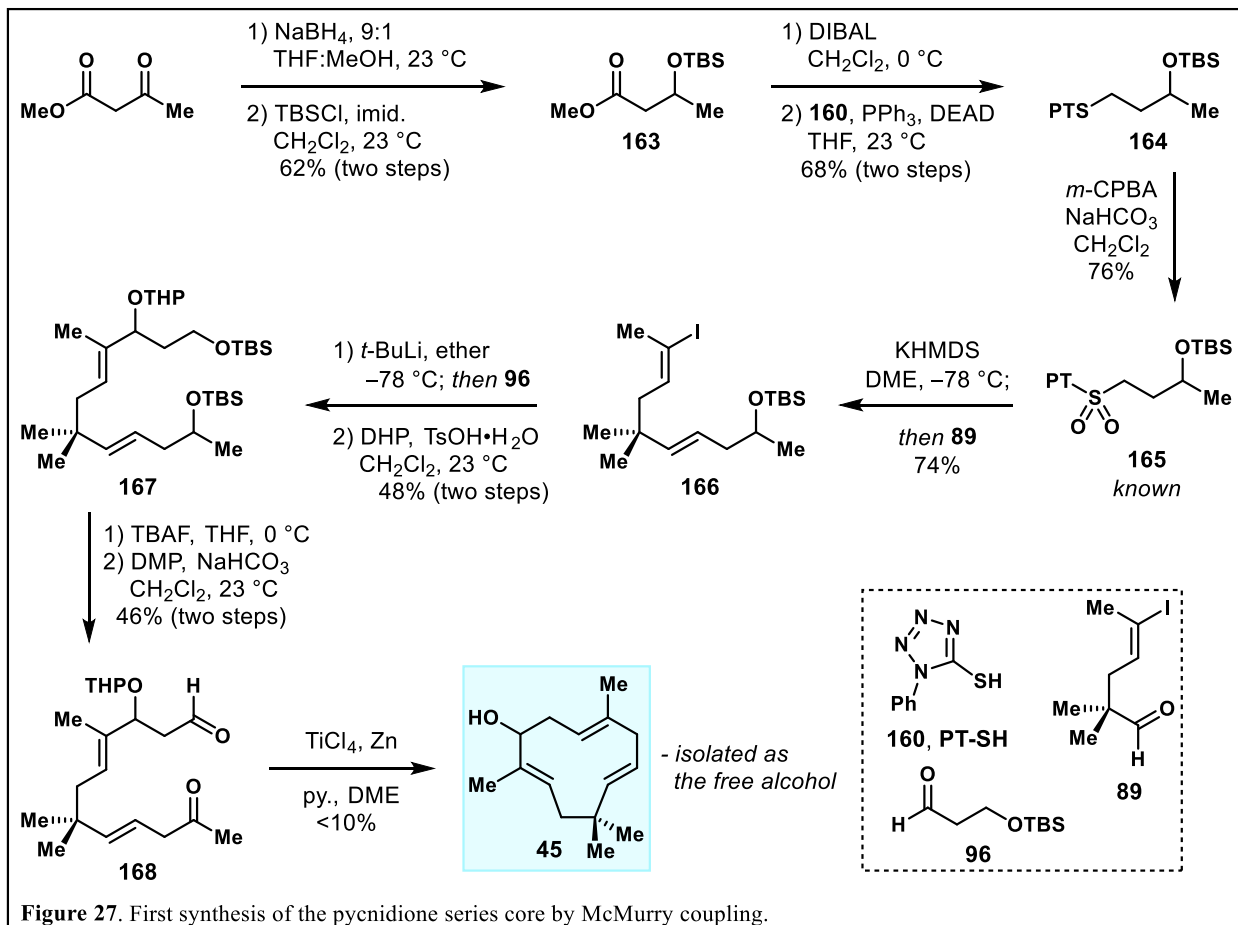
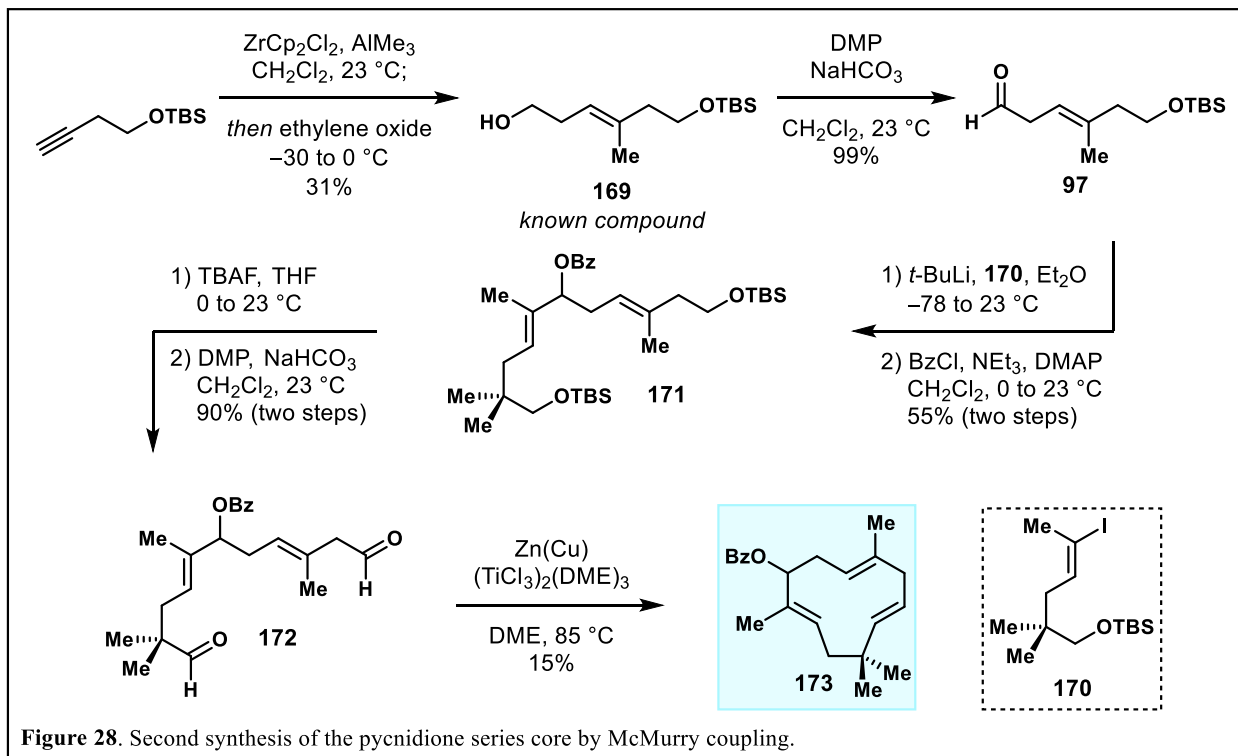


Figure 27. First synthesis of the pycnidione series core by McMurry coupling.

We decided to pursue concurrently a second synthesis utilizing the McMurry reaction and the same bond disconnection pursued during our RCM studies (Figure 28). At first, we attempted to synthesize intermediate **97** from ester **136**, but initial studies to afford selective oxidative cleavage of the terminal olefin to an aldehyde or alcohol were fruitless. Fortunately, alcohol **169** is a known compound synthesized *via* zirconium mediated carboalumination of TBS protected 3-butyn-1-ol, then trapping the vinyl aluminum intermediate with ethylene oxide.<sup>30</sup> After reproducing the literature preparation, we oxidized the alcohol with DMP to give aldehyde **97** in 99% yield. Lithiation of vinyl iodide **170** (an intermediate in the synthesis of **89**) gave the corresponding alcohol product, which was protected as the benzoate to give **171** in 55% yield over two steps. As before, this ether was converted to dicarbonyl compound **172** *via* the orthogonal deprotection of the TBS ethers with TBAF and oxidation with DMP, which

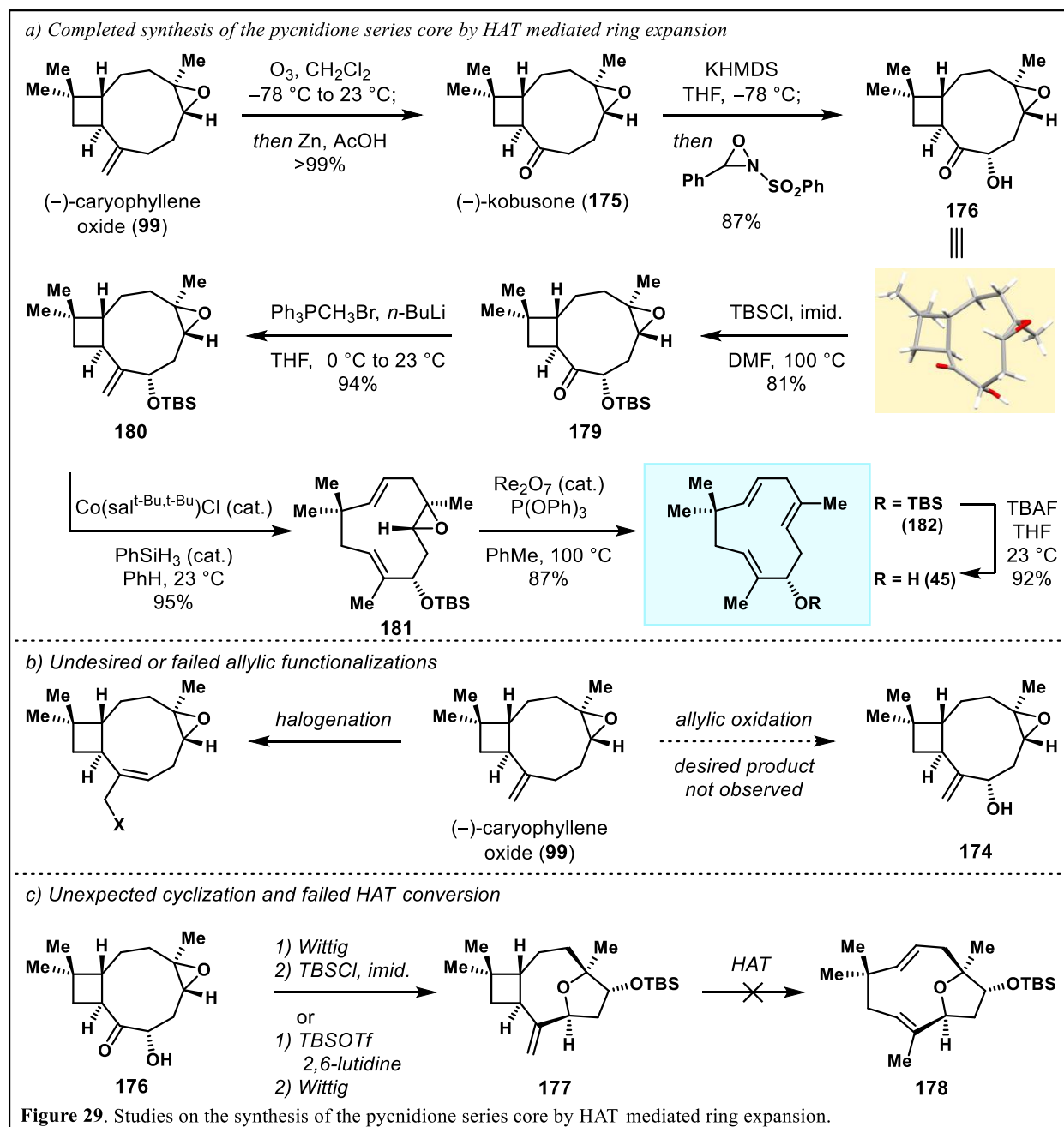




proceeded in 90% yield over two steps. After screening McMurry conditions, the best results in this case utilized titanium(III) chloride as its dimethoxyethane complex and zinc-copper couple as the reductant. The reaction was again low yielding and never exceeded a yield of 15% of benzoate ester **173**. Since both McMurry coupling strategies worked poorly for the synthesis of **45**, we decided to abandon this reaction for this purpose. Moreover, the McMurry coupling still depended on dilute reaction conditions, so this issue that was present in both the NHK and RCM strategies remained unsolved.

### 3.3.4. Hydrogen Atom Transfer Strategy

The multiple macrocyclization strategies discussed so far were successful but failed to deliver quantities of material needed for late stage synthetic studies. Instead of continuing to find a more successful macrocyclization, we decided instead to synthesize the macrocycle *via* a ring expansion (Figure 29a). Employing the Shenvi group's HAT methodology, we anticipated that macrocycle **45** could be obtained from the appropriately oxygenated derivative of (–)-



caryophyllene oxide.<sup>10</sup> Initial attempts using selenium dioxide to affect an allylic oxidation all failed to deliver the desired product (**174**) (Figure 29b). On the other hand, allylic halogenation methodologies were considered with the anticipation that we could convert the halide to an alcohol. However, these reactions delivered constitutional isomers of the desired product wherein the olefin was transposed to the endocyclic rather than exocyclic position. Rather than

continue to screen allylic functionalizations, we recognized the ease with which we could oxygenate the  $\alpha$ -position of a ketone rather than an olefin.

Thus, (-)-caryophyllene oxide (**99**) was ozonolyzed to (-)-kobusone (**175**), which proceeds in quantitative yield when zinc in acetic acid is used to cleave the ozonide. Notably, (-)-kobusone is another commercially available natural product, but its synthesis from (-)-caryophyllene oxide is more economically feasible. Oxygenation of **175** was accomplished by treating the corresponding potassium enolate with Davis oxaziridine providing the alcohol **176** in 87% yield. This compound was produced as a single diastereomer, and we showed by X-ray crystallography that the configuration of the carbon bearing the alcohol is *S*, identical to that in pycnidione. In order to return to the path of our originally planned synthesis, we intended to reinstall the olefin with a Wittig reaction. Performing a Wittig reaction on the unprotected alcohol with excess base triggered a 5-*endo*-tet cyclization of the alcohol into the epoxide to form tetrahydrofuran, which when TBS protected gave compound **177** (Figure 29c). It also appeared that this cyclization occurred any time the unprotected allylic alcohol was present, which could be a reason for the failure of the allylic oxidation. To remedy this undesired result, we attempted to protect the alcohol as the TBS ether, but found that standard conditions with TBS chloride returned unreacted starting material. When more reactive TBS triflate was used instead, the same cyclization to open the epoxide was observed. Olefination of this intermediate delivered the same product observed previously, **177**. We saw an opportunity to convert **177** into **178** via Shenvi's HAT conditions. This would be advantageous because the most reactive olefin in the  $\alpha$ -humulene system would be masked in compound **178**, which might allow for the second trisubstituted olefin to react in a HDA reaction selectively. However, **177** was unreactive under these HAT conditions.

We avoided the cyclization by employing standard conditions with TBS chloride but in DMF and heated to 100 °C, which successfully delivered the desired silyl ether **179** in 79% yield. The Wittig reaction on this intermediate was now successful, delivering olefin **180** in 98% yield. With **180** in hand, we attempted Shenvi's HAT conditions and were delighted to find that 11-membered ring **181** was formed in 94% yield, nearly identical to the yield obtained by the Shenvi group in their synthesis of (-)-humulene oxide II. After a brief screen of conditions, we found that **181** could be deoxygenated to triene **182** using Takai's method in 85% yield.<sup>31</sup> TBS ether can then be deprotected with TBAF to alcohol **45** in quantitative yield. This route is in stark contrast to all of our macrocyclization routes in that it is more concise, higher yielding, and can produce decagram quantities of material in a single pass. While it does employ the ozonolysis and Wittig reaction as a workaround for a failed allylic functionalization, it is still by far our most efficient and reliable route to **45**.

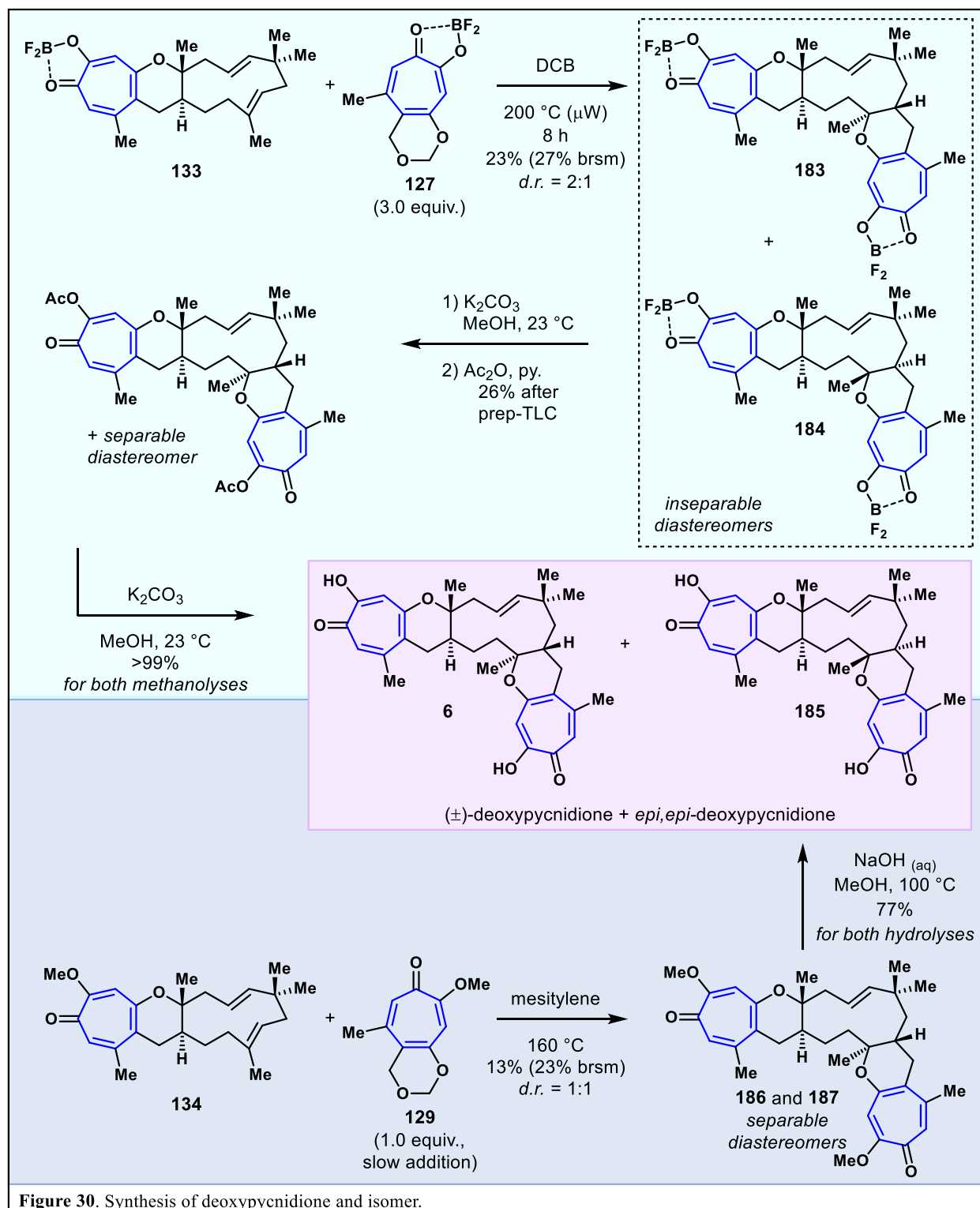
### 3.4. Synthesis of Sesquiterpene-Tropolones

#### 3.4.1. Synthesis of Deoxyptycnidione

The Baldwin group reported only a single example of the occurrence of a second HDA reaction with an *o*-QM.<sup>1</sup> The tropolone in this case, **46** (Figure 7) was protected as the methyl ether and benefited from the added stability of a second aromatic ring fused to the tropolone. Since the second cycloaddition of tropolone *o*-QM precursor **49** to deliver deoxyptycnidione (**6**) was not discussed in Baldwin's work, we supposed that the reaction may have been attempted but did not succeed.<sup>19</sup> We anticipated that the second cycloaddition would be similarly challenging in our hands, though we were encouraged by the effectiveness of the difluoroborate complex of the tropolone (**127**) and the efficiency of the microwave reaction conditions that were previously unexplored.

Our early studies on the second cycloaddition were modeled after Baldwin's example and knowledge from our own work. Thus, heating three equivalents of tropolone *o*-QM precursor **127** with monocycloadduct **133**, both difluoroborate complexes, for eight hours in *o*-dichlorobenzene (DCB) at 200 °C under microwave irradiation delivered two products (**183** and **184**, tentatively presumed to be diastereomers) in a ratio of 2:1 and 27% yield that could be separated from unreacted **127** (Figure 30). By <sup>1</sup>H NMR, we could identify that the trisubstituted olefin was now absent and two tropolone structures were present on each product. Attempts to separate these two compounds by preparative thin layer chromatography (TLC) failed, as the retention factors of both compounds were nearly identical. We eventually resolved the compounds by decomplexation of the boron difluoride with potassium carbonate in methanol to give a mixture of deoxypycnidione isomers, then reprotecting the tropolones as their acetate derivatives. Notably, only two compounds were formed here, while each tropolone could theoretically form four compounds if both oxygen atoms on each tropolone were acetylated. While this is the case for methylation of the tropolones, acetate is a much more labile protecting group and the two possible constitutional isomers may be able to equilibrate to the more thermodynamically stable isomer. This fortunate result allowed for a much more facile separation of the two isomers by preparative TLC, but the yield after this sequence was a low 26%. Regardless, quantitative methanolysis of the acetates revealed deoxypycnidione and (presumably) *epi,epi*-deoxypycnidione (**6** and **185**).

As stated during the discussion of the tropolone synthesis, we found that methyl tropolone **129** was required for studies on the synthesis of pycnidione. We also attempted to use this intermediate in the synthesis of deoxypycnidione from methylated deoxyepolone B (**134**). Syringe pump addition of an ethanol solution of one equivalent of the tropolone over 16 hours to



**Figure 30.** Synthesis of deoxypycnidione and isomer.

a stirring 160 °C solution of **134** in mesitylene, then continued reaction at this temperature until the tropolone is consumed as monitored by LCMS (about 24 hours) produces methylated derivatives of deoxypycnidione (**186** and **187**) in approximately a 1:1 ratio of diastereomers and

13% yield (23% brsm) (Figure 30). (These specific but required conditions were the result of several months of exploration and will be discussed in section 3.4.3.) The yield for this reaction is lower than that for the tropolone difluoroboronate complex **127**, but the two cycloadducts are more easily separated by preparative TLC or preparative HPLC. However, compounds **186** and **187** can be hydrolyzed by refluxing aqueous sodium hydroxide in 77% yield to deliver separately both diastereomers of deoxypycnidione (**6** and **185**).

After completing our synthesis, we contacted the isolation chemists and requested that they send us the NMR data for the isolated material, even though the data was not publication quality.<sup>32</sup> We were grateful for their assistance, and were delighted to find that the major component of our mixture matched the data for the natural product, allowing us to claim the first total synthesis of deoxypycnidione. However, the stereochemistry of deoxypycnidione remains ambiguous, and we cannot definitively claim that the relative stereochemistry of the dihydropyran fusions matches that of pycnidione. The only other known compound with this core is lucidene (**3**), and it possesses the opposite configuration wherein the methyl groups on the dihydropyrans share a *syn*-relationship with respect to the macrocycle. We are currently working to crystallize the natural product or a derivative in order to unambiguously prove its relative stereochemistry.

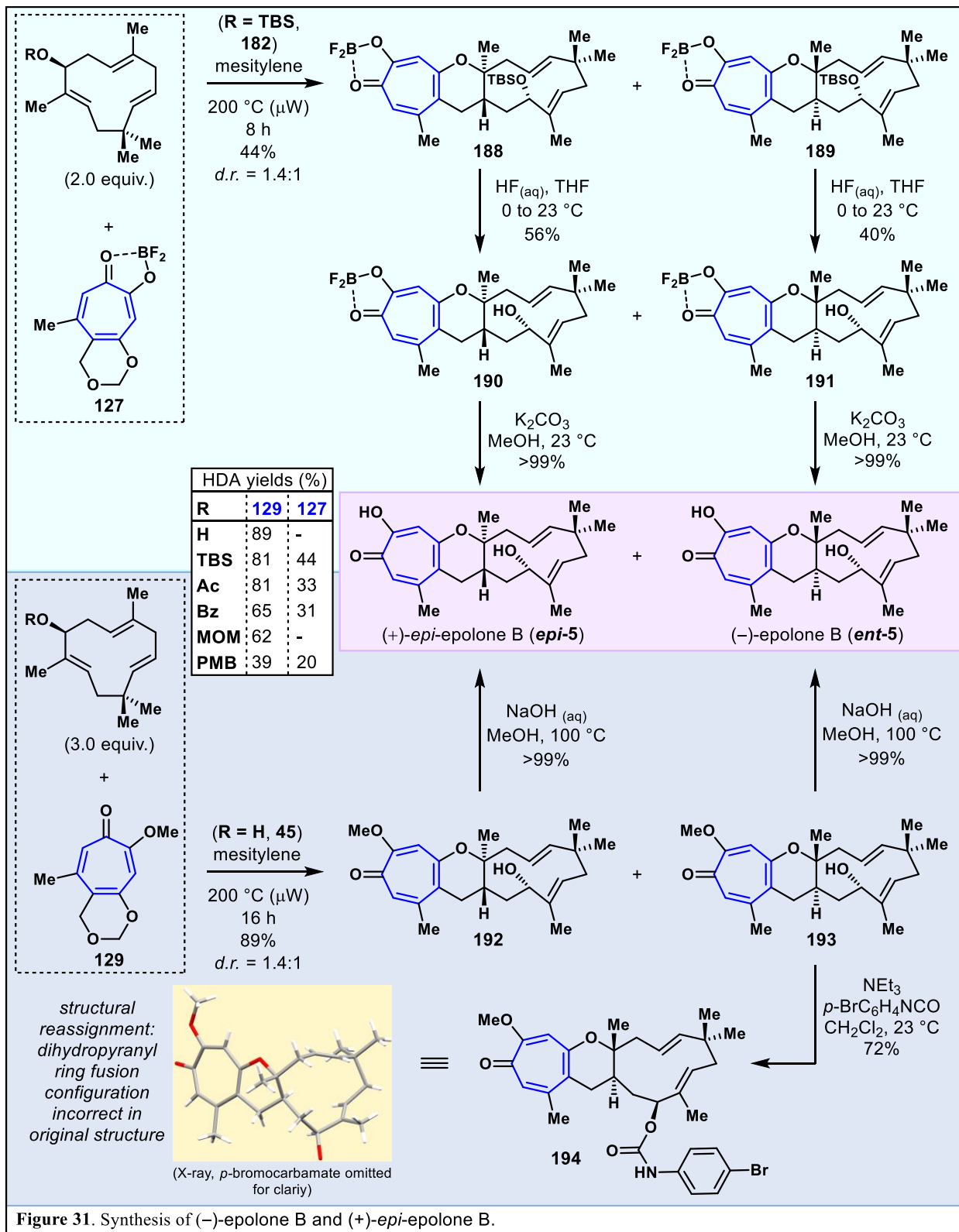
### 3.4.2. Synthesis of Epolone B

The syntheses of deoxyepolone B and deoxypycnidione served as appropriate model systems that enabled the development of reliable HDA cycloaddition conditions. By the time the first synthesis of hydroxyhumulene **45** was developed, we had a grasp on the cycloaddition using microwave irradiation to generate the *o*-QM from tropolone difluoroborate **127**. Our first attempts at the synthesis of epolone B were between macrocyclic alcohol **45** and either

unprotected tropolone **128** or difluoroborate **127** with microwave irradiation for eight hours at 200 °C. In the former case, the cycloaddition appeared to be successful, but the cycloadducts could not be purified by standard silica gel chromatography. On the other hand, **127** did not give observable cycloadducts with free alcohol, which may be a result of the alcohol decomplexing the difluoroborate or leading to alternative reaction pathways. When the macrocyclic alcohol was protected as the TBS ether (**182**), the cycloaddition with difluoroborate **127** was successful and two cycloadducts (**188** and **189**) were produced in a yield of 44% and a diastereomeric ratio of 1.4:1 (Figure 31). A two to three-fold excess of the macrocycle is typically used in order to favor the cycloaddition over *o*-QM dimerization, but the unreacted macrocycle may be recovered and reused without additional purification. Deprotection of the TBS group was surprisingly difficult, as all basic fluoride sources failed to form the product. However, treating **188** or **189** with excess hydrofluoric acid successfully gave conversion to the free alcohols **190** and **191** in 40% and 56% yield, respectively. These were determined to be diastereomers because oxidation of the alcohol with DMP gives two compounds with identical <sup>1</sup>H NMR spectra. The tropolone difluoroborate was then cleaved by standard methanolysis to give (+)-*epi*-epolone B (*epi*-**5**) (major product) and (–)-epolone B (*ent*-**5**) (minor product) both quantitatively, constituting the first total synthesis of epolone B.

The optical rotation of our synthetic epolone B is nearly identical in value but opposite in sign to naturally occurring epolone B.<sup>33</sup> Since the absolute stereochemistry of the alcohol is known from the crystal structure obtained during the synthesis of **45**, we have validated that the reported configuration of the alcohol of epolone B is correct. However, there was still no justification for the configuration of the dihydropyran provided in the original structural determination. Attempts to crystallize any of the difluoroborates in Figure 31 failed and all





**Figure 31.** Synthesis of (-)-epolone B and (+)-epi-epolone B.

compounds could only be obtained as powders. Finally, while a detailed discussion is not warranted, the monocycloaddition with tropolone **127** was successful with a variety of protecting

groups on the alcohol, including triethylsilyl, acetate, benzoate, and *p*-methoxybenzyl, though TBS ether **182** was the highest yielding substrate.

Methyl tropolone **129** was also employed in the monocycloaddition toward epolone B and was significantly more effective than the tropolone **127** (Figure 31). Most importantly, the free alcohol **45** could be used in the cycloaddition producing the cycloadducts in yields as high as 89% and the in same ratio of 1.4:1. The reaction requires about twice the amount of time to fully consume the tropolone, but this is a suitable compromise for the greatly improved yield. In this case, nearly all of the unreacted macrocycle can be recovered and the purity of the recovered material is nearly that of freshly prepared macrocycle. Hydrolysis of the tropolones in **192** or **193** is quantitative and delivers *epi-5* and *ent-5*. Overall, the yields of the cycloaddition with the methyl tropolone were nearly double those with the tropolone difluoroborate for every protected alcohol that was run with both tropolones. Yields higher than 80% are obtained consistently for the cycloaddition with **129** regardless of scale. The only limitation to scale that has been observed so far is the volume of the microwave vessels (35-mL), but the reaction has been performed on as much material as 1.8 mmol of **129** at once.

Finally, in an effort to unambiguously prove the configuration of all stereogenic centers in epolone B, we spent a considerable amount of time attempting to crystallize a cycloadduct intermediate toward epolone B or a derivative. Eventually, we found that the *p*-bromocarbamate derivative (**194**) of compound **193** crystallizes from methanol to form needles suitable for X-ray analysis. As expected, the configuration of the carbon bearing the alcohol is (*S*)-configured in synthetic (–)-epolone B, confirming that the assigned (*R*)-configuration for natural (+)-epolone B is correct. However, both dihydropyranyl stereogenic centers are (*R*)-configured in synthetic (–)-epolone B. These two stereogenic centers were also assigned to be (*R*)-configured in natural (+)-

epolone B, which cannot be correct.<sup>33</sup> Thus, the true structure of natural (+)-epolone B must have (*S*)-configured dihydropyranyl stereogenic centers.

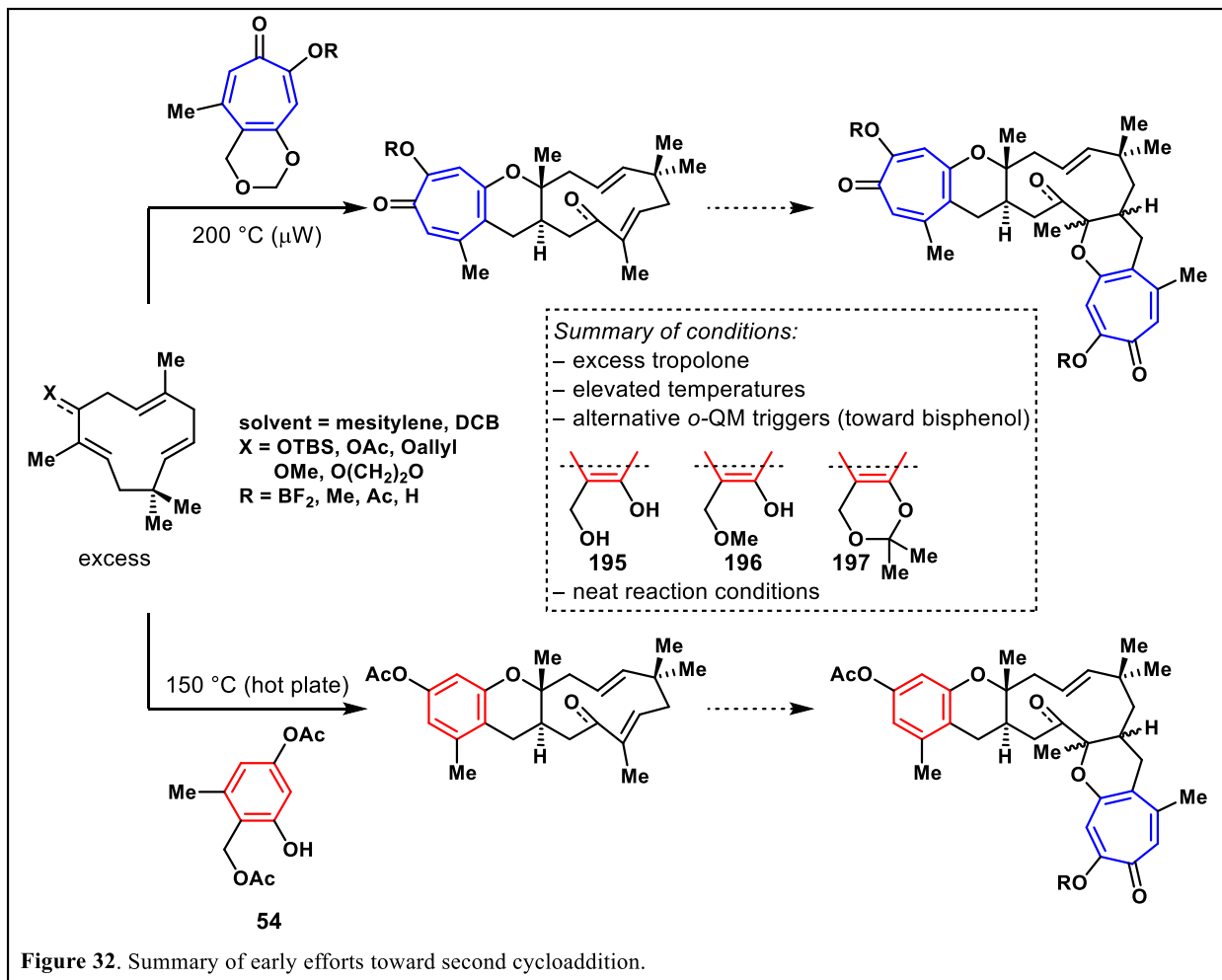
### 3.4.3. Synthesis of Pycnidione

The determination of the structure of epolone B reveals that intermediate **193**, which is hydrolyzed to (–)-epolone B, is our desired synthetic precursor to pycnidione. As with the first cycloaddition, two HDA products with the trisubstituted olefin could be expected: addition to the *re*-face of the olefin would give the desired stereochemical configuration of pycnidione and addition to the *si*-face of the olefin would give the undesired stereochemical configuration present in lucidene (or *epi,epi*-pycnidione). The regioselectivity of the cycloaddition is typically predictable, but the formation of two additional constitutional isomers resulting from a change in orientation of the tropolone *o*-QM approach is theoretically possible. In the same manner, compound **192** could undergo a cycloaddition to give two expected bistropolones, one of which is the epimer of the enantiomer of pycnidione.

Prior to our structural correction of epolone B, we subjected both monocycloadducts to HDA conditions due to our suspicion that the structure may have been reported incorrectly. Moreover, we believed it to be beneficial to develop second cycloaddition conditions on either substrate to increase our chances of discovering successful conditions. We began our studies on the tropolone difluoroborate complex of TBS protected epolone B derivatives (**188** and **189**) employing the conditions that were successful for the synthesis of deoxypycnidione. In this case, we used three equivalents of tropolone **127** relative to the monocycloadduct in DCB or mesitylene, a crystal of BHT, and microwave irradiation at 200 °C. These conditions were unsuccessful and all that could be observed was consumption of the tropolone, partial decomposition of the monocycloadduct, and no identifiable products. We initially believed that

this result could be attributed to the large size of the TBS group and its proximity to the targeted olefin sterically inhibiting the approach of the tropolone *o*-QM. This seemed reasonable because the cycloaddition was successful, albeit low yielding, with the deoxy-series of sesquiterpene-tropolones that do not bear the allylic alcohol functionality.

We continued to employ the same conditions since they were previously successful, but varied the nature of the protecting group on the alcohol. (A summary of all early cycloaddition efforts is shown in Figure 32.) As we saw before, the unprotected alcohol was entirely unsuccessful with tropolone difluoroborates. In order to obtain the protected monocycloadducts, we performed the first cycloaddition with the appropriately protected macrocycle rather than suffer the loss of material in a TBS deprotection and reprotection sequence of the monocycloadducts. Decomposition and partially recovered starting material also occurred when the alcohol was protected as the acetate or allyl ether. In an attempt to use the smallest possible group, we even explored the second cycloaddition with the methyl ether but were still unsuccessful. We then decided to remove the allylic alcohol functionality altogether by investigating the cycloaddition on the ketone or corresponding ethylene glycol ketal. Notably, we found that oxidation of the macrocyclic alcohol **45** to the ketone ablated optical activity, which would render our synthesis racemic. The first cycloaddition was not successful with the ketone, however, the tropolone difluoroborate complex underwent a rather clean cycloaddition with the glycol ketal. Again, the second cycloaddition failed. Turning to the protection of the tropolone in an attempt to modulate its reactivity, we decomplexed the difluoroborate and acetylated or methylated the tropolone. The second cycloaddition with these two tropolones, as well as unprotected tropolone **128**, all failed to produce an observable or isolable bistropolone under these conditions.



Concurrently, we also pursued the second cycloaddition with acetylphenol monocycloadducts *en route* to epolone A. We synthesized the phenol *o*-QM precursor **54** using Baldwin's method.<sup>34</sup> The Baldwin group's conditions for the first cycloaddition (hot plate at 150 °C) were also successful for our monocycloadditions with all protected hydroxyhumulenes, though we typically employed mesitylene rather than xylene as the solvent. However, none of the second cycloadditions with tropolone difluoroborate gave rise any desired second cycloadduct. Since the conditions for the generation of the phenol *o*-QM are milder than those for generation of the difluoroborate tropolone *o*-QM, we also attempted the second cycloaddition with compound **54** toward bisphenol products with the expectation that decomposition would be reduced. Again, this endeavor was fruitless.

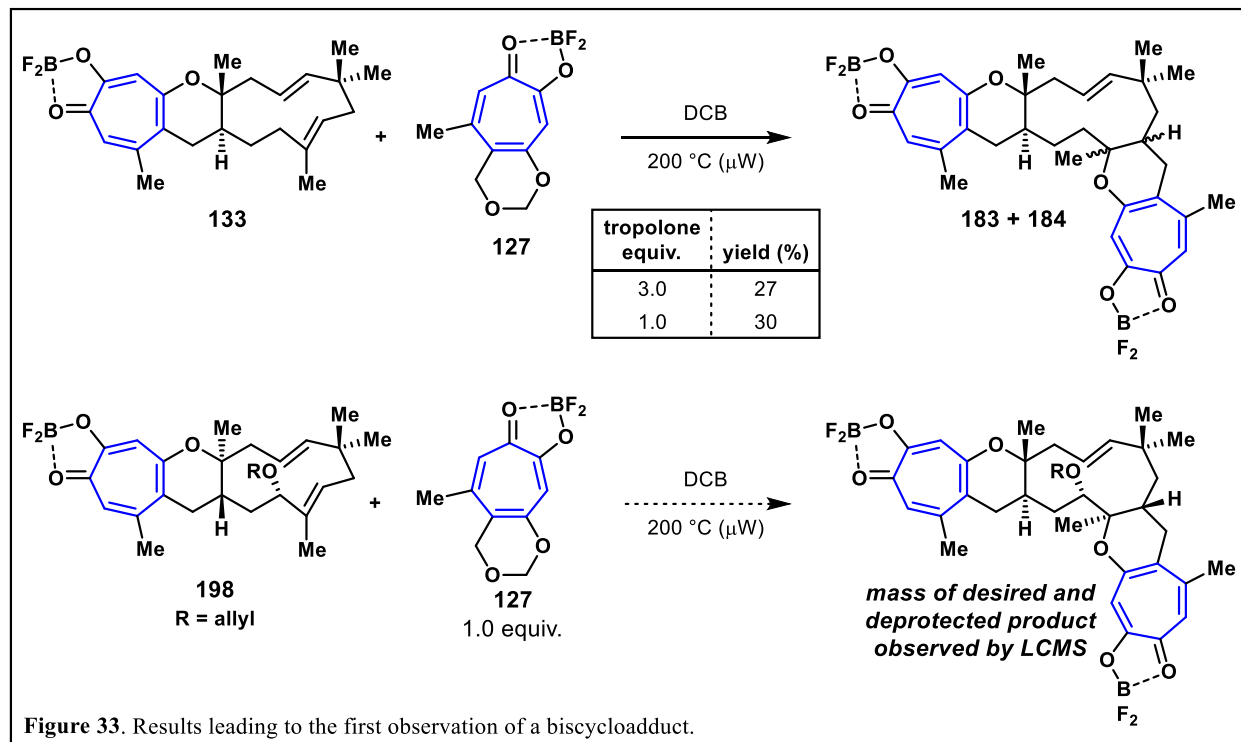
Generation of the *o*-QM intermediates derived from tropolone **127** or phenol **54** produced formaldehyde and acetic acid as byproducts, respectively. We considered the possibility that these byproducts may be having a deleterious effect on the second cycloaddition, especially at high temperatures. We then sought to modify the *o*-QM trigger on these precursors through the installation of a more benign leaving group. The tropolone proved to be resilient to modification. We attempted to oxidize the methylene acetal to the carbonate under various conditions, but only recovered unreacted starting material or decomposition under more forcing conditions. The acetal could not be deprotected to the methylene hydroxy group under acidic conditions without decomposition, potentially *via* uncontrolled *o*-QM formation, so a protecting group exchange was not possible. Generation of the *o*-QM in the presence of nucleophiles in an attempt to trap the *o*-QM with a new trigger were also unsuccessful, likely due to the methylene acetal being a less reactive trigger than any of those we attempted to introduce. Alternatively, photolysis or thermolysis of the acetylphenol *o*-QM precursor **54** in the presence of methanol or water in acetonitrile produced *o*-QM precursors **195** and **196**. In turn, **195** could be protected as the acetonide, **197**. The byproducts for these *o*-QM precursors would be water, methanol, or acetone, respectively, which we anticipated would be much less destructive than acetic acid at 150 °C. However, second cycloaddition attempts with these precursors continued to fail under standard conditions.

More aggressive conditions were also employed to persuade the second cycloaddition. Using a melting point apparatus, we heated neat reactions in capillary tubes as high as 300 °C. Effective *o*-QM formation was evident by the observed evaporation of acetic acid or formaldehyde, but no cycloaddition was observed before decomposition occurred. Likewise, higher temperatures in the microwave using higher boiling solvents such as 1-methylnaphthalene

or 1-chloronaphthalene led only to decomposition, and in one case, the failure of a microwave vessel. Increasing the quantity of the *o*-QM precursor only increased the amount of decomposition. We considered the possibility of employing extreme pressures to effect the cycloaddition, however, increased pressure would likely disfavor *o*-QM formation *via* cycloreversion as much as it would favor the cycloaddition.<sup>35</sup> Moreover, the temperatures needed for *o*-QM formation are much higher than are typically employed with the high-pressure apparatus in question.

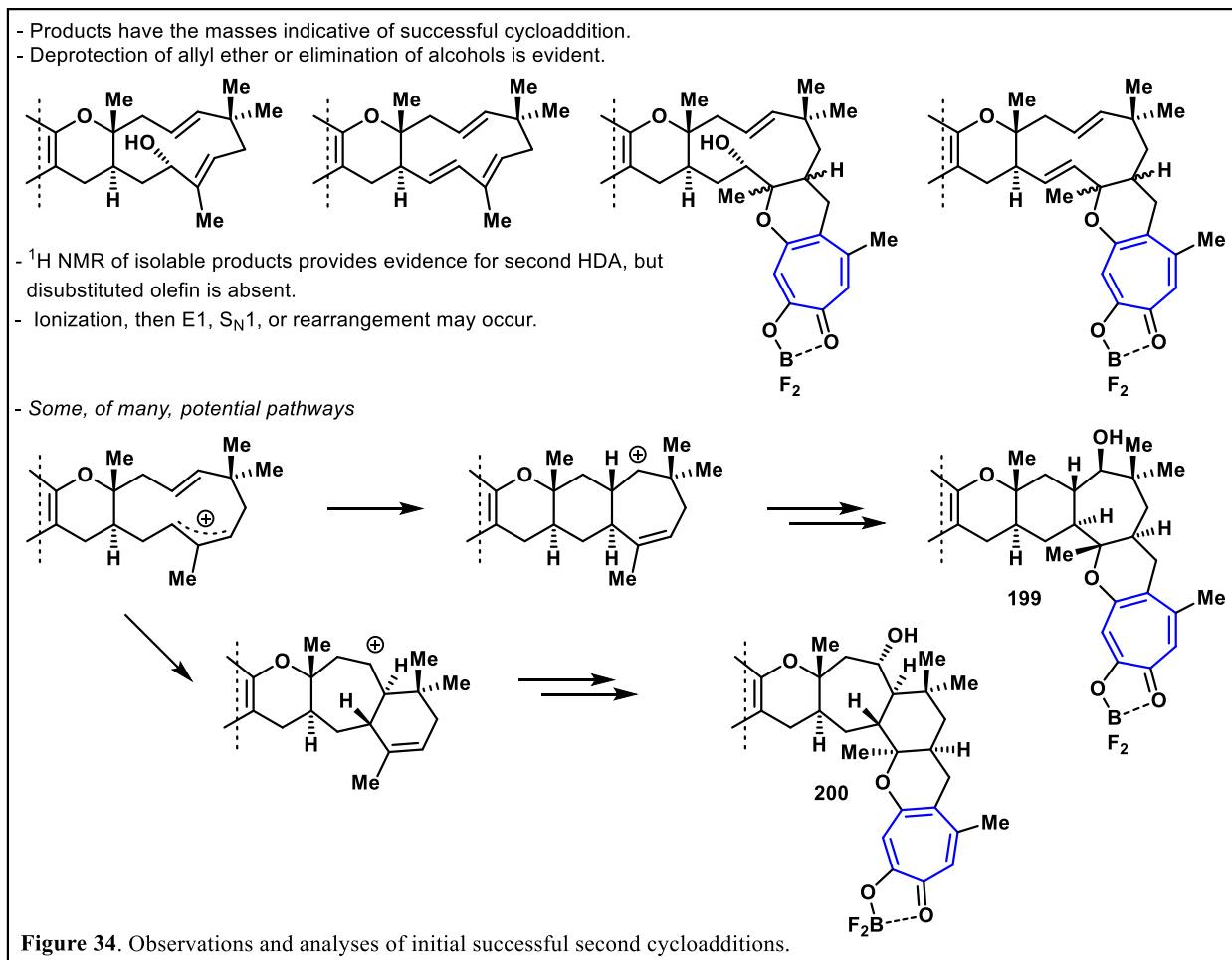
After we thought we had exhausted all of our ideas, we turned our attention to the optimization of the second cycloaddition on the deoxy-sesquiterpene-tropolone series and characterization of the products (Figure 33). Since the yield of this reaction was still rather low, consumption of three equivalents of tropolone difluoroborate **127** for every reaction put a significant strain on the throughput of the synthesis of this intermediate. To mitigate this, we attempted the second cycloaddition toward the difluoroborate complex of deoxypycnidione using a single equivalent of **127** and found that the yield was identical to that when three equivalents were used. Moreover, the reaction was cleaner and purification of the two cycloadducts was more facile.

Encouraged by this new result, we returned to the second cycloaddition toward pycnidione. The HDA reaction with allyl protected (+)-*epi*-epolone B (**198**) as the difluoroborate complex was attempted (Figure 33). Conveniently, this reaction was run around the same time that our group obtained an LCMS instrument, which accelerated the analysis of the crude cycloadditions. We found that products with the molecular weight of the desired second cycloadduct were present, as well as products with the molecular weight corresponding to mono- and biscycloadducts with the loss of the allyl group or elimination of the allyl ether. Deprotection



of an allyl group would not be expected under these reaction conditions so this result was rather puzzling. After continued experimentation and isolation of the new products, it became evident that the cycloadducts were undergoing structural rearrangement (Figure 34). Evidence for this was provided by the isolation of a compound with the mass of the deprotected bicycloadduct that showed no vinyl protons by  $^1\text{H}$  NMR, indicating an olefin rearrangement. While we did not fully characterize this compound, we expect that this product or others observed with the same molecular weight could have the structure of compounds **199**, **200**, or several other potential products that one could imagine resulting from rearrangements. Formation of these products could be a result of ionization of the allylic ether to the secondary carbocation, then subsequent olefin or sigmatropic rearrangements, with or without the introduction of the second tropolone. Regardless, this realization led us to consider the cause of the putative ionization and suppress it.





We first conducted the cycloaddition reaction at various temperatures and found that reactions below  $170\text{ }^\circ\text{C}$  produced cleaner mixtures but did not completely eliminate formation of the undesired products. More polar solvents, even relatively non-polar aromatic solvents such as DCB, tended to favor a broader spectrum of products. Thus, mesitylene was an optimal solvent for this reaction. Returning to our suspicion that the acidity of the glassware may have an effect on the reaction, we attempted the reaction in a silylated vial and saw no change in the product distribution. Moreover, running the reaction in a Teflon insert in the microwave vial also had no effect. Finally, we considered that the Lewis acidity of the tropolone difluoroborate may be the cause of ionization. High boiling amines were added to the reaction but increased decomposition. We instead resolved to eliminate the potential source of the ionization and use the methylated

tropolone (**129**). While this was part of our original exploration, we previously used an excess of this reactant and had yet to attempt reactions with only a single equivalent.

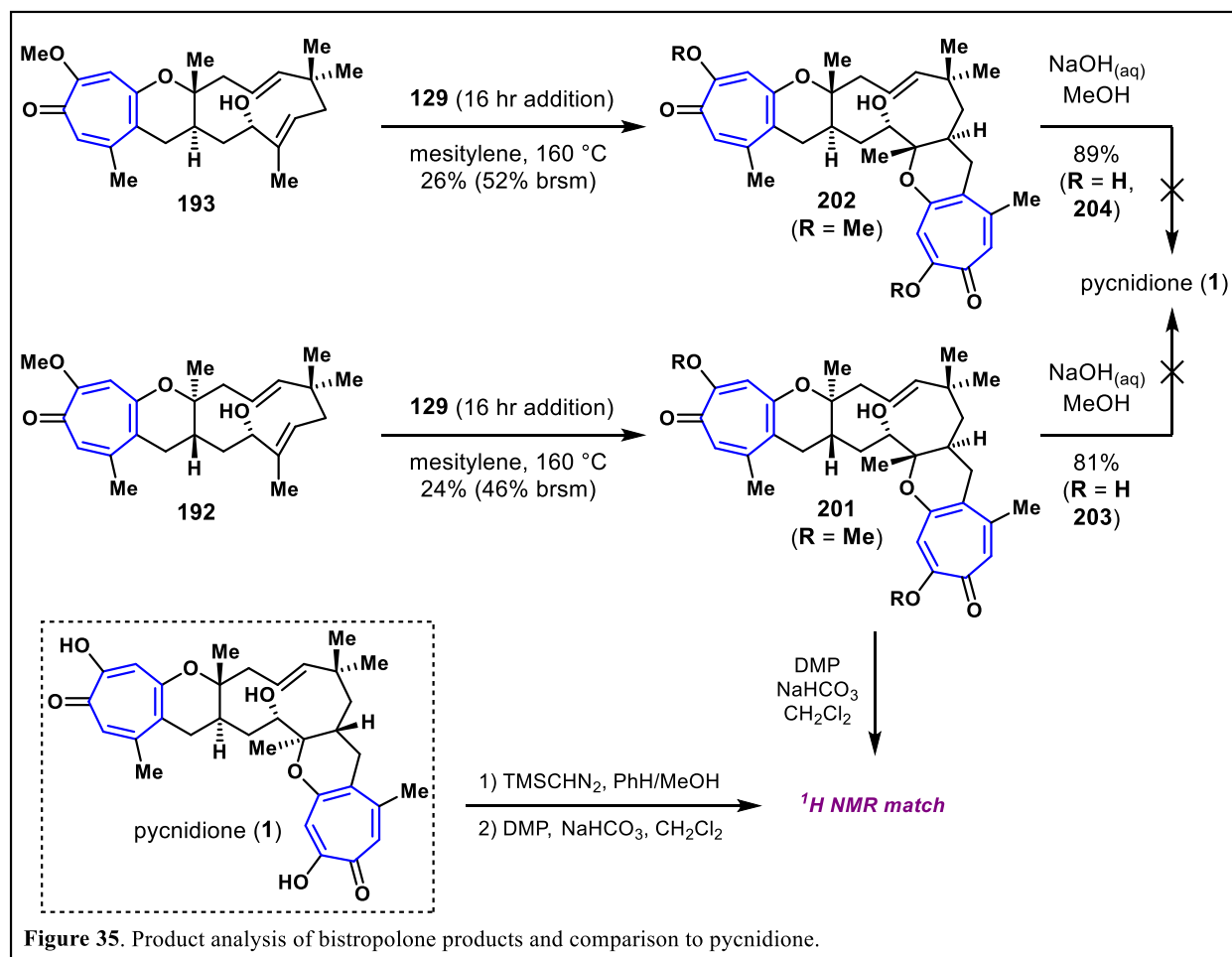
At the time we suspected that ionization may be occurring, we were performing most of our cycloaddition reactions on the allyl protected alcohol. When we attempted the second cycloaddition on the corresponding monocycloadduct with methylated tropolones, we isolated a product with the desired mass. However, the <sup>1</sup>H NMR showed the absence of the allyl group and presence of the trisubstituted olefin. Evidently, the allyl group underwent a HDA reaction with the tropolone *o*-QM, which is a testament to the difficulty of the desired reaction because monosubstituted olefins should be significantly less reactive than trisubstituted olefins in inverse electron demand Diels–Alder reactions. However, no ionization was observed and the reaction was rather clean, which was quite encouraging. When the alcohol protecting group on the methyl epolone B derivatives was changed to a TBS or acetate, traces of the mass of the desired product were observed by LCMS and the starting material was unchanged.

As stated earlier in the discussion of the synthesis of the methyltropolone monocycloadducts, we realized that the unprotected macrocycle undergoes a cycloaddition with the methylated tropolone in yields as high as 89%, and the products can be isolated in exceptional purity. Since the unprotected alcohol was now an option in the cycloaddition, we attempted using methylated monocycloadducts with no alcohol protecting group in the second cycloaddition. At long last, using a single equivalent of the methyl tropolone **129** with either monocycloadduct **201** or **202** provided second cycloadducts **203** or **204**, respectively, in yields great enough that the products could be isolated and characterized. The defining features of the products by <sup>1</sup>H NMR are the presence of four downfield singlets corresponding to the protons on seven membered ring, two resonances corresponding to the coupled vinyl protons, a resonance

corresponding to the proton bonded to the carbon bearing the alcohol, two singlets corresponding to two methoxy groups, and two singlets corresponding to two methyl groups on the tropolone, and four upfield singlets corresponding to the remaining methyl groups. Each monocycloadduct produced one compound that fit these criteria.

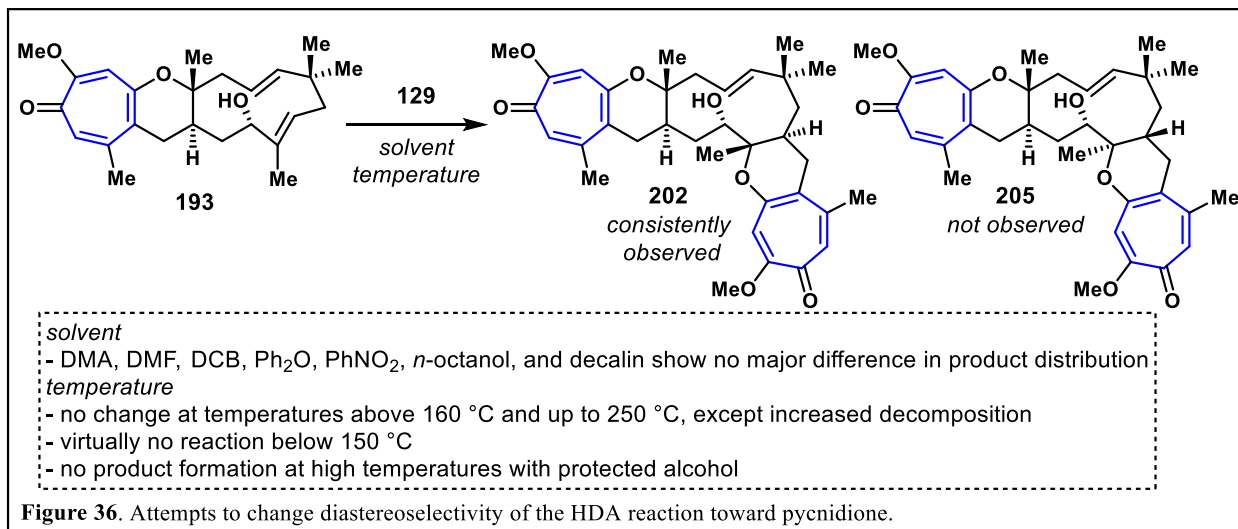
The synthesis of the biscycloadducts was further improved by running the reactions at 160 °C on a hot plate rather than 200 °C in the microwave (Figure 35). The reaction times were longer, but decomposition was suppressed. Moreover, to increase the effective equivalents of the monocycloadduct relative to the tropolone, thus decreasing the probability of tropolone *o*-QM dimerization, we experimented with a slow addition of a solution of the tropolone to a heated solution of the macrocycle. This improved the yields of **201** and **202** to 24% (46% brsm) and 26% (52% brsm), respectively. Current standard conditions are the delivery of the tropolone as a solution in ethanol over 16 hours *via* syringe pump, then approximately 24 hours of continued reaction to complete the consumption of the tropolone. While the tropolone is not as soluble in ethanol as it may be in other solvents, solutions in solvents such as dichloromethane cause the syringes to swell and leak.

At the time that we obtained this exciting result, we still had not confirmed the true structure of epolone B and were uncertain about the stereochemical configurations of the biscycloadducts. Regardless, we hydrolyzed both biscycloadducts **201** and **202** with aqueous sodium hydroxide with the anticipation that one of products, **203** or **204** (obtained in 81% and 89%, respectively), would be identical to pycnidione. Most unfortunately, the spectroscopic data of both compounds contained the same features as those of pycnidione, but the data were not identical. However, the <sup>1</sup>H NMR spectrum of compound **204** very closely resembled that of pycnidione save for a few key differences. It is most likely that compound **204** is the cycloadduct



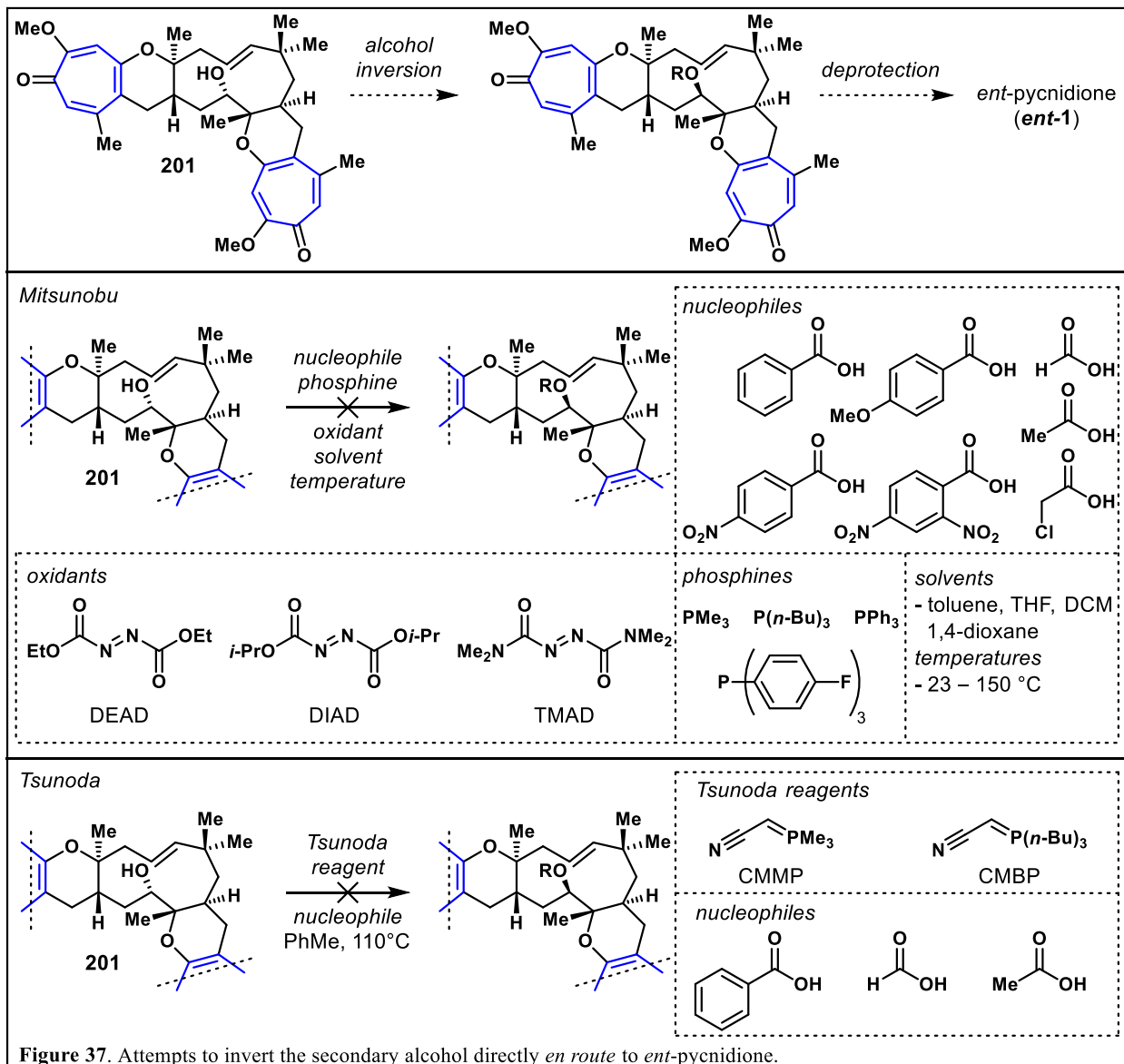
resulting from the HDA reaction occurring on the undesired face of the trisubstituted olefin. We were very grateful to have obtained a sample of pycnidione from Merck & Co., and confirmed by obtaining an NMR of the standard that we did not synthesize the natural product.<sup>36</sup> However, methylation of the pycnidione standard with TMS diazomethane using the reported procedure, then oxidation of the alcohol gave a mixture of ketones wherein the  $^1\text{H NMR}$  spectrum of the major component was identical to the ketone produced from **201**.<sup>33</sup> Thus, **201** was determined to be the epimer of the enantiomer of pycnidione.

These new results left us with two options for the completion of pycnidione: change the selectivity of the cycloaddition between tropolone **129** and monocycloadduct **193**, or invert the stereochemical configuration of the carbon bearing the alcohol in compound **201** to synthesize



the enantiomer of pycnidione. In regard to the former, we began our efforts by increasing the temperature of the cycloaddition (Figure 36). Temperatures as high as 250 °C caused the cycloaddition to proceed rapidly, but only **202** could be observed by LCMS and <sup>1</sup>H NMR and never **205**. Temperatures as low as 100 °C were also attempted, but the consumption of the tropolone *o*-QM precursor was impractically slow at temperatures below 150 °C. Various solvents were screened in an effort to encourage more conformational flexibility of the monocycloadduct. Dimethylacetamide (DMA), *n*-octanol, DCB, DMF, nitrobenzene, diphenyl ether, and decalin showed almost no difference in product distribution as observed by LCMS and <sup>1</sup>H NMR. We revisited the application of protecting groups on the alcohol with the expectation that they may influence the conformation of the macrocycle, but the second cycloaddition still did not occur to any meaningful extent with any protecting group, even at high temperatures. Under certain conditions, a second cycloadduct is obtained from compound **193**, however the <sup>1</sup>H NMR of this compound and the corresponding hydrolysis product indicate that it is not the structure of pycnidione. Preliminary characterization indicates that it may be a constitutional isomer formed as a result of the reversal in regioselectivity of the cycloaddition, however full characterization of this compound is needed to verify this anomalous result.

Our second proposed solution circumvents the selectivity issue altogether by inverting the stereochemical configuration of the alcohol on **201**, which is the methylated form the epimer of the enantiomer of pycnidione (Figure 37). While this would not provide the natural configuration of pycnidione, alcohol inversion at an earlier stage of the synthesis would allow for the synthesis of the natural configuration after the second inversion. We began our studies with the Mitsunobu reaction, the most straightforward approach to alcohol inversion. In summary, all conditions attempted had no effect on the alcohol except decomposition under forcing conditions. Several combinations and variations on the equivalents of acid, phosphine, and phosphine oxidant, as well as solvent and temperature were investigated. Acids screened include benzoic acid, 4-nitrobenzoic acid, 2,4-dinitrobenzoic acid, 4-methoxybenzoic acid, acetic acid, formic acid, and chloroacetic acid. Phosphines screened include triphenylphosphine, tributylphosphine, trimethylphosphine, and tris(4-fluorophenyl)phosphine. Phosphine oxidants employed were diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), and tetramethylazodicarboxamide (TMAD). Refluxing toluene was typically used as the solvent, though 1,4-dioxane, tetrahydrofuran, and dichloromethane were also tested. Under the most forcing conditions, temperatures as high as 150 °C were used and reagent stoichiometry up to 20 equivalents were tested. In no case were even traces of the desired compounds observed by LCMS. Since alcohol **201** seemed to be stable against all conditions, it is likely that the rate of nucleophilic attack of the alcohol on the phosphine is slow enough to prevent any productive formation of the product. In an effort to accelerate this step of the reaction, we followed the guidance of mechanistic investigations into the Mitsunobu reaction and employed three equivalents of formic acid in order to maintain a formic acid:formate ratio of 2:1 in solution.<sup>37</sup> Still, the alcohol was unreactive.



**Figure 37.** Attempts to invert the secondary alcohol directly *en route* to *ent*-pycnidione.

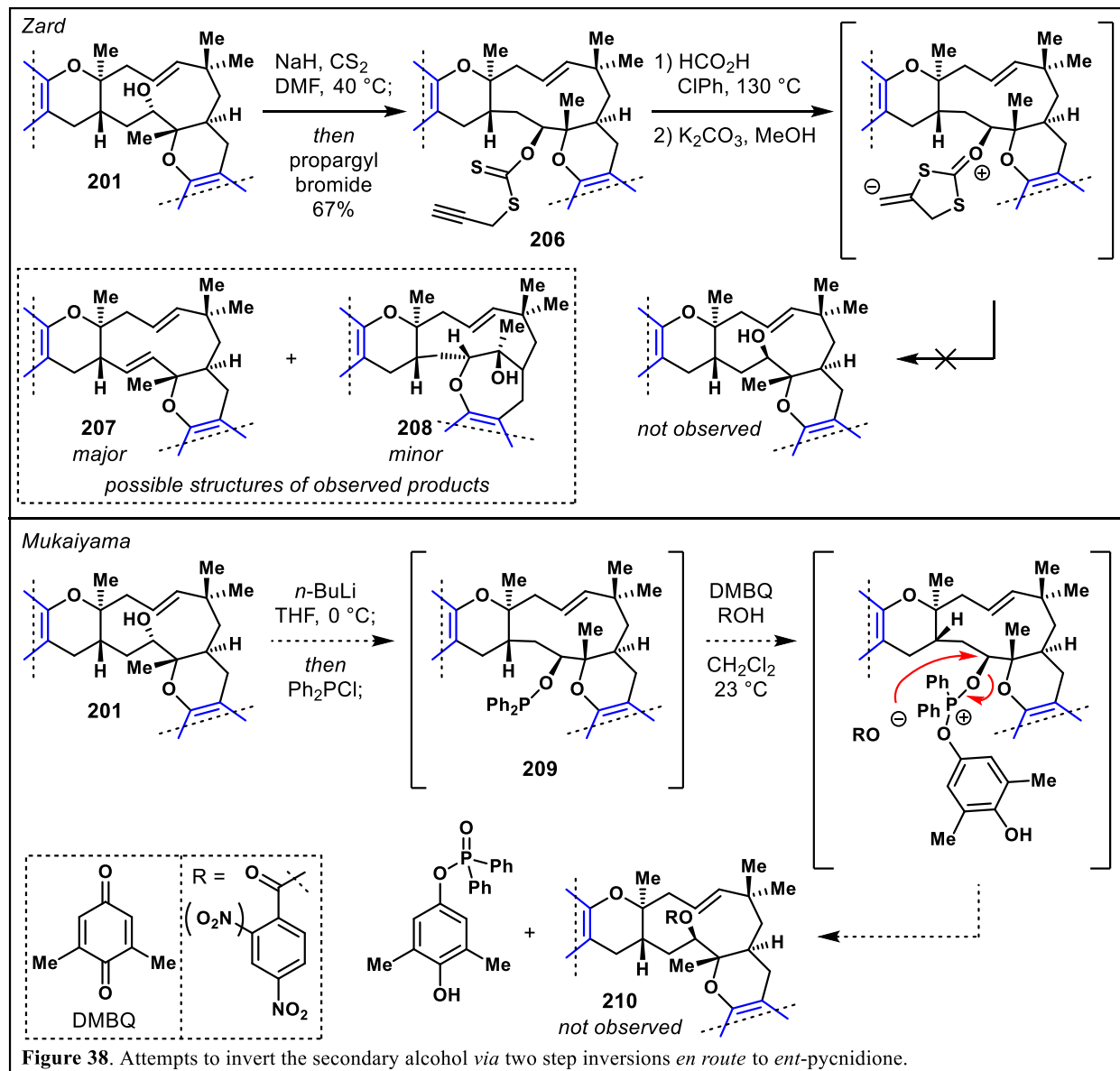
Several variations on the Mitsunobu reaction are known. One that appeared particularly attractive to us was the use of (cyanomethylene)tributylphosphorane (CMBP) or (cyanomethylene)trimethylphosphorane (CMMP), two reagents developed by Tsunoda for alcohol inversions with a variety of nucleophiles (Figure 37).<sup>38</sup> These react in a manner similar to that of the complex between a phosphine and a diazodicarboxylate in the Mitsunobu reaction. Conditions only require a Tsunoda reagent and a nucleophile, rather than three components. Moreover, we were encouraged to use these reagents due to their smaller size in comparison to

the Mitsunobu complex, which might allow for a more facile nucleophilic attack by the alcohol. We prepared CMBP based upon the literature procedure, but again observed no conversion of the product with this reagent, even when smaller acids were used. We attempted to invert the alcohol using CMMP prepared *in situ* but still saw no reaction.

Another methodology that we tested was developed by the Zard group and involves the inversion of a propargyl xanthate derivative of an alcohol by nucleophiles with a large  $pK_a$  range (Figure 38).<sup>39</sup> When heated in the presence of a nucleophile, the propargyl xanthate undergoes a 5-*exo*-dig cyclization that generates a zwitterionic intermediate composed of a vinyl anion and an oxocarbenium. The former deprotonates the nucleophile, then the resulting anion displaces the activated leaving group. While the alcohol in compound **201** was completely unreactive in the Mitsunobu or Tsunoda reaction, we were grateful to find that forcing conditions produced the propargyl xanthate **206** in 67%. When the xanthate was heated to 100 °C in toluene with benzoic acid, we observed by LCMS the rapid consumption of **206** in exchange for a compound with a mass corresponding to elimination. We considered it possible that the approach a large nucleophile like benzoic acid may be encumbered by the crowded steric environment around the xanthate. We performed the same reaction with acetic acid and formic acid at the nucleophile and were delighted to find that with formic acid, two new compounds with the mass of the formate and the alcohol were present. However, under these conditions, the presumed elimination product was still the dominant component of the mixture.

It seemed possible that high temperatures could have been causing a Chugaev elimination, though temperatures required for this reaction are typically closer to 200 °C. When the temperature was decreased to 80 °C and the reaction was performed in benzene with formic acid, the elimination product became even more abundant, leading us to believe that elimination





is occurring through the cyclized intermediate rather than a Chugaev elimination. Increasing the temperature and the quantity of formic acid present decreased the amount of the elimination product relative to the presumed formate and alcohol. Though at temperatures as high as 180 °C, unproductive decomposition occurred. Likewise, insolubility of **206** in formic acid was problematic at high enough formic acid loadings and caused further decomposition.

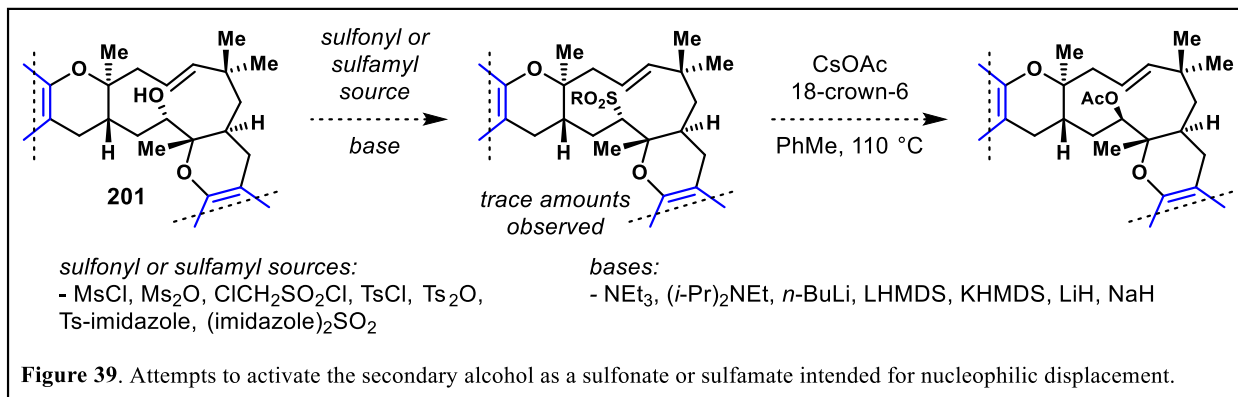
Optimal conditions employed a 1:1 ratio between chlorobenzene and formic acid at 130 °C for about 3 hours, or until the starting material was consumed as observed by LCMS. The

crude reaction contained mixtures of related compounds and the  $^1\text{H}$  NMR was nearly indecipherable. Moreover, the high polarity of the bistropolone cycloadducts made separation of these compounds by standard column chromatography impractical. Instead, the mixture was methanolized to convert the remainder of the formate to the free alcohol. The  $^1\text{H}$  NMR at this stage did not appear to align with the known spectra of dimethylpycnidione. This reaction sequence was run on a scale that allowed for effective separation of the presumed elimination product and alcohol by preparative HPLC. The identity of the elimination product was validated by the presence of two new peaks in the  $^1\text{H}$  NMR corresponding to the vinyl protons that would be expected from elimination of the xanthate. A possible structure for this compound is **207**. We did not confirm the identity of the product with the desired mass, though the absence of the proton bound to the carbon bearing the alcohol suggests that rearrangement of the dihydropyran to a dehydrooxepane may have occurred to generate a more stable tertiary carbocation that would be quenched by water or formic acid, potentially generating compound **208** after methanolysis. As a final test to prove that this is not the structure of pycnidione, hydrolysis of the tropolone methyl ethers produced a compound that did not match the  $^1\text{H}$  NMR spectrum of pycnidione.

We considered Mukaiyama's oxidation-reduction condensation methodology for our system due to its success and high selectivity for the inversion of tertiary alcohols and sterically hindered secondary alcohols.<sup>40</sup> In this methodology, the alcohol is activated as the diphenylphosphinite, then treatment with 2,6-dimethylbenzoquinone (DMBQ) and an acid induces a simultaneous oxidation of phosphorus and displacement of the alcohol with the acid nucleophile. The phosphinites are typically prepared by deprotonation of the alcohol with *n*-butyllithium and subsequent quenching with chlorodiphenylphosphine. Alternatively, these intermediates could be prepared by refluxing *N,N*-dimethylaminodiphenylphosphine. The former

method proved to be unsuccessful for alcohol **201**, and in no case was the diphenylphosphinite **209** or the desired product **210** observed when *p*-nitrobenzoic acid or 2,4-dinitrobenzoic acid was used as the nucleophile (Figure 38). Alternatively, LCMS indicated that **209** could be formed when triethylamine was used as the base. Isolation of this intermediate was not attempted due to the lability of these intermediates. Encouraged by this result, and the finding in our experimentation with the Zard methodology that smaller nucleophiles appear to be more successful with this system, we are continuing to investigate the oxidative inversion of the phosphinite.

A more conventional two-step approach to the inversion of an alcohol is conversion to a sulfonate or sulfamate, then inversion with cesium acetate in the presence of 18-crown-6 (Figure 39).<sup>41</sup> We have spent a considerable amount of time attempting to form and isolate various sulfonate derivatives of compound **201** without much success. In most cases, the consumption of the starting material is observed by LCMS and <sup>1</sup>H NMR, but no other identifiable products are present. The spectroscopic data of the crude reaction mixtures indicate almost complete decomposition. Conditions that have been attempted include the use of methanesulfonyl chloride, methanesulfonic anhydride, chloromethanesulfonyl chloride, *p*-toluenesulfonyl chloride, *p*-toluenesulfonyl anhydride, *p*-toluenesulfonyl imidazole, and sulfonyl diimidazole. When triethylamine is employed as the base, the reactions appear to be much more controlled, and traces of the methansulfonate derivative of **201** can be observed by LCMS when methanesulfonic anhydride is the sulfonyl source. Likewise, when LHMDs and sulfonyl diimidazole are paired, the sulfamate can also be observed in trace amounts by LCMS. However, decomposition still appears to be the major results of both reactions. The use of stronger bases such as *n*-BuLi, larger bases such as Hunig's base, lower temperatures, and extreme excess of



reagents, all fail to deliver the desired intermediates in measurable quantities. We are encouraged by the fact that **201** is reacting at all, so current efforts are being devoted to taming the sulfonate or sulfamate formation, and converting them to the inverted acetates without isolation.

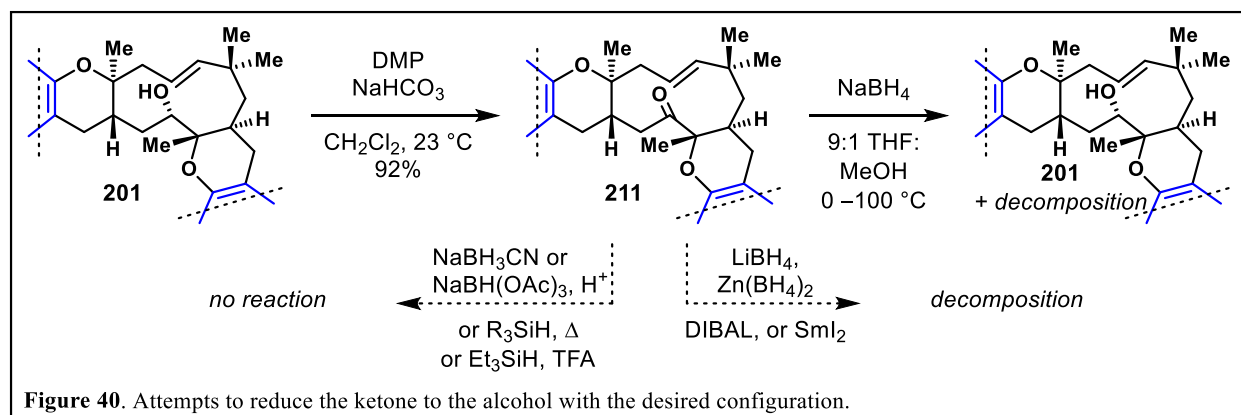
Another methodology that we attempted was developed by the Barrett group, which involves activation of alcohols to their (alkoxymethylene)dimethylammonium chloride derivatives by the Vilsmeier reagent.<sup>42</sup> These intermediates may then undergo nucleophilic displacement by potassium carboxylate salts. We believed this relatively small reagent would be less hindered by the congested environment around the alcohol in **201**. While the methodology was successful in our hands using menthol as a test substrate, the reaction failed for compound **201** and several products were observable by LCMS, none of which had the desired mass. Some masses that were observed corresponded to demethylation of the tropolone, suggesting that the Vilsmeier reagent may have reacted with the tropolone.

Since we were able to synthesize the propargyl xanthate **206**, we briefly explored radical generation from the corresponding methyl xanthate and trapping with molecular oxygen to give, ideally, the desired alcohol after peroxide reduction. To the best of our knowledge, this transformation is unprecedented. We attempted to generate the radical under various conditions including tributyltin hydride with azobisisobutyronitrile (AIBN), tributyltin hydride with oxygen, hexabutyltin with AIBN, triethylborane with oxygen, and di-*tert*-butylperoxide with AIBN.

While we were able to observe a mixture of alcohol products for the menthol test substrate when tributyltin hydride and oxygen in refluxing chlorobenzene were employed, these conditions as well as all others failed to deliver identifiable products. In most cases, the starting material was resilient to reaction.

In addition to exploring alcohol inversion strategies, we also attempted to oxidize the alcohol to the ketone and reduce it to give either a mixture of alcohols or the desired alcohol selectively (Figure 40). Ketone **211** was readily formed from the oxidation of alcohol **201** with DMP in 92% yield. Several hydride sources were used in an attempt to reduce the ketone, however, only sodium borohydride was effective and regenerated only alcohol **201**. Stronger reducing agents such as lithium borohydride, zinc borohydride, or DIBAL led to decomposition. Tropolones are known to be reduced in the presence of strong aluminum hydride reducing agents, so it is probable that this was a source of decomposition. Weaker reducing agents such as sodium cyanoborohydride or sodium triacetoxyborohydride failed to reduce the ketone. Attempted reduction with sodium borohydride in refluxing dioxane gave no reaction until water was added, at which point the tropolones were hydrolyzed. These conditions may be useful if the reduction gives only the desired product as the free tropolone, but separation of these species can be challenging. Ionic reduction with triethylsilane in trifluoroacetic acid gave no conversion, even at reflux. Likewise, hydrogen atom transfer induced by the thermolysis of silanes failed to convert the starting material. Single electron reduction with samarium diiodide gave only decomposition.

In summary, the synthesis of pycnidione has proven to be much more difficult than we had originally anticipated after securing a synthesis of the monocycloadduct fragments. The second cycloaddition requires an artificial excess of the monocycloadduct relative to the



tropolone due to the poor reactivity of the targeted olefin. Moreover, maintaining structural integrity of the macrocyclic portion of the structure could only be achieved using the methylated tropolone instead of the Lewis acidic tropolone difluoroborate complex. The reaction is only effective when the alcohol of the monocycloadduct is unprotected, most likely due to the steric hindrance introduced by protecting groups. Once appropriate conditions for the cycloaddition were established, we unfortunately found that the reaction is entirely selective for the undesired diastereomer of the pycnidione framework. We are not entirely out of options for changing the diastereoselectivity of the cycloaddition, as we have not pursued all combinations of protecting groups, solvent, and temperature, but the best that we can expect is a mixture of diastereomers. However, the enantiomer of pycnidione is still within our reach because we can produce a structure that is epimeric to pycnidione at the carbon bearing the secondary alcohol. This alcohol appears to be resistant to inversion when subjected to most standard conditions that should produce the desired epimer, but we are currently pursuing a few promising leads that will finally reveal the pycnidione structure.

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## CHAPTER 4: SUMMARY AND FUTURE DIRECTIONS

### 4.1. Summary

In summary, we have been pursuing the total synthesis of the sesquiterpene-tropolones in an effort to make available the tools needed for their synthesis and to enable the study of their potent biological activities. In particular, bistropolones pycnidione (**1**) and eupenifeldin (**7**) exhibit nanomolar activities against cancer cell lines, so exploration of this structural motif and its incorporation into drug candidates is warranted. Mechanism of action studies have suggested biological pathways that may be influenced by tropolones, but specific biological targets for pycnidione and related compounds have not been unambiguously identified.<sup>1,2</sup>

Our approach to the synthesis of the sesquiterpene-tropolones involves the convergence of the  $\alpha$ -humulene derived macrocyclic alcohol core and two tropolone units by reacting a trisubstituted olefin in the former with an *o*-QM formed from the latter in a HDA reaction. Therefore, our first challenges were the synthesis of both of these fragments. After two failed routes, we identified that a Lewis acid mediated de Mayo-type fragmentation was suitable for producing a tropolone *o*-QM precursor. Later, we discovered that this type of fragmentation can be induced by irradiation with UV light, which is a new reaction, to the best of our knowledge. These tropolones undergo retro-HDA reactions to release the *o*-QM and formaldehyde, then the *o*-QM reacts with  $\alpha$ -humulene with predictable selectivity for the most reactive olefin. The macrocyclic alcohol portion of the compounds was successfully synthesized in five ways: RCM, the NHK reaction, two McMurry couplings, and a HAT mediated ring expansion of a (-)-caryophyllene oxide derivative, the last of which is the most practical route. The HDA reaction between the tropolone *o*-QM and the macrocyclic alcohol is successful under a wide range of conditions and with a variety of protecting groups on the tropolone and macrocyclic alcohol.

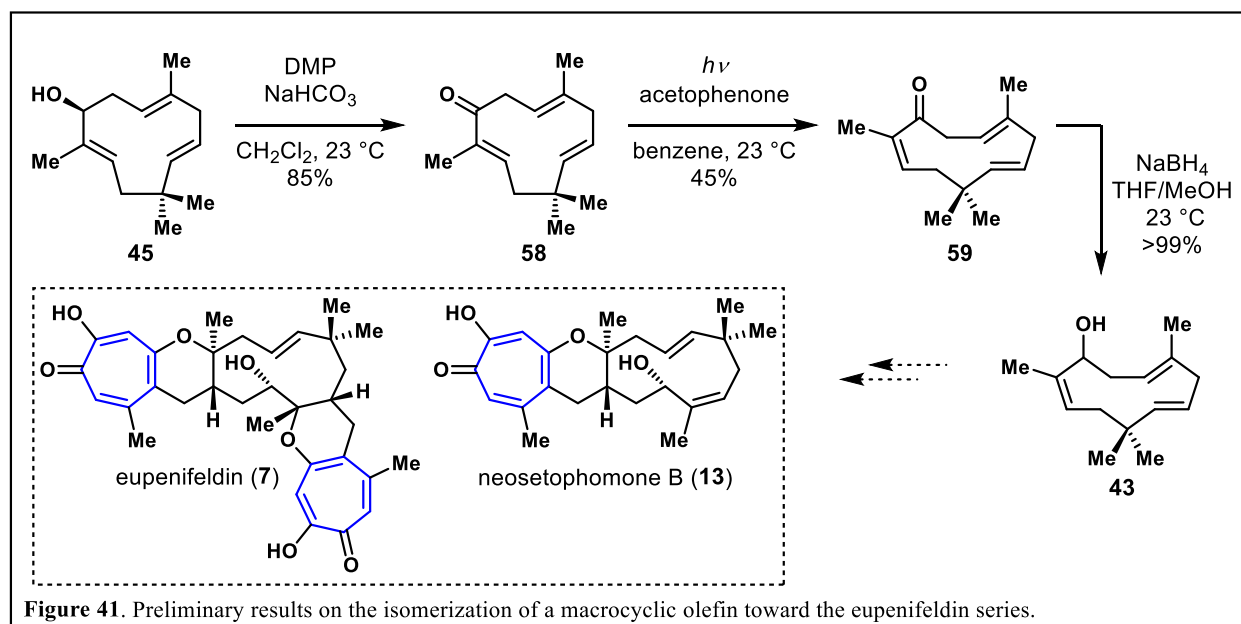
Removal of protecting groups reveals (–)-epolone B (*ent-5*), concluding its first total synthesis and (+)-*epi*-epolone B (*epi-5*). Moreover, we unambiguously proved the structure of this natural product by X-ray crystallography and confirmed that the original report contained a stereochemical misassignment.

The second cycloaddition toward the more active bistropolone natural products was far more challenging than the first. The cycloaddition was moderately successful under standard conditions for the deoxygenated natural products, allowing for the first synthesis of the natural product deoxypycnidione and its isomer (**6** and **185**). The epolone B scaffold, however, resisted a second cycloaddition despite our best efforts. We eventually found that the cycloaddition is only successful and practical when the tropolone is added slowly to the monocycloadduct as the unprotected alcohol. However, both **192** and **193** produce biscycloadducts **201** and **202**, neither of which have the stereochemical configuration of pycnidione. Our initial efforts to change the diastereoselectivity of the cycloaddition have failed, but there are still more conditions to be explored on this front. Alternatively, the stereochemistry of cycloadduct **201** corresponds to the alcohol epimer of the enantiomer of pycnidione, so inversion of the configuration of the alcohol should allow for the completion of the synthesis of pycnidione. The alcohol appears to be resistant to all standard alcohol inversion techniques. It is either unreactive, undergoes undesired rearrangements, or decomposes. There are a few promising leads that we are still pursuing.

#### **4.2. Synthesis of Eupenifeldin Series Natural Products**

While the second cycloaddition toward pycnidione produced the wrong diastereomer, it is still important that we now have the synthetic tools to install a second tropolone onto this humulene scaffold. This creates ample opportunities for the synthesis of known and new bistropolone congeners. Our first focus will be toward the eupenifeldin series of sesquiterpene-

tropolones. The synthesis of these compounds could be achieved by isomerization of the second trisubstituted olefin in the macrocycle and from *E*- to *Z*-configuration, corresponding to the *syn*-relationship between the methyl group and hydrogen on the second dihydropyran in the eupenifeldin series. Preliminary results show that this olefin macrocyclic alcohol **45** can be inverted by photochemical isomerization of the corresponding enone **58** to **59**, then reduction to **43** (Figure 41).<sup>3</sup> We can perform this sequence in 38% yield over three steps. Current efforts are focused on increasing the throughput of this reaction to generate enough material for cycloaddition studies. However, we would ultimately want to perform an olefin isomerization on a chiral compound in order to allow for an enantioselective synthesis. We will also pursue olefin isomerizations without ablation of the configuration of the alcohol, or perform the photochemical isomerization on the enones corresponding to monocycloadducts **192** or **193**.



Currently, we are nearly prepared to initiate cycloaddition studies with alcohol **43** and tropolone **129**. The first cycloaddition is expected to give the methylated form of neosetophomone B (**13**) and its stereoisomer. Deprotection of these cycloadducts and comparison to the literature spectrum of neosetophomone B will allow us to assign their relative

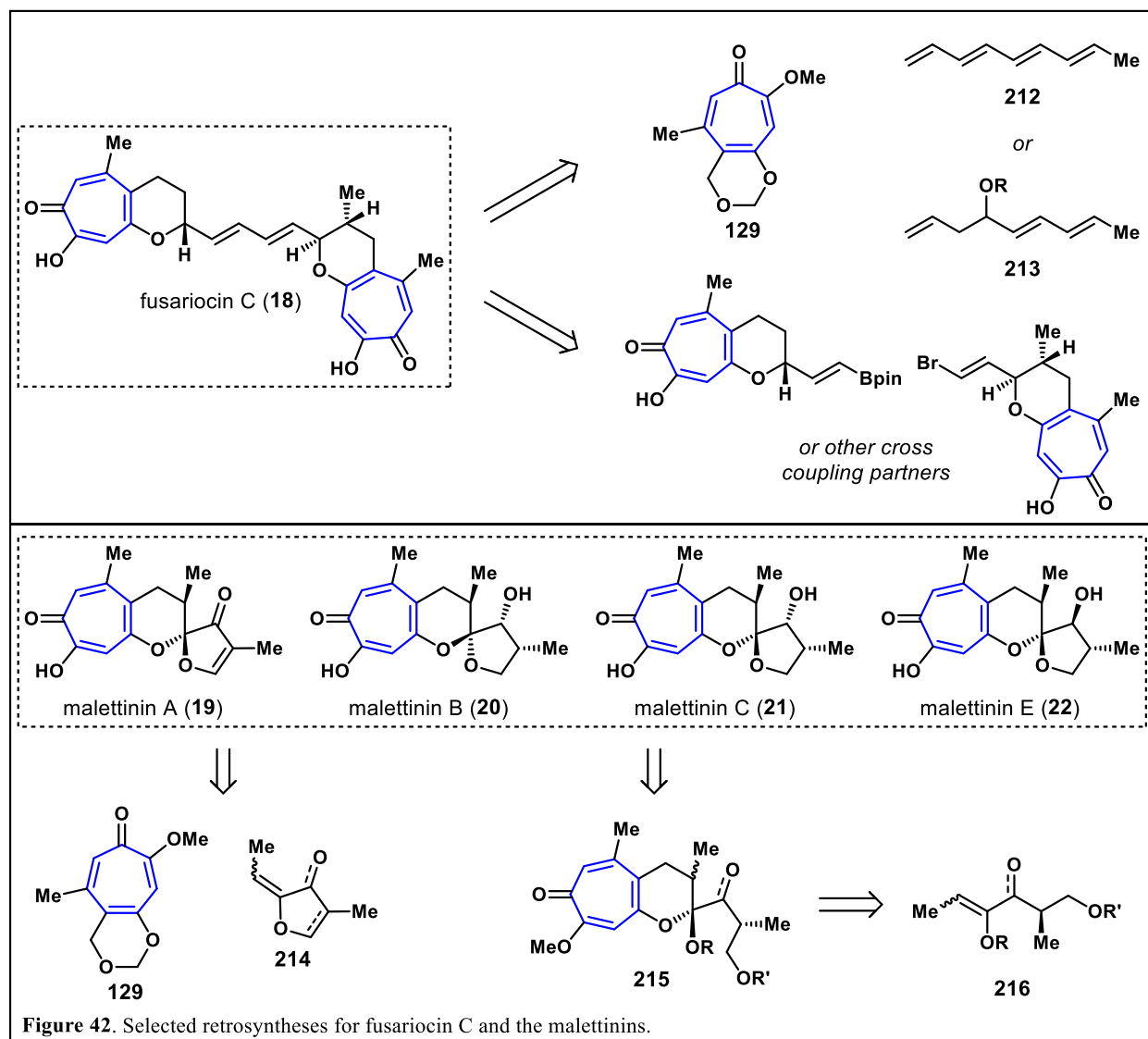
stereochemistry, since the crystal structure of neosetophomone B is known. This will also constitute another total synthesis of a natural sesquiterpene-tropolone. Then, whichever monocycloadduct corresponds to neosetophomone B will be subjected to our conditions for the second cycloaddition. The best case scenario will be complete diastereoselectivity for methylated form of eupenifeldin and the worst being complete diastereoselectivity for the wrong isomer, as we are observed in the pycnidione series. Even a mixture of diastereomers would be acceptable. These experiments that could lead to the synthesis of new natural products are within immediate reach and are being pursued by other members in our group.

### 4.3. Synthesis of Tropolone-Containing Natural Products

As discussed in chapter 1, there are additional biologically active natural products that bear a tropolone-dihydropyran fragment identical to the one found in the sesquiterpene-tropolones, namely fusariocin C (**18**) and malettinins A, B, C, and E, (**19**, **20**, **21**, **22**). Since we have devoted such effort into the synthesis and introduction of this fragment into much more complicated scaffolds, the synthesis of these smaller natural products would be an interesting and low-stakes pursuit for our group. In a retrosynthetic analysis, we found that there are several ways to disconnect these compounds. A few of our ideas are presented in Figure 42.

For the synthesis of fusariocin C, the most straightforward approach would be the HDA reaction between the *o*-QM generated from **129** and nonatetraene **212**. However, the terminal olefins may not react selectively over the internal olefins. Alternatively, the nine carbon chain could be traced back to triene **213**, where the allylic ether could be protected such that the only internal olefin is blocked by a large protecting group. Synthesis of this intermediate would be readily achieved by the addition of allylmagnesium chloride to sorbic aldehyde. If two cycloadditions on the nine carbon chain proves to be challenging, another alternative would be to





perform the cycloadditions on separate olefin fragments, then unite the two tropolone fragments in a cross coupling reaction.

The tropolone containing malettinin natural products all have the same carbon skeleton with varying stereochemistry and oxidation. Our first foray into the synthesis of this class will be focused only on constructing the skeleton with oxygen-based functional groups in the proper locations. Stereochemistry and oxidation state will be a secondary concern, because if the stereochemistry of compounds **21** or **22** is not directly achieved, oxidation to compound **19** will still enable the synthesis of a natural product in this class. Reduction of **19** may also produce

stereoisomers with the natural configuration of the malettinins. That being stated, the malettins can be traced back to the tropolone *o*-QM precursor **129** and generic compound **214**. Alternatively, the malettinin structure contains a ketal that could be cleaved to trace their structure back to compound generic compound **215**. This could be disconnected to cycloaddition partners **129** and **216**. While these natural products do not exhibit the biological activity found in the sesquiterpene-tropolones, their synthesis will be a test for the *o*-QM generation and HDA reactions of **129** in a new context.

#### 4.4. Synthesis of Bistropolones for Biological Studies

The biological activity and limited studies on the mechanism of action were discussed in section 1.4. It is clear from the available biological activity data that the bistropolones are significantly more active than monotropolones. Likewise, work from the Yamato group corroborates this in their SAR studies of mono- and bistropolones.<sup>4</sup> In work by the Houck group, it was suggested that the HIF-1 $\alpha$  pathway is targeted by pycnidione to mimic hypoxic conditions in the cell.<sup>1</sup> We are curious to see if this pathway is also targeted in other cell lines, specifically if it is related to the growth inhibition observed by the Chung group in their studies of pycnidione in A549 cells.<sup>2</sup> To this end, we propose that our modular synthetic platform may be used to construct and test bistropolones derived directly from the sesquiterpene-tropolones scaffold, or from linkers designed to vary the relative positions between tropolones in three dimensional space.

A consequence of the HDA reactions employed in the synthesis of natural sesquiterpene-tropolones is the generation of unnatural stereoisomers with the same constitution as the natural products. We have obtained some preliminary biological activity data with (–)-epolone B (*ent*-**5**), *epi*-(+)-epolone B (*epi*-**5**), (±)-deoxyepolone B (**50**), and (±)-deoxypycnidione (**6**) wherein all

compounds were cytotoxic against A549 and HCT-116 cells (Table 2). It is evident that conformational changes of the macrocyclic core resulting from stereochemical differences may have a

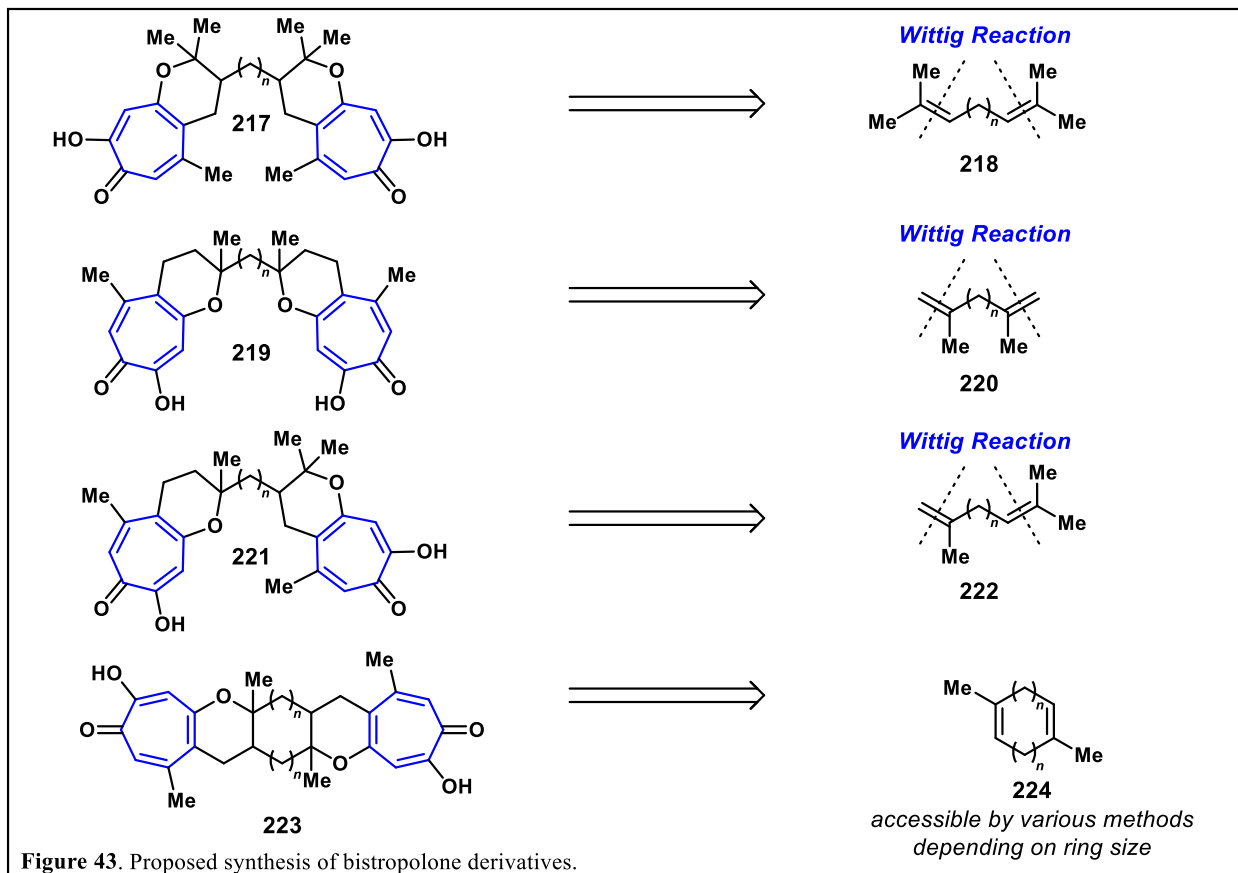
**Table 2.** Preliminary biological activity data for synthetic sesquiterpene-tropolones.

<i>Compound</i>	<b>A549</b> (mM)*	<b>HCT-116</b> (mM)*
(-)-epolone B ( <i>ent</i> - <b>5</b> )	27 ± 3	18.6
<i>epi</i> -(+)-epolone B ( <i>epi</i> - <b>5</b> )	33 ± 5	22.6
(±)-deoxyepolone B ( <b>50</b> )	65 ± 2	66.5
(±)-deoxypycnidione ( <b>6</b> )	18 ± 5	12 ± 5

\*48 hr IC<sub>50</sub> values

slight impact on the biological activity of the sesquiterpene-tropolones. Moreover, relative orientation of tropolones in bistropolone structures has already been shown to impact activity in prior work.<sup>4</sup> These data also confirm that our synthetic bistropolones are more active than the corresponding monotropolones. Thus, we propose that it will be a worthwhile endeavor to evaluate all natural and unnatural stereoisomers of the sesquiterpene-tropolones resulting from the HDA cycloaddition reactions, especially those that are immediately available to us by our current synthetic efforts. Should the acquired data indicate a significant dependence of activity on macrocycle conformation or structure, the core may be further derivatized *via* manipulation of the disubstituted olefin and secondary alcohol.

In addition to sesquiterpene-tropolone derivatives, we envision the synthesis of a series of bistropolones derived from simple, readily constructed aliphatic linkers capable of undergoing HDA reactions with the *o*-QM generated from **129** (Figure 43). For linear compounds such as **217**, we anticipate that the unadorned linker may be readily synthesized using simple olefination chemistry. For example, linker precursor **218** may be synthesized using a Wittig reaction, tracing the compound back to the corresponding bisphosphonium ylide and acetone. Additionally, the orientation of the two tropolones may have a significant impact on the activity of these analogues. Thus, we expect that by taking advantage of the native regioselectivity of the cycloadditions, we can modify the substitution pattern of the olefins to change the orientation of



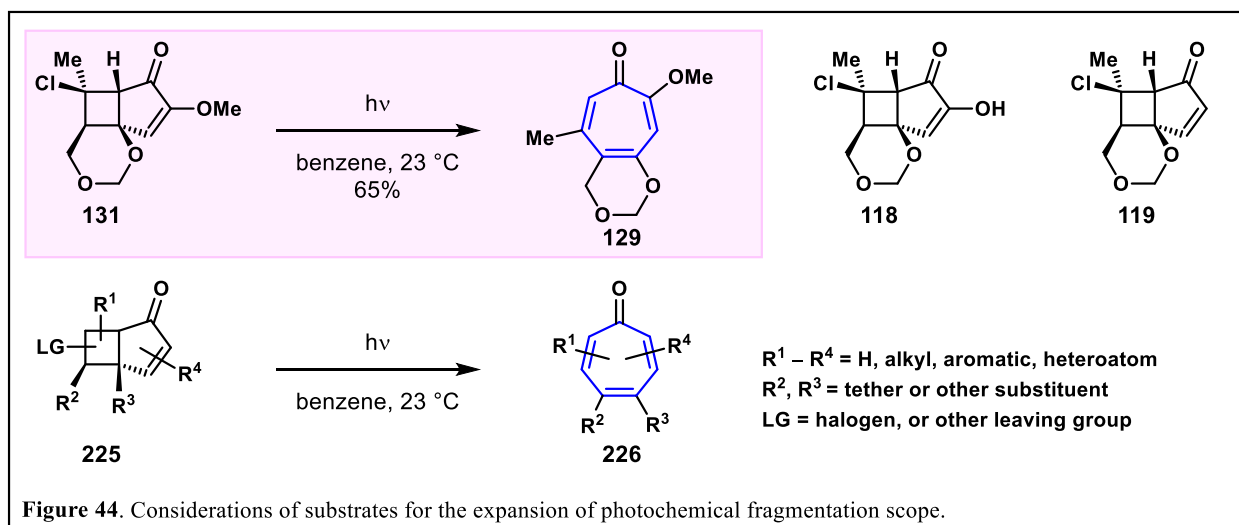
the tropolones, generating compounds such as **219**. Again, diene **220** may be retrosynthetically disconnected *via* Wittig reactions between the corresponding diketone and methylenephosphonium ylide. Finally, compounds such as **221**, which resemble the tropolone orientation of the sesquiterpene-tropolones, may also be derived from linkers such as **222**, synthesized using olefination chemistry.

Cyclic bistropolones such as **223** will likely be significant in our proposed SAR study, as they more closely resemble the sesquiterpene-tropolones. Symmetrical structures such as **224** containing trisubstituted olefins can be readily synthesized from their parent structures *via* introduction of a methyl group. Simple bicyclic structures may also be converted into bistropolones. However, we predict that in some cases the synthesis of desired linkers may not be trivial. Regardless, we can supplement these gaps in our systematic analogue development

with the addition of commercially available terpenes as scaffolds to rapidly introduce complexity to our library of bistropolone

#### 4.5. Development of the Photochemical Fragmentation

To the best of our knowledge, the photochemical fragmentation that converts compound **131** to tropolone **129** is unprecedented (Figure 44). Notably, a recent publication describes a one-pot photochemical [2+2] enone-alkyne cycloaddition that spontaneously fragments to ring-expanded products, however, this proceeds over a photochemical electrocyclic ring opening of the intermediate cyclobutene. A compound very similar to **129** was generated, though no tropolones were formed using this methodology. Instead, our photochemical fragmentation must be mechanistically distinct, since an electrocyclic ring opening is not possible in our case, and ring expanded products were never observed during the photochemical [2+2] enone-olefin cycloaddition that produces **116** and **117** (Figure 17).



In an effort to explore the nature and scope of our new reaction, we are initiating a methodological study for the fragmentation of bicyclo[3.2.0]heptenones such as generic compound **225** to ring expanded products such as **226**. While we performed our reaction on a methylated hydroxyenone, perhaps the unprotected hydroxyenone (such as **118**) or enone (such

as **119**) will undergo the same fragmentation. Presumably, the presence of a leaving group such as a halogen is required, but we plan to test substrates that lack this substituent to verify our suspicion. Moreover, we can test substrates with the substituent at various positions on the cyclobutane and measure its impact on the reaction. We are especially interested to learn if other bicyclic systems, such as a bicyclo[4.2.0]octenone system will undergo fragmentation, as this would have implications on the electron flow during the fragmentation. Finally, we would like to test the tolerance of substituents of various functionality at different positions in the bicyclic ring system. The conversion of compound **131** to **129** is a particularly useful way to synthesize this tropolone fragment, but we believe that exploring the generality may be beneficial to other chemists seeking to synthesize intricate ring systems.

#### 4.6 References

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## CHAPTER 5: EXPERIMENTAL

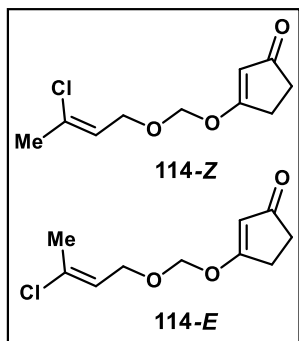
**General Procedures.** All reactions were performed under nitrogen atmosphere in oven or heat-gun dried glassware unless otherwise indicated. Diethyl ether (ACS grade), dichloromethane (ACS grade), tetrahydrofuran (HPLC grade), and toluene (ACS grade) were dried for reactions using the MB-SPS solvent purification system containing activated alumina manufactured by MBRAUN. Reaction temperatures correspond to the external temperature of the reaction vessel. Photochemical reactions were performed with LSE Lighting 15W 120V Compact Germicidal UV (CFL/UV/MED) bulbs. Microwave reactions were performed in CEM Discover and Discover S Microwave Synthesis System.

Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Macherey-Nagel silica gel plates (SIL G-25 UV<sub>254</sub>). The same plates were used for preparative TLC. Plates were visualized by UV and KMnO<sub>4</sub>. Silicycle SiliaFlash<sup>®</sup> P60 (SiO<sub>2</sub>, 40–63 μm particle size, 230–400 mesh) was used for flash column chromatography. Preparative HPLC was performed on a Shimadzu Prominence LC-20AP Preparative Liquid Chromatograph system with SPD-20A UV/VIS detector and a Kinetex<sup>®</sup> 5 μm EVO C18 100Å, 250 x 100 mm column. UHPLC-MS experiments were performed on a Shimadzu Nexera XR LC-20AD XR liquid chromatograph system with a SPD-M30A diode array detector and a Kinetex<sup>®</sup> 1.7 μm EVO C18 100Å, 50 x 2.1 mm column.

<sup>1</sup>H-NMR spectra were obtained at 500 MHz and <sup>13</sup>C-NMR were obtained at 126 MHz. NMR spectra were recorded using a Bruker 500 MHz spectrometer and were referenced to residual chloroform (7.26 ppm, <sup>1</sup>H; 77.0, <sup>13</sup>C) or residual dichloromethane (5.32 ppm, <sup>1</sup>H; 53.8 ppm, <sup>13</sup>C). Chemical shifts are reported in parts per million (ppm) and multiplicities are as indicated: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling



constants,  $J$ , are reported in Hertz. High resolution mass spectrometry (HRMS) data were collected on an Agilent 6230 TOF LCMS instrument using the electrospray ionization-time of flight (ESI-TOF) technique with positive ionization, or collected at the University of Illinois Mass Spectrometry Laboratory with ESI-TOF or electron impact-time of flight (EI-TOF). Infrared (IR) spectra were measured neat on a Perkin-Elmer Spectrum Two FT-IR spectrometer. Peaks are reported in  $\text{cm}^{-1}$  with indicated relative intensities: s (strong, 0–33% T); m (medium, 34–66% T), w (weak, 67–100% T), and br (broad). Melting points were measured on a Buchi B-540 melting point apparatus and are uncorrected. Optical rotations were recorded on a Jasco P-2000 polarimeter at 589 nm and are reported in units of  $10^{-1}$  ( $\text{deg cm}^2 \text{g}^{-1}$ ). The X-ray diffraction experiments were conducted using a Bruker D8 Venture/Photon 100 diffractometer. Using Olex2 the structures were solved with ShelXT structure solution program using the intrinsic phasing solution method and the XT refinement package using least squared minimization.



**Synthesis of Compounds 114-Z and 114-E** : 3-Chloro-2-buten-1-ol

(**113**, 10.7 g, 100 mmol, 1.1 equiv, mixture of *E* and *Z* olefin isomers)

was added dropwise to a stirring suspension of paraformaldehyde (3.00 g, 100 mmol, 1.1 equiv) and TMSCl (30 mL) prepared in a 100-mL

flask at 0 °C. The flask was equipped with a drying tube containing

anhydrous CaCl<sub>2</sub>, then the reaction was warmed to room temperature and became homogenous over two hours. The reaction was carefully concentrated *in vacuo* at 10 °C, then the mixture of the chloromethyl ether (**115**) and hexamethyldisiloxane was added slowly to a stirring solution of 1,3-cyclopentadione (**112**, 8.92 g, 91.0 mmol, 1.0 equiv) and potassium carbonate (18.9 g, 136 mmol, 1.5 equiv) in DMF (400 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 12 h. The suspension was decanted over a packed bed of celite and vacuum filtered. The reaction flask and filter cake were washed with ethyl acetate (100 mL) then the orange filtrate was concentrated to 50 mL by rotary evaporation. The residue was partitioned between water (50 mL) and ethyl acetate (50 mL) then the organic and aqueous layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 50 mL) then the combined organic extracts were washed with brine (50 mL), dried over magnesium sulfate, and concentrated. The crude reaction mixture was purified by flash column chromatography (silica gel, 1:1 hexane:EtOAc) to afford an inconsequential mixture of compounds **114-Z** and **114-E** as a pale yellow oil (17.6 g, 81.1 mmol, 89%). **114-Z** could be completely separated from **114-E** by column chromatography. However, **114-E** could not be similarly obtained without impurities from **114-Z**. Thus, characterization of **114-E** was less extensive.

**114-Z:**

**R<sub>f</sub>** = 0.38 (SiO<sub>2</sub>, hexanes:EtOAc = 1:1, UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 5.62 (tq, *J* = 6.3, 1.3 Hz, 1H), 5.43 (t, *J* = 1.3 Hz, 1H), 5.16 (s, 2H), 4.32 (dq, *J* = 6.3, 1.3 Hz, 2H), 2.66 – 2.63 (m, 2H), 2.46 – 2.43 (m, 2H), 2.14 (dt, *J* = 1.3 Hz, 3H).

**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 206.2, 187.7, 134.9, 121.3, 107.1, 94.4, 66.6, 34.0, 28.6, 26.4.

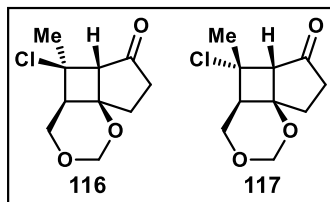
**HRMS:** (ESI-TOF, *m/z*) calcd. for C<sub>10</sub>H<sub>13</sub>ClO<sub>3</sub> [M]<sup>+</sup> calc.: 216.0553; found: 216.0551.

**IR:** (ATR, neat, cm<sup>-1</sup>) 2959 (w), 2924 (w), 1702 (m), 1678 (m), 1589 (s), 1438 (w), 1344 (m), 1287 (w), 1183 (m), 1105 (m), 997 (m), 925 (s), 832 (m), 632 (m), 522 (w), 485 (w).

#### **114-E:**

**R<sub>f</sub>** = 0.30 (SiO<sub>2</sub>, hexanes:EtOAc = 1:1, UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 5.77 (tq, *J* = 7.4, 1.3 Hz, 1H), 5.45 (t, *J* = 1.3 Hz, 1H), 5.16 (s, 2H), 4.18 (d, *J* = 7.4 Hz, 2H), 2.67 – 2.63 (m, 2H), 2.47 – 2.43 (m, 2H), 2.14 (s, 3H).



**Synthesis of Compounds 116 and 117:** A mixture of **114** isomers

(4.20 mL, 5.00 g, 23.1 mmol) was added to a 1-L quartz vessel

containing a stir bar, and the oil was dissolved in dichloromethane

(600 mL, 0.04 M). The vessel was sealed with a rubber septum and the solution was degassed

with argon at 0 °C for 20 min, then the reaction was irradiated using six UV lamps for 30 h. The

mixture was concentrated and subjected to flash column chromatography (silica gel, 3:2

hexanes:EtOAc) to give [2+2] cycloadducts **116** and **117** as a pale yellow solid (3.70 g, 17.1

mmol, 74%, d.r. = 4.9:1). The diastereomers were partially separable by column

chromatography. Further purification of compound **116** or **117** could be achieved by

recrystallization from dichloromethane and diethylether. Alternatively, the crude reaction

mixture could be concentrated to give a tan solid mixture of **116** and **117**. Suspension of this

residue in diethyl ether and filtration of the solid through a fritted funnel gave **116** with only trace quantities of **117** as a colorless solid.

**116:**

**R<sub>f</sub>** = 0.33 (SiO<sub>2</sub>, hexanes:EtOAc = 3:2, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 4.97 (d, *J* = 6.3 Hz, 1H), 4.70 (d, *J* = 6.3 Hz, 1H), 4.23 (d, *J* = 12.8 Hz, 1H), 3.99 (dd, *J* = 12.8, 6.3 Hz, 1H), 3.01 (s, 1H), 2.63 – 2.52 (m, 1H), 2.46 – 2.35 (m, 3H), 2.02 – 1.91 (m, 1H), 1.52 (s, 3H).

**<sup>13</sup>C NMR:** (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 212.9, 89.4, 77.3, 65.6, 63.7, 63.5, 46.3, 39.2, 32.4, 29.0.

**HRMS:** (EI-TOF, *m/z*) calcd. for C<sub>10</sub>H<sub>13</sub>ClO<sub>3</sub> [M]<sup>+</sup> calc.: 216.0553; found: 216.0555.

**IR:** (ATR, neat, cm<sup>-1</sup>) 3448 (w), 2985 (w), 2941 (w), 2859 (w), 2787 (w), 1732 (s), 1381 (w), 1334 (w), 1156 (s), 1009 (s), 914 (m), 795 (w), 760 (w), 646 (w), 602 (w), 512 (m), 461 (m).

**mp:** 133 – 136 °C

**117:**

**R<sub>f</sub>** = 0.49 (SiO<sub>2</sub>, hexanes:EtOAc = 3:2, KMnO<sub>4</sub>)

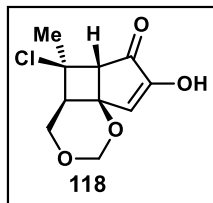
**<sup>1</sup>H NMR:** (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 4.92 (d, *J* = 6.6 Hz, 1H), 4.61 (d, *J* = 6.5 Hz, 1H), 4.26 (d, *J* = 13.2 Hz, 1H), 3.91 (dd, *J* = 13.2, 5.7 Hz, 1H), 2.69 (s, 1H), 2.67 (d, 5.7 Hz, 1H), 2.58 – 2.49 (m, 2H), 2.45 (ddd, 12.7, 7.4, 2.6, 1H), 2.02 (s, 3H), 1.88 (td, 11.7, 9.5 1H).

**<sup>13</sup>C NMR:** (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 211.1, 89.7, 77.5, 64.1, 62.6, 62.5, 47.7, 39.2, 31.8, 28.1.

**HRMS:** (EI-TOF, *m/z*) calcd. for C<sub>10</sub>H<sub>13</sub>ClO<sub>3</sub> [M]<sup>+</sup> calc.: 216.0553; found: 216.0547.

**IR:** (ATR, neat, cm<sup>-1</sup>) 2977 (w), 2881 (w), 1724 (s), 1491 (w), 1458 (w), 1412 (w), 1384 (m), 1216 (m), 1161 (s), 1006 (s), 963 (s), 801 (m), 737 (m), 643 (m), 456 (m)

**mp:** 142 – 143 °C



**Synthesis of Compound 118:** To a 250-mL round-bottom flask equipped with a stir bar was added compound **116** (2.50 g, 11.5 mmol, 1.0 eq.) and a 1:1 mixture of DMSO and toluene (120 mL, 0.1 M). Iodine (0.293 g, 1.15

mmol, 0.10 equiv) was added to the resulting solution then the neck of the flask was fitted with an air condenser open to the atmosphere. The dark red solution was stirred at 75 °C in a dark hood and the consumption of the starting material was monitored by TLC (silica gel, 1:2 hexanes:Et<sub>2</sub>O). After 2.5 days, the reaction was ended before full consumption of the starting material to mitigate over-oxidation of the desired product. The reaction was cooled to room temperature and quenched with aqueous 10% sodium thiosulfate (75 mL). The mixture was extracted with ethyl acetate (4 × 50 mL) then the combined organic extracts were washed with water (3 × 50 mL), brine (50 mL), dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The brown residue was subjected to column chromatography (silica gel, 3:2 to 1:2 hexanes:Et<sub>2</sub>O gradient) to give recovered **116** (0.287 g, 1.32 mmol) and compound **118** as a pale yellow solid (1.384 g, 6.00 mmol, 52%, 59% brsm).

**R<sub>f</sub>** = 0.39 (SiO<sub>2</sub>, hexanes:EtOAc = 1:1, UV, KMnO<sub>4</sub>)

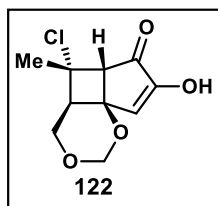
**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 6.47 (d, *J* = 0.7 Hz, 1H), 5.67 (s, 1H), 5.10 (d, *J* = 5.6 Hz, 1H), 4.89 (d, *J* = 5.6 Hz, 1H), 4.45 (ddd, *J* = 12.4, 2.5 Hz, 1H), 4.12 (dd, *J* = 12.4, 7.0 Hz, 1H), 3.49 (dd, *J* = 1.2, 0.7 Hz, 1H), 2.48 (ddd, *J* = 7.0, 2.5, 1.2 Hz, 1H), 1.54 (s, 3H).

**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 197.5, 154.9, 127.2, 90.6, 71.6, 64.5, 62.6, 61.2, 46.5, 29.1.

**HRMS:** (EI-TOF, *m/z*) calcd. for C<sub>10</sub>H<sub>11</sub>ClO<sub>4</sub> [M]<sup>+</sup> calc.: 230.0346; found: 230.0341.

**IR:** (ATR, neat, cm<sup>-1</sup>) 3284 (br), 3124 (br), 3010 (w), 2859 (w), 1713 (s), 1646 (m), 1387 (m), 1231 (w), 1208 (m), 1117 (s), 1033 (s), 990 (s), 963 (m), 801 (m), 683 (m), 549 (m), 485 (m).

**mp:** 138 – 140 °C



**Synthesis of Compound 122:** Employing a procedure identical to that for the formation of compound **118** from **116**, compound **117** (2.50 g, 11.5 mmol, 1.0 eq.) in a 1:1 mixture of DMSO and toluene (120 mL, 0.1 M) was treated with iodine (0.293 g, 1.15 mmol, 0.10 equiv), heated at 75 °C for 2.5 days, and monitored by TLC (silica gel, 1:1 hexanes:EtOAc). After work-up, the crude product mixture was purified by column chromatography (silica gel, 4:1 to 1:1 hexanes:EtOAc gradient) to produce recovered **117** (0.947 g, 4.37 mmol) and compound **122** as a pale yellow solid (0.741 g, 3.21 mmol, 28%, 45% brsm).

**R<sub>f</sub>** = 0.31 (SiO<sub>2</sub>, hexanes:EtOAc = 3:1, UV, KMnO<sub>4</sub>)

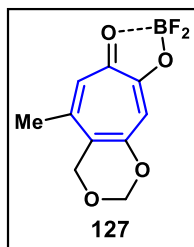
**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 6.64 (s, 1H), 5.92 (s, 1H), 5.02 (d, *J* = 6.1 Hz, 1H), 4.73 (d, *J* = 6.1 Hz, 1H), 4.29 (d, *J* = 13.0 Hz, 1H), 3.99 (dd, *J* = 13.0, 6.1 Hz, 1H), 3.06 (d, *J* = 1.2 Hz, 1H), 2.65 (d, *J* = 6.1 Hz, 1H), 2.04 (s, 3H).

**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 196.4, 155.2, 128.1, 90.3, 72.9, 62.9, 60.0, 59.6, 50.0, 28.7.

**HRMS:** (EI-TOF, *m/z*) calcd. for C<sub>10</sub>H<sub>11</sub>ClO<sub>4</sub> [M]<sup>+</sup> calc.: 230.0346; found: 230.0341.

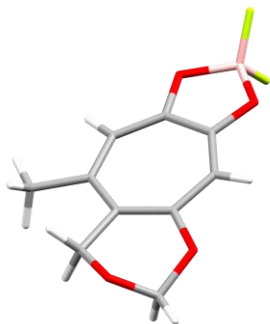
**IR:** (ATR, neat, cm<sup>-1</sup>) 3341 (br), 2974 (w), 2872 (w), 1706 (m), 1644 (m), 1396 (m), 1231 (m), 1171 (m), 1115 (s), 1131 (s), 986 (s), 921 (m), 799 (m), 701 (m), 644 (m), 610 (m), 571 (m).

**mp:** 142 – 145 °C



**Synthesis of Compound 127:** To a dry 250-mL round-bottom flask equipped with a stir bar was added compound **118** (3.11 g, 13.5 mmol, 1.0 equiv) and anhydrous dichloromethane (135 mL, 0.1 M). The resulting solution was

cooled to 0 °C, then boron trifluoride diethyletherate (10.0 mL, 80.8 mmol, 6.0 equiv.) was slowly added to the flask *via* syringe. The reaction was slowly warmed to room temperature and stirred for two days, after which the starting material was shown to have been consumed by TLC (silica gel, 1:1 hexanes:EtOAc). The reaction was quenched with saturated aqueous sodium bicarbonate (50 mL) and transferred to a separatory funnel. The dichloromethane layer was drained and the aqueous layer was extracted with ethyl acetate (4 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated to a brown solid. The residue was purified by column chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>) to afford compound **127** as a colorless solid (1.91 g, 7.88 mmol, 59%). Compound **122** (0.782 g, 3.39 mmol) may be converted to compound **127** (0.356 g, 1.47 mmol, 43%) using an analogous procedure.



**R<sub>f</sub>** = 0.33 (SiO<sub>2</sub>, hexanes:EtOAc = 2:3, CH<sub>2</sub>Cl<sub>2</sub> = 0.59, UV, KMnO<sub>4</sub>)

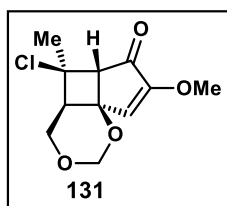
**<sup>1</sup>H NMR:** (500 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) δ 7.57 (s, 1H), 7.31 (s, 1H), 5.50 (s, 2H), 5.08 (s, 2H), 2.60 (s, 3H).

**<sup>13</sup>C NMR:** (126 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) δ 169.03, 168.96, 168.0, 157.3, 128.6, 122.5, 115.6, 92.6, 67.6, 25.1.

**HRMS:** (EI-TOF, m/z) calcd. for C<sub>10</sub>H<sub>9</sub>BF<sub>2</sub>O<sub>4</sub> [M]<sup>+</sup> calc.: 241.0598; found: 241.0589.

**IR:** (ATR, neat,  $\text{cm}^{-1}$ ) 3042 (w), 2922 (w), 1714 (w), 1608 (m), 1452 (s), 1335 (s), 1214 (s), 1005 (s), 979 (s), 858 (s), 761 (s).

**mp:** 203 – 204 °C



**Synthesis of Compound 131:** To a 250-mL recovery flask equipped with a stir bar was added compound **118** (3.65 g, 15.8 mmol, 1.0 equiv.) and the solid was dissolved in a 9:1 acetone:water mixture (100 mL), and potassium

carbonate (8.75 g, 63.3 mmol, 4.0 equiv.) was added to the solution. The flask was sealed with a rubber septum and placed under nitrogen. Dimethylsulfate (4.50 mL, 47.5 mmol, 3.0 equiv.) was transferred to the reaction by syringe. The reaction started as a suspension and gradually became a yellow solution over 1.5 hours. After stirring for 24 hours, the reaction was checked by TLC (1:1 hexanes:EtOAc) and appeared to be nearly complete. Brine (50 mL) was added to the reaction, then mixture was transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 x 50 mL), then the combined organic extracts were again washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 9:1 to 1:1 hexanes:EtOAc) to give recovered **118** (0.528 g, 2.29 mmol) and **131** (2.239 g, 9.15 mmol, 58%, 68% brsm) as pale solids.

**R<sub>f</sub>** = 0.33 (SiO<sub>2</sub>, hexanes:EtOAc = 1:1, UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.31 (s, 1H), 5.03 (d,  $J$  = 5.7 Hz, 1H), 4.83 (d,  $J$  = 5.7 Hz, 1H), 4.37 (ddd,  $J$  = 12.5, 2.5, 1.1, 1H), 4.07 (dd,  $J$  = 12.5, 7.1 Hz, 1H), 3.72 (s, 3H), 3.38 (s, 1H), 2.43 (ddd,  $J$  = 7.1, 2.5, 1.1 Hz, 1H), 1.50 (s, 3H).

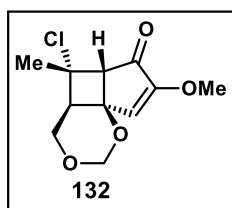


**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 195.6, 159.4, 125.2, 90.3, 71.2, 64.3, 62.8, 61.8, 57.7, 46.7, 29.0.

**HRMS:** (ESI-TOF, m/z) calcd. for C<sub>11</sub>H<sub>14</sub>ClO<sub>4</sub> [M+H]<sup>+</sup> calc.: 245.0581; found: 245.0570.

**IR:** (ATR, neat, cm<sup>-1</sup>) 3078 (w), 2975 (w), 2944 (w), 2854 (w), 1711 (s), 1617 (s), 1439 (m), 1368 (m), 1290 (m), 1208 (m), 1177 (m), 1123 (s), 1043 (s), 974 (m), 929 (m), 690 (m), 599 (m), 501 (m).

**mp:** 90 – 91 °C



**Synthesis of Compound 132:** Employing a procedure identical to that used for the conversion of **118** to **131** subsequent purification, **122** (0.543 g, 2.40 mmol, 1.0 equiv) was methylated with potassium carbonate (1.50 g, 14.0

mmol, 6.0 equiv.) and dimethylsulfate (1.10 mL, 12.0 mmol, 5.0 equiv.) in 9:1 acetone:water (30 mL) to give **132** (0.432 g, 1.77 mmol, 74%).

**R<sub>f</sub>** = 0.40 (SiO<sub>2</sub>, hexanes:EtOAc = 1:1, UV, KMnO<sub>4</sub>)

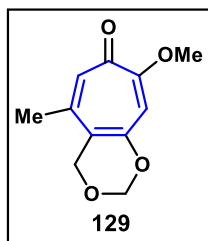
**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 6.48 (s, 1H), 5.02 (dd, *J* = 6.1, 1.1 Hz, 1H), 4.75 (d, *J* = 6.1 Hz, 1H), 4.29 (dd, *J* = 13.0, 1.1 Hz, 1H), 3.99 (dd, *J* = 13.0, 6.1 Hz, 1H), 3.78 (s, 3H), 3.04 (s, 1H), 2.66 (d, *J* = 6.1 Hz, 1H), 2.02 (s, 3H).

**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 194.5, 159.9, 125.8, 90.3, 72.4, 62.9, 60.3, 60.0, 57.8, 50.4, 28.7.

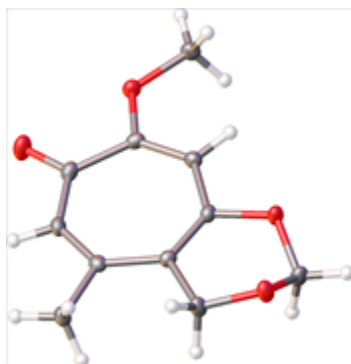
**HRMS:** (ESI-TOF, m/z) calcd. for C<sub>11</sub>H<sub>14</sub>ClO<sub>4</sub> [M+H]<sup>+</sup> calc.: 245.0581; found: 245.0570.

**IR:** (ATR, neat, cm<sup>-1</sup>) 3080 (w), 2949 (w), 2867 (w), 1716 (s), 1617 (s), 1439 (w), 1318 (m), 1234 (m), 1111 (s), 1039 (s), 982 (s), 803 (m), 706 (m), 609 (m).

**mp:** 143 – 145 °C



**Synthesis of Compound 129:** To a dry 1-L quartz vessel was added a solution of **131** (1.10 g, 4.48 mmol.) in benzene (0.45 L, 0.010 M). The vessel was sealed with a rubber septum and the solution was degassed with nitrogen for 20 min, then the reaction was irradiated using six UV lamps for 18 h. After this time period, the solution had become a suspension and the solid was poorly soluble in most common organic solvents except methanol. Thus, the suspension was concentrated under reduced pressure to about 100 mL of benzene, then treated with a saturated aqueous sodium bicarbonate (25 mL), which led to dissolution of the solid. The aqueous layer was extracted with ethyl acetate (5 x 25 mL) then a 4:1 mixture of ethyl acetate:isopropyl alcohol (2 x 25 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (EtOAc to 9:1 EtOAc:*i*-PrOH) to give **129** as a tan solid (0.627 g, 2.96 mmol, 66%). A mixture of compounds **131** and **132** (2.20 g, 8.98 mmol) in benzene (0.70 L, 0.013 M) may be converted to compound **129** (1.14 g, 5.47 mmol, 61%) using an analogous procedure. Compound **129** was recrystallized from dichloromethane to produce crystals suitable for X-ray diffraction analysis.



$R_f = 0.35$  ( $\text{SiO}_2$ , EtOAc:*i*-PrOH = 9:1, UV,  $\text{KMnO}_4$ )

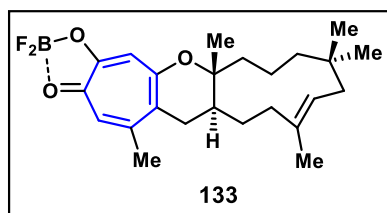
**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 6.97 (s, 1H), 6.44 (s, 1H), 5.19 (s, 2H), 4.68 (s, 2H), 3.90 (s, 3H), 2.16 (s, 3H).

**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 177.7, 162.3, 155.8, 145.1, 132.1, 116.4, 109.7, 90.4, 65.8, 56.2, 23.9.

**HRMS:** (ESI-TOF, m/z) calcd. for C<sub>11</sub>H<sub>13</sub>O<sub>4</sub> [M+H]<sup>+</sup> calc.: 209.0814; found: 209.0807.

**IR:** (ATR, neat, cm<sup>-1</sup>) 3004 (w), 2907 (w), 2848 (w), 1608 (s), 1562 (s), 1494 (s), 1431 (m), 1280 (s), 1181 (s), 1016 (s), 974 (s), 963 (s), 893 (m), 673 (m), 607 (m), 549 (s).

**mp:** 146 – 150 °C



**Synthesis of 133:** To a 10-mL microwave vial containing a stir bar was added tropolone **127** (0.100 g, 0.413 mmol, 1.0 eq.), α-humulene (**2**, 0.253 g, 1.24 mmol, 3.0 eq.), a crystal of BHT,

and mesitylene (4.1 mL, 0.1 M). The vial was sealed and heated at 200 °C for eight hours in a microwave reactor. Tropolone **127** was then determined to be mostly consumed by TLC (silica gel, 1:1 hexanes:EtOAc). The brown solution was transferred to a recovery flask and concentrated under reduced pressure. The residue was then loaded onto silica gel and purified by flash column chromatography (silica gel, 3:1 hexanes:EtOAc to EtOAc) to give recovered **127** (0.0229 g, 0.0946 mmol) and compound **133** (0.0878 g, 0.211 mmol, 51%, 66% brsm).

**R<sub>f</sub>** = 0.29 (SiO<sub>2</sub>, hexanes:EtOAc = 2:1, UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 7.33 (s, 1H), 7.25 (s, 1H), 5.18 (dd, *J* = 15.8, 2.1 Hz, 1H), 5.02 (dd, *J* = 12.2, 4.1 Hz, 1H), 4.98 (ddd, *J* = 15.8, 10.6, 2.1 Hz, 1H), 2.95 (dd, *J* = 17.9, 5.1 Hz, 1H), 2.66 (dt, *J* = 14.8, 2.1 Hz, 1H), 2.60 (s, 3H), 2.40 (dd, *J* = 17.9, 12.8 Hz, 1H), 2.34 (dd, *J* = 14.8, 10.6 Hz, 1H), 2.21 – 2.14 (m, 2H), 1.90 (ddd, *J* = 12.8, 8.0, 5.1 Hz, 1H), 1.82 (dd, *J* = 12.0, 11.5

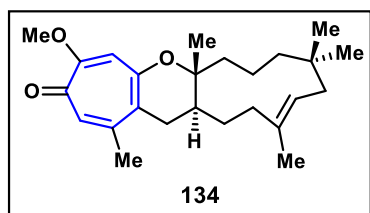
Hz, 1H), 1.77 (dd,  $J = 12.2, 4.1$  Hz, 1H), 1.63 (s, 3H), 1.37 (dd,  $J = 13.9, 11.5$  Hz, 1H), 1.23 (dd,  $J = 15.0, 8.0$  Hz, 1H), 1.19 (s, 3H), 1.06 (s, 3H), 1.00 (s, 3H).

**$^{13}\text{C}$  NMR:** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.8, 167.6, 167.6, 156.4, 144.2, 136.1, 128.8, 123.8, 120.7, 119.0, 115.7, 85.1, 42.7, 41.5, 38.4, 37.8, 34.5, 31.6, 30.1, 29.8, 28.1, 24.3, 20.6, 17.2.

**HRMS:** (EI-TOF,  $m/z$ ) calcd. for  $\text{C}_{24}\text{H}_{30}\text{O}_3$   $[\text{M}-\text{H}]^+$  calc.: 415.23706; found: 415.23662.

**IR:** (ATR, neat,  $\text{cm}^{-1}$ ) 2954 (w), 2932 (w), 1618 (m), 1524 (w), 1371 (m), 1360 (m), 1195 (m), 1046 (s), 986 (m), 903 (m), 836 (m), 734 (m), 562 (w), 518 (w), 469 (w).

**mp:** 252 – 255 °C



**Synthesis of 134:** To a 35-mL microwave vial containing a stir bar was added tropolone **129** (0.150 g, 0.720 mmol, 1.0 eq.),  $\alpha$ -humulene (**2**, 0.442 g, 3.60 mmol, 3.0 eq.), a crystal of BHT, and

mesitylene (7.2 mL, 0.1 M). The vial was sealed and heated at 200 °C for 16 hours in a microwave reactor. Tropolone **129** was then determined to be consumed by TLC (silica gel, 9:1 EtOAc:*i*-PrOH). The brown solution was transferred to a recovery flask and concentrated under reduced pressure. The residue was then loaded onto silica gel and purified by flash column chromatography (silica gel, 1:3 hexanes:EtOAc to pure EtOAc) to give compound **134** (0.225 g, 0.588 mmol, 82%).

**R<sub>f</sub>** = 0.58 (SiO<sub>2</sub>, EtOAc, UV, KMnO<sub>4</sub>)

**$^1\text{H}$  NMR:** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.01 (s, 1H), 6.50 (s, 1H), 5.14 (dd,  $J = 15.8, 1.6$  Hz, 1H), 5.08 (ddd,  $J = 16.0, 9.9, 2.3$  Hz, 1H), 5.02 (dd,  $J = 11.5, 3$  Hz, 1H), 3.89 (s, 3H), 2.77 (dd,  $J = 17.5, 5.4$  Hz, 1H), 2.53 (d,  $J = 14.5$  Hz, 1H), 2.30 (s, 3H), 2.30 – 2.24 (m, 1H), 2.20 – 2.09 (m, 3H),

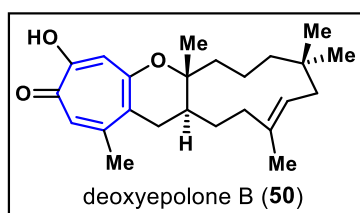
1.83 – 1.73 (m, 3H), 1.61 (s, 3H), 1.32 (dd,  $J = 13.8, 10.9$  Hz, 1H), 1.13 (dt,  $J = 14.2, 8.3$  Hz, 1H), 1.08 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H).

$^{13}\text{C}$  NMR: (126 MHz,  $\text{CDCl}_3$ )  $\delta$  177.6, 161.6, 156.8, 148.5, 143.1, 136.4, 130.5, 123.4, 120.1, 117.5, 111.3, 81.3, 56.0, 42.7, 41.5, 38.4, 38.0, 35.1, 30.6, 30.3, 30.3, 26.8, 24.4, 20.1, 17.2.

HRMS: (EI-TOF,  $m/z$ ) calcd. for  $\text{C}_{25}\text{H}_{35}\text{O}_3$   $[\text{M}+\text{H}]^+$  calc.: 383.2586; found: 383.2579.

IR: (ATR, neat,  $\text{cm}^{-1}$ ) 2929 (w), 2857 (w), 1737 (w), 1602 (s), 1566 (s), 1486 (s), 1454 (m), 1426 (m), 1266 (m), 1177 (s), 1151 (s), 1011 (s), 875 (m), 729 (w).

mp: 147 – 150 °C



**Synthesis of 50 from 133:** To a 4-mL vial containing a stir bar and compound **133** (0.0318 g, 73.6  $\mu\text{mol}$ , 1.0 equiv.) was added methanol (0.74 mL, 0.1 M) followed by potassium carbonate

(0.102 g, 0.736  $\mu\text{mol}$ , 10.0 equiv.). The suspension was vigorously stirred until the starting material was consumed. After 24 hours, the reaction was transferred to a separatory funnel containing pH = 7 phosphate buffer (2 mL) and washed with ethyl acetate (2 mL). The aqueous layer was drained and acidified with citric acid until a neutral pH was obtained. The aqueous layer was transferred back into the separatory funnel and extracted with the previously retained organic extract. The aqueous layer was subsequently washed with ethyl acetate (3 x 2 mL), then the combined organic extracts were washed with brine (4 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give **50** as an orange solid (0.0283 g, 0.0736  $\mu\text{mol}$ , quant.).

**Synthesis of 50 from 134:** To a 4-mL vial containing a magnetic stir bar and **134** (0.0250 g, 0.0654 mmol, 1.0 equiv.) was added methanol (0.65 mL) then a solution of sodium hydroxide (1.0 M, 0.65 mL, 0.65 mmol, 10 equiv.). The reaction was heated at 100 °C for eight hours, after which the reaction was checked by TLC (EtOAc) and the starting material spot became an undefined streak. The reaction was quenched with pH = 7 phosphate buffer (1.0 mL), then 1M HCl (0.65 mL) was added to neutralize the pH of the crude reaction. The aqueous mixture was transferred to a separatory funnel and extracted with ethyl acetate (3 x 1 mL), then the combined organic extracts were washed with brine (2 mL), dried over Magnesium sulfate, filtered, and concentrated, to give **50** as an orange solid (0.0193 g, 0.052 mmol, 80%).

**R<sub>f</sub>** = 0.36 (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 19:1, UV, KMnO<sub>4</sub>)

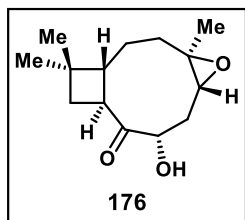
**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 7.13 (s, 1H), 7.01 (s, 1H), 5.14 (dd, *J* = 15.9, 1.6 Hz, 1H), 5.07 (ddd, *J* = 16.0, 10.1, 2.6 Hz, 1H), 5.02 (dd, *J* = 11.5, 3.0 Hz, 1H), 2.82 (dd, *J* = 17.4, 5.2 Hz, 1H), 2.56 (d, *J* = 14.3 Hz, 1H), 2.40 (s, 3H), 2.28 (dd, *J* = 14.5, 10.1 Hz, 1H), 2.22 (dd, *J* = 17.4, 12.2 Hz, 1H), 2.20 – 2.11 (m, 2H), 1.86 – 1.74 (m, 3H), 1.62 (s, 3H), 1.34 (dd, *J* = 13.8, 11.0 Hz, 1H), 1.20 – 1.12 (m, 1H), 1.11 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H).

**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 172.7, 163.3, 161.5, 150.2, 143.3, 136.4, 124.6, 123.7, 120.9, 120.2, 113.6, 82.0, 43.0, 41.7, 38.5, 38.1, 35.2, 31.2, 30.3, 29.9, 27.5, 24.6, 20.4, 17.4.

**HRMS:** (EI-TOF, *m/z*) calcd. for C<sub>24</sub>H<sub>32</sub>O<sub>3</sub> [M]<sup>+</sup> calc.: 368.23514; found: 368.23532.

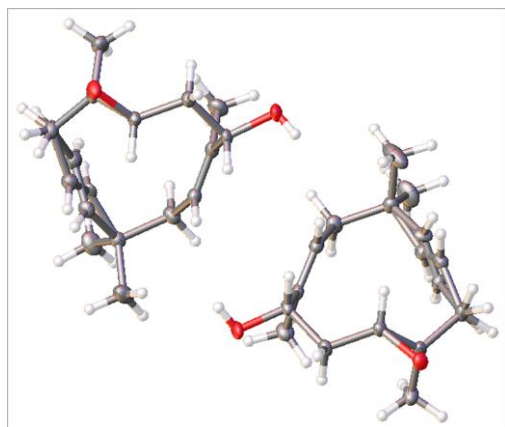
**IR:** (ATR, neat, cm<sup>-1</sup>) 3180 (w), 2925 (m), 2856 (m), 1733 (w), 1588 (m), 1438 (s), 1367 (m), 1280 (m), 1756 (s), 1134 (s), 1046 (s), 890 (m), 747 (w).

**mp:** 181 – 184 °C



**Synthesis of 176:** To a solution of (–)-kobusone (**175**, 20 g, 90 mmol, 1.0 equiv.) in anhydrous THF (450 mL) cooled to  $-78\text{ }^{\circ}\text{C}$  was added dropwise freshly prepared KHMDS (198 mL, 0.5 M in PhMe, 99 mmol, 1.10 equiv.).

The resulting yellow solution was stirred at  $-78\text{ }^{\circ}\text{C}$  for a half hour and thereafter treated dropwise with a solution of Davis oxaziridine (28.2 g, 108 mmol, 1.2 equiv.) in anhydrous THF (50 mL). The contents were stirred an additional three hours at  $-78\text{ }^{\circ}\text{C}$  and thereafter quenched with saturated aqueous ammonium chloride (300 mL). After warming to room temperature, the THF was removed *in vacuo*. The aqueous layer was extracted with ethyl acetate (3 x 300 mL), and the combined organics were washed with brine (800 mL), dried over magnesium sulfate, filtered, and concentrated. The crude oil was purified *via* flash chromatography (silica gel, hexane:EtOAc = 10:1 to 1:1) to afford the **176** as a white solid (18.6 g, 78.0 mmol, 87%). Crystals suitable for X-ray crystallographic analysis were grown from dichloromethane and methanol.



$R_f = 0.50$  (SiO<sub>2</sub>, hexanes:EtOAc = 1:1, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.73 – 4.68 (m, 1H), 3.43 (q,  $J = 9.5$  Hz, 1H), 2.83 (dt,  $J = 12.1, 5.0$  Hz, 2H), 2.67 – 2.60 (m, 1H), 2.20 (t,  $J = 10.3$  Hz, 1H), 2.15 (dt,  $J = 13.0, 3.8$  Hz, 1H), 1.96 (t,  $J = 10.4$  Hz, 1H), 1.85 (dd,  $J = 10.9, 8.8$  Hz, 1H), 1.73 – 1.67 (m, 1H), 1.53 (dddd,  $J = 15.3,$

13.3, 11.1, 4.6 Hz, 1H), 1.42 (ddd,  $J = 13.2, 11.2, 7.8$  Hz, 1H), 1.22 (d,  $J = 0.6$  Hz, 3H), 1.08 (s, 6H), 1.02 (td,  $J = 13.2, 4.8$  Hz, 1H).

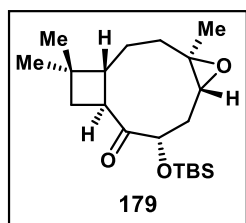
**$^{13}\text{C}$  NMR:** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  215.2, 71.4, 60.1, 59.9, 47.9, 47.5, 38.3, 37.6, 35.6, 35.0, 29.8, 26.5, 21.8, 16.6.

**HRMS:** (ESI-TOF,  $m/z$ ) calcd. For  $\text{C}_{14}\text{H}_{22}\text{O}_3$   $[\text{M}+\text{Na}]^+$  calc.: 261.1461; found: 261.1455.

**IR:** (ATR, neat,  $\text{cm}^{-1}$ ) 3469 (w), 2935 (s), 2866 (w), 1697 (s), 1448 (m), 1340 (m), 1164 (s), 1066 (m).

**mp:** 97 – 99 °C

**$[\alpha]_{\text{D}}^{23}$**  = -4.4 ( $c = 1.00$  in  $\text{CHCl}_3$ )



**Synthesis of 179:** To a solution of hydroxyl-ketone **176** (16.35 g, 68.6 mmol, 1.0 equiv.) and imidazole (20.7 g, 137.2 mmol, 3.0 equiv) in anhydrous DMF (275 mL) was added TBSCl (14.0 g, 205.8 mmol, 2.0 equiv). The resulting yellow solution was heated at 100 °C for 12 hours.

Thereafter, the reaction was cooled in an ice bath and quenched with saturated aqueous sodium bicarbonate (275 mL) and the aqueous phase was extracted with diethyl ether (3 x 300 mL). The combined organics were washed with brine (900 mL), dried over magnesium sulfate, filtered, and concentrated. The crude oil was purified *via* flash chromatography (silica gel, hexanes:EtOAc = 10:1) to afford the **179** as a clear oil (19.74 g, 78.0 mmol, 81%).

**$R_f$**  = 0.42 ( $\text{SiO}_2$ , hexanes:EtOAc = 10:1,  $\text{KMnO}_4$ )

**$^1\text{H}$  NMR:** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.31 (dd,  $J = 7.2, 1.0$  Hz, 1H), 3.92 (dt,  $J = 9.4, 8.3$  Hz, 1H), 2.65 (ddd,  $J = 13.9, 7.2, 5.3$  Hz, 1H), 2.47 (dd,  $J = 10.7, 5.3$  Hz, 1H), 2.12 (dt,  $J = 13.1, 3.7$  Hz, 1H), 2.03 (dd,  $J = 10.6, 9.4$  Hz, 1H), 1.91 (ddd,  $J = 11.3, 6.6, 3.2$  Hz, 1H), 1.62 – 1.52 (m, 3H),



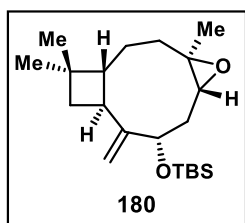
1.41 (s, 3H), 1.36 (ddd,  $J = 13.9, 10.7, 1.0$  Hz, 1H), 1.05 (s, 3H), 1.04 (s, 3H), 0.94 – 0.84 (m, 10H), 0.04 (s, 3H), 0.00 (s, 3H).

$^{13}\text{C}$  NMR: (126 MHz,  $\text{CDCl}_3$ )  $\delta$  217.1, 75.8, 60.1, 60.0, 51.8, 41.0, 39.7, 36.1, 34.2, 34.1, 29.3, 26.5, 25.8, 23.0, 18.2, 17.9,  $-5.0, -5.2$ .

HRMS: (ESI-TOF,  $m/z$ ) calcd. For  $\text{C}_{20}\text{H}_{36}\text{O}_3\text{Si}$   $[\text{M}+\text{Na}]^+$  calc.: 375.2326; found: 375.2322.

IR: (ATR, neat,  $\text{cm}^{-1}$ ) 2952 (w), 2930 (w), 2858 (w), 1703 (w), 1471 (w), 1254 (w), 1111 (m), 1050 (m), 907 (m), 829 (m), 777 (m).

$[\alpha]_{\text{D}}^{23} = -73.8$  ( $c = 1.00$  in  $\text{CHCl}_3$ )



**Synthesis of 180:** To a flask containing a solution of methyltriphenylphosphonium bromide (31.6 g, 84.0 mmol, 1.5 equiv, 95%) in anhydrous THF (200 mL) at 0 °C was added dropwise *n*-butyllithium (49.0 mL, 1.6 M in hexanes, 78.4 mmol, 1.4 equiv.). The resulting

heterogeneous orange solution was stirred at this temperature for 30 minutes and thereafter treated dropwise with a solution of ketone **179** (19.74 g, 56.0 mmol, 1.00 equiv.) in anhydrous THF (100 mL). The contents were warmed to room temperature and allowed to stir an additional 12 h. Thereafter, the reaction was quenched with saturated aqueous ammonium chloride (100 mL), THF was removed *in vacuo* and extracted with ethyl acetate (3 x 300 mL). The combined organics were washed with saturated aqueous sodium chloride (900 mL), dried over magnesium sulfate, filtered, and concentrated. The crude material was purified *via* flash chromatography (silica gel, hexanes:EtOAc = 20:1,  $\text{KMnO}_4$ ) to afford **180** as a colorless oil (18.47 g, 52.7 mmol, 94%).

**R<sub>f</sub>** = 0.50 (SiO<sub>2</sub>, hexanes:EtOAc = 10:1, KMnO<sub>4</sub>)

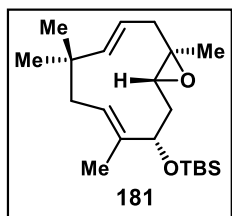
**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 5.07 (s, 1H), 5.05 (s, 1H), 4.57 (dd, *J* = 6.2, 3.4 Hz, 1H), 3.09 – 2.98 (m, 1H), 2.75 (dd, *J* = 10.8, 4.5 Hz, 1H), 2.44 (dddd, *J* = 13.4, 6.2, 4.6, 0.8 Hz, 1H), 2.09 (dt, *J* = 12.9, 3.6 Hz, 1H), 1.76 (ddd, *J* = 10.9, 8.8, 0.8 Hz, 1H), 1.71 – 1.64 (m, 2H), 1.58 (dtd, *J* = 14.7, 4.1, 1.9 Hz, 1H), 1.53 – 1.40 (m, 2H), 1.30 (s, 3H), 1.03 (s, 3H), 1.01 (s, 3H), 0.97 – 0.90 (m, 1H), 0.89 (s, 9H), 0.03 (s, 3H), –0.02 (s, 3H).

**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 155.9, 110.9, 71.9, 61.3, 60.5, 53.8, 41.3, 39.9, 38.6, 38.4, 33.3, 30.2, 27.5, 25.9, 22.7, 18.3, 17.8, –4.8, –5.0.

**HRMS:** (ESI-TOF, *m/z*) calcd. For C<sub>21</sub>H<sub>38</sub>O<sub>2</sub>Si [M+Na]<sup>+</sup> calc.: 373.2533; found: 373.2528.

**IR:** (ATR, neat, cm<sup>-1</sup>) 2952 (w), 2928 (w), 2858 (w), 1472 (w), 1387 (w), 1255 (w), 1046 (w), 830 (m), 775 (m).

**[α]<sub>D</sub><sup>23</sup>** = –47.5 (*c* = 1.00 in CHCl<sub>3</sub>)



**Synthesis of 181:** To a flask charged with **180** (18.47 g, 52.68 mmol) and Co(saI<sup>*t*-Bu, *t*-Bu</sup>)Cl (0.673 g, 1.05 mmol, 0.02 equiv.) was added benzene (263 mL) and was thereafter degassed with argon for one hour at 0 °C. After warming to room temperature, degassed phenylsilane (0.26 mL, 2.10 mmol, 0.04 equiv.) was added to the reaction, which immediately turned from dark green to bright red.

The contents were allowed to stir at room temperature 24 hours. Thereafter, solvent was removed *in vacuo* and the resulting crude oil was purified *via* flash chromatography (silica gel, hexanes:EtOAc = 20:1) to afford **181** as a dark red solid (17.56 g, 50.1 mmol, 95%).

**R<sub>f</sub>** = 0.61 (SiO<sub>2</sub>, hexanes:EtOAc = 10:1, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 5.27 (m, 2H), 5.19 (d, *J* = 16.1 Hz, 1H), 4.22 (dd, *J* = 7.7, 5.0 Hz, 1H), 2.56 – 2.46 (m, 2H), 2.20 (d, *J* = 13.8 Hz, 1H), 2.04 (t, *J* = 7.1 Hz, 1H), 1.93 (dd, *J* = 13.8, 6.2 Hz, 1H), 1.70 (dd, *J* = 12.8, 9.1 Hz, 1H), 1.58 – 1.47 (m, 4H), 1.29 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H).

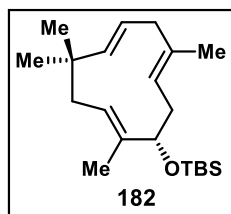
**<sup>13</sup>C NMR:** (126 MHz, DMSO-*d*<sub>6</sub>, 80 °C) δ 141.6, 134.6, 123.0, 122.4, 75.3, 62.4, 58.5, 40.6, 40.1, 35.3, 33.3, 27.6, 26.7, 25.3, 17.9, 17.4, 10.9, –5.4.

**HRMS:** (ESI-TOF, *m/z*) calcd. For C<sub>21</sub>H<sub>38</sub>O<sub>2</sub>Si [M+NH<sub>4</sub>]<sup>+</sup> calc.: 368.2979; found: 368.2965.

**IR:** (ATR, neat, cm<sup>-1</sup>) 2954 (w), 2927 (w), 2856 (w), 1470 (w), 1249 (w), 1069 (m), 1047 (m), 900 (m), 833 (m), 779 (m).

**mp:** 40 – 42 °C

**[α]<sub>D</sub><sup>23</sup>** = –77.2 (*c* = 1.00 in CHCl<sub>3</sub>)



**Synthesis of 182:** To a pressure tube charged with epoxide **181** (3.54 g, 1.10 mmol, 1.0 equiv.), and rhenium(VII) oxide (0.122 g, 0.252 mmol, 0.025 equiv.) was added anhydrous toluene (33 mL) followed by triphenyl phosphite (2.8 mL, 10.6 mmol, 1.05 equiv.). The resulting mixture was

heated at 100 °C for three hours and thereafter cooled to room temperature. The solvent was removed *in vacuo* and the crude material was purified *via* flash chromatography (silica gel, hexanes:EtOAc = 40:1-20:1) to afford **181** as a pale yellow oil (2.93 g, 8.76 mmol, 87%).

**R<sub>f</sub>** = 0.83 (SiO<sub>2</sub>, hexanes:EtOAc = 25:1, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 5.52 (dt, *J* = 15.8, 7.4 Hz, 1H), 5.14 (d, *J* = 15.8 Hz, 1H), 4.91 (d, *J* = 10.9 Hz, 1H), 4.82 (t, *J* = 8.0 Hz, 1H), 3.95 (dd, *J* = 9.1, 6.2 Hz, 1H), 2.46 (d, *J* = 7.4 Hz, 2H), 2.27 (ddd, *J* = 13.4, 7.0 Hz, 1H), 2.12 (t, *J* = 12.4 Hz, 1H), 2.05 (ddd, *J* = 13.2, 8.9 Hz, 1H),

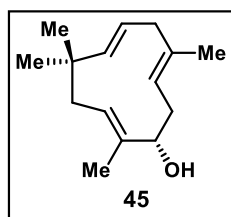
1.80 (d,  $J = 12.1$  Hz, 1H), 1.64 – 1.59 (s, 3H), 1.39 (t,  $J = 1.3$  Hz, 3H), 1.05 (s, 3H), 1.03 (s, 3H), 0.84 (s, 9H), 0.00 (s, 3H), –0.04 (s, 3H).

$^{13}\text{C NMR}$ : (126 MHz, DMSO- $d_6$ , 90 °C)  $\delta$  140.5, 138.5, 134.9, 126.5, 123.1, 122.2, 77.9, 41.3, 39.5, 36.1, 32.5, 28.6, 25.2, 24.2, 17.3, 17.2, 10.1, –5.3.

**HRMS**: (ESI-TOF,  $m/z$ ) calcd. For  $\text{C}_{21}\text{H}_{38}\text{OSi}$   $[\text{M}+\text{Na}]^+$  calc.: 357.2584; found: 357.2579.

**IR**: (ATR, neat,  $\text{cm}^{-1}$ ) 2955 (w), 2928 (w), 2856 (w), 1472 (w), 1251 (w), 1070 (m), 1053 (m), 967 (w), 834 (m), 773 (m).

$[\alpha]_{\text{D}}^{23} = -59.2$  ( $c = 1.00$  in  $\text{CHCl}_3$ )



**Synthesis of 45 from 182**: To a solution of **182** (1.70 g, 4.85 mmol, 1.0 equiv.) in anhydrous THF (5.1 mL) cooled to 0 °C was added dropwise TBAF (9.7 mL, 1.0 M in THF, 9.7 mmol, 2.0 equiv.). The contents were warmed to room temperature and stirred 48 hours. Thereafter, the reaction was quenched with saturated aqueous ammonium chloride (20 mL) and THF was removed *in vacuo*. The organics were extracted with ethyl acetate (3 x 20 mL) and the combined organics were washed with brine (60 mL), dried over magnesium sulfate, filtered, and concentrated. The crude oil was purified *via* flash chromatography (silica gel, hexanes:EtOAc = 15:1 to 6:1) to afford **45** as a white solid (1.05 g, 4.44 mmol, 92%).

**Synthesis of 45 from 181**: To a vial charged with epoxide **181** (0.050 g, 0.14 mmol, 1.0 equiv.), and rhenium(VII) oxide (0.0021 g, 0.0043 mmol, 0.030 equiv.) was added anhydrous toluene (0.71 mL) followed by triphenyl phosphite (0.039 mL, 0.14 mmol, 1.00 equiv., 97%). The resulting mixture was heated at 100 °C for three hours and thereafter cooled to room

temperature. The solvent was removed *in vacuo* and the crude material was treated with TBAF (0.7 mL, 1.0 M in THF, 0.7 mmol, 5.0 equiv.). The contents were heated at 50 °C for 36 hours and thereafter cooled to room temperature and quenched with saturated aqueous ammonium chloride (2 mL). The organics were extracted with ethyl acetate (3 x 4 mL) and the combined organics were washed with brine (10 mL), dried over magnesium sulfate, filtered, and concentrated. The crude oil was purified *via* flash chromatography (silica gel, hexanes:EtOAc = 20:1 to 6:1) to afford **45** as a white solid (0.023 g, 0.10 mmol, 73%).

**R<sub>f</sub>** = 0.36 (SiO<sub>2</sub>, hexanes:EtOAc = 4:1, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (400 MHz, CDCl<sub>3</sub>) δ 5.55 (m, 1H), 5.17 (d, *J* = 15.8, 1H), 5.10 – 5.02 (m, 1H), 4.87 (m, 1H), 4.07 (dd, *J* = 9.2, 6.2 Hz, 1H), 2.55-2.55 (m, 3H), 2.24 – 2.03 (m, 2H), 1.85 (dd, *J* = 13.8, 3.4 Hz, 1H), 1.66 (s, *J* = 1.5 Hz, 3H), 1.48 (t, *J* = 1.3 Hz, 3H), 1.08 (s, 3H), 1.07 (s, 3H).

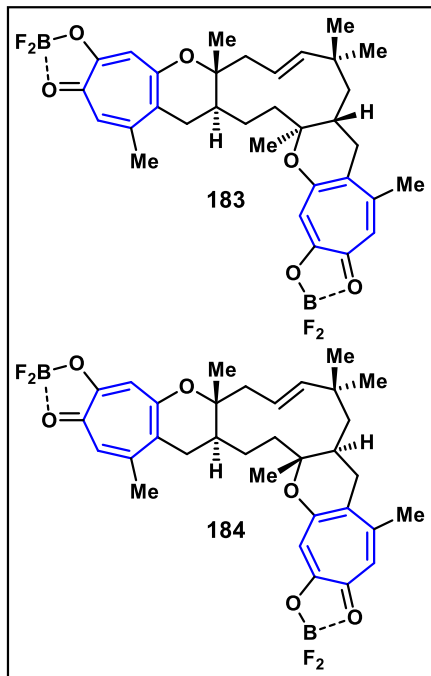
**<sup>13</sup>C NMR:** (126 MHz, DMSO-*d*<sub>6</sub>, 80 °C) δ 140.5, 137.9, 135.8, 126.6, 122.9, 122.6, 76.4, 41.4, 39.5, 36.2, 31.9, 28.8, 24.2, 17.3, 10.3.

**HRMS:** (ESI-TOF, *m/z*) calcd. For C<sub>15</sub>H<sub>24</sub>O [M+Na]<sup>+</sup> calc.: 243.1725; found: 243.1724.

**IR:** (ATR, neat, cm<sup>-1</sup>) 3335 (br), 2956 (s), 2952 (s), 2862 (s), 1659 (m), 1446 (m), 1383 (m), 1362 (m), 1017 (m), 966 (m), 823 (m).

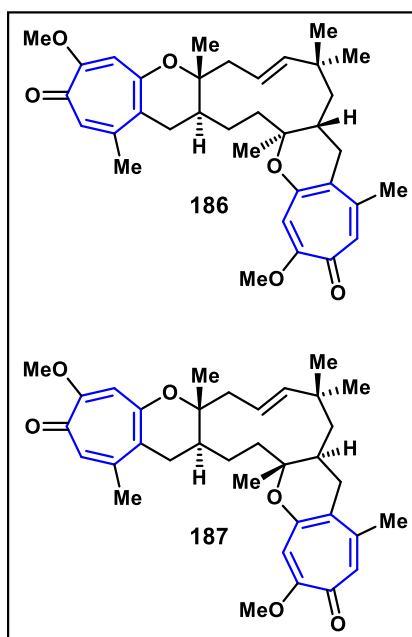
**mp:** 55 – 56 °C

**[α]<sub>D</sub><sup>23</sup>** = -121.5 (c = 1.00 in CHCl<sub>3</sub>)



**Synthesis of 183 and 184:** To a 10-mL microwave vial containing a stir bar was added tropolone **127** (0.298 g, 1.23 mmol, 3.0 eq.), **133** (0.171 g, 0.411 mmol, 1.0 equiv.), a crystal of BHT, and mesitylene (4.1 mL). The vial was sealed and heated at 200 °C for eight hours in a microwave reactor. The reaction was checked by TLC (silica gel, 1:3 hexanes:EtOAc) and the tropolone was determined to be fully consumed. The brown suspension was transferred to a recovery flask and concentrated under reduced pressure. The residue was then loaded onto silica gel and purified by flash

column chromatography (silica gel, 3:1 to 1:1 hexanes:EtOAc) to give recovered **133** (0.0256 g, 0.0614 mmol) and a mixture of compounds **183** and **184** in a 2:1 ratio (0.0598 g, 0.0952 mmol, 23%, 27% brsm). The two products were inseparable and were taken forward as a mixture.



**Synthesis of 186 and 187:** To a 50-mL screw-cap tube containing a stir bar was added **134** (0.287 g, 0.749 mmol, 1.0 equiv.) and a crystal of BHT. The solids were dissolved in mesitylene (7.5 mL), the tube was sealed with a septum cap, the septum was vented with two 18-gauge needles, and the vessel was placed in an aluminum block preheated to 160 °C. A syringe pump was positioned next to the hotplate. Separately, a solution of tropolone **129** (0.156 g, 0.749 mmol, 1.0 equiv.) in ethanol (8 mL) was prepared. **129** does not

readily dissolve in ethanol so sonication and gentle heating is required to achieve full dissolution. The solution of **129** was drawn into a 10-mL Luer lock glass syringe with a Teflon-tipped plunger and using an 18 gauge metal needle, then the syringe was fitted into syringe pump with the needle positioned about three inches above the reaction level. It is important that this type of syringe is used with the ethanolic solution, as other syringe and solvent combinations cause the solution to leak. The solution of **129** was added dropwise to the reaction over about 16 hours, then the reaction was monitored by LCMS and TLC (2:1 EtOAc:*i*-PrOH). About 24 hours after the addition of **129** was complete, it was determined to be fully consumed. At this time, the reaction was cooled to room temperature, then transferred to a recovery flask and concentrated by rotary evaporation. The crude reaction was purified by column chromatography (silica gel, EtOAc to 1:1 EtOAc:*i*-PrOH gradient) to give recovered **134** (0.127 g, 0.332 mmol) and a mixture of **186** and **187** (1:1 ratio, 0.0544 g, 0.097 mmol, 13%, 23% brsm). The two isomers can be separated by preparative TLC (silica gel, 2:1 EtOAc:*i*-PrOH) or preparative HPLC (C18, 50% to 95% MeCN in H<sub>2</sub>O).

**186:**

**R<sub>f</sub>** = 0.27 (SiO<sub>2</sub>, EtOAc:*i*-PrOH = 2:1, UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 7.02 (s, 1H), 7.01 (s, 1H), 6.47 (s, 1H), 6.45 (s, 1H), 5.56 (d, *J* = 15.7 Hz, 1H), 5.47 (ddd, *J* = 15.2, 9.2, 5.1 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.75 (dd, *J* = 17.2, 5.3 Hz, 1H), 2.70 – 2.61 (m, 2H), 2.42 – 2.35 (m, 1H), 2.34 (s, 3H), 2.29 (d, *J* = 1.0 Hz, 3H), 2.28 – 2.22 (m, 2H), 1.99 (dd, *J* = 13.4, 6.2 Hz, 1H), 1.91 (d, *J* = 13.5 Hz, 1H), 1.89 – 1.83 (m, 1H), 1.69 – 1.52 (m, 3H), 1.49 (dt, *J* = 11.7, 6.2 Hz, 1H), 1.26 (dt, *J* = 12.1, 3.0 Hz, 1H), 1.23 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H).

**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 177.7, 177.7, 161.8, 161.7, 156.2, 156.1, 148.3, 148.0, 144.1, 130.8, 130.8, 121.3, 117.7, 117.3, 111.1, 111.0, 81.4, 80.3, 56.1, 56.0, 48.5, 47.3, 40.8, 38.0, 36.7, 33.7, 31.8, 31.1, 30.4, 26.9, 26.8, 24.8, 23.0, 20.9, 19.0.

**HRMS:** (ESI-TOF, m/z) calcd. for C<sub>35</sub>H<sub>45</sub>O<sub>6</sub> [M+H]<sup>+</sup> calc.: 561.3216; found: 561.3203.

**IR:** (ATR, neat, cm<sup>-1</sup>) 2930 (w), 2851 (w), 1716 (w), 1600 (m), 1562 (m), 1481 (m), 1377 (w), 1182 (m), 1140 (m), 1010 (m), 984 (m), 914 (m), 879 (m), 726 (s), 643 (m).

**mp:** 259 – 263 °C

**187:**

**R<sub>f</sub>** = 0.20 (SiO<sub>2</sub>, EtOAc:*i*-PrOH = 2:1, UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 7.08 (s, 1H), 7.06 (s, 1H), 6.50 (s, 1H), 6.47 (s, 1H), 5.86 (d, *J* = 15.9 Hz, 1H), 5.68 (ddd, *J* = 15.4, 8.8, 6.4 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 2.76 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.69 – 2.54 (m, 3H), 2.41 (s, 3H), 2.37 – 2.30 (m, 1H), 2.34 (s, 3H), 2.20 – 2.13 (m, 1H), 2.12 – 2.01 (m, 1H), 1.98 – 1.90 (m, 2H), 1.90 – 1.80 (m, 2H), 1.69 (d, *J* = 11.7 Hz, 1H), 1.62 (d, *J* = 14.0 Hz, 1H), 1.32 (s, 3H), 1.23 (s, 3H), 1.20 – 1.13 (m, 1H), 1.19 (s, 3H), 1.16 (s, 3H).

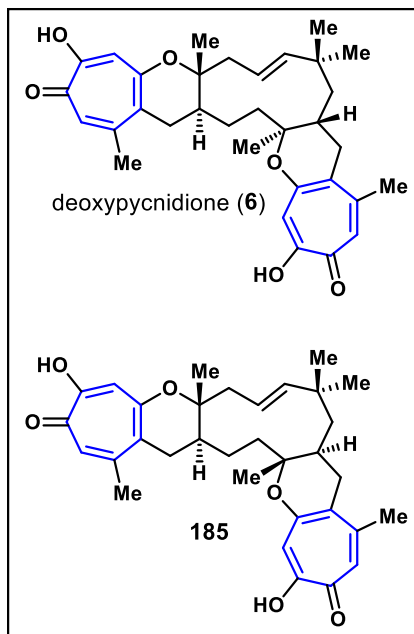
**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 177.6, 177.6, 161.8, 161.7, 156.3, 156.1, 148.3, 148.1, 144.6, 130.8, 130.8, 121.2, 118.1, 117.5, 111.4, 110.8, 80.8, 80.0, 56.0, 56.0, 45.8, 36.6, 36.0, 33.7, 33.6, 30.6, 30.4, 30.1, 26.9, 26.7, 26.7, 21.1, 20.9, 19.4, 19.0.

**HRMS:** (ESI-TOF, m/z) calcd. for C<sub>35</sub>H<sub>45</sub>O<sub>6</sub> [M+H]<sup>+</sup> calc.: 561.3216; found: 561.3210.

**IR:** (ATR, neat, cm<sup>-1</sup>) 2927 (w), 2844 (w), 1713 (w), 1601 (m), 1560 (m), 1481 (m), 1180 (m), 1139 (m), 1004 (m), 914 (m), 725 (s), 641 (m).

**mp:** 280 °C (decomp)





**Synthesis of 6 and 185 from 183 and 184 mixture:** To a 4-mL vial containing a stir bar and a mixture of **183** and **184** (0.0834 mg, 0.133 mmol, 1.0 equiv.) was added methanol (1.3 mL) followed by potassium carbonate (0.367 g, 2.65 mmol, 20.0 equiv.). The reaction was stirred for 24 hours and determined to be complete by TLC (silica gel, EtOAc). The reaction was quenched with pH = 7 buffer and transferred to a separatory funnel, rinsing the vial with ethyl acetate. The aqueous layer was acidified to neutral pH with citric acid and

was then extracted with EtOAc (3 x 2 mL). The combined organic extracts were washed with brine (2 mL), dried over magnesium sulfate, filtered, and concentrated to give an inseparable mixture of **6** and **185**. The crude mixture was dissolved in a 2:1 mixture of pyridine and acetic anhydride (1.2 mL) and stirred for 18 hours, after which the reaction was determined to be complete by TLC (silica gel, EtOAc). The reaction was concentrated and purified by column chromatography (silica gel, EtOAc) to give a mixture of acetylated bistropolones. These two products were separated by preparative TLC (silica gel, EtOAc) to give acetylated forms of **6** (0.0107 g, 0.0178 mmol, 13%) and **185** (0.0101 g, 0.0168 mmol, 13%). Separately, these compounds were dissolved in methanol (0.36 mL) in 4-mL vials, then potassium carbonate (0.0123 g, 0.0178 mmol, 5.0 equiv.) as added. The reactions were stirred for 12 hours and determined to be complete by TLC (silica gel, EtOAc). Both reactions were quenched with pH = 7 buffer and transferred to a separatory funnel with ethyl acetate. The aqueous layers were acidified to a neutral pH with citric acid then extracted with EtOAc (3 x 1 mL). The combined organic extracts were washed with brine (1 mL), dried over magnesium sulfate, filtered, and

concentrated to give **6** (0.0092 mg, 0.0178 mmol, quant.) and **185** (0.0086 mg, 0.0166 mmol, 99%).

**Synthesis of 6 from 186:** To a 4-mL vial containing a stir bar was added **186** (0.0033 g, 0.0059 mmol, 1.0 equiv.) which was suspended in methanol (0.20 mL) and 1M sodium hydroxide (0.20 mL, 0.20 mmol, 34 equiv.) The suspension was stirred at 100 °C and gradually became homogenous. The reaction was monitored by LCMS and the starting material was determined to be consumed after about 5 hours. The reaction was diluted with pH 7 phosphate buffer, then 1M hydrochloric acid (0.20 mL) was added. The reaction was transferred to separatory funnel and extracted with ethyl acetate (3 x 1 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated to give **6** as an orange solid (0.0024 g, 0.0045 mmol, 77%).

$R_f = 0.29$  (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 19:1, UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.13 (s, 1H), 7.11 (s, 1H), 6.97 (s, 1H), 6.96 (s, 1H), 5.52 (d,  $J = 15.6$  Hz, 1H), 5.44 (ddd,  $J = 15.5, 9.8, 4.7$  Hz, 1H), 2.77 (dd,  $J = 17.1, 5.2$  Hz, 1H), 2.70 – 2.62 (m, 2H), 2.44 (s, 3H), 2.38 (s, 3H), 2.36 – 2.24 (m, 3H), 2.03 – 1.94 (m, 2H), 1.87 – 1.76 (m, 2H), 1.64 (t,  $J = 13.0$  Hz, 1H), 1.56 (dd,  $J = 14.9, 2.6$  Hz, 1H), 1.47 (dt,  $J = 11.9, 5.7$  Hz, 1H), 1.36 – 1.27 (m, 1H), 1.23 (s, 3H), 1.13 (s, 2H), 1.12 (s, 3H), 1.10 – 1.08 (m, 1H), 1.07 (s, 3H).

**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>)  $\delta$  172.6, 171.9, 163.9, 163.1, 160.6, 160.5, 149.9, 149.1, 143.5, 124.4, 124.1, 121.6, 121.2, 120.1, 113.5, 112.8, 81.9, 80.6, 48.4, 46.7, 40.8, 37.8, 36.7, 33.9, 32.3, 31.3, 30.1, 29.7, 27.3, 27.2, 24.7, 21.1, 18.8.

**HRMS:** (ESI-TOF, m/z) calcd. for C<sub>33</sub>H<sub>41</sub>O<sub>6</sub> [M+1]<sup>+</sup> calc.: 533.2903; found: 533.2900.

**IR:** (ATR, neat,  $\text{cm}^{-1}$ ) 2922.5 (m), 2851 (w), 1738 (s), 1591 (w), 1439 (s), 1375 (s), 1285 (m), 1174 (s), 891 (m), 730 (m).

**mp:** 230 – 235 °C (decomp)

**Synthesis of 185 from 187:** Employing a procedure that is identical to that used for the conversion of **186** to **6**, **187** (0.0042 g, 0.0075 mmol, 1.0 equiv.) was hydrolyzed in methanol (0.22 mL) and 1M sodium hydroxide (0.22 mL, 0.22 mmol, 29 equiv.) at 100 °C to give **185** (0.0031 g, 0.0058 mmol, 77%).

**R<sub>f</sub>** = 0.29 (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 19:1, UV, KMnO<sub>4</sub>)

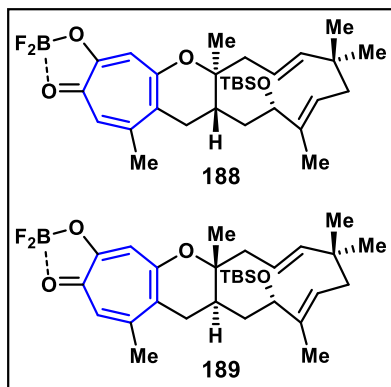
**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.13 (s, 1H), 7.10 (s, 1H), 6.94 (s, 1H), 6.93 (s, 1H), 5.72 (d,  $J$  = 15.9 Hz, 1H), 5.61 – 5.53 (m, 1H), 2.71 (dd,  $J$  = 17.4, 5.6 Hz, 1H), 2.62 – 2.51 (m, 3H), 2.43 (s, 3H), 2.36 (s, 3H), 2.12 (d,  $J$  = 11.2 Hz, 1H), 2.03 – 1.86 (m, 3H), 1.83 – 1.69 (m, 3H), 1.55 (d,  $J$  = 14.3 Hz, 1H), 1.37 – 1.26 (m, 2H), 1.23 (s, 3H), 1.15 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H).

**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>)  $\delta$  172.9, 172.5, 163.3, 163.3, 160.8, 160.8, 150.6, 149.8, 144.6, 133.7, 133.6, 124.9, 124.6, 121.2, 113.6, 113.2, 81.4, 80.5, 45.6, 36.4, 34.0, 32.2, 31.5, 30.2, 30.0, 29.6, 27.5, 27.3, 23.9, 22.9, 21.8, 19.6, 14.4.

**HRMS:** (ESI-TOF,  $m/z$ ) calcd. for C<sub>33</sub>H<sub>41</sub>O<sub>6</sub> [M+1]<sup>+</sup> calc.: 533.2903; found: 533.2908.

**IR:** (ATR, neat,  $\text{cm}^{-1}$ ) 3016 (w), 2970 (s), 2924 (w), 1738 (s), 1693 (w), 1439 (m), 1366 (w), 1217 (m), 894 (w), 723 (w), 528 (w).

**mp:** 270 – 275 °C (decomp)



**Synthesis of Compounds 188 and 189:** To a 10-mL

microwave vial containing a stir bar was added tropolone **127** (0.075 g, 0.31 mmol, 1.0 eq.), TBS ether **182** (0.207 g, 0.620 mmol, 2.0 eq.), a crystal of BHT, and mesitylene (3.1 mL, 0.1 M). The vial was sealed and heated at 200 °C for eight hours in a microwave reactor. Tropolone **127** was then determined to be

fully consumed by TLC (silica gel, 1:1 hexanes:EtOAc). The brown suspension was transferred to a recovery flask and concentrated under reduced pressure. The residue was then loaded onto silica gel and purified by flash column chromatography (silica gel, 9:1 to 4:1 hexanes:EtOAc gradient) to give cycloadduct **188** (0.0441 g, 0.0807 mmol, 26%) and **189** (0.0301 g, 0.0551 mmol, 18%) (44% total yield, 1.4:1 dr).

**188:**

$R_f$  = 0.49 (SiO<sub>2</sub>, hexanes:EtOAc = 3:1, UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 7.35 (s, 1H), 7.26 (s, 1H), 5.37 (dd,  $J$  = 12.0, 5.8 Hz, 1H), 5.19 (dd,  $J$  = 15.6, 2.3 Hz, 1H), 4.98 (ddd,  $J$  = 15.6, 9.6, 2.3 Hz, 1H), 4.30 (d,  $J$  = 5.5 Hz, 1H), 3.35 (dd,  $J$  = 18.0, 5.6 Hz, 1H), 2.69 – 2.59 (m, 1H), 2.56 (s, 3H), 2.40 (dd,  $J$  = 18.0, 11.7 Hz, 1H), 2.26 (dd,  $J$  = 15.6, 9.6 Hz, 1H), 2.19 – 2.07 (m, 2H), 1.85 (dd,  $J$  = 12.0, 5.8 Hz, 1H), 1.57 (d,  $J$  = 14.0, 1H), 1.52 (s, 3H), 1.51 – 1.46 (m, 1H), 1.17 (s, 3H), 1.08 (s, 3H), 1.02 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 168.7, 167.7, 167.6, 155.9, 143.1, 137.9, 129.6, 122.0, 120.8, 119.5, 115.8, 85.1, 74.6, 42.5, 41.0, 38.9, 36.3, 35.0, 29.8, 29.2, 27.9, 26.2, 24.4, 20.7, 18.7, 16.4, –4.6, –4.8.

**HRMS:** (EI-TOF,  $m/z$ ) calcd. for C<sub>30</sub>H<sub>44</sub>BF<sub>2</sub>O<sub>4</sub>Si [M]<sup>+</sup> calc.: 545.31845; found: 545.31026.

**IR:** (ATR, neat,  $\text{cm}^{-1}$ ) 2926 (w), 2855 (w), 1715 (w), 1616 (w), 1526 (w), 1441 (m), 1375 (m), 1199 (m), 1060 (s), 895 (w), 834 (m), 742 (w), 659 (w), 516 (w).

**mp:** 147–120 °C

**$[\alpha]_{\text{D}}^{23}$ :** +36.2 (c = 1.00 in  $\text{CHCl}_3$ )

**189:**

**$R_f$**  = 0.63 ( $\text{SiO}_2$ , hexanes:EtOAc = 3:1, UV,  $\text{KMnO}_4$ )

**$^1\text{H NMR}$ :** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 (s, 1H), 7.27 (s, 1H), 5.20 (dd,  $J = 15.4, 2.2$  Hz, 1H), 5.08 (dd,  $J = 11.9, 3.3$  Hz, 1H), 4.95 (ddd,  $J = 15.4, 10.7, 2.2$  Hz, 1H), 3.86 (d,  $J = 9.2$  Hz, 1H), 3.01 (dd,  $J = 17.9, 5.1$  Hz, 1H), 2.67 (dt,  $J = 15.4, 2.2$  Hz, 1H), 2.58 (s, 3H), 2.51 (dd,  $J = 17.9, 12.4$  Hz, 1H), 2.32 – 2.21 (m, 2H), 1.81 – 1.74 (m, 2H), 1.61 (s, 3H), 1.55 (d,  $J = 9.2$  Hz, 1H) 1.18 (s, 3H), 1.12 (dd,  $J = 13.6, 9.2$  Hz, 1H) 1.07 (s, 3H), 0.99 (s, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H).

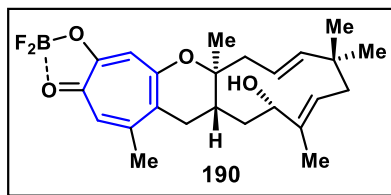
**$^{13}\text{C NMR}$ :** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.6, 168.0, 167.8, 156.1, 143.8, 139.5, 128.0, 122.2, 120.8, 119.1, 115.8, 84.7, 78.3, 42.6, 40.8, 40.3, 38.6, 33.1, 32.3, 30.2, 29.9, 27.9, 26.0, 24.1, 20.7, 18.4, 10.9, -4.6, -4.8.

**HRMS:** (EI-TOF, m/z) calcd. for  $\text{C}_{30}\text{H}_{45}\text{BF}_2\text{O}_4\text{Si}$   $[\text{M}]^+$  calc.: 545.3184; found: 545.3168.

**IR:** (ATR, neat,  $\text{cm}^{-1}$ ) 2928 (w), 2856 (w), 1715 (w), 1618 (w), 1527 (w), 1440 (m), 1374 (m), 1188 (m), 1063 (s), 835 (s), 777 (m), 669 (w), 587 (w), 517 (w).

**mp:** 174 – 177 °C

**$[\alpha]_{\text{D}}^{23}$ :** –88.5 (c = 0.60 in  $\text{CHCl}_3$ )



**Synthesis of Compound 190:** To a 10-mL plastic vial containing a stir bar was added a solution of compound **188** (0.0450 g, 0.0823 mmol, 1.0 equiv) in THF (0.80 mL). The

solution was cooled to 0 °C, then hydrofluoric acid (0.149 mL, 48% aq., 4.12 mmol, 50 equiv) was delivered dropwise to the vial using a mechanical pipette. The reaction was warmed to room temperature and stirred for one day, after which another portion of hydrofluoric acid (0.149 mL, 48% aq., 4.12 mmol, 50 equiv) was added in the manner previously described. After another day, the reaction was determined to be complete by TLC analysis (silica gel, 1:3 hexanes:EtOAc). The reaction was slowly poured onto cold saturated aqueous sodium bicarbonate (2 mL) in a Nalgene beaker. The quenched reaction was transferred to a separatory funnel and extracted with ethyl acetate (3 x 1 mL). The combined organic extracts were washed with brine (2 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The reaction was purified by column chromatography (silica gel, 1:2 to 1:3 hexanes:EtOAc) to give alcohol **190** (0.0198 g, 0.0458 mmol, 56%).

**R<sub>f</sub>** = 0.44 (SiO<sub>2</sub>, hexanes:EtOAc = 1:2, UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 7.35 (s, 1H), 7.25 (s, 1H), 5.41 (dd, *J* = 12.1, 4.9 Hz, 1H), 5.19 (dd, *J* = 15.9, 2.2 Hz, 1H), 4.97 (ddd, *J* = 15.9, 10.3, 2.2 Hz, 1H), 4.38 (d, *J* = 7.2 Hz, 1H), 3.42 (dd, *J* = 18.1, 5.0 Hz, 1H), 2.68 (dt, *J* = 15.0, 2.2 Hz, 1H), 2.58 (s, 3H), 2.41 (dd, *J* = 18.1, 12.1 Hz, 1H), 2.25 (dd, *J* = 15.0, 10.3 Hz, 1H), 2.21 (t, *J* = 12.1 Hz, 1H), 2.09 (ddd, *J* = 12.1, 7.2, 5.0 Hz, 1H), 1.84 (dd, *J* = 12.1, 4.9 Hz, 1H), 1.63 (dt, *J* = 14.4, 7.2 Hz, 1H), 1.56 (s, 3H), 1.51 (d, *J* = 14.4 Hz, 1H), 1.20 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H).

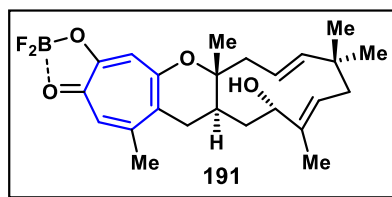
**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 168.7, 167.7, 167.5, 156.1, 143.0, 139.2, 129.9, 121.1, 120.9, 119.7, 115.7, 85.3, 73.5, 42.6, 40.9, 38.9, 34.5, 34.2, 29.9, 29.0, 28.1, 24.2, 21.0, 16.5.

**HRMS:** (EI-TOF, m/z) calcd. for C<sub>24</sub>H<sub>31</sub>BF<sub>2</sub>O<sub>4</sub> [M]<sup>+</sup> calc.: 431.2320; found: 431.2330.

**IR:** (ATR, neat, cm<sup>-1</sup>) 3573 (br), 2929 (w), 2863 (w), 1723 (w), 1615 (m), 1526 (w), 1441 (m), 1374 (m), 1299 (w), 1199 (m), 1045 (s), 895 (m), 840 (w), 745 (m), 659 (m), 516 (w).

**mp:** 107 – 109 °C

**[α]<sub>D</sub><sup>23</sup>:** +65.8 (c = 0.83 in CHCl<sub>3</sub>)



**Synthesis of Compound 191:** In a procedure analogous to that for the conversion of compound **188** to **190** and subsequent purification, compound **189** (0.0320 g, 0.0585 mmol, 1.0 equiv)

in THF (0.60 mL) was treated with hydrofluoric acid (0.106 mL, 48% aq., 2.93 mmol, 50 equiv) and stirred for one day. A second portion of hydrofluoric acid (0.053 mL, 48% aq., 1.47 mmol, 25 equiv) was added and the reaction was determined to be complete by TLC (silica gel, 1:3 hexanes:EtOAc) after another day. After the standard work-up, the crude reaction mixture was purified by column chromatography (silica gel, 1:2 to 1:3 hexanes:EtOAc) to give compound **191** (0.0102, 0.0624 mmol, 40%).

**R<sub>f</sub>** = 0.24 (SiO<sub>2</sub>, hexanes:EtOAc = 1:2, UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 7.36 (s, 1H), 7.26 (s, 1H), 5.22 (dd, *J* = 15.8, 2.1 Hz, 1H), 5.20 (dd, *J* = 11.9, 4.4 Hz, 1H) 4.97 (ddd, *J* = 15.8, 10.6, 2.1 Hz, 1H), 3.97 (d, *J* = 10.2 Hz, 1H), 3.04 (dd, *J* = 18.0, 5.2 Hz, 1H), 2.69 (dt, *J* = 13.7, 2.1 Hz, 1H), 2.61 (s, 3H), 2.55 (dd, *J* = 18.0, 12.4 Hz, 1H), 2.31 (dd, *J* = 14.9, 10.2 Hz, 1H), 2.25 (t, *J* = 13.7 Hz, 1H), 1.80 (dd, *J* = 11.9, 4.4 Hz, 2H), 1.76 (m, 1H), 1.66 (s, 3H), 1.64 – 1.60 (m, 1H), 1.26 – 1.21 (m, 1H), 1.20 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H).

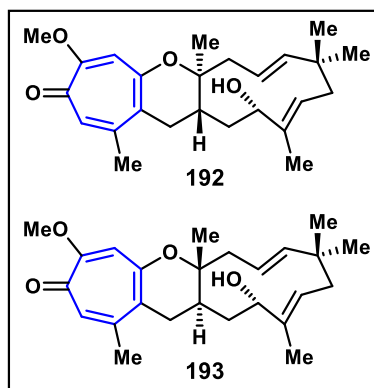
**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 168.5, 167.9, 167.8, 156.4, 143.4, 138.3, 128.1, 124.3, 120.8, 119.4, 115.8, 84.6, 77.9, 42.6, 40.7, 38.8, 38.3, 33.1, 32.1, 30.1, 28.2, 24.1, 20.7, 10.7.

**HRMS:** (EI-TOF,  $m/z$ ) calcd. for  $C_{24}H_{30}BF_2O_4$   $[M-H]^+$  calc.: 431.23198; found: 431.23392.

**IR:** (ATR, neat,  $cm^{-1}$ ) 3566 (br), 2923 (w), 2858 (w), 1680 (w), 1618 (m), 1526 (w), 1439 (m), 1374 (m), 1199 (m), 1138 (m), 1058 (s), 895 (m), 842 (m), 730 (m), 586 (w), 517 (w).

**mp:** 134 – 137 °C

**$[\alpha]_D^{23}$ :** -96.3 ( $c = 1.00$  in  $CHCl_3$ )



**Synthesis of Compounds 192 and 193:** To a 35-mL microwave vial containing a stir bar was added tropolone **129** (0.212 g, 1.02 mmol, 1.0 eq.), alcohol **45** (2.49 g, 3.05 mmol, 3.0 eq.), a crystal of BHT, and the mixture was suspended in mesitylene (10.0 mL, 0.1 M). The vial was sealed and heated at 200 °C for 16 hours in a microwave reactor. Analysis by of the reaction by LCMS

showed full consumption of **129** and a *d.r.* of 1.4:1 for two products. The brown suspension was transferred to a recovery flask and concentrated under reduced pressure. The residue was then loaded onto silica gel and purified by flash column chromatography (silica gel, 3:1 hexanes:EtOAc to EtOAc to 7:1 EtOAc:*i*-PrOH) to give recovered excess **45** and cycloadducts **192** and **193** as a mixture (0.362 g, 0.908 mmol, 89%). Compounds **192** and **193** were then separated using a Biotage Isolera One chromatography system (SNAP Ultra C18 30 g column, 4:1  $H_2O$ :MeCN to 1:4  $H_2O$ :MeCN gradient).

**192:**

$R_f = 0.43$  ( $SiO_2$ , EtOAc:*i*-PrOH = 9:1, UV,  $KMnO_4$ )

**$^1H$  NMR:** (500 MHz,  $CDCl_3$ )  $\delta$  7.01 (s, 1H), 6.50 (s, 1H), 5.43 (dd,  $J = 11.8, 4.9$  Hz, 1H), 5.16 (dd,  $J = 16.0, 1.5$  Hz, 1H), 5.09 (ddd,  $J = 16.0, 9.6, 1.9$  Hz, 1H), 4.35 (d,  $J = 6.7$  Hz, 1H), 3.89 (s,



3H), 3.16 (dd,  $J = 17.7, 5.4$  Hz, 1H), 2.56 (d,  $J = 14.8$  Hz, 1H), 2.30 (s, 3H), 2.23 – 2.15 (m, 3H), 2.00 (dt,  $J = 12.0, 6.0$  Hz, 1H), 1.84 (dd,  $J = 12.4, 4.8$  Hz, 1H), 1.68 (d,  $J = 4.4$  Hz, 1H), 1.54 (s, 3H), 1.58 – 1.46 (m, 2H), 1.09 (s, 3H), 1.09 (s, 3H), 1.07 (s, 3H).

**$^{13}\text{C}$  NMR:** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  177.6, 161.6, 156.5, 148.8, 141.8, 139.5, 130.6, 120.9, 120.6, 118.7, 111.4, 81.4, 73.6, 56.0, 42.5, 40.9, 38.9, 34.8, 33.8, 30.2, 29.1, 26.9, 24.2, 20.4, 16.5.

**HRMS:** (ESI-TOF,  $m/z$ ) calcd. for  $\text{C}_{25}\text{H}_{35}\text{O}_4$   $[\text{M}+\text{H}]^+$  calc.: 399.2535; found: 399.2522.

**IR:** (ATR, neat,  $\text{cm}^{-1}$ ) 3369 (br), 2935 (w), 1599 (m), 1547 (m), 1480 (m), 1272 (m), 1179 (s), 1132 (s), 1011 (s), 881 (m), 726 (s), 643 (m), 564 (m).

**mp:** 148 – 152 °C

**$[\alpha]_{\text{D}}^{23}$ :** +130 ( $c = 1.0$  in  $\text{CHCl}_3$ )

**193:**

**$R_f$**  = 0.37 ( $\text{SiO}_2$ ,  $\text{EtOAc}:\textit{i}\text{-PrOH} = 9:1$ , UV,  $\text{KMnO}_4$ )

**$^1\text{H}$  NMR:** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.01 (s, 1H), 6.48 (s, 1H), 5.22 – 5.16 (m, 2H), 5.06 (ddd,  $J = 15.9, 10.4, 2.5$  Hz, 1H), 3.96 (d,  $J = 9.9$  Hz, 1H), 3.89 (s, 3H), 2.86 (dd,  $J = 17.6, 5.4$  Hz, 1H), 2.56 (dt,  $J = 14.7, 2.3$  Hz, 1H), 2.31 (s, 3H), 2.32 – 2.20 (m, 4H), 1.79 (dd,  $J = 12.8, 4.7$  Hz, 1H), 1.74 (dd,  $J = 13.6, 9.9$  Hz, 1H), 1.65 (s, 3H), 1.16 – 1.10 (m, 1H), 1.10 (s, 3H), 1.07 (s, 3H), 1.03 (s, 3H).

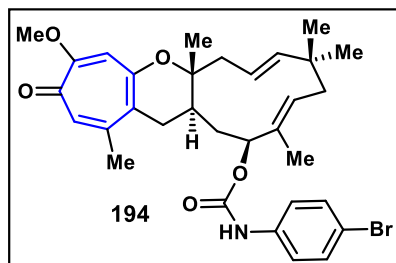
**$^{13}\text{C}$  NMR:** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  177.6, 161.7, 156.7, 148.5, 142.3, 138.7, 130.6, 123.7, 120.5, 117.2, 111.2, 81.0, 78.1, 56.0, 42.6, 40.7, 39.0, 38.8, 33.6, 30.9, 30.3, 26.9, 24.2, 20.1, 10.7.

**HRMS:** (ESI-TOF,  $m/z$ ) calcd. for  $\text{C}_{25}\text{H}_{35}\text{O}_4$   $[\text{M}+\text{H}]^+$  calc.: 399.2535; found: 399.2522.

**IR:** (ATR, neat,  $\text{cm}^{-1}$ ) 3366 (br), 2941 (w), 1599 (m), 1548 (m), 1478 (m), 1178 (s), 1134 (s), 1009 (s), 879 (m), 727 (s), 642 (m), 552 (m).

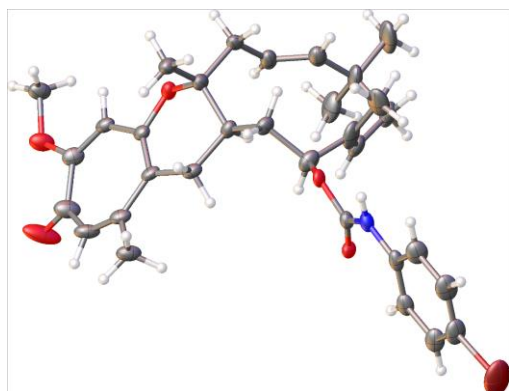
**mp:** 156 – 160 °C

$[\alpha]_D^{23}$ :  $-121.4$  ( $c = 1.00$  in  $\text{CHCl}_3$ )



**Synthesis of Compounds 194:** To a 4-mL vial containing a stir bar and a solution of **193** (0.0200 g, 0.0502 mmol, 1.0 equiv.) in anhydrous dichloromethane (0.50 mL, 0.1 M) was added triethylamine (0.014 mL, 0.0102 g, 0.100 mmol, 2.0 equiv.)

followed by *p*-bromophenyl isocyanate (0.0149 g, 0.0753 mmol, 1.5 equiv.). The reaction gradually became a yellow suspension and stirring was continued overnight. The starting material was determined to be consumed in exchange for two products by TLC (EtOAc). The reaction was quenched with saturated aqueous ammonium chloride (1 mL), then the mixture was transferred to a separatory funnel and the vial was rinsed with ethyl acetate (1 mL). The layers were separated, and the aqueous layer was washed with ethyl acetate (3 x 1 mL). The combined organic extracts were washed with brine (2 mL), dried over magnesium sulfate, filtered, and concentrated. The crude material was purified by column chromatography (silica gel, EtOAc) to give **194** (0.0216 g, 0.0362 mmol, 72%). The two products were separated by prep-TLC (silica gel, EtOAc), and the major, later eluting product was recrystallized from methanol to produce crystals suitable for X-ray diffraction. Through single crystal X-ray analysis, the structure was unambiguously proven.



$R_f = 0.31$  (SiO<sub>2</sub>, EtOAc, UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.41 (d,  $J = 8.0$  Hz, 2H), 7.29 (d,  $J = 8.0$  Hz, 2H), 7.04 (s, 1H), 6.65 (s, 1H), 6.49 (s, 1H), 5.33 (dd,  $J = 11.9, 3.6$  Hz, 1H), 5.19 (d,  $J = 15.9$  Hz, 1H), 5.11 (ddd,  $J = 15.9, 10.0, 2.0$  Hz, 1H), 4.88 (d,  $J = 9.9$  Hz, 1H), 3.90 (s, 3H), 3.14 (dd,  $J = 17.9, 5.4$  Hz, 1H), 2.59 (d,  $J = 14.8$  Hz, 1H), 2.37 (s, 3H), 2.29 (dd,  $J = 15.8, 10.8$  Hz, 1H), 2.24 (dd,  $J = 11.7, 8.4$  Hz, 1H), 1.85 (dd,  $J = 13.0, 4.6$  Hz, 1H), 1.81 – 1.72 (m, 2H), 1.67 (s, 3H), 1.29 – 1.22 (m, 2H), 1.10 (s, 3H), 1.09 (s, 3H), 1.07 (s, 3H).

**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>)  $\delta$  177.7, 161.7, 156.4, 152.6, 148.7, 142.5, 137.1, 134.8, 132.2, 130.8, 125.4, 120.5, 120.2, 117.3, 116.1, 111.2, 80.6, 56.0, 42.7, 40.6, 38.6, 37.0, 33.7, 30.5, 30.4, 29.8, 26.9, 24.3, 20.1, 11.6.

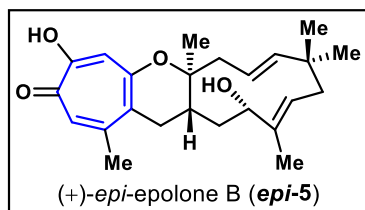
**HRMS:** (ESI-TOF,  $m/z$ ) calcd. for C<sub>32</sub>H<sub>39</sub>BrNO<sub>5</sub> [M+H]<sup>+</sup> calc.: 596.2012; found: 596.2005.

**IR:** (ATR, neat, cm<sup>-1</sup>) 3366 (br), 2922 (m), 1721 (m), 1598 (s), 1538 (s), 1474 (s), 1398 (s), 1308 (m), 1276 (m), 1178 (s), 1136 (s), 1012 (s), 824 (m), 504 (s).

1480 (m), 1272 (m), 1179 (s), 1132 (s), 1011 (s), 881 (m), 726 (s), 643 (m), 564 (m).

**mp:** 220 – 223 °C

**$[\alpha]_D^{23}$ :** –83 (c = 0.46 in CHCl<sub>3</sub>)



**Synthesis of *epi-5* from **190**:** To a 4-mL vial containing a stir bar and compound **190** (0.0754 g, 0.174 mmol, 1.0 equiv.) was added methanol (1.7 mL, 0.1 M) followed by potassium carbonate (0.121 g, 0.872 mmol, 5.0 equiv.). The suspension was vigorously stirred until the starting material was consumed. After 24 hours, the reaction was transferred to a separatory funnel containing pH = 7 phosphate buffer (2 mL) and washed with ethyl acetate (2 mL). The aqueous

layer was drained and acidified with citric acid until a neutral pH was obtained. The aqueous layer was transferred back into the separatory funnel and extracted with the previously retained organic extract. The aqueous layer was subsequently washed with ethyl acetate (3 x 2 mL), then the combined organic extracts were washed with brine (4 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give *epi-5* as an orange solid (0.0671 g, 0.174 mmol, quant.).

### Synthesis of *epi-5* from **192**:

To a 4-mL vial containing a stir bar and compound **192** (0.0100 g, 0.025 mmol, 1.0 equiv) was added methanol (0.25 mL) and 1M sodium hydroxide (0.25 mL, 0.25 mmol, 10.0 equiv.). The suspension was heated to 100 °C and vigorously stirred, eventually becoming homogenous. Consumption of the starting material was observed after six hours, then the reaction was transferred to a separatory funnel containing pH = 7 phosphate buffer (1 mL) and rinsed with ethyl acetate (1 mL). 1M Hydrochloric acid (0.25 mL) was added to the separatory funnel to neutralize residual sodium hydroxide. The pH of the aqueous layer was measured and determined to be about pH = 3. The aqueous layer was extracted with ethyl acetate (3 x 2 mL), then the combined organic extracts were washed with brine (2 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give *epi-5* as an orange solid (0.0095 g, 0.025 mmol, quant.).

$R_f = 0.36$  (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> = 19:1, UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 7.11 (s, 1H), 7.00 (s, 1H), 5.42 (dd,  $J = 11.7, 5.1$  Hz, 1H), 5.16 (dd,  $J = 15.9, 1.8$  Hz, 1H), 5.07 (ddd,  $J = 15.9, 9.8, 2.4$  Hz, 1H), 4.36 (d,  $J = 6.6$  Hz, 1H), 3.23 (dd,  $J = 17.6, 5.3$  Hz, 1H), 2.58 (dt,  $J = 14.8, 2.1$  Hz, 1H), 2.39 (s, 3H), 2.26 (dd,  $J = 17.7, 11.8$

Hz, 1H), 2.23 – 2.16 (m, 2H), 2.02 (dt,  $J = 12.0, 6.1$  Hz, 1H), 1.85 (dd,  $J = 12.6, 5.1$  Hz, 1H), 1.56 – 1.52 (m, 1H), 1.55 (s, 3H), 1.50 (d,  $J = 14.2$  Hz, 1H), 1.12 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H).

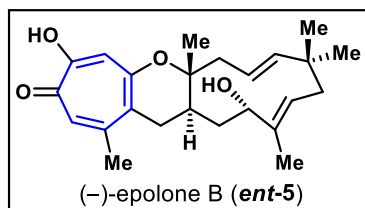
$^{13}\text{C}$  NMR: (126 MHz,  $\text{CDCl}_3$ )  $\delta$  172.4, 163.4, 161.2, 150.1, 142.0, 139.4, 124.4, 122.0, 120.9, 120.8, 113.5, 82.1, 73.8, 42.8, 40.9, 38.9, 34.7, 34.2, 30.0, 29.3, 27.4, 24.3, 20.6, 16.5.

HRMS: (EI-TOF,  $m/z$ ) calcd. for  $\text{C}_{24}\text{H}_{32}\text{O}_4$   $[\text{M}]^+$  calc.: 384.2301; found: 384.2320.

IR: (ATR, neat,  $\text{cm}^{-1}$ ) 3365 (br), 3187 (br), 2932 (w), 2861 (w), 1591 (m), 1525 (w), 1443 (s), 1375 (m), 1280 (m), 1176 (s), 1131 (s), 1092 (s), 1031 (m), 983 (m), 891 (m), 729 (s), 568 (w), 469 (w).

mp: 107 – 109 °C

$[\alpha]_{\text{D}}^{23}$ : +65.8 ( $c = 1.00$  in  $\text{CHCl}_3$ )



**Synthesis of *ent-5* from **191**:** Employing a procedure identical to that which converted **190** to *epi-5*, **191** (0.0318 g, 73.6  $\mu\text{mol}$ , 1.0 equiv.) was treated with potassium carbonate (0.102 g, 0.736

$\mu\text{mol}$ , 10.0 equiv.) in methanol (0.74 mL) to give (-)-epolone B (*ent-5*) as an orange solid (0.0283 g, 0.0736  $\mu\text{mol}$ , quant.).

**Synthesis of *ent-5* from **193**:** Employing a procedure identical to that which converted **192** to *epi-5*, **193** (0.0103 g, 0.0258  $\mu\text{mol}$ , 1.0 equiv.) was heated to 100 °C in 1M sodium hydroxide (0.26 mL, 0.26  $\mu\text{mol}$ , 10 equiv.) in methanol (0.26 mL) to give *ent-5* as an orange solid (0.0099 mg, 0.0285  $\mu\text{mol}$ , quant.).

$R_f = 0.34$  ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2 = 19:1$ , UV,  $\text{KMnO}_4$ )

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 7.12 (s, 1H), 6.99 (s, 1H), 5.23 – 5.15 (m, 2H), 5.05 (ddd, *J* = 15.9, 10.4, 2.6 Hz, 1H), 3.97 (d, *J* = 9.8 Hz, 1H), 2.90 (dd, *J* = 17.0, 4.0 Hz, 1H), 2.58 (d, *J* = 14.8 Hz, 1H), 2.40 (s, 3H), 2.39 – 2.33 (m, 1H), 2.28 – 2.22 (m, 2H), 1.82 – 1.72 (m, *J* = 23.1, 13.1, 7.2 Hz, 2H), 1.70 – 1.66 (m, 1H), 1.65 (s, 3H), 1.18 – 1.14 (m, 1H), 1.12 (s, 3H), 1.07 (s, 3H), 1.01 (s, 3H).

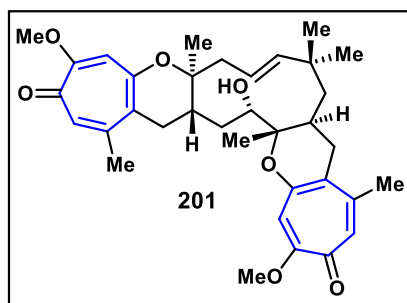
**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 172.8, 163.1, 161.1, 150.1, 142.3, 138.5, 124.6, 124.0, 120.4, 120.2, 113.3, 81.5, 78.1, 42.7, 40.8, 38.8, 38.8, 33.6, 31.5, 30.2, 27.5, 24.2, 20.3, 10.8.

**HRMS:** (EI-TOF, *m/z*) calcd. for C<sub>24</sub>H<sub>32</sub>O<sub>4</sub> [M]<sup>+</sup> calc.: 384.23006; found: 384.23107.

**IR:** (ATR, neat, cm<sup>-1</sup>) 3377 (br), 3195 (br), 2935 (m), 2862 (w), 1590 (m), 1443 (s), 1376 (m), 1233 (m), 1159 (s), 1135 (m), 1051 (m), 1001 (m), 754 (m).

**mp:** 169 – 173 °C

**[α]<sub>D</sub><sup>23</sup>:** –84 (*c* = 0.35 in CHCl<sub>3</sub>)



**Synthesis of 201:** Employing a procedure identical to that used for the preparation and purification of **186** and **187**, **192** (0.249 g, 0.624 mmol, 1.0 equiv.) was reacted with tropolone **129** (0.130 g, 0.624 mmol, 1.0 equiv.) to give recovered **192** (0.120 g, 0.301 mmol) and **201** (0.0847 g, 0.147 mmol, 24%,

46% brsm).

**R<sub>f</sub>** = 0.29 (SiO<sub>2</sub>, EtOAc:*i*-PrOH = 2:1, UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 7.01 (s, 1H), 6.92 (s, 1H), 6.43 (s, 1H), 6.41 (s, 1H), 5.74 (d, *J* = 15.7 Hz, 1H), 5.35 (ddd, *J* = 15.4, 10.5, 4.3 Hz, 1H), 4.94 (s, 1H), 4.13 (dt, *J* = 11.4, 5.4 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 2.89 (t, *J* = 13.1 Hz, 1H), 2.72 – 2.63 (m, 3H), 2.59 (dd, *J* = 17.5, 5.7

Hz, 1H), 2.38 (t,  $J = 11.7$  Hz, 1H), 2.34 – 2.36 (m, 2H), 2.31 (s, 3H), 2.30 (s, 3H), 2.13 – 2.03 (m, 2H), 1.96 (dt,  $J = 9.4, 4.2$  Hz, 1H), 1.42 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 1.06 (s, 3H), 0.90 (dd,  $J = 14.6, 4.2$  Hz, 1H).

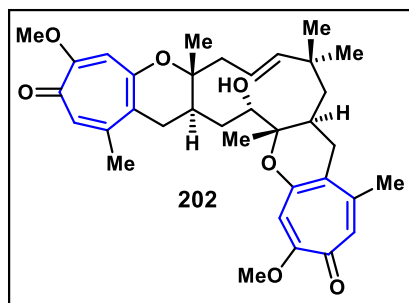
**$^{13}\text{C}$  NMR:** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  177.7, 176.8, 161.7, 161.1, 156.7, 155.8, 149.7, 148.8, 148.4, 130.7, 129.6, 120.6, 118.5, 117.8, 111.6, 111.1, 82.1, 81.0, 75.1, 56.2, 56.1, 49.2, 45.2, 37.4, 34.9, 33.1, 31.8, 31.5, 31.4, 30.4, 27.2, 26.7, 21.8, 19.4, 18.7.

**HRMS:** (ESI-TOF,  $m/z$ ) calcd. for  $\text{C}_{35}\text{H}_{45}\text{O}_7$   $[\text{M}+\text{H}]^+$  calc.: 577.3165; found: 577.3151.

**IR:** (ATR, neat,  $\text{cm}^{-1}$ ) 3348 (br), 2927 (w), 2855 (w), 1715 (w), 1599 (m), 1547 (m), 1478 (m), 1455 (m), 1375 (w), 1184 (s), 1152 (s), 1068, 1011 (m), 879 (m), 733 (w), 666 (w).

**mp:** 238 – 240  $^\circ\text{C}$

**$[\alpha]_{\text{D}}^{23}$ :** +160 ( $c = 0.47$  in  $\text{CHCl}_3$ )



**Synthesis of 202:** Employing a procedure identical to that used for the preparation and purification of **186** and **187**, **193** (0.172 g, 0.432 mmol, 1.0 equiv.) was reacted with tropolone **129** (0.0900, 0.432 mmol, 1.0 equiv.) to give recovered **193** (0.0853 g, 0.214 mmol) and **202** (0.0655 g, 0.114 mmol, 26%,

52% brsm).

**$R_f$**  = 0.18 ( $\text{SiO}_2$ ,  $\text{EtOAc}:\textit{i}\text{-PrOH} = 2:1$ , UV,  $\text{KMnO}_4$ )

**$^1\text{H}$  NMR:** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.10 (s, 1H), 7.03 (s, 1H), 6.49 (s, 1H), 6.44 (s, 1H), 5.49 (ddd,  $J = 13.8, 7.9, 5.6$  Hz, 1H), 5.43 (d,  $J = 15.8$  Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.71 (t,  $J = 4.0$  Hz, 1H), 2.98 – 2.90 (m, 2H), 2.65 (dd,  $J = 14.2, 5.4$  Hz, 1H), 2.53 – 2.43 (m, 3H), 2.38 – 2.26 (m, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 2.19 – 2.11 (m, 1H), 1.90 (dddd,  $J = 25.9, 12.5, 6.0, 3.2$  Hz, 1H),

1.57 (d,  $J = 15.1$  Hz, 1H), 1.17 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H), 1.07 – 1.03 (m, 1H), 0.93 (dd,  $J = 14.8, 5.2$  Hz, 1H).

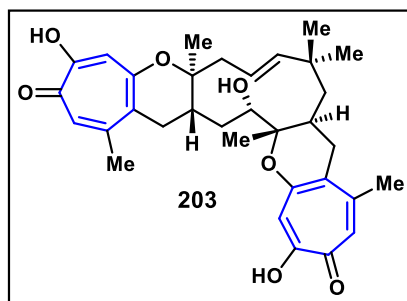
$^{13}\text{C}$  NMR: (126 MHz,  $\text{CDCl}_3$ )  $\delta$  177.7, 177.7, 162.6, 161.7, 156.3, 156.3, 148.5, 146.6, 143.5, 132.6, 130.9, 122.7, 117.5, 117.5, 111.2, 110.7, 87.6, 79.8, 78.4, 56.3, 56.0, 45.8, 44.1, 40.1, 37.7, 36.3, 33.0, 32.9, 30.7, 29.8, 29.4, 26.8, 24.0, 18.8, 16.1.

HRMS: (ESI-TOF,  $m/z$ ) calcd. for  $\text{C}_{35}\text{H}_{45}\text{O}_7$   $[\text{M}+\text{H}]^+$  calc.: 577.3165; found: 577.3152.

IR: (ATR, neat,  $\text{cm}^{-1}$ ) 3410 (br), 2960 (m), 2931 (m), 2869 (m), 1715 (w), 1601 (s), 1556 (s), 1483 (s), 1430 (m), 1266 (m), 1183 (s), 1151 (s), 1009 (m), 881 (w), 750 (s), 662 (w).

mp: 204 – 206 °C

$[\alpha]_{\text{D}}^{23}$ : +33 ( $c = 0.49$  in  $\text{CHCl}_3$ )



**Synthesis of 203:** Employing a procedure that is identical to that used for the conversion of **186** to **6**, **201** (0.010 g, 0.0173 mmol, 1.0 equiv) was hydrolyzed in methanol (0.50 mL) and 1M sodium hydroxide (0.52 mL, 30 equiv.) at 100 °C to give **203** as an orange solid (0.0077 g, 0.014 mmol, 81%).

$R_f = 0.19$  ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2:\text{MeOH} = 19:1$ , UV,  $\text{KMnO}_4$ )

$^1\text{H}$  NMR: (500 MHz,  $\text{CDCl}_3$ )  $\delta$   $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  7.14 (s, 1H), 7.08 (s, 1H), 6.97 (s, 1H), 6.94 (s, 1H), 5.63 (d,  $J = 15.8$  Hz, 1H), 5.38 (ddd,  $J = 15.8, 10.6, 4.6$  Hz, 1H), 4.00 – 3.95 (m, 1H), 2.80 – 2.60 (m, 3H), 2.52 – 2.44 (m, 2H), 2.41 (s, 3H), 2.38 (s, 3H), 2.36 – 2.25 (m, 2H), 2.00 – 1.92 (m, 1H), 1.69 – 1.60 (m, 2H), 1.37 (s, 3H), 1.33 – 1.28 (m, 2H), 1.22 (s, 3H), 1.14 (s, 3H), 1.06 (s, 3H), 1.04 – 1.00 (m, 1H).



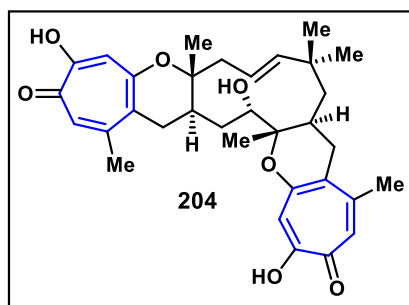
**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 176.8, 176.3, 165.5, 165.3, 157.9, 156.5, 147.6, 145.1, 144.3, 130.6, 130.0, 124.5, 123.0, 121.9, 114.8, 113.5, 81.6, 81.6, 75.6, 45.1, 41.0, 37.5, 35.2, 32.2, 31.9, 30.6, 29.9, 29.6, 27.5, 27.3, 22.9, 19.2, 14.4.

**HRMS:** (ESI-TOF, m/z) calcd. for C<sub>33</sub>H<sub>41</sub>O<sub>7</sub> [M]<sup>+</sup> calc.: 549.2852; found: 549.2852.

**IR:** (ATR, neat, cm<sup>-1</sup>) 3452 (br), 3199 (br), 2923 (s), 2852 (m), 1716 (w), 1594 (m), 1448 (s), 1377 (m), 1279 (m), 1178 (s), 1074 (m), 908 (w), 734 (w).

**mp:** 180 – 185 °C

**[α]<sub>D</sub><sup>23</sup>:** +95.2 (c = 0.29 in CHCl<sub>3</sub>)



**Synthesis of 204:** Employing a procedure that is identical to that used for the conversion of **186** to **6**, **202** (0.0039 g, 0.0067 mmol, 1.0 equiv) was hydrolyzed in methanol (0.20 mL) and 1M sodium hydroxide (0.20 mL, 30 equiv.) at 100 °C to give **204** as an orange solid (0.0033 g, 0.0060 mmol, 89%).

**R<sub>f</sub>** = 0.22 (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 19:1, UV, KMnO<sub>4</sub>)

**<sup>1</sup>H NMR:** (500 MHz, CDCl<sub>3</sub>) δ 7.18 (s, 1H), 7.14 (s, 1H), 6.99 (s, 2H), 5.46 (ddd, *J* = 14.3, 8.9, 5.1 Hz, 1H), 5.36 (d, *J* = 15.8 Hz, 1H), 3.66 (t, *J* = 4.5 Hz, 1H), 3.00 (dd, *J* = 17.8, 4.9 Hz, 1H), 2.66 (dd, *J* = 14.4, 5.1 Hz, 1H), 2.60 – 2.49 (m, 2H), 2.47 – 2.31 (m, 3H), 2.43 (s, 3H), 2.42 (s, 3H), 2.10 – 2.02 (m, 1H), 1.89 (td, *J* = 11.8, 4.2 Hz, 1H), 1.84 – 1.81 (m, 1H), 1.51 (d, *J* = 14.7 Hz, 1H), 1.18 (s, 3H), 1.15 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.95 – 0.84 (m, 1H).

**<sup>13</sup>C NMR:** (126 MHz, CDCl<sub>3</sub>) δ 172.7, 169.6, 167.5, 163.3, 162.7, 160.9, 150.5, 145.9, 143.8, 129.4, 124.8, 122.6, 122.1, 120.8, 117.2, 113.5, 88.7, 80.1, 78.1, 45.5, 40.2, 37.8, 36.2, 33.1, 32.6, 30.5, 29.8, 29.6, 27.4, 26.8, 23.9, 19.2, 16.4.

**HRMS:** (ESI-TOF, m/z) calcd. for  $C_{33}H_{41}O_7$   $[M]^+$  calc.: 549.2852; found: 549.2847.

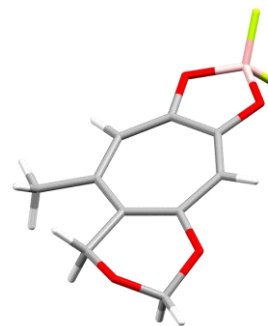
**IR:** (ATR, neat,  $cm^{-1}$ ) 3397 (br), 3211 (br), 2925 (m), 2855 (w), 1709 (w), 1588 (m), 1443 (s), 1376 (m), 1262 (s), 1069 (m), 908 (w), 732 (m).

**mp:** 220 – 225 °C (decomp.)

**$[\alpha]_D^{23}$ :**  $-14.8$  (c = 0.19 in  $CHCl_3$ )

## Crystallographic Data for Compound 127

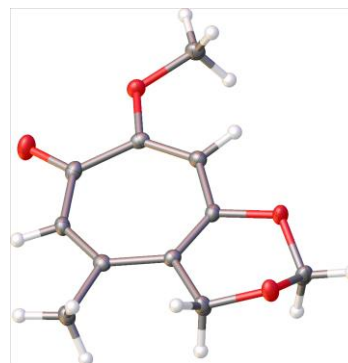
Single crystals of compound **127** were obtained by slow recrystallization from acetone. A suitable crystal was selected and diffraction data were collected on a Bruker D8 Venture/Photon 100 diffractometer. The crystal was kept at 100 K during data collection.



Identification code	tropolone_BF2	
Empirical formula	C10 H9 B F2 O4	
Formula weight	241.98	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2 <sub>1</sub> /c	
Unit cell dimensions	a = 10.0111(5) Å	α = 90°.
	b = 8.1247(4) Å	β = 95.6560(17)°.
	c = 12.1157(6) Å	γ = 90°.
Volume	980.66(8) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.639 Mg/m <sup>3</sup>	
Absorption coefficient	0.147 mm <sup>-1</sup>	
F(000)	496	
Crystal size	0.894 x 0.397 x 0.128 mm <sup>3</sup>	
2θ range for data collection	3.023 to 28.303°.	
Index ranges	-13 ≤ h ≤ 13, -10 ≤ k ≤ 10, -16 ≤ l ≤ 16	
Reflections collected	16421	
Independent reflections	2434 [R(int) = 0.0304]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.98670 and 0.91307	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	2434 / 0 / 156	
Goodness-of-fit on F <sup>2</sup>	1.063	
Final R indices [I > 2σ(I)]	R1 = 0.0360, wR2 = 0.0887	
R indices (all data)	R1 = 0.0387, wR2 = 0.0910	
Extinction coefficient	0.159(7)	
Largest diff. peak and hole	0.264 and -0.392 e.Å <sup>-3</sup>	

## Crystallographic Data for Compound 129

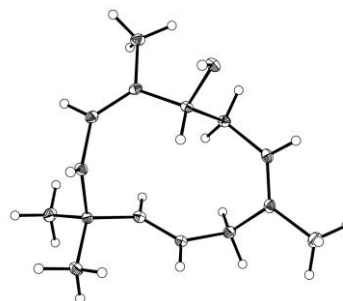
Single crystals of compound **129** were obtained by slow recrystallization from dichloromethane. A suitable crystal was selected and diffraction data were collected on a Bruker D8 Venture/Photon 100 diffractometer. The crystal was kept at 100 K during data collection.



Identification code	mo_dd80r_0m	
Empirical formula	C11 H12 O4	
Formula weight	208.21	
Temperature	100.03 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.8779(3) Å b = 10.6084(4) Å c = 12.5217(4) Å	$\alpha = 92.0813(9)^\circ$ $\beta = 107.3012(9)^\circ$ $\gamma = 109.5163(8)^\circ$
Volume	930.95(6) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.486 Mg/m <sup>3</sup>	
Absorption coefficient	0.113 mm <sup>-1</sup>	
F(000)	440.0	
Crystal size	0.528 × 0.39 × 0.212 mm <sup>3</sup>	
2 $\theta$ range for data collection	4.958 to 56.742 °	
Index ranges	-10 ≤ h ≤ 10, -14 ≤ k ≤ 14, -16 ≤ l ≤ 16	
Reflections collected	52758	
Independent reflections	52758 [R <sub>int</sub> = ?, R <sub>sigma</sub> = 0.0482]	
Completeness to theta = 25.242°	99.9 %	
Data / restraints / parameters	52758/0/277	
Goodness-of-fit on F <sup>2</sup>	1.048	
Final R indices [I > 2σ(I)]	R <sub>1</sub> = 0.0445, wR <sub>2</sub> = 0.1049	
R indices (all data)	R <sub>1</sub> = 0.0575, wR <sub>2</sub> = 0.1123	
Largest diff. peak and hole	0.41 and -0.23 Å <sup>-3</sup>	

### Crystallographic Data for Compound 139

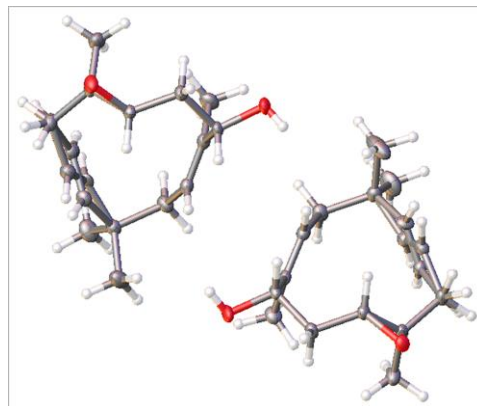
Single crystals of compound **139** were obtained by slow recrystallization from dichloromethane and *n*-heptane. A suitable crystal was selected and diffraction data were collected on a Bruker D8 Venture/Photon 100 diffractometer. The crystal was kept at 100 K during data collection.



Identification code	cm84s_a	
Empirical formula	C <sub>15</sub> H <sub>24</sub> O	
Formula weight	220.34	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P <sub>2</sub> <sub>1</sub> /c	
Unit cell dimensions	a = 13.9713(10) Å	α = 90°.
	b = 21.2153(14) Å	β = 99.134(3)°.
	c = 9.4185(7) Å	γ = 90°.
Volume	2756.3(3) Å <sup>3</sup>	
Z	8	
Density (calculated)	1.062 Mg/m <sup>3</sup>	
Absorption coefficient	0.064 mm <sup>-1</sup>	
F(000)	976	
Crystal size	0.536 x 0.181 x 0.136 mm <sup>3</sup>	
2θ range for data collection	2.391 to 27.202°.	
Index ranges	-17 ≤ h ≤ 17, -27 ≤ k ≤ 27, -12 ≤ l ≤ 12	
Reflections collected	71142	
Independent reflections	6113 [R(int) = 0.0337]	
Completeness to theta = 25.242°	99.9 %	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	6113 / 0 / 289	
Goodness-of-fit on F <sup>2</sup>	1.045	
Final R indices [I > 2σ(I)]	R1 = 0.0712, wR2 = 0.2176	
R indices (all data)	R1 = 0.0783, wR2 = 0.2265	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.951 and -0.832 e.Å <sup>-3</sup>	

## Crystallographic Data for Compound 179

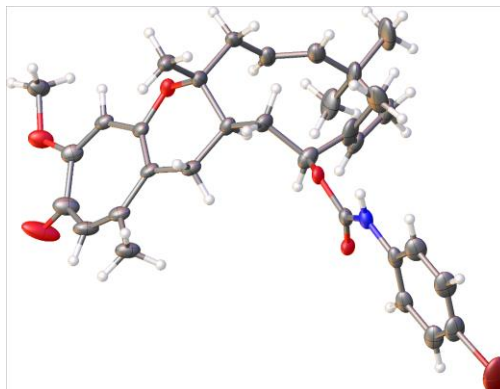
Single crystals of compound **179** were obtained by slow recrystallization from dichloromethane and methanol. A suitable crystal was selected and diffraction data were collected on a Bruker D8 Venture/Photon 100 diffractometer. The crystal was kept at 100 K during data collection.



Identification code	dm66g	
Empirical formula	C <sub>15</sub> H <sub>24</sub> O <sub>2</sub>	
Formula weight	236.34	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	
Unit cell dimensions	a = 9.7164(3) Å	α = 90°.
	b = 12.4263(5) Å	β = 90°.
	c = 22.9456(9) Å	γ = 90°.
Volume	2770.43(18) Å <sup>3</sup>	
Z	8	
Density (calculated)	1.133 Mg/m <sup>3</sup>	
Absorption coefficient	0.073 mm <sup>-1</sup>	
F(000)	1040.0	
Crystal size	0.343 x 0.306 x 0.186 mm <sup>3</sup>	
2θ range for data collection	5.322 to 56.754°	
Index ranges	-12 ≤ h ≤ 12, -16 ≤ k ≤ 16, -30 ≤ l ≤ 30	
Reflections collected	64113	
Independent reflections	6908 [R(int) = 0.0264]	
Data / restraints / parameters	6908 / 92 / 359	
Goodness-of-fit on F <sup>2</sup>	1.049	
Final R indices [I > 2σ(I)]	R1 = 0.0391, wR2 = 0.0994	
R indices (all data)	R1 = 0.0436, wR2 = 0.1031	
Largest diff. peak and hole	0.45 and -0.26 e.Å <sup>-3</sup>	

## Crystallographic Data for Compound 194

Single crystals of compound **194** were obtained by slow recrystallization from methanol. A suitable crystal was selected and diffraction data were collected on a Bruker D8 Venture/Photon 100 diffractometer. The crystal was kept at 100 K during data collection.



Identification code	mo_dd84r_0m
Empirical formula	C <sub>33</sub> H <sub>43</sub> BrNO <sub>6.5</sub>
Formula weight	637.59
Temperature	99.99 K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Unit cell dimensions	a = 13.6047(3) Å      α = 90° b = 17.4760(4) Å      β = 90° c = 28.4885(8) Å      γ = 90°
Volume	6773.3(3) Å <sup>3</sup>
Z	8
Density (calculated)	1.250 Mg/m <sup>3</sup>
Absorption coefficient	1.256 mm <sup>-1</sup>
F(000)	2680.0
Crystal size	0.622 × 0.184 × 0.09 mm <sup>3</sup>
2θ range for data collection	4.054 to 50.894°
Index ranges	-16 ≤ h ≤ 16, -19 ≤ k ≤ 21, -34 ≤ l ≤ 34
Reflections collected	97186
Independent reflections	12478 [R <sub>int</sub> = 0.0494, R <sub>sigma</sub> = 0.0264]
Data / restraints / parameters	12478/1208/1086
Goodness-of-fit on F <sup>2</sup>	1.054
Final R indices [I > 2σ(I)]	R <sub>1</sub> = 0.0402, wR <sub>2</sub> = 0.0970
R indices (all data)	R <sub>1</sub> = 0.0463, wR <sub>2</sub> = 0.1002
Extinction coefficient	n/a
Largest diff. peak and hole	0.45/-0.38 e.Å <sup>-3</sup>
Flack parameter	0.0006(19)