ABSTRACT

A straightforward synthesis of topopyrones B and D is described. The key reaction involved a convergent avenue to the anthraquinone core utilizing a tandem directed $\sigma$-metalation – metal halogen exchange methodology. The chemistry should be suitable for future SAR studies.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Calcd.</td>
<td>calculated</td>
</tr>
<tr>
<td>Conc.</td>
<td>concentrated</td>
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<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>(N, N)-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple Bond Correlation</td>
</tr>
<tr>
<td>IBX</td>
<td>iodoxybenzoic acid</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LiTMP</td>
<td>lithium 2,2,6,6-Tetramethylpiperidide</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>NBS</td>
<td>(N)-bromosuccinimide</td>
</tr>
<tr>
<td>NCS</td>
<td>(N)-chlorosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>Sat.</td>
<td>saturated</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>(t)-butyldimethylsilyl</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
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</table>
TMEDA
$N, N, N', N'$-tetramethylethylenediamine
TMS
trimethylsilyl
Ts
tosyl
TOTAL SYNTHESIS OF TOPOPYRONES B AND D
1.1 Introduction

Topoisomerases I and II ("topo I" and "topo II") are essential nuclear enzymes involved in DNA replication, transcription, and repair events. They are responsible for the relaxation of supercoiled DNA by reversibly breaking one (topo I) or both (topo II) DNA strands, and by unwinding the severed strand(s), thereby releasing the build up of torsional strain. Inhibition of topoisomerases interferes with the relaxation process, inhibiting cellular growth and reproduction, ultimately proving fatal to the cell. The high replication rate of tumor cells and their tendency to overexpress topoisomerases have made topoisomerase inhibitors an important class of anti-tumor agents.

A number of anti-tumor drugs target topo-II, but selective inhibition of topo-I is also a valid strategy in cancer therapy. Currently, the only topo-I inhibitors approved by the FDA as antineoplastic drugs are derived from camptothecin (CPT): topotecan (Hycamtin, GlaxoSmithKline) and irinotecan (also known as CPT-11, Camptosar, Yakult Honsha KK). Topotecan is currently used as a second-line treatment for ovarian cancers and for the treatment of small cell lung cancer, while irinotecan is currently for colon cancers. Several other camptothecin derivatives are in clinical trials.

The success of CPT derivatives as chemotherapy agents has promoted the search of other, non-CPT, topo-I inhibitors. An interesting development in this area is the recent discovery of a family of tetracyclic compounds, termed topopyrones (Scheme 1), that are...
potent and selective inhibitors of topo-I. These substances were isolated by Kanai\(^8\) and shown to possess an anthraquinone moiety with an angularly (topopyrone A and C) or linearly (topopyrone B and D) fused 4-pyrone ring. Bioactivity is especially pronounced in topopyrone B (IC\(_{50}\) 0.15 ng/mL), which shows activity comparable to that of CPT (IC\(_{50}\) 0.10 ng/mL).

\begin{center}
\begin{tabular}{|c|c|}
\hline
\textbf{Compound} & \textbf{IC\(_{50}\) (ng/mL)} \\
\hline
Topopyrone A & 1.22 \\
Topopyrone B & 0.15 \\
Topopyrone C & 4.88 \\
Topopyrone D & 19.63 \\
Camptothecin & 0.10 \\
\hline
\end{tabular}
\end{center}

\begin{center}
\textbf{Scheme 1: Structure and Topo-I Inhibitory Activity of Topopyrones A-D}
\end{center}

Our laboratory cultivates a long-standing interest in topo-I inhibitors. The discovery of 1-4 has thus provided us with an incentive to investigate structure-activity relationship (SAR) aspects of these substances. In order to attain this objective, we required access to topopyrone congeners. Derivatization of the natural products appears to be a poor strategy for analog synthesis, on accounts of anticipated difficulties with the selective functionalization of the tetracyclic nucleus of the natural products, as well as of the poor efficiency of the fermentation process. In the latter respect, the yield of the especially active topopyrone B is a meager 1.8 mg / 2.5 L of culture broth. Therefore, we have endeavored to devise a concise avenue to fully synthetic topopyrones. Moreover, we have focused on the most potent 3 and its closely related congener 4.

1.2 Background

No synthetic work on topopyrones has been recorded in the primary literature as of this writing, although approaches to these molecules have been described in a dissertation\textsuperscript{10} and in a poster presentation.\textsuperscript{11} The isolation paper\textsuperscript{8} indicates that the "angular" members of the family transpose to their "linear" isomers under basic conditions, signifying that the B and D series of topopyrones is thermodynamically favored. This observation allowed us to chart an avenue to the natural products that involves cyclization of an intermediate such as 5 (X = H or Cl, Scheme 2) under thermodynamically controlled conditions. Accordingly, the problem of synthesizing topopyrones may be reduced to that of assembling anthraquinone 6. The acetoacetyl substituent in 5 may be built into the precursors leading to the anthraquinone segment, or it may be introduced on an unsubstituted anthraquinone 6 at an opportune time. The same holds true for the chloro substituent found in 3.

\begin{center}
\includegraphics[width=\textwidth]{Scheme2.png}
\end{center}

\textbf{Scheme 2: Retrosynthetic Analysis}

Implementation of the foregoing strategy requires access to appropriately substituted anthraquinone educts. Methodology for the construction of such motifs will be reviewed in the following section.

\textsuperscript{11} Gattinoni, S. University of Milan, Italy, 2006.
1.3 Synthesis of Anthraquinones

There are hundreds of naturally occurring anthraquinones that have been discovered and numerous syntheses have been reported in the literature.\textsuperscript{12} A classical anthraquinone construction involves a double Friedel-Crafts condensation of substituted phthalic acids or anhydrides (cf. 7 in Scheme 3) with appropriate aryl acceptors, initially producing an o-benzoylbenzoic acid 8 which ultimately cyclizes to 9.

\begin{center}
\includegraphics[width=0.7\textwidth]{scheme3.png}
\end{center}

**Scheme 3**: Friedel-Crafts Route to Anthraquinones

The method, however, is limited to the preparation of certain symmetrical anthraquinones, because of complications posed by the so-called Hayashi rearrangement during the second Friedel-Crafts step (cf. $8 \rightarrow 9$ Scheme 3).\textsuperscript{13} Such difficulties lead to the formation of mixtures of regioisomeric anthraquinones from homogeneous $o$-benzoylbenzoic acid. To illustrate (Scheme 4), activation of 10 under protic or Lewis acidic conditions reversibly forms an acylium ion 11, which partitions between two reaction pathways. An ordinary Friedel-Crafts cyclization produces anthraquinone regioisomer 12. However, cyclization of 11 to spirocyclic intermediate 14 may also occur.


\textsuperscript{13} Hayashi, M. *J. Chem. Soc.* 1927, 2516.
Agent 14 can now undergo 1,2-acyl shift. Either carbonyl group may migrate (cf. pathways a and b), resulting in formation of a mixture of anthraquinone regioisomers 12 and 15. Alternatively, 14 could fragment back to 11 or to 13, promoting "scrambling" of the acyl substituent on ring C, i.e. Hayashi rearrangement. Cyclization of the emerging 13 again leads to the formation of anthraquinone regioisomer 15. This equilibration of o-benzoylbenzoic acid intermediates creates ambiguous mixtures of regioisomers and is understandably impractical in the synthesis of many anthraquinones.

Scheme 4: Hayashi Rearrangement

To obviate the above inconveniences, a number of regioselective routes to anthraquinones have been developed. Many such avenues rely on a Diels-Alder reaction between a diene and a quinone. Thus, a regiochemically defined anthraquinone is assembled by the addition of a diene to a naphthoquinone, or by the successive addition
of two dienes to a benzoquinone. A representative example is the synthesis of an insect pigment ceroalbolinic acid by Cameron (Scheme 5).\(^{14}\) The adduct 18 of 2,6-dichlorobenzoquinone 16 with diene 17 underwent aromatization upon contact with silica gel to furnish naphthoquinone 19 in 57% yield. A second cycloaddition between naphthoquinone 20 and diene 21 afforded anthraquinone 22 in 55% yield.

\[ \text{Cl}_2\text{C}_{\text{O}}\text{O} \quad \text{MeO}\text{C}_{\text{O}}\text{OMe} \quad \text{Cl}_2\text{C}_{\text{OTMS}}\text{O} \quad \text{MeO}\text{C}_{\text{OTMS}}\text{O} \quad \text{Cl}_2\text{C}_{\text{O}}\text{OH} \quad \text{MeO}\text{C}_{\text{O}}\text{OH} \]

a. THF; b. SiO\(_2\) (57%, a-b); c. Ac\(_2\)O; d. 80 °C; e. SiO\(_2\) (55%, d-e); f. AlCl\(_3\), NaCl (69%).

**Scheme 5**: Synthesis of Ceroalbolinic Acid

---

Danishefsky's total synthesis of Vineomycinone B₂ methyl ester is another demonstration of the Diels-Alder approach to anthraquinones (Scheme 6).¹⁵ Cycloaddition of diene 24 to 16 afforded naphthoquinone 26 in 71% yield after methylation. Following isomerization of 26 to the more stable propenyl isomer 27, a subsequent cycloaddition using diene 28 was employed to give anthraquinone 29 (79% yield after methylation). Further elaboration of the side chains at C-2 and C-6 ultimately gave the product 30.

Scheme 6: Synthesis of Vineomycinone B₂ Methyl Ester

An alternative anthraquinone synthesis that offers strict regiocontrol relies on Hauser's phthalide annulation reaction. This is illustrated in the synthesis of chrysophanol 35 (Scheme 7).\(^ {16} \) Michael addition of phthalide 31 to cyclohexenone 32 gave intermediate 33 which was eventually advanced to 35.

![Scheme 7: Synthesis of Chrysophanol](image)

An interesting variant of the Hauser annulation relies on the addition of the anion of a phthalide to a benzyne. The technique is nicely illustrated in the Townsend synthesis of the mold metabolite, averufin, 42 (Scheme 8).\(^ {17} \) Thus, exposure of a mixture of phthalide 36 and aryl bromide 37 to excess LiTMP afforded 41 in 35% yield upon air oxidation. The sequence of events leading to 41 is believed to involve mettallation of 37 with consequent elimination of LiBr, resulting in formation of benzyne 39. The MOM protecting group directs the regiochemical sense of addition of the phthalide anion 38 to the 39 and favors formation of product 40. It is unclear whether 40 obtains through a


\(^{17}\) Townsend, C. A.; Christensen, S. B.; Davis, S. G. J. C. S. Perkin Trans. I. 1988, 839.
stepwise addition of 38 to 39, leading to a MOM-chelated aryllithium intermediate which then adds intramolecularly to the carbonyl group of the phthalide, or through a directed Diels-Alder-type reaction.

![Scheme 8: Synthesis of Averufin](image)

a. LiTMP, then air (O₂) (35%); b. 5% HCl aq., MeOH (80%).

Another regioselective route to anthraquinones relies on directed ortho metalation (DoM) technology. This method permits selective deprotonation of aromatic rings at the ortho position of appropriate substituents termed “directed metalation groups” (DMG’s). Good DMG’s are complexing or chelating substituents, such as OMe, OMOM, and many others, that can coordinate external organolithium agents such as BuLi and direct them toward an ortho-hydrogen, thereby increasing the kinetic acidity thereof (cf. “Z” in 43, Scheme 9). Subsequent treatment of the ortho-lithiated species 45 with an appropriate electrophile provides an ortho-substituted product 46 with full regiocontrol.

---

Scheme 9: Directed ortho Metallation

The deprotonation step is greatly accelerated by additives such as TMEDA, which break down aggregates of alkylolithiums through ligation. This is exemplified in Scheme 10 with a generic R-Li tetramer. The use of Lewis basic solvents such as THF also aid in the separation of alkylolithium aggregates. The resulting dimeric and — especially — monomeric species display substantially enhanced basicity.

Scheme 10: Breakdown of R-Li oligomers

---

Especially useful in the context of anthraquinone construction is the Snieckus ortho metalation of $N,N$-dialkylbenzamides, which are among the most powerful DMG’s.\textsuperscript{20} The technique is demonstrated in the synthesis of soranjidiol, \textit{52},\textsuperscript{21} (Scheme 11). Reaction of ortho-lithiated benzamide \textit{47} with benzaldehyde \textit{48} provided hydroxyamide \textit{49}, which upon treatment with acid lactonized to phthalide \textit{50}. Friedel-Crafts cyclization afforded anthrone \textit{51} in 71% yield. Oxidation and demethylation provided anthraquinone \textit{52} (70% yield). An analogous approach was used for the synthesis of islandicin, digitopurpone, erythroglaucin, and cynodontin.

\begin{center}
\begin{tikzpicture}

\begin{scope}[every node/.style={scale=0.7}]
\node (a1) at (0,0) {a. s-BuLi, TMEDA, THF; b. TsOH (76%); c. TFAA (71%); d. CrO$_3$, HOAc; e. py HCl (70%).};
\node (a2) at (-2,1) {\textit{47}};
\node (a3) at (2,1) {\textit{48}};
\node (a4) at (0,2) {\textit{49}};
\node (a5) at (0,3) {\textit{50}};
\node (a6) at (0,4) {\textit{51}};
\node (a7) at (0,5) {\textit{52}};
\node (b1) at (0,0) {\textbf{Scheme 11: Synthesis of Soranjidiol}};
\end{scope}
\end{tikzpicture}
\end{center}

Eventually, Snieckus showed that anthraquinones can be obtained in a one-pot reaction using a tandem DoM – halogen-metal exchange approach (Scheme 12).\textsuperscript{22} This process involves the merger of an ortho-lithiated benzamide \textit{53} with an $o$-

\textsuperscript{22} Wang, X.; Snieckus, V. \textit{Synlett} \textbf{1990}, 313.
bromobenzaldehyde 54 to give intermediate 55, which is treated in situ with additional R-Li (usually t-BuLi) to effect a lithium-bromine exchange, thereby triggering cyclization to 57. Oxidation in air finally affords anthraquinone 58.

Scheme 12: Tandem DoM – Metal Halogen Exchange

The broad scope of this reaction allows for the rapid construction of complex anthraquinones using readily accessible benzamide and benzaldehyde synthons. Thus, we chose to apply this technology to assemble the anthraquinone core in topopyrones. Our synthetic strategy is illustrated in Scheme 13. We considered both an avenue relying on functionalization of unsubstituted anthraquinone 6, and a more convergent route leading directly to 5 through the merger of fragments 59-60 and 62. Our results are detailed in the next section.
Scheme 13: Improved Synthetic Strategy
1.4 Synthesis and Elaboration of 1,3,6,8-tetramethoxyanthraquinone

The synthesis of anthraquinone 6 served as a test of the Snieckus tandem DoM methodology. Amide 59 and aldehyde 61 were prepared by the method of Kamila\textsuperscript{23} and Broering, \textsuperscript{24} respectively, as shown in Scheme 14.

\begin{scheme}

\begin{align*}
\text{a. } & \quad \text{OMe} \quad \text{OMe} \\
\text{MeO} \quad \text{R} \\
\text{b. } & \quad \text{OMe} \\
\text{X} \quad \text{OMe}
\end{align*}

\text{a. } \text{Et}_2\text{NH, toluene, } 0 \, ^\circ\text{C} (89\%); \text{b. } \text{Br}_2, \text{AcOH, r.t.} (90\%)

\textbf{Scheme 14:} Synthesis of Amide 59 and Aldehyde 61

Benzamide 59 was o-lithiated (s-BuLi/TMEDA/THF/-78 \, ^\circ\text{C}; Scheme 15) and the resulting organometallic was added to benzaldehyde 61. The presumed intermediate 65 was treated \textit{in situ} with t-BuLi, resulting in cyclization to a new compound believed to be 66. Air oxidation provided anthraquinone 6 in 60\% yield. The balance of the crude product (40\%) was 68. Recrystallization from EtOAc afforded pure 6 in 40\% yield.


The formation of byproduct 68 may be explained by invoking protonation of aryllithium species 66. Premature quenching of the reaction was quickly dismissed as a possible cause, since reactions that were allowed to proceed for up to 24 h at room temperature showed no improvement in yields. Thus protonation must have transpired during the reaction. Available evidence suggests that the proton source is the substrate itself, or possibly the solvent (THF). Indeed, intermediate 66 possesses a doubly benzylic hydrogen (marked with an arrow) that may be anticipated to be rather acidic, activated as it is by a pair of aryl groups, one of which permits delocalization of negative charge into the amide carbonyl. Formation of 68 may thus reflect a rate of proton transfer that is
comparable to that of nucleophilic addition to the amide carbonyl. We note that proton transfer is more likely to occur in a bimolecular mode than in an intramolecular one, because the intramolecular reaction would have to proceed through an unfavorable four-center transition state. Alternatively, kinetic barriers to the addition of the aryllithium unit in 66 to the amide carbonyl may open the door to competitive deprotonation of THF. This event would be accelerated by the presence of TMEDA in the medium.

Scheme 16: Montmorillonite K-10 Catalyzed Chromone Synthesis

With anthraquinone 6 in hand, we attempted construction of the pyrone subunit by the use of noteworthy reaction that was described in a recent paper dealing with the synthesis of 73 (Scheme 16). The authors of this work reported a straightforward route to chromone 73 by coupling of phloroglucinol 69 and acid chloride 70 catalyzed by montmorillonite K-10. The reaction proceeds through esterification of 69 to 71, which

\[ a. \text{ montmorillonite K-10, nitrobenzene, } 120^\circ \text{C, (62%).} \]

References:

then undergoes a Fries rearrangement to give intermediate 72. This substance is transformed to pyrone 73 following an intramolecular 1,4-addition of the phenolic OH group to the unsaturated ester.

We hoped that the described method could be applied to the resorcinlylic system in anthraquinone 6 (Scheme 17). Thus, 6 was first converted to the hydroxyanthraquinone 74 by refluxing in conc. HBr/AcOH. Treatment of 74 with 2-butynoyl chloride 76 and montmorillonite K-10 in nitrobenzene failed to generate any of the desired pyrone 4, even after heating at 130 °C overnight. Only starting 74 was recovered from these attempts.

Scheme 17: Attempted Synthesis of 4

The above results provided no indication as to the nature of the problem that was preventing formation of 4. In particular, it was unclear whether the initial phenol esterification reaction was occurring at all. Accordingly, a monoester of 74 believed to be 77 was prepared in a separate operation, and then subjected to the action of montmorillonite K-10 under the described conditions (Scheme 18). Interestingly, the
substrate was converted quantitatively back to 74. This seems to suggest that Montmorillonite K-10 does promote formation of acylium ion 79 at some point in the reaction, but that the subsequent electrophilic acylation of presumed intermediate 78 is thwarted by the deactivating effects of the quinone carbonyls.

\[
\begin{align*}
74 & \xrightarrow{a. \text{ Et}_3\text{N, EtOAc, then 76}} \xrightarrow{b. \text{ Montmorillonite K-10, nitrobenzene, 130 °C.}} \\
\text{Scheme 18: Unsuccessful Fries Rearrangement}
\end{align*}
\]

This reluctance of 74 toward electrophilic substitution has also been observed in connection with the synthesis of averufin 42.\(^{27}\) Castonguay and Brassard thoroughly investigated the functionalization of C-2 in systems of type 74 under a variety of Friedel-Crafts acylation, Fries rearrangement, and \textit{ortho}-lithiation conditions. All such attempts were uniformly unsuccessful. They eventually achieved conversion of 74 to 42 by treatment with 5-oxohexanal 81 and aqueous sodium bicarbonate, followed by mild acid treatment to trigger internal acetal formation (Scheme 19). The yield was an ungenerous

6.5%. These observations, as well as our own results, induced us to refocus on a route that avoids functionalization of 6 and 74. This means that the anthraquinone must be constructed using fragment 62 (cf. Scheme 13).

\[
\begin{align*}
74 + \text{81} & \rightarrow 42 \\
a. \text{NaHCO}_3, 90 \, ^\circ \text{C} (6.5\%)
\end{align*}
\]

**Scheme 19:** Brassard's Synthesis of Averufin
1.5 Synthesis of Fragment 62

We sought to create 62 through hydroxyalkylation of an appropriate arylmetallic reagent with the known \(^{28}\) aldehyde 85. The latter was prepared in 3 steps from ethyl acetoacetate 82 by simple modifications of literature procedures (Scheme 20).

\[ \text{Scheme 20: Synthesis of Aldehyde 85} \]

The arylmetallic agent that would add to 85 may be the recently described dianion \(^{29}\) 86, which is prepared by deprotonation of 86 by use of so-called “super base\(^{30}\)” (Scheme 21). Super bases are alkylpotassium species generated \textit{in situ} through the reaction of alkillylithium species and a tertiary potassium alkoxide such as \(t\)-BuOK.

\[ \text{Scheme 21: Dianion Formation Using “Super Base”} \]


The formation of a more ionic organo-potassium complex at the expense of a more covalent organo-lithium one may seem to violate the principles governing transmetallation reactions. In fact, the success of this apparently contrathermodynamic transmetallation process is believed to be due to precipitation of t-BuOLi, which is largely insoluble in solvents such as THF. By a LeChatelier effect, subtraction of t-BuOLi shifts the equilibrium of the reaction toward formation of the organo-potassium species. As anticipated from considerations of metal-C bond polarization, potassium alkyls are exceptionally powerful bases: they are capable of deprotonating even simple alkanes.31

Unfortunately, no reaction was observed upon treatment of 86 with n-BuLi and t-BuOK, followed by addition of aldehyde 85. An alternative approach involving lithium-bromine exchange of t-butyl ester 90, again followed by addition of 85 was equally unsuccessful. The reaction afforded only traces of 92: the major product (>90% yield) was the dehalogenated form of 90, which arguably arises through protonation of 91 (Scheme 22).

```
OMe
OMe

89 R = H
90 R = t-Bu

OMe
OMe

91

OMe
OMe

92

a. H₂SO₄, MgSO₄, t-BuOH, DCM, r.t. (26%); b. t-BuLi, THF, -78 °C; c. 85.
```

Scheme 22: Synthesis of 92

---

After further experimentation, it was found that silyl ether 94 is a competent substrate for this reaction (Scheme 23). Compound 94 was obtained by reduction of 93 with BH$_3$-SMe$_2$ followed by protection with TBSCI. Subjection of 94 to lithium-bromine exchange then reaction with aldehyde 85 afforded 95 in 67% yield. The balance of starting 94 was recovered as the dehalogenated product 96. The moderate yield was perhaps due to competitive deprotonation of the aldehyde by the aryllithium intermediate.

Scheme 23: Synthesis of 95

The next step in the elaboration of 95 to 62 was the electrophilic bromination of the aromatic ring. Interestingly, reaction of 95 with NBS in CH$_3$CN gave an essentially 1 : 1 mixture of desired 97 and side products 98 and 99 (Scheme 24).

Scheme 24: Bromination of 95
The formation of 98 is clearly due to an *ipso* substitution,\(^{32}\) which may be rationalized by assuming an initial electrophilic bromination at the carbon atom situated between the two methoxy groups (Scheme 25). Intermediate 100 may then fragment into a molecule of 98 and one of aldehyde 85. The aromaticity of 98 is a likely driving force for such a fragmentation.

![Scheme 25: Fragmentation of Intermediate 100](image)

The formation of side-product 99 likely occurs through NBS oxidation of the benzylic alcohol and deketalization of 99 by traces of HBr present in the medium. Oxidations of 1° and 2° alcohols to aldehydes or ketones by NBS are not uncommon.\(^{33}\) They are believed to proceed via a hypobromite intermediate 102, which undergoes 1,2-elimination of HBr (Scheme 26). The HBr thus released could be responsible for loss of the ketal.

![Scheme 26: Oxidation of Alcohols by NBS](image)


An alternative interpretation based on radical bromination of the benzylic position leading to 99 (Scheme 27) is less plausible, because the reaction is carried out under conditions that do not promote radical chain processes.

Scheme 27: Radical Bromination Route

It was envisioned that protection of the benzylic alcohol in 95 would suppress – or at least limit – formation of by-products 98 - 99. Therefore, alcohol 95 was protected as a TIPS ether (Scheme 28). The resulting 107 was successfully converted to 108 in
quantitative yield. The action of TBAF on 108 induced selective deprotection of the less hindered primary alcohol to give 109. Swern oxidation then provided aldehyde 62. The overall yield of fragment 62 was 76% yield from TBS ether 95.
1.6 Synthesis of Topopyrone D

The stage was now set for the merger of benzamide 59 and aldehyde 62 in the tandem DoM route to anthraquinone 111 (Scheme 29). To our dismay, this sequence provided the desired 111 in only a meager 17% yield, the major product of the reaction being the uncyclized adduct 112 (mixture of diastereomers). This was a far cry from the 60% crude yield obtained in the synthesis of anthraquinone 6 (see Scheme 15).

Interestingly, NMR spectra of compound 111 indicated that the material exists as a 2 : 1 mixture of atropisomers, seemingly due to restricted rotation about the aryl-CHOTIPS bond. This conclusion is supported by the observation that atropisomerism vanished upon release of the TIPS group.

\[ 110 \]

\[ 111 \]
\[ 112 \]

a. s-BuLi, TMEDA, THF, -78 °C, then 62; b. t-BuLi, -78 °C - r.t., then H₂O, O₂ (17% of 111 a-b).

**Scheme 29:** Synthesis of Anthraquinone 111
Intractable mixtures containing no desired product

\[ 114 - 115 \]

a. s-BuLi, TMEDA, THF, -78 °C, then 62 (70%); b. H₂O; c. IBX, CH₃CN, reflux (83%); d. imidazole, DMAP, TIPSCI, DMF, r.t. (74%); e. HOCH₂CH₂OH, p-TsOH, benzene, reflux dean-stark; f. t-BuLi, THF, -78 °C.

**Scheme 30: Optimization of the Cyclization Step**

Investigations directed toward improving the yield of 111 were fruitless. Initially, we reasoned that if proton transfer from the diaryl substituted carbon was in fact the cause of the poor yield, then protection of the OH group in 113 with a bulky silyl group may disfavor approach of a basic agent to the acidic C-H bond (Scheme 30). Thus, the addition product 113 was isolated in good yield (70%), as a mixture of diastereomers, by quenching the reaction after addition of 62 to the anion of the diethylbenzamide 59. Next, 113 was converted to silyl ether 115. Attempts to cyclize 115 by treatment with t-BuLi produced an intractable mixture of products, none of which was the desired one. In a like manner, IBX oxidation of 113 to the corresponding benzophenone 114, followed again
by treatment with t-BuLi, gave a complex mixture containing no desired anthraquinone. Attempts to generate a ketal derivative of 114 failed, barring us from examining the possible t-BuLi-promoted cyclization of 116.

Despite this discouraging result, we continued the synthesis with TBAF desilylation of 111 to give alcohol 117 cleanly and quantitatively (Scheme 31). Oxidation of 117 with IBX in refluxing CH$_3$CN delivered ketone 118 in 88% yield. Finally, treatment of 118 with concentrated aqueous HBr in refluxing AcOH effected global deblocking and cyclization to fully synthetic topopyrone D. This material was of excellent quality and required no further purification.

\[
\begin{align*}
\text{111} & \xrightarrow{\text{a.}} \text{117} \\
\text{117} & \xrightarrow{\text{b.}} \text{118} \\
\text{4} & \xrightarrow{\text{c.}} \text{119} \\
\end{align*}
\]

a. TBAF, THF, r.t., (quantitative); b. IBX, CH$_3$CN, reflux (88%); c. 48% HBr, AcOH, reflux (quantitative); d. pyridine, Ac$_2$O, r.t.

**Scheme 31:** Synthesis of Topopyrone D

To our delight, only the thermodynamically favored linear topopyrone was formed in the last step. The linear arrangement of rings was verified by a 2D-HMBC NMR experiment, which showed $^4J$ correlations of the C-3 carbon with the
C-4 proton and with the C-14 protons. Such a correlation has been observed for natural
topopyrone D, but obviously not for its angularly fused congener, topopyrone C.8

Due to the poor solubility of topopyrones in common organic solvents (except
DMSO), the isolation paper provided no spectral data of free topopyrones 3 and 4.34
Instead, these were characterized as the respective triacetate 119 and trimethyl ether (cf.
138 in Scheme 39) derivatives. Therefore, 4 was converted to the triacetate 119 by
treatment with pyridine and acetic anhydride. As expected, 1H and 13C NMR spectra of
119 were in full accordance with the reported data.

34 We were able to obtain clean 1H and 13C NMR spectra of free topopyrone D in a solution of DMSO – d6, see experimental.
1.7 Synthesis of Topopyrone B

Armed with the successful synthesis of topopyrone D, our attention now turned toward topopyrone B, for which we needed to utilize chloroamide 60, in lieu of 59, in the sequence leading to the anthraquinone. Several avenues to 60 may be envisaged. Initially, we considered the union of metallated 2-chlororesorcinol dimethyl ether 120 with an appropriate carboxylating agent (Scheme 32). Methoxy groups are strong DMGs and metallation of anisoles via DoM are well known. Furthermore, chloro substituents are generally regarded as compatible with metatllation reactions, and may themselves behave as DMG’s. Consequently, the presence of a Cl atom in 124 was not anticipated to be problematic.

\[
\begin{align*}
\text{Cl} & \quad \text{OMe} \\
\text{MeO} & \quad \text{OMe} \\
\text{Li} & \quad \text{OMe} \\
\text{MeO} & \quad \text{OMe} \\
\end{align*}
\]

Scheme 32: Synthetic Strategy Towards 60

Contrary to such optimistic expectations, we were unable to deprotonate 124, at least by the use of s-BuLi (Scheme 33). A slightly different approach involved lithium-bromine exchange of 126 followed by addition of the aryllithium intermediate to \( N,N \)-diethyl carbamoyl chloride, 121. Compound 126 was prepared from commercial 2-chlororesorcinol by \( O \)-methylation and bromination. Reaction with \( t \)-BuLi followed by

121 produced amide 60 in a low 20% yield. An alternative route involving formylation of 122 under Vilsmeier-Haack conditions gave 123 in a modest 30% yield.

![Chemical Structures]

**Scheme 33:** Avenues Towards 60

Parallel investigations centered on the introduction of chlorine by direct halogenation of substrates such as 127. As shown in **Scheme 34**, both NCS and SO₂Cl₂ preferentially chlorinated the less hindered C-5 position of 2,4-dimethoxybenzaldehyde 127.
One report demonstrated the regioselective C-3 chlorination of 2,4-dihydroxybenzaldehyde with NaOCl under basic conditions (Scheme 35). Application of this method to substrate 129 furnished 123 in quantitative yield. O-Methylation followed by oxidation of the aldehyde to carboxylic acid 125 (NaClO₂) proceeded efficiently. Transformation of 125 to amide 60 was effected by treatment with SOCl₂ followed by Et₂NH. Although this less direct approach required more steps, gram scale quantities of 60 was effortlessly prepared in excellent overall yield.

Scheme 35: Synthesis of Amide 60

---

The next step should have been the simple merger of 60 and 62 as outlined in Scheme 29 for the preparation of topopyrone D. Unexpectedly, amide 60 proved to be entirely resistant to deprotonation under standard conditions (s-BuLi/TMEDA, THF, -78 °C). Even an eight-hour exposure to five molar equivalents of s-BuLi/TMEDA complex failed to effect ortho-lithiation, as determined by the failure to incorporate deuterium following CD$_3$OD quenching (Scheme 36). Attempts to force deprotonation by operating at temperatures as high as 0 °C were likewise fruitless. Temperatures higher than 0 °C promoted dechlorination of 60. Furthermore, reaction of THF with the s-BuLi/TMEDA complex becomes rapid at such temperatures, resulting in destruction of active base.

This roadblock in our synthetic plans was finally overcome by using the more basic t-BuLi/TMEDA complex, which promoted complete metallation of 60 (as judged by deuterium incorporation following quenching with CD$_3$OD) after three hours at -78 °C.

\[
\begin{align*}
60 & \xrightarrow{a.} \quad \text{OMe} \quad \text{OMe} \\
\text{Cl} & \quad \text{MeO} \\
\text{MeO} & \quad \text{NET}_2
\end{align*}
\]

\[
\begin{align*}
\text{D} & \quad \text{OMe}
\end{align*}
\]

a. 5 eq. s-BuLi, 5 eq. TMEDA, THF, -78 °C - 0 °C, then CD$_3$OD b. 1 eq. t-BuLi, 1 eq. TMEDA, THF, -78 °C, then CD$_3$OD.

Scheme 36: Deprotonation of 60

The reasons for the encountered difficulties remain unclear. The resistance of amide 60 towards deprotonation cannot solely be attributed to the chlorine substituent since a number of chlorinated amides undergo deprotonation without incident. 39

Furthermore, explanations involving sequestration of the base by chelation/coordination\textsuperscript{40} effects involving the chlorine atom are implausible, because amide 60 was immune to deprotonation even after addition of excess base, and because 2,3,4-trimethoxybenzamide (an analog of 60 where the chloro substituent is replaced by a methoxy group) undergoes deprotonation in a normal fashion,\textsuperscript{41} even though the triad of adjacent methoxy groups can undoubtedly chelate/coordinate/sequester the base as effectively as the 2,4-dimethoxy-3-chloro arrangement present in 60.

\[ \text{Scheme 37: Synthesis of 133} \]

Reaction of 60 and 62 under the newly modified conditions proceeded through intermediate 132, which upon treatment with \( t \)-BuLi followed by air oxidation gave anthraquinone 133 in 20% yield (Scheme 37). As seen earlier for the case of topopyrone

D, the desired 133 was accompanied by a significant quantity of debrominated adduct 134 (70 % yield). It should be noted that deprotonation of 60 was conducted in the presence of only one molar equivalent of t-BuLi/TMEDA complex. Use of excess reagent caused formation of dechlorinated products, probably through an unusual lithium-chlorine exchange reaction followed by protonation of the resultant aryllithium species.

The synthesis continued according to Scheme 38. Desilylation of 133 with TBAF gave alcohol 135, which was oxidized to ketone 136 by IBX. Deprotection/cyclization of 136 using conc. HBr did not proceed as cleanly as with the dechloro analog (cf. 118 Scheme 31). Instead, this treatment resulted in formation of a mixture of 3 and a mono-methyl ether thereof, the precise structure of which was not determined.

\[
133 \rightarrow \begin{array}{c}
\text{a. TBAF, THF, r.t., (91%)} \rightarrow 135 \\
\text{b. IBX, CH\textsubscript{3}CN, reflux (90%)} \rightarrow 136 \\
\text{c. 48% HBr, AcOH, reflux} \rightarrow 3 + 137 \\
\end{array}
\]

\[
137 \quad R = H, H, Me
\]

Scheme 38: Synthesis of Topopyrone B
The addition of a phase transfer catalyst\textsuperscript{42} had no effect on the reaction. The monomethyl ether persisted even after refluxing a solution of 136 in aq. conc. HBr / AcOH for 48 hours. Fortunately, this was not of immediate concern since, as mentioned previously, topopyrone B was characterized as the trimethyl ether 138. Therefore the mixture of the two products was subjected to permethylation by use of Meerwein’s salt. The spectra and physical data of compound 138 thus obtained were in full accordance with the literature data.

It should be noted that permethylation of 3 and 137 was not a trivial proposition. Thus, a variety of standard methylation procedures failed to provide 138 in satisfactory yield (Scheme 39).

\begin{verbatim}
3 + 137 \rightarrow a. \begin{array}{c}
\text{38}
\end{array}
\end{verbatim}

<table>
<thead>
<tr>
<th>Procedure (a.)</th>
<th>Yield 138</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{K}_2\text{CO}_3$, Mel, acetone, reflux, 48 h</td>
<td>none</td>
</tr>
<tr>
<td>$\text{Cs}_2\text{CO}_3$, Mel, DMF, 45 °C, 48 h</td>
<td>none</td>
</tr>
<tr>
<td>$\text{CH}_2\text{N}_2$, Et$_2$O, r.t., 48 h</td>
<td>trace</td>
</tr>
<tr>
<td>$\text{Ag}_2\text{O}$, Mel, DCM, reflux, 48 h</td>
<td>30%</td>
</tr>
<tr>
<td>Me$_3$OBF$_4$, DCM, r.t., 2 h</td>
<td>95%</td>
</tr>
</tbody>
</table>

\textbf{Scheme 39: Synthesis of Trimethyl Ether 138}

\textsuperscript{42}\text{Landini, D.; Montanari, F.; Rolla, F.} \textit{Synthesis} 1978, 771.
In the interest of obtaining a sample of free 3 for biological assays, we now set out to demethylate a portion of 138. Just like many other aspects of topopyrone B chemistry, this transformation was problematic. It is rather ironic that having overcome the troublesome methylation of 3, we were now seeking to optimize the demethylation of 138. Consequently, other more efficient methods for the deprotection of 136 were explored (Scheme 40). Attack of 136 with TMS-I\textsuperscript{43} engendered extensive decomposition. Use of 12 M BBr\textsubscript{3} competently cleaved the methyl ethers, but the product was 139: cyclization to topopyrone B had not occurred under such conditions. The problem was corrected by exposing 139 to the action of conc. HBr in refluxing AcOH to give 3.

\begin{center}
\begin{tabular}{|c|c|}
\hline
\textbf{Condition (a.)} & \textbf{Result} \\
\hline
48\% HBr, AcOH, n-C\textsubscript{16}H\textsubscript{39}P(C\textsubscript{4}H\textsubscript{9})\textsubscript{3}Br, reflux & 3 and 137 \\
\hline
TMS-I, CHCl\textsubscript{3}, reflux & decomposition \\
\hline
i) BBr\textsubscript{3}, DCM, -78 °C - 0 °C; ii) 48\% HBr, AcOH, reflux & 3 \\
\hline
\end{tabular}
\end{center}

\textbf{Scheme 40: Deprotection of 136}

\textsuperscript{43} Jung, M. E.; Lyster, M. A. \textit{J. Org. Chem.} 1977, 42, 3761
A new set of difficulties awaited us at this juncture. Topopyrone B was poorly soluble in all common organic solvents, including polar ones such as MeOH, CH₂Cl₂, EtOAc, MeCN and acetone. Purification of 3 was therefore replete with a host of technical problems. Normal phase column chromatography was impractical. Even preparative TLC was troublesome: for instance, the compound produced a long streak on a TLC plate upon elution with 10% MeOH in CH₂Cl₂.

A promising alternative is to convert 3 to the more soluble triacetate 140, which may be readily purified by standard chromatographic methods as a prelude to release of the acetyl groups (Scheme 41). Deacetylation of 140 by using the standard K₂CO₃ / MeOH treatment has failed to produce satisfactory results. We are currently exploring techniques for the cleavage of the acetyl groups under neutral conditions in an effort to reach pure topopyrone B.

\[ \text{Scheme 41: Acetylation of Topopyrone B} \]
In conclusion, and the above difficulties notwithstanding, we feel that the straightforward synthesis of topopyrones B and D developed in the course of this research should prove valuable for the preparation of analogues for SAR studies. Various solutions aiming to improve overall yields of 3 – 4 are currently under study in our laboratories.

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44 Tan, J. S.; Ciufolini, M. A. *Org. Lett.* ASAP article, September 15, 2006.
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Experimental Protocols.

Unless otherwise stated, $^1$H and $^{13}$C NMR spectra were obtained from CDCl$_3$ solutions. Chemical shifts are reported in parts per million (ppm) on the $\delta$ scale and coupling constants, $J$, are in hertz (Hz). Multiplicities are reported as “s” (singlet), “d” (doublet), “t” (triplet), “q” (quartet), “dd” (doublet of doublets), “td” (triplet of doublets), “m” (multiplet), “c” (complex), “br” (broad). FT-IR spectra (cm$^{-1}$) were from thin films deposited on NaCl plates. Low- and high-resolution mass spectra (m/z) were obtained in the electrospray (ESI) mode. Melting points are uncorrected. All reagents and solvents were commercial products and used without further purification except THF (freshly distilled from Na/benzophenone under Ar) and CH$_2$Cl$_2$ (freshly distilled from CaH$_2$ under Ar). Commercial n-BuLi was titrated against N-benzylbenzamide in THF at -78 °C until persistence of a light blue color. Flash chromatography was performed on Silicycle 230 – 400 mesh silica gel. All reactions were performed under dry Ar in flame or over dried flasks equipped with Teflon$^\text{TM}$ stirbars. All flasks were fitted with rubber septa for the introduction of substrates, reagents, and solvents via syringe.
A solution of ethyl acetoacetate (100.0 g, 0.77 mol), ethylene glycol (143.0 g, 2.30 mol), and p-TsOH•H₂O (6.5 g, 34.2 mmol) in benzene (1000 mL; CAUTION: cancer suspect agent) was refluxed for 5 h with continuous azeotropic H₂O separation (Dean-Stark trap). The mixture was then cooled to RT, concentrated to 500 mL in vacuo., washed sequentially with sat. aq. NaHCO₃ (2 x 100 mL) and brine (100 mL), dried (Na₂SO₄), filtered and concentrated to afford the ketal ester 83 (120.5 g, 90%) as a colorless oil. This material was of excellent purity as judged by NMR and required no further purification.

¹H: 4.06 (q, 2H, J = 6.6), 3.88 (s, 4H), 2.57 (s, 2H), 1.41 (s, 3H), 1.17 (t, 3H, J = 6.6). ¹³C: 169.2, 107.4, 64.5, 60.2, 44.0, 24.2, 13.9.

IR: 1747.

Scheme 42 NMR Spectra of 83
Scheme 43 IR Spectra of 83
A solution of the above ketal ester 83 (9.0 g, 51.7 mmol) in dry THF (20 mL) was added dropwise to a cold (−5 °C; ice-NaCl bath) suspension of LAH (1.97 g, 51.7 mmol) in dry THF (80 mL). The reaction mixture was stirred at 0 °C for 1.5 h then quenched carefully with aq. sat. Na / K tartrate soln. (100 mL. CAUTION: vigorous evolution of highly flammable H₂ gas). The organic layer was separated and the aqueous layer was extracted with Et₂O (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried (Na₂SO₄) and concentrated to give alcohol 84 (6.2 g, 91%) as a colorless oil. This material was of excellent purity as judged by NMR and required no further purification.

\[ ^1H: \text{3.99 (s, 4H), 3.76 (broad s, 2H), 2.76 (broad s, 1H), 1.95 (t, 2H, } J = 5.2), 1.36 (s, 3H). \]

\[ ^{13}C: 110.3, 64.6, 58.8, 40.5, 23.9. \]

IR: 3440.

Scheme 44 NMR Spectra of 84
Scheme 45 IR Spectra of 84
Dry DMSO (2.79 mL, 39.3 mmol) was added dropwise to a cold (-78 °C) solution of oxalyl chloride (3.38 mL, 39.3 mmol) in dry DCM (130 mL; **CAUTION:** a vigorous exotherm ensues that produces poisonous CO gas). The mixture was stirred at -78 °C for 15 min, then solution of alcohol 84 (4.0 g, 30.3 mmol) in dry DCM (20 mL) was added dropwise. The resultant solution was stirred at -78 °C for 30 min, then Et$_3$N (16.9 mL, 121 mmol) was added. The mixture was stirred at -78 °C for 5 min then it was allowed to warm to RT over 40 min, with continued stirring. The reaction mixture was washed successively with aq. sat. NH$_4$Cl (3 x 50 mL), dried (Na$_2$SO$_4$) and concentrated to give 85 (3.6 g, 91%) as a pale yellow oil. This material was of excellent purity as judged by NMR and required no further purification.

$^1$H: 9.75 (t, 1H, $J =$ 2.8), 4.01 (m, 4H), 2.71 (d, 2H, $J =$ 2.8), 1.43 (s, 3H).

$^{13}$C: 200.3, 107.6, 64.8, 52.2, 24.9.

**IR:** 1724.

**HRMS** calcd for C$_6$H$_{10}$O$_3$ [M + Na]$^+$ = 153.0528, found 153.05.
Scheme 46 NMR Spectra of 85
Scheme 47 IR Spectra of 85
Diethylamine (7.12 mL, 68.5 mmol) was carefully added to a cold (0 °C) solution of 2,4-dimethoxybenzoyl chloride (4.58 g, 22.8 mmol) in dry toluene (70 mL), and the mixture was stirred at 0 °C for 1 h then warmed to RT and stirred for another 5 h. The solution was concentrated and the residue was partitioned between ethyl acetate (50 mL) and aq. sat. NaHCO₃ (50 mL). The organic layer was washed successively with 1M HCl (50 mL), H₂O (50 mL), and brine (50 mL), dried (Na₂SO₄) and concentrated to give pure amide 59 (4.8 g, 89%) as a pale yellow oil.

^{1}H: 7.05 (d, 1H, J = 8.4), 6.43 (dd, 1H, J = 8.4, 2.0), 6.39 (d, 1H, J = 2.0), 3.74 (s, 3H), 3.73 (s, 3H), 3.49 (broad q, 2H), 3.09 (q, 2H, J = 7.2), 1.16 (t, 3H, J = 7.6), 0.97 (t, 3H, J = 7.2).

^{13}C: 168.6, 161.0, 156.3, 128.1, 119.6, 104.4, 98.4, 55.3, 55.2, 42.6, 38.7, 13.8, 12.7.

IR: intense band with fine structure between 1680 and 1615.

HRMS calcd for C_{13}H_{18}^{35}ClNO₃ [M + Na]^+ = 294.0873, found 294.0870.
Scheme 48 NMR Spectra of 59
Scheme 49 IR Spectra of 59
A suspension of 2,4-dihydroxybenzaldehyde (2.0 g, 14.5 mmol, Fluka) in H₂O (10 mL) was sequentially treated at RT with a solution of KOH (2.0 g, 35.6 mmol) in H₂O (15 mL), followed by commercial bleach containing 6% NaOCl (21 mL, 16 mmol). The reaction mixture was stirred at RT for 3 h then it was acidified with 6M HCl (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated. Purification by flash chromatography (EtOAc:hexanes, 1:1) gave pure aldehyde 123 (2.4 g, quantitative) as a white solid, m.p. 146-148 °C (no m.p. was recorded in the literature).

^1H (acetone-\textit{d}₆): 9.80 (s, 1H), 7.60 (d, 1H, J = 8.8), 6.75 (d, 1H, J = 8.8).

^13C: 197.1, 162.5, 161.6, 135.5, 117.1, 110.5, 109.1.

IR: 1634.

HRMS calcld for C₇H₇O₃Cl [M + H]^+ = 173.0005, found 173.0007.
Scheme 50 NMR Spectra of 123
Scheme 51 IR Spectra of 123
Neat MeI (7.9 mL, 127 mmol CAUTION: toxic, volatile, cancer suspect agent) was added at RT to a solution of the aldehyde \textbf{123} (2.2 g, 12.7 mmol) in acetone (50 mL) containing suspended K$_2$CO$_3$ (17.6 g, 127 mmol). The mixture was refluxed for 5 h, then it was filtered and concentrated, and the residue was purified by flash chromatography (EtOAc : hexanes, 1:4) to give \textbf{130} (2.2 g, 85\%) as a white solid. This material was of excellent purity as judged by NMR and required no further purification.

\textbf{m.p.} 105-107 °C (lit. 109-111 °C).\textsuperscript{45}

\textbf{H}: 10.19 (s, 1H), 7.75 (d, 1H, $J = 9.1$), 6.81 (d, 1H, $J = 9.1$), 3.96 (s, 3H), 3.95 (s, 3H).

\textbf{C}: 187.9, 161.1, 160.5, 127.8, 123.8, 116.6, 107.7, 62.9, 56.6.

\textbf{IR}: 1681.

\textbf{HRMS} calcd for C$_9$H$_9$Cl$_3$O$_3$ [M + H]$^+$ = 201.0318, found 201.0317.

Scheme 52 NMR Spectra of 130
Scheme 53 IR Spectra of 130
A solution of NaClO₂ (80%, 1.4 g, 12.3 mmol) in a NaH₂PO₄ buffer (pH 3.5, 50 mL) was carefully added to a solution of aldehyde 130 (2.06 g, 10.3 mmol) in t-butanol (50 mL) containing 2-methyl-2-butene (2.0 M in THF, 6.2 mL, 12.4 mmol). The mixture was stirred at RT overnight, then it was basified with 1 M NaOH (10 mL) and the aqueous layer was washed with EtOAc (2 x 25 mL). The aqueous layer was reacidified with 6 M HCl (5 mL) and extracted with EtOAc (2 x 40 mL). The combined extracts were dried (Na₂SO₄) and concentrated to give pure 125 (2.0 g, 90%) as a white solid.

m.p. 168-170 °C.

¹H: 8.07 (d, 1H, J = 9.1), 6.88 (d, 1H, J = 9.1), 4.08 (s, 3H), 3.99 (s, 3H).

¹³C (acetone-d₆): 165.8, 160.4, 158.5, 131.9, 119.0, 118.1, 108.2, 62.0, 57.0.

IR: 1695.

HRMS calcd for C₉H₉ClO₄ [M + Na]⁺ = 239.0087, found 239.0089.
Scheme 54 NMR Spectra of 125
Scheme 55 IR Spectra of 125
Thionyl chloride (1.0 mL, 13.8 mmol; CAUTION: corrosive, toxic) was carefully added to a solution of 125 (2.0 g, 9.2 mmol) in dry benzene (65 mL; CAUTION: cancer suspect agent) and the mixture was refluxed for 3 h (CAUTION: evolution of corrosive HCl gas). The mixture was then cooled to 0 °C prior to dropwise addition of a solution of diethylamine (7.65 mL, 73.6 mmol) in dry benzene (10 mL CAUTION: cancer suspect agent). The mixture was stirred overnight at RT, then it was washed with 1M aq. NaOH (2 x 50 mL), dried (Na2SO4) and concentrated. The residue of crude amide was recrystallized (EtOAc:hexanes, 1:1) to afford pure 60 (1.9 g, 76%) as tan crystals.

m.p. 70-72 °C.

1H: 7.11 (d, 1H, J = 8.7), 6.73 (d, 1H, J = 8.7), 3.91 (s, 3H), 3.87 (s, 3H), 3.74, 3.36 (br s, 2H), 3.15 (q, 2H, J = 7.3), 1.24 (t, 3H, J = 7.3), 1.02 (t, 3H, J = 7.3).

13C: 167.8, 156.8, 153.4, 125.8, 125.6, 116.8, 107.7, 61.9, 56.6, 43.2, 39.2, 14.1, 12.9. IR: 1634.

HRMS calcd for C15H1835ClNO3 [M + Na]+ = 294.0873, found 294.0870.
Scheme 56 NMR Spectra of 60
Scheme 57 IR Spectra of 60
Commercial BH$_3$•SMe$_2$ solution (36.3 mL, 0.38 mol) was added dropwise to a solution of 3,5-dimethoxy-4-bromobenzoic acid (50.0 g, 0.19 mol) in dry THF (600 mL). The mixture was stirred at 40 °C overnight, then it was quenched with 1M aq. HCl (200 mL. CAUTION: evolution of highly flammable H$_2$ gas) and the volatiles were removed in vacuo. The aqueous residue was extracted with EtOAc (3 x 200 mL), and the combined extracts were dried (Na$_2$SO$_4$) and concentrated to give the pure alcohol 94a (47 g, quantitative) as a white solid.

m.p. 100 – 102 °C (lit. 100-102 °C).

$^1$H: 6.51 (s, 2H), 4.59 (s, 2H), 3.84 (s, 6H), 2.41 (s, 1H).

$^{13}$C: 156.8, 141.7, 102.8, 99.3, 64.8, 56.3.

IR: 3310.

HRMS calcd for C$_9$H$_{17}$BrO$_3$ [M + Na]$^+$ = 268.9789, found 268.979.

---

Scheme 58 NMR Spectra of 94a
Scheme 59 IR Spectra of 94a
A solution of the alcohol 94a (47.0 g, 0.19 mol), imidazole (25.9 g, 0.38 mol), 4-DMAP (1.8 g, 15 mmol), and TBSCl (30.1 g, 0.20 mol) in dry CH₂Cl₂ (400 mL) was stirred at RT overnight, then it was concentrated. The residue was taken up with sat. NH₄Cl aq. (200 mL) and extracted with EtOAc (3 x 150 mL). The combined extracts were dried (Na₂SO₄) and concentrated, and the residue was purified by flash chromatography (hexanes → EtOAc:hexanes, 1:1) to afford silyl ether 94 (68 g, quantitative) as a waxy solid.

m.p. 34 – 36 °C.

¹H: 6.57 (s, 2H), 4.71 (s, 2H), 3.89 (s, 6H), 0.96 (s, 9H), 0.11 (s, 6H).

¹³C: 157.1, 142.7, 102.3, 64.8, 56.5, 26.1, 18.6, -5.1.

IR: 2856, 1589, 1233.

Scheme 60 NMR Spectra of 94

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Scheme 61 IR Spectra of 94
A pentane solution of $t$-BuLi (1.45M 10.5 mL, 15.2 mmol) was added dropwise to a cold (-78 °C) solution of 94 (2.5 g, 6.9 mmol) in dry THF (25 mL), followed by a solution of aldehyde 85 (0.90 g, 6.9 mmol) in dry THF (5 mL). The mixture was stirred at -78 °C for 1 h then it was allowed to warm to RT overnight. The reaction was quenched with sat. NH$_4$Cl aq. (30 mL) and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined extracts were dried ($\text{Na}_2\text{SO}_4$) and concentrated. Chromatographic purification of the residue (EtOAc:hexanes, 1:1) gave 95 (1.9 g, 67%) as a pale orange oil.

$^1$H: 6.53 (s, 2H), 5.43 (ddd, 1H, $J = 9.6, 9.6, 3.9$), 4.70 (s, 2H), 3.97 (m, 4H), 3.82 (s, 6H), 3.54 (d, 1H, $J = 9.6$), 2.43 (dd, 1H, $J = 15.0, 9.6$), 1.97 (dd, 1H, $J = 15.0, 3.9$), 1.45 (s, 3H), 0.95 (s, 9H), 0.10 (s, 6H).

$^{13}$C: 157.7, 142.4, 118.8, 109.9, 101.9, 65.1, 64.7, 64.3, 63.8, 55.8, 45.2, 26.3, 24.3, 18.5, -4.8.

$\text{IR: 3565.}$

$\text{HRMS calcd for C}_{21}\text{H}_{36}\text{O}_6\text{Si} [\text{M + Na}]^+ = 435.2179$, found 435.2178.
Scheme 62 NMR Spectra of 95
Scheme 63 IR Spectra of 95
Neat TIPS-OTf (1.85 mL, 6.9 mmol) was carefully added to a solution of 95 (2.7 g, 6.6 mmol), imidazole (0.9 g, 13.2 mmol), and 4-DMAP (64.0 mg, 0.53 mmol) in dry DMF (13 mL), and the mixture was stirred at RT overnight. The reaction was quenched with aq. sat. NaHCO₃ (50 mL) and extracted with EtOAc (2 x 50 mL). The combined extracts were washed with brine (50 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (hexanes → EtOAc:hexanes, 1:4) to afford silyl ether 107 (3.5 g, 94%) as colorless oil.

\[ \text{^1H: } 6.50 \text{ (br s, 1H), 6.46 (br s, 1H), 5.57 (dd, } 1H, J = 9.2, 4.4), 4.70 \text{ (br s, 2H), 3.85-3.78 (c, 4H), 3.78 (s, 3H), 3.77 (s, 3H), 2.76 (dd, } 1H, J = 14.4, 9.2), 2.23 \text{ (dd, } 1H, J = 14.4, 4.4), 1.24 \text{ (s, 3H), 1.00-0.98 (m, 12H), 0.94 (s, 9H), 0.89-0.85 (m, 9H), 0.08 (s, 6H).} \]

\[ \text{^13C: } 160.1, 157.0, 142.1, 120.0, 109.5, 102.8, 101.1, 65.3, 64.4, 64.3, 63.1, 55.6, 55.6, 45.1, 26.0, 24.5, 18.2, 18.0, 17.9, 12.5, -5.0. \]

\[ \text{IR: } 2865, 1610, 1228. \]

\[ \text{HRMS calcd for } C_{30}H_{56}O_{6}Si_{2} [M+ Na]^+ = 591.3513, \text{ found } 591.3518. \]
Scheme 64 NMR Spectra of 107
Scheme 65 IR Spectra of 107
A solution of 107 (3.5 g, 6.2 mmol) and NBS (1.1 g, 6.2 mmol) in CH$_3$CN (20 mL) was stirred at RT for 1.5 h, then it was diluted with aq. sat. NaHCO$_3$ aq. (30 mL) and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with brine (50 mL), dried (Na$_2$SO$_4$) and concentrated to give pure 108 (4.0 g, quantitative) as a colorless oil. Proton and $^{13}$C NMR spectra indicated that this material exists as a ca. 4:1 mixture of atropisomers.

$^1$H (Major atropisomer): 6.94 (s, 1H), 5.57 (dd, 1H, $J = 10.5$, 3.6), 4.70 (br AB-type system, 2H, $J = 15.1$), 3.93 (s, 3H), 3.80 (s, 3H), 3.81-3.69 (c, 4H), 3.14 (dd, 1H, $J = 14.2$, 10.5), 2.12 (dd, 1H, $J = 14.2$, 3.6), 1.18 (s, 3H), 1.11-0.84 (c, 21H), 0.97 (s, 9H), 0.13 (s, 6H).

$^{13}$C (Major atropisomer): 157.2, 156.4, 141.1, 126.5, 109.0, 108.2, 105.4, 64.9, 64.5, 64.4, 63.2, 62.1, 55.6, 44.7, 26.1, 24.4, 18.4, 18.2, 12.5, -5.1.

IR: 2866.

HRMS calcd for C$_{30}$H$_{55}$O$_6^{79}$BrSi$_2$ [M + Na]$^+$ = 669.2618, found 669.2614.
Scheme 66 NMR Spectra of 108
Scheme 67 IR Spectra of 108
A solution of 108 (4.0 g, 6.2 mmol) and TBAF (1.0M in THF, 5.9 mL, 6.2 mmol) in THF (20 mL) was stirred at RT for 20 min, then it was quenched with aq. sat. NaHCO₃ (30 mL) and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with brine (50 mL), dried (Na₂SO₄) and concentrated to give 109 (3.2 g, quantitative) as a colorless oil. Proton and \(^{13}\text{C}\) NMR spectra indicated that this material exists as a ca. 4:1 mixture of atropisomers.

\(^{1}\text{H}\) (major atropisomer): 6.84 (s, 1H), 5.58 (dd, 1H, \(J = 10.5, 3.5\)), 4.71 (br AB-type system, 2H, \(J = 14.0\)), 3.93 (s, 3H), 3.82 (s, 3H), 3.78-3.68 (c, 4H), 3.13 (dd, 1H, \(J = 14.0, 10.5\)), 2.26 (br, 1H, OH), 2.13 (dd, 1H, \(J = 14.0, 3.5\)), 1.40-0.80 (m, 21H), 1.17 (s, 3H).

\(^{13}\text{C}\) (major atropisomer): 157.4, 156.4, 140.9, 127.0, 109.4, 108.9, 106.0, 64.3, 64.2, 63.0, 62.0, 55.7, 53.7, 44.5, 28.5, 24.2, 20.9, 18.2, 18.1, 12.4.

IR: 3430.

HRMS calc'd for C\(_{24}\)H\(_{44}\)\(^{79}\)BrO\(_6\)Si [M + Na]\(^+\) = 555.1753, found 555.1755.
Scheme 68 NMR Spectra of 109
Scheme 69 IR Spectra of 109
Dry DMSO (0.35 mL, 4.8 mmol) was cautiously added to a cold (-78 °C) solution of oxalyl chloride (0.42 mL, 4.8 mmol) in dry DCM (15 mL. CAUTION: a vigorous exotherm ensues that produces poisonous CO gas). The mixture was stirred at -78 °C for 15 min, then a solution of 109 (2.0 g, 3.7 mmol) in dry DCM (5 mL) was added and the reaction was stirred at -78 °C for 1 h. Triethylamine (2.1 mL, 14.8 mmol) was injected and the mixture was stirred at -78 °C for 5 min, then it was allowed to warm to RT with continued stirring. The reaction mixture was washed successively with aq. sat. NH₄Cl aq. (3 x 50 mL), dried (Na₂SO₄) and concentrated. Chromatography of the residue (EtOAc:hexanes, 1:2) gave pure aldehyde 62 (1.6 g, 81%) as a colorless semisolid. Proton and ¹³C NMR spectra indicated that this material exists as a ca. 6:1 mixture of atropisomers.

¹H (major atropisomer): 10.36 (s, 1H), 7.21 (s, 1H), 5.61 (dd, 1H, J = 10.5, 3.2), 3.99 (s, 3H), 3.90-3.60 (m, 4H), 3.85 (s, 3H), 3.17 (dd, 1H, J = 14.2, 10.5), 2.17 (dd, 1H, J = 14.2, 3.2), 1.20 (s, 3H), 1.15-0.84 (m, 21H).

¹³C (major atropisomer): 191.9, 158.2, 156.6, 135.4, 133.6, 116.3, 108.7, 106.3, 64.4, 64.3, 63.1, 62.5, 56.0, 44.5, 24.3, 18.2, 18.1, 12.4.

IR: 1694.

HRMS calcd for C₂₄H₃⁹⁷⁹BrO₆Si [M + Na]⁺ = 553.1597, found 553.1596.
Scheme 70 NMR Spectra of 62
Scheme 71 IR Spectra of 62
A solution of benzamide 59 (200 mg, 0.86 mmol) in dry THF (2 mL) was added to a cold (-78 °C) solution of s-BuLi (0.68 mL, 0.90 mmol) and TMEDA (0.14 mL, 0.95 mmol) in dry THF (4 mL), followed, after 3 h, by a solution of 62 (460 mg, 0.86 mmol) in dry THF (2 mL). The mixture was stirred for 1 h, then t-BuLi (1.32 mL of 1.45M pentane solution 1.9 mmol) was added. The reaction was stirred at -78 °C for 2 h and allowed to warm to RT overnight. The mixture was quenched with H₂O (1 mL) and stirred for 1 h while bubbling air through the solution, then it was diluted with aq. sat. NaHCO₃ (20 mL) and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with brine (50 mL), dried (Na₂SO₄) and concentrated. The yellow residue was purified by flash chromatography (EtOAc:hexanes, 1:1) to give 111 (80 mg, 17%) as a bright yellow solid. Proton and ¹³C NMR spectra indicated that this material exists as a ca. 2:1 mixture of atropisomers.

¹H (major atropisomer): 7.48 (s, 1H), 7.33 (d, 1H, J = 2.7), 6.78 (d, 1H, J = 2.7), 5.63 (dd, 1H, J = 10.5, 3.2), 4.01 (s, 3H), 3.96 (br s, 6H), 3.95 (s, 3H), 3.90-3.70 (cm, 4H), 3.27 (dd, 1H, J = 14.2, 10.5), 2.15 (dd, 1H, J = 14.2, 3.2), 1.23 (s, 3H), 1.05-0.85 (m, 21 H).

¹³C (major atropisomer): 184.1, 181.2, 163.8, 162.7, 162.0, 160.2, 136.6, 134.8, 134.5, 122.5, 118.5, 108.8, 105.5, 104.1, 102.3, 64.5, 64.4, 63.7, 63.1, 56.8, 56.1, 44.4, 24.3, 18.3, 18.2, 12.5.
IR: 1670.

HRMS calcd for C\textsubscript{33}H\textsubscript{46}O\textsubscript{9}Si [M + Na]\textsuperscript{+} = 637.2809, found 637.2807.
Scheme 72 NMR Spectra of 111
Scheme 73 IR Spectra of 111
A solution of 111 (45 mg, 0.073 mmol) and TBAF (1.0M in THF, 0.15 mL, 0.15 mmol) in THF (0.5 mL) was stirred at RT overnight, then it was diluted with aq. sat. NaHCO₃ (30 mL) and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with brine (50 mL), dried (Na₂SO₄) and concentrated. Chromatographic purification of the residue (EtOAc ; hexanes, 1:1) gave 117 (30 mg, quantitative) as a yellow solid. Unlike the case of 111, proton and ¹³C NMR spectra of the present compound indicated the existence of a single species in solution.

¹H: 7.54 (s, 1H), 7.33 (d, 1H, J = 2.8), 6.78 (d, 1H, J = 2.0), 5.53 (ddd, 1H, J = 8.4, 8.4, 3.2), 4.02-3.96 (m, 4H), 4.02 (s, 3H), 3.99 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.47 (d, 1H, J = 10.0), 2.55 (dd, 1H, J = 14.4, 9.2), 2.02 (dd, 1H, J = 14.4, 3.0), 1.46 (s, 3H).

¹³C: 183.8, 181.1, 164.1, 162.1, 161.5, 159.6, 136.5, 134.9, 133.3, 122.4, 118.3, 109.9, 105.6, 105.0, 102.5, 64.9, 64.6, 64.3, 63.5, 44.9, 24.5.

IR: 3500, 1669.

HRMS calcd for C₂₄H₂₆O₉ [M + Na]⁺ = 481.1475, found 481.1478.
Scheme 74 NMR Spectra of 117
Scheme 75 IR Spectra of 117
A mixture of the 117 (7.0 mg, 0.015 mmol) and IBX (13 mg, 0.045 mmol) in CH$_3$CN (1 mL) was refluxed for 45 min, then it was cooled to RT, filtered and concentrated. Purification of the residue by preparative TLC (EtOAc) provided 118 (6.0 mg, 88%) as a yellow solid. Proton and $^{13}$C NMR spectra of 118 indicated the existence of a single species in solution.

$^1$H (7.55 (s, 1H), 7.35 (d, 1H, $J = 2.8$), 6.80 (d, 1H, $J = 2.8$), 3.98 (s, 3H), 3.97 (s, 3H), 3.97 (s, 3H), 3.96-3.91 (m, 4H), 3.94 (s, 3H), 3.18 (s, 2H), 1.54 (s, 3H).

$^{13}$C: 199.8, 183.5, 180.4, 164.3, 162.3, 159.5, 158.8, 136.5, 136.3, 132.3, 122.3, 117.9, 107.9, 105.7, 105.2, 102.8, 64.8, 64.2, 56.8, 56.6, 56.2, 52.8, 24.6.

IR: 1718, 1670.

HRMS calcd for C$_{24}$H$_{24}$O$_9$ [M + Na]$^+$ = 479.1318, found 479.1320.
Scheme 76 NMR Spectra of 118
Scheme 77 IR Spectra of 118
A solution of 118 (6.0 mg, 0.013 mmol) in AcOH (1.5 mL) and aq. 48% HBr (1.0 mL) was refluxed overnight. The mixture was diluted with H₂O (10 mL) and extracted with EtOAc (2 x 40 mL). The combined extracts were washed with brine (50 mL), dried (Na₂SO₄) and concentrated to give fully synthetic topopyrone D (5 mg, quantitative) as an orange solid.

^1H (DMSO-d₆): 7.55 (s, 1H), 7.07 (d, 1H, J = 2.3), 6.60 (d, 1H, J = 2.3), 6.52 (s, 1H), 2.47 (s, 3H).

^13C (DMSO-d₆): 185.4, 182.1, 180.8, 169.9, 164.6, 164.45, 164.41, 164.0, 159.1, 138.1, 134.0, 113.5, 110.4, 110.0, 108.7, 107.6, 106.6, 20.0.
Scheme 78 NMR Spectra of 4
Synthetic 4 was acetylated as described in the literature (ref. 8) to afford the corresponding triacetate 119, which was purified by preparative TLC (EtOAc).

This material produced $^1$H and $^{13}$C NMR spectra in complete accord with the literature (values in brackets, ref. 8).

$^1$H: 8.19 [8.19] (s, 1H), 7.97 [7.97] (d, 1H, $J = 2.1$), 7.28 [7.28] (d, 1H, $J = 2.1$), 6.13 [6.13] (s, 1H), 2.52 [2.52] (s, 3H), 2.45 [2.45] (s, 3H), 2.40 [2.40] (s, 3H), 2.36 [2.36] (s, 3H).

$^{13}$C: 180.4 [180.2], 178.5 [178.4], 175.9 [175.7], 169.3 (2 overlapping resonances) [169.0], 168.2 [169.0], 165.9 [165.6], 159.7 [159.4], 154.9 (2 overlapping resonances) [154.7], 151.8 [151.6], 136.5 [136.3], 135.5 [135.3], 124.3 [124.1], 124.2 [124.1], 122.4 [122.3], 121.4 [121.2], 118.7 [118.4], 115.6 [115.3], 113.1 [112.8], 21.34 [21.1], 21.27 [21.0], 21.2 [20.9], 20.4 [20.1].

HRMS calcd for C$_{24}$H$_{16}$O$_{10}$ [M + Na]$^+$ = 487.0641, found 487.0645.
A solution of 60 (0.20 g, 0.74 mmol) in dry THF (1 mL) was added to a cold (-78 °C) solution of t-BuLi (1.5M pentane solution, 0.49 mL, 0.74 mmol) and TMEDA (0.11 mL, 0.78 mmol) in dry THF (3 mL). After 3 h, a solution of 62 (0.39 g, 0.74 mmol) in dry THF (1 mL) was added, and after stirring for 1 h, t-BuLi (1.5M pentane solution, 0.97 mL, 1.48 mmol) was injected. The solution was stirred at -78 °C, then it was allowed to warm to RT overnight, and finally it was quenched with H₂O (1mL) and stirred under a stream of air for 2 h. The mixture was diluted with aq. sat. NaHCO₃ (30 mL) and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with brine (50 mL), dried (Na₂SO₄) and concentrated. Chromatographic purification of the residue (EtOAc:hexanes, 1:4) gave 133 (97 mg, 20%) as an orange oil. Proton and C NMR spectra indicated that this material exists as a ca. 2:1 mixture of atropisomers.

**H (major atropisomer):** 7.57 (s, 1H), 7.50 (s, 1H), 5.63 (dd, 0.5H, J = 10.5, 3.1), 4.06 (s, 3H), 4.04 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H), 3.90-3.70 (m, 4H), 3.25 (dd, 1H, J = 14.0, 10.5 Hz), 2.19 (dd, 1H, J = 14.4, 3.1), 1.23 (s, 3H), 1.10-0.81 (c, 21H).

**C (major atropisomer):** 183.0, 180.5, 162.8, 160.6, 159.3, 134.8, 134.7, 133.4, 125.7, 123.3, 122.0, 108.9, 105.1, 104.3, 64.5, 64.4, 63.4, 63.0, 62.2, 57.1, 56.2, 44.7, 24.3, 18.3, 18.2, 12.5.
$^1$H (minor atropisomer): 7.57 (s, 1H), 7.51 (s, 3H), 5.76 (dd, 0.5H, $J = 7.4$, 5.2), 4.06 (s, 3H), 4.04 (s, 3H), 3.98 (s, 3H), 3.92 (s, 3H), 2.58 (dd, 1H, $J = 14.4$, 7.4), 2.41 (dd, 1H, $J = 14.4$, 5.2), 1.32 (s, 3H), 1.10-0.81 (c, 21H).

$^{13}$C (minor atropisomer): 182.96, 180.7, 163.4, 159.2, 157.9, 157.8, 134.8, 134.6, 134.3, 125.6, 123.4, 120.2, 109.1, 105.2, 64.5, 64.3, 63.9, 62.8, 62.2, 56.1, 56.0, 45.2, 24.6, 18.2, 18.1, 12.6.

IR: 1672.

HRMS calcd for C$_{33}$H$_{45}$ClO$_9$Si [M + Na]$^+$ = 671.2419, found 671.2422.
Scheme 80 NMR Spectra of 133
Scheme 81 IR Spectra of 133
A solution of 133 (84 mg, 0.13 mmol) and TBAF (1.0 M in THF, 0.26 mL, 0.26 mmol) in THF (1 mL) was stirred at RT overnight, then it was diluted with aq. sat. NaHCO₃ (30 mL) and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with brine (50 mL), dried (Na₂SO₄) and concentrated. Chromatographic purification of the residue (EtOAc : hexanes, 1:1) gave the alcohol 135 (58 mg, 91%) as a yellow solid. Unlike the case of 133, proton and $^{13}$C NMR spectra of the present compound indicated the existence of a single species in solution.

$^1$H: 7.58 (s, 1H), 7.55 (s, 1H), 5.55 (td, 1H, $J = 9.2, 3.1$ Hz), 4.07 (s, 3H), 4.04 (s, 3H), 4.00 (s, 3H), 4.02-3.98 (m, 4H), 3.97 (s, 3H), 3.48 (c, 1H), 2.56 (dd, 1H, $J = 14.8, 9.2$), 2.00 (dd, 1H, $J = 14.8, 3.5$), 1.46 (s, 3H).

$^{13}$C: 182.7, 180.4, 161.8, 160.1, 159.4, 158.0, 134.9 (2 overlapping resonances), 133.3, 125.9, 123.0, 121.7, 109.9,* 105.2,* 105.1, 64.9, 64.6, 64.1, 63.4, 62.2, 57.1, 56.6, 44.8, 24.5.

IR: 3520, 1671.

HRMS calcd for $\text{C}_{24}\text{H}_{25}^{35}\text{ClO}_{9} \ [\text{M + Na}]^{+} = 515.1085$, found 515.1087.
Scheme 82 NMR Spectra of 135
Scheme 83 IR Spectra of 135
A solution of the 135 alcohol (100 mg, 0.20 mmol) IBX (114 mg, 0.40 mmol) in EtOAc (2 mL) was refluxed for 3 h, then it was cooled to RT, diluted with more EtOAc (30 mL) and washed with 1M NaOH (2 x 50 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated. Purification of the residue by preparative TLC afforded 136 (90 mg, 90%) as a yellow solid.

$^1$H: 7.59 (s, 1H), 7.55 (s, 1H), 4.08 (s, 3H), 4.02 (s, 3H), 3.98 (s, 3H), 3.94 (c, 4H), 3.91 (s, 3H), 3.18 (s, 2H), 1.54 (s, 3H).

$^{13}$C: 199.6, 182.5, 179.8, 160.0, 159.6, 159.0, 158.2, 136.2, 133.2, 132.9, 126.2, 122.6, 121.6, 107.9, 105.4 (two overlapping resonances), 64.8, 64.0, 62.1, 57.2, 56.7, 52.9, 29.9.

IR: 1718, 1672.

HRMS calcd for C$_{24}$H$_{23}$CIO$_9$ [M + H]$^+$ = 491.1109, found 491.1106.
Scheme 85 IR Spectra of 136
A solution of ketone 136 (17 mg, 0.035 mmol) in conc. HBr (48%, 1 mL) and acetic acid (1.5 mL) was refluxed overnight, then it was concentrated to give crude topopyrone B (13 mg, quantitative), which without further purification was suspended in dry CH$_2$Cl$_2$ (0.8 mL) and treated with solid Meerwein’s salt (30 mg, 0.2 mmol) while stirring at RT for 2h. The mixture was partitioned between EtOAc (10 mL) and sat. NaHCO$_3$ aq. (10 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated. Purification of the residue by preparative TLC (4% MeOH in DCM containing 0.5% triethylamine) gave pure 138 (3.0 mg, 30%) as a yellow solid. This material produced $^1$H and $^{13}$C NMR spectra in complete accord with the literature (values in brackets, ref. 8).

$^1$H: 8.00 [8.00] (s, 1H), 7.59 [7.59] (s, 1H), 6.16 [6.16] (s, 1H), 4.13 [4.13] (s, 3H), 4.08 [4.08] (s, 3H), 4.04 [4.05] (s, 3H), 2.38 [2.38] (s, 3H).

$^{13}$C: 181.9 [181.7], 179.7 [179.5], 176.4 [176.2], 165.0 [164.8], 162.5 [162.3], 160.2 [160.0], 159.7 [159.5], 158.2 [158.0], 136.9 [136.7], 133.2 [133.0], 126.3 [126.1], 124.8 [124.6], 123.7 [123.5], 122.9 [122.7], 113.2 [113.0], 112.9 [112.6], 105.1 [104.9], 64.1 [63.9], 62.3 [62.1], 57.2 [57.0], 20.2 [20.0].

IR: 1734, 1673.

HRMS calcd for C$_{21}$H$_{15}^{35}$ClO$_7$ [M + H]$^+$ = 415.0585, found 415.05.
Scheme 86 NMR Spectra of 138
Scheme 87 IR Spectra of 138