Expedient Single Step Access to Strained Tricyclic Ketals

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Abstract

The synthesis of cyclopropyl methyl ketones and highly strained fused substituted dihydrobenzopyran cyclopropyl lactones derived from coumarin carboxylates and chloroacetone in the presence of potassium carbonate is reported. One step synthetic access to the previously unknown dihydrobenzopyran cyclopropyl tricyclic ketals is achieved with wide substrate scope. Substituted coumarin carboxylates, phenylamides or a quinolin-2(1H)-one possessing alkyl electron donating (methyl, t-butyl) and electron withdrawing groups (F, Cl, Br, NO_2) in the 4 or 6 positions formed the highly strained dihydrobenzopyran cyclopropyl tricyclic ketals in moderate yield alongside the expected coumarin carboxylate. Saturation or substitution at the 5-position or 6-OMe afforded no tricyclic ketal compound but solely coumarin carboxylates. The formation of both structures in selected derivatives was confirmed by X-ray crystallography. A plausible mechanism is proposed for the formation of the fused lactone; via intramolecular rearrangement of *cis* cyclopropyl methyl ketones with phenolic acetate via the formation of a hemiacetal.

The search for novel chemical space in pharmaceutical discovery has correlated increasing three-dimensional space with an increased propensity to identify a clinical candidate. Thus, sp^3 rich scaffolds have garnered increased attention from the medicinal chemistry community, leading to a new predictive metric Fsp^3; the fraction of sp^3 carbon atoms within a compound.[1-3] Of specific interest has been the introduction of multi-cyclic, fused, bridged, or spiro-fused rings.[4-6]

The cyclopropane ring is a constituent of many compounds that have biological activity, including numerous natural products and pharmaceuticals used in the clinical management of cardiovascular, inflammatory diseases, diabetes and cancer.[7] Furthermore, coumarin derivatives have been extensively studied due to their wide-ranging biological profiles, including activity as anticancer, anti-inflammatory, antibacterial, antifungal, and anticoagulant agents.[8] Despite the potential for increased biological activity, cyclopropanated derivatives of coumarins have not been extensively investigated.

In the course of our continued efforts to identify new aldo-keto reductase 1C3 (AKR1C3) inhibitors, we desired access to cyclopropyl-fused coumarins.[9-13] Thus, we investigated the utility of a Michael initiated ring closure (MIRC) reaction. Prior precedent demonstrates cyclopropanation can be achieved at α,β-unsaturated alkenes, such as those present in the coumarin structure, with activated methylene substrates via the MIRC reaction,[14, 15] which includes the use of 1,2-dicarboxylate substituted alkenes[16] and 1,1,2-trisubstituted alkenes,[17] among others.[18] However, reaction with highly activated halomethylene ketones has been understudied due to high reactivity and potential for self-polymerization.[19]

While this work was in progress, Sun *et. al.* reported the reaction of a coumarin carboxylate with *tert*-butyl 2-bromoacetate using a chiral Lewis base catalyst and Cs_2CO_3 which provided polycyclic ketones in predominantly high yields (Figure 1).[20] However, when the reaction was performed without either base at room temperature, either there was no reaction, or in the case of carbonyl coumarins, a set of complex products prevented the purification of the desired cyclopropanation derivative. Guo *et. al.* reported an enatioselective cyclopropanation reaction employing a phenyliodonium ylide that was tolerative of unsubstituted or 6-methyl substituted coumarins.[21] The synthesis of functionalized strained

bicylic ketals, where n = 1 or 2 (Figure 1), from bis-homopropargylic diols via use of a Au^I or Au^{III} catalyst was reported by Antoniotti *et. al.*[22]
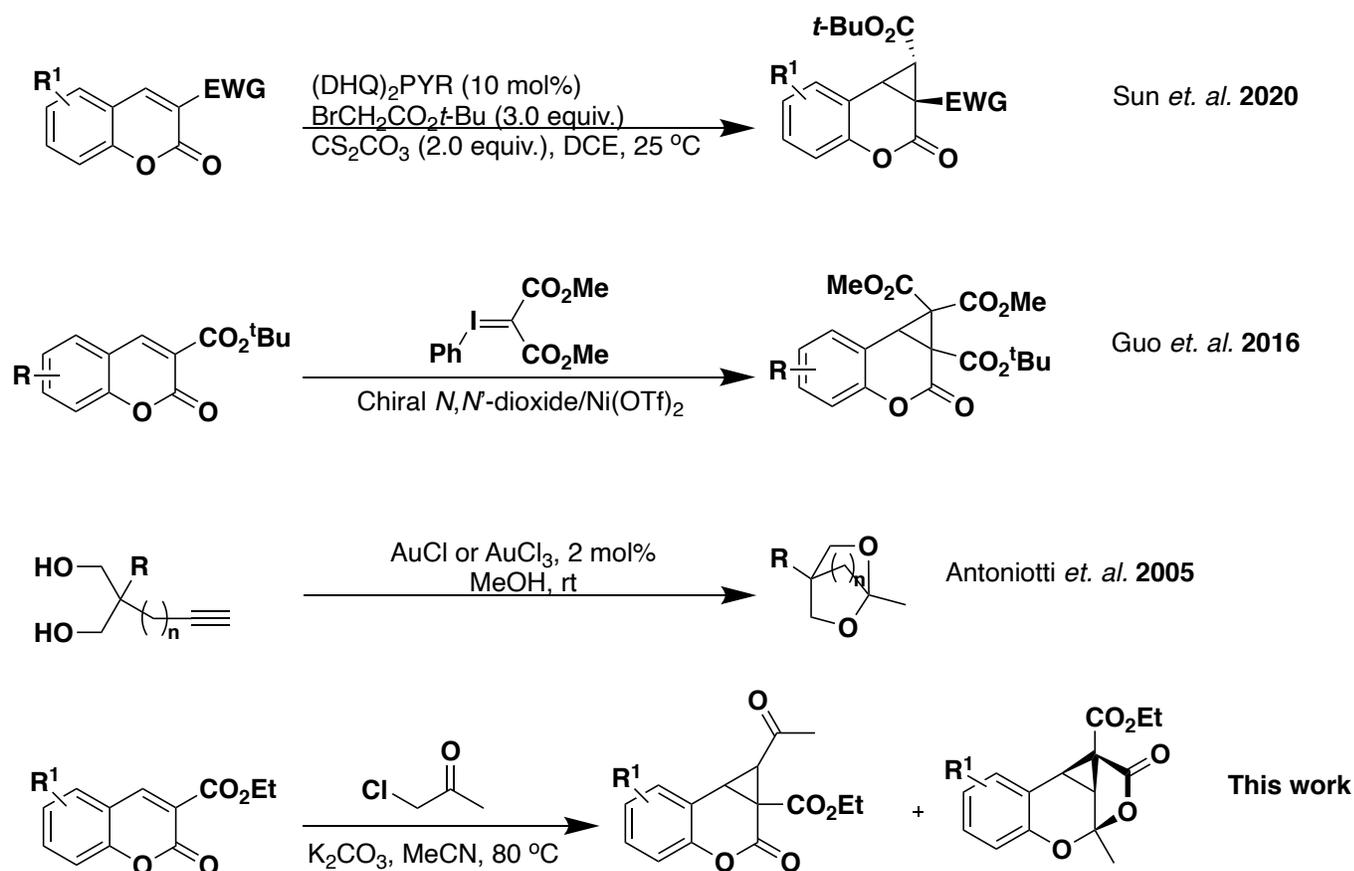

Figure 1. Comparison of the reported work and that of cyclopropanation of coumarins (Sun *et. al.* and Guo *et. al.*) and the formation of strained bicyclic ketals (Antoniotti *et. al.*).

The reaction of coumarin carboxylates with bromoacetophenones leads to the formation of cyclopropanated benzophenone and/or benzofuran derivatives.[23, 24] During the course of our synthetic efforts to access cyclopropanated coumarins we intriguingly isolated and characterized a unique tricyclic ketal that, to the best of our knowledge, has not previously been disclosed.

Reaction yields were found to be highly dependent on the substituents of the coumarin starting material. To this end, we first exposed 5-hydroxy coumarin ethyl ester (**1**) to base and stoichiometric amounts of chloroacetone. Total consumption of the starting material was not observed and so addition of excess chloroacetone and K_2CO_3 was attempted. These conditions led to the formation of the

cyclopropanated methyl ketone derivative (**1a**) complete with reaction of the chloroacetone with the alcohol to afford the respective ether (Scheme 1).
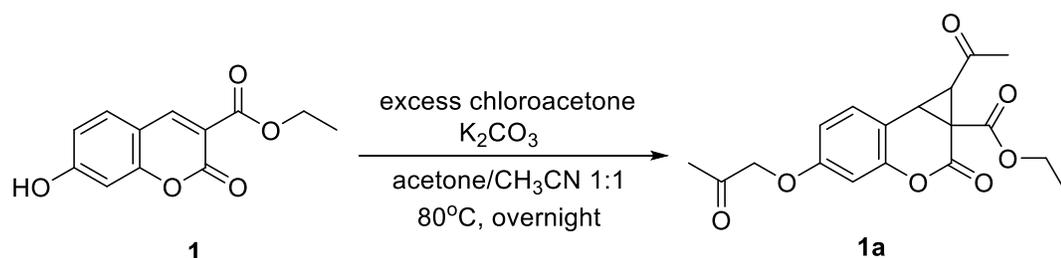
Scheme 1: Cyclopropanation of hydroxy coumarin carboxylic acid ethyl ester

We next switched to an unsubstituted coumarin ethyl ester as starting material which resulted in the formation of a complex mixture of products with the desired fused cyclopropyl product in trace yield. Optimization of reaction conditions using the 6-bromocoumarin ethyl ester (**9a**) began with a base scan (Table 1). However, no to low yields of product were formed with the use of Na_2CO_3, $CaCO_3$, NaOMe, NaOEt, KOEt, $NaHCO_3$, or $KHCO_3$. Furthermore, no significant improvement in yield was observed with additives including a 2:1 ratio of Na_2CO_3+DABCO, Na_2CO_3+Et_3N, or Na_2CO_3+K_2CO_3. In all cases, final products were isolated via silica gel column chromatography and recrystallized in 20% EtOAc:Hexanes. These purification conditions identified the unusual highly strained tricyclic ketal **9b** as the major product alongside fused cyclopropyl coumarin **9a**. The structures of **9a** and **9b** were confirmed by ^{1}H and ^{13}C spectroscopy. Representative examples for the structures of type **a** and **b**, and *cis* and *trans* isomers of **a** were confirmed by 2D NMR and X-ray crystallography.

Table 1: Reaction condition optimization for cyclopropanation
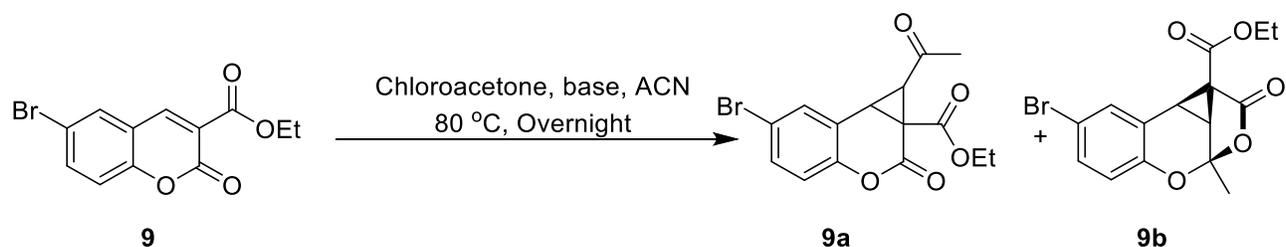
Entry	Base	Combined yield
1	Na$_2$CO$_3$	no product/trace
2	CaCO$_3$	no product/trace
3	K$_2$CO$_3$	40%
4	Cs$_2$CO$_3$	38%
5	Na$_2$CO$_3$+DABCO (2:1)	40%
6	Na$_2$CO$_3$+Et$_3$N (2:1)	35% (difficulty in isolation)
7	Na$_2$CO$_3$+K$_2$CO$_3$ (2:1)	40%
8	NaHCO$_3$	no product/trace
9	KHCO$_3$	no product/trace
10	NaOMe	no product/trace
11	NaOEt	no product/trace
12	KOEt	no product/trace
13	KO^{t}Bu	15% (difficulty in isolation)
14	Et$_3$N	no product/trace
15	Aqueous K$_2$CO$_3$	Polymerized products

We utilized K$_2$CO$_3$ as the base for further synthesis of substituted derivatives due to the ease of purification and isolation of products. Synthesis of a library of derivatives from substituted coumarins including electron donating groups; 6-methyl (**3**), 4-methoxy (**4**), 6-methoxy (**5**), 4-*tert*-butyl (**6**), and electron withdrawing groups; 5-OH (**1**), 6-fluoro (**7**), 6-chloro (**8**), 6-bromo (**9**), 4,6-dibromo (**10**), 6-nitro (**11**) and *O*-benzyl (**14**) were utilized. These substrates resulted in consistent formation of the fused cyclopropyl coumarin and the tricyclic ketal in low to moderate, but still synthetically useful yields in all case with starting material bearing 4-, 6- or 4,6-substitution. To further probe the substrate scope coumarin benzamide (**12**), quinolin-2(1*H*)-one (**13**) and 4-diethylamine (**15**) were also investigated (Figure 2).

5-Hydroxy, saturated, and 5-OBn coumarins (**1**, **2** and **14** respectively) resulted in isolation of the cyclopropylated coumarin (overall 31%, 35% and 31% yield) as the major product with only trace tricyclic product detected. The 6-methyl (**3**), 6-fluoro (**7**), 6-chloro (**8**) and benzamide (**12**) coumarin

substrates all provided preference to the tricyclic ketal as the sole isolated product (22%, 40%, 13% and 31% yield respectively). It should be noted that when the 6-fluoro coumarin cyclopropylated product was purified by silica gel chromatography without a methanol wash, decomposition of the product was observed. However, washing the product with methanol followed by silica gel chromatography resulted in *trans* isomerization of ethyl ester to methyl ester **7b**. Similar results was observed with 4-*tert* butyl isomerized methyl ester **6b**. Interestingly switching an unsubstituted coumarin ethyl ester to the respective unsubstituted benzamide (**12**) resulted in switch of major product from the cyclopropylated coumarin to the tricyclic ketal (Figure 2).

The 4-methoxy (**4**), 6-bromo (**9**) and 4,6-dibromo (**10**) substituted coumarin substrates provided an approximate 1:1 ratio of fused cyclopropyl coumarin and the tricyclic ketal. Lower equivalents of chloroacetone did not lead to the consumption of starting material in the case of 5-hydroxy and 6-nitro coumarins, hence, excess chloroacetone (5 equiv.) was used for these reactions. Difficulty in purification was observed if the starting material was not consumed. Use of excess chloroacetone (5 equiv.) with 6-nitro coumarin **11** lead to the formation of tricyclic ketal **11b** and a ring-opened alkylated diester **11c** (supporting information).

Interestingly, 6-methoxy substituted starting material (**5**) afforded the cyclopropyl coumarin as the major and only product in a 1:1 mixture of *cis* and *trans* isomers as confirmed by X-ray crystallography (Figure 3C/D). Substrate scope was further extended with quinolin-2(1*H*)-one (**13**) which afforded a mixture of the respective *N*-alkylated compound and the cyclopropyl coumarin (**13a**) in equivalent yield but with no tricyclic ketal isolated.

Cyclopropanation of 5-diethylamine coumarin **15** yielded no isolated product under the conditions depicted in Figure 2. However, when the conditions were modified to KO^{t}Bu in THF at -78 °C the cyclopropyl coumarin was isolated in poor yield with no evidence of ketal formation (Scheme 2), again suggesting that substitution at the 5-position is unfavorable for tricyclic ketal formation.
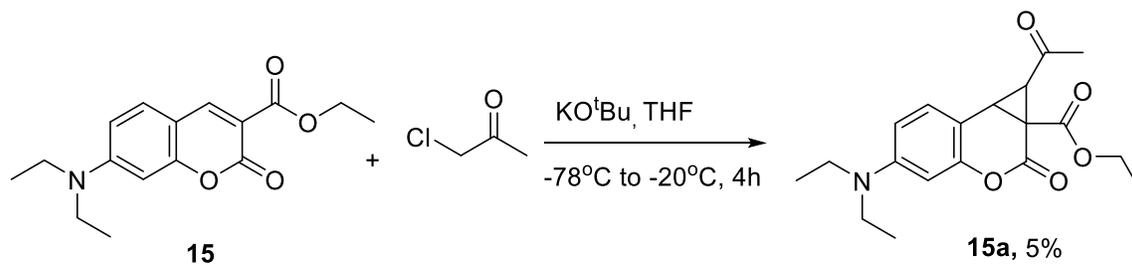
Scheme 2: Cyclopropanation of *N,N*-diethyl coumarin carboxylic acid ethyl ester.

Table 2: Substrate scope and isolate product yields

Substrate	Equiv. Chloroacetone	Products isolated and yields
1	5	**1a**, 35%
2	2	**2a**, 31%
3	2	**3b**, 22%
4	2	**4a**, 5% + **4b**, 10%
5	2	*cis:trans* 1:1 **5a**, 44%
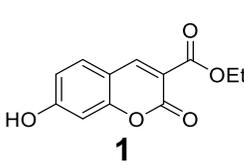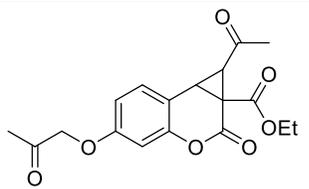
6	2	**6a**, 15% + **6b***, 14%
7	2	**7b***, 40%
8	2	**8b**, 13%
9	2	**9a**, 17% + **9b**, 20%
10	2	**10a**, 17% + **10b**, 17%
11	5	**11b**, 18% + **11c**, 20%
12	2	**12b**, 31%
13	3	**13.1**, 16% + **13a**, 13% each *cis*:*trans* 1:1
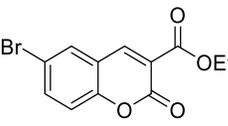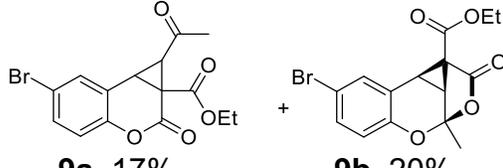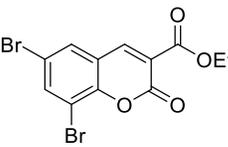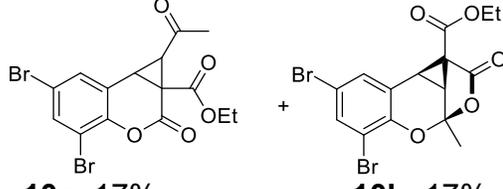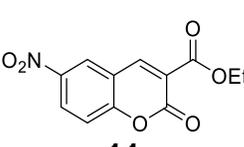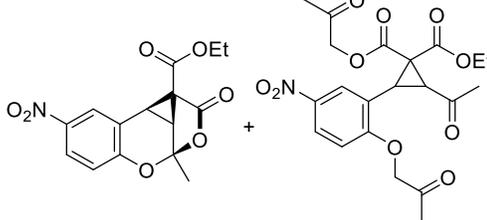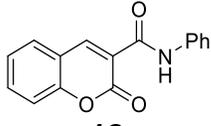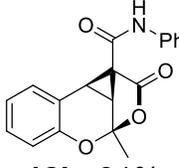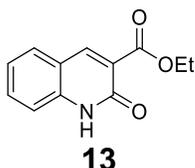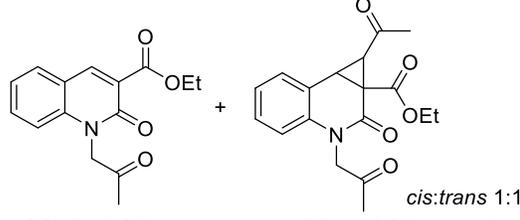
14	2	**14a**, 31% *cis:trans* 1:1
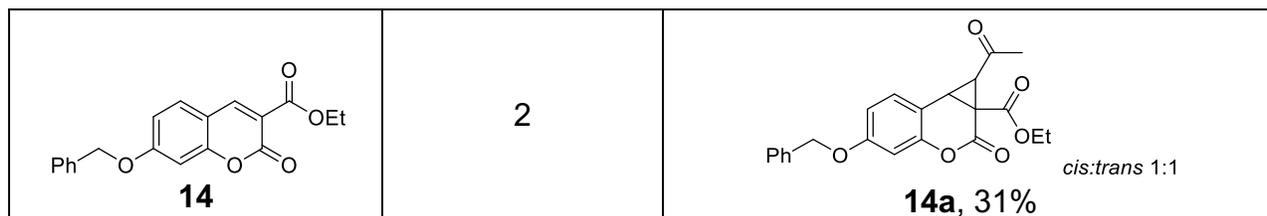
*Methyl ester of the product was observed when the reaction mixture was washed with methanol.

The structures of the 4,6-dibromo cyclopropylated coumarin **10a**, 4,6-dibromo tricyclic ketal **10b**, and *cis* and *trans* 6-methoxy cyclopropylated coumarins **5a** and **5a'** were confirmed using X-ray crystallography (Figure 3). The crystal structure for **10a** showed twinned (more than one crystal) structure. Initial attempts to solve the crystal structure without accounting for the twin lead to flat anisotropic displacement parameters (ADPs). After further analysis, it was found that the data contained a smaller twin component that resulted in significant overlap with the larger twin component. This overlap complicates the integration of the reflections and is likely the main culprit in the large ADP ratios. The dataset was reprocessed as a twin to improve Rint data statistics. Only the data associated with the primary/larger component was used for structural analysis. Merge outliers were rejected upon creation of the HKL5 files. While twin refinement improved ADP behavior, several ADP associated irregularities (high max/min ADP ratios) remain.
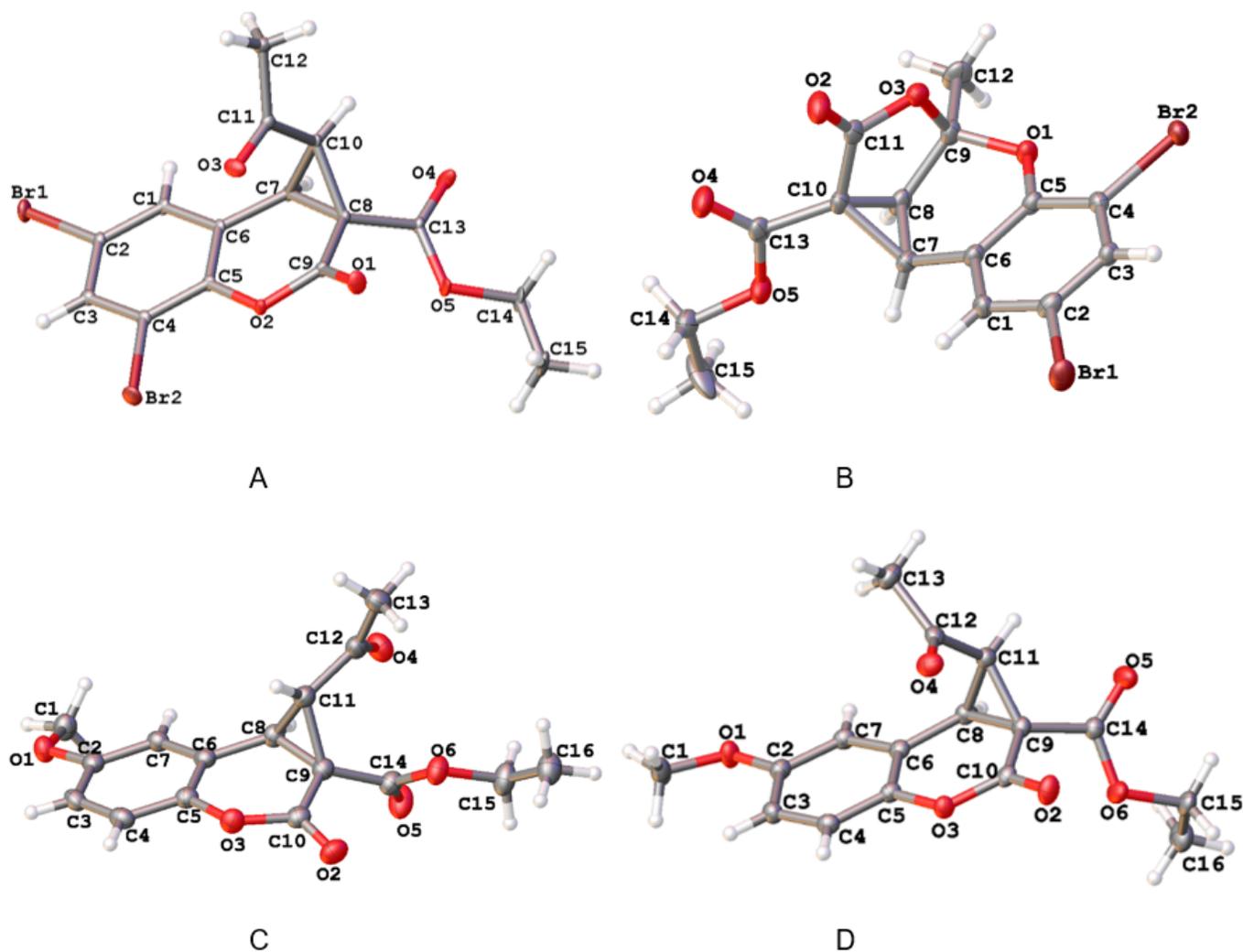
Figure 3. Crystal structures of cyclopropanated (A) dibromo coumarin ketone **10a**, (B) dibromo coumarin lactone **10b**, (C) *cis* 6-methoxy coumarin ketone **5a** and (D) *trans* 6-methoxy coumarin ketone **5a'** derivatives

In most of the cases, formation of the *trans* cyclopropylated product along with isomerized tricyclic ketal derivatives were observed, however, in the case of 6-methoxy, both *cis* and *trans* ketones were isolated, leading us to postulate that *cis* ketones undergo intermolecular rearrangement resulting in the formation of the lactone derivative by a potential mechanism delineated in Figure 3.
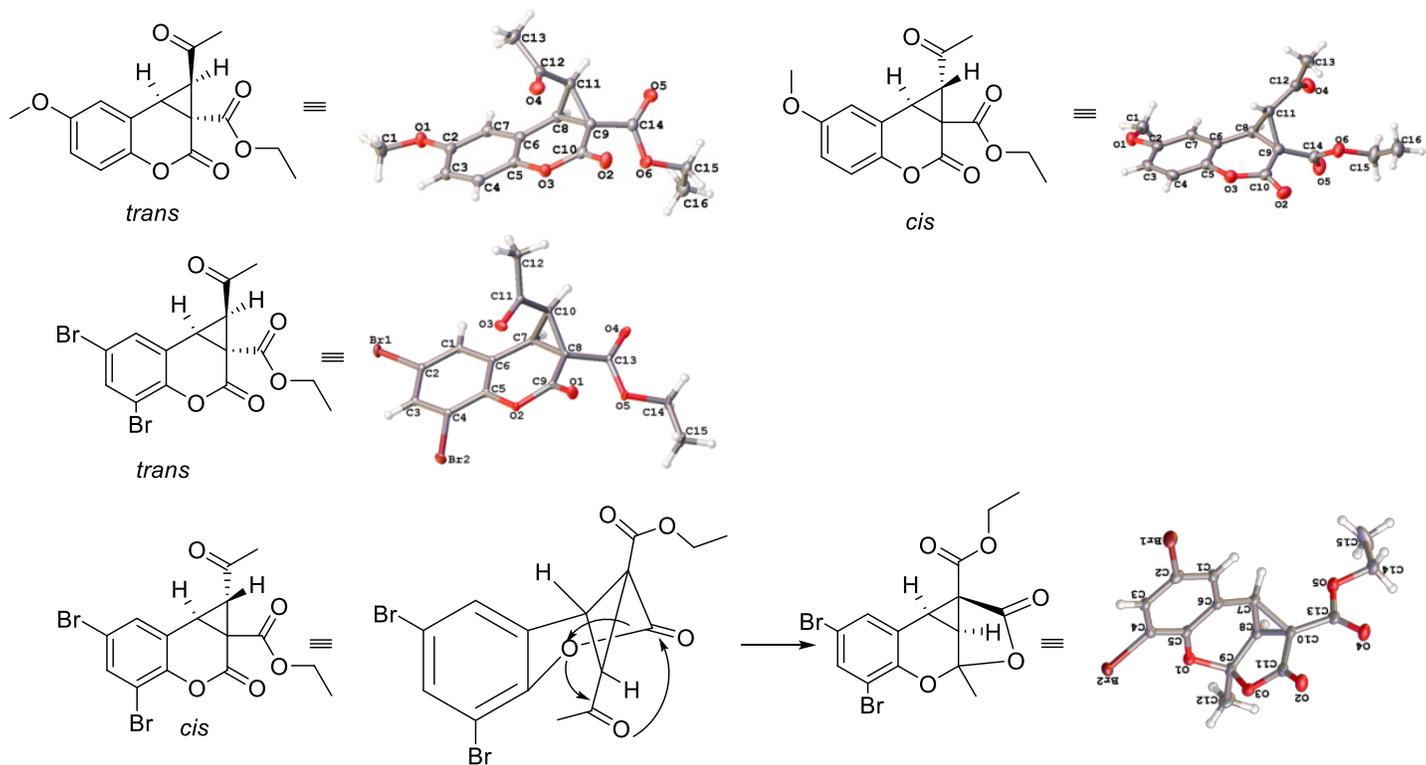
Figure 3: Possible mechanism for the formation of tricyclic ketals from the cyclopropyl caboxylate *cis* isomer.

To understand the potential antineoplastic effects of these scaffolds, representative compounds were tested for cytotoxicity in the triple negative breast cancer cell line MDA-MB-468 using an MTS assay (Figure 4). None of the compounds tested showed potent inhibition of cell proliferation at either 50 or 100 µM with the exception of 5-diethylamide **15a** which was determined to possess an IC_{50} = 21 µM.
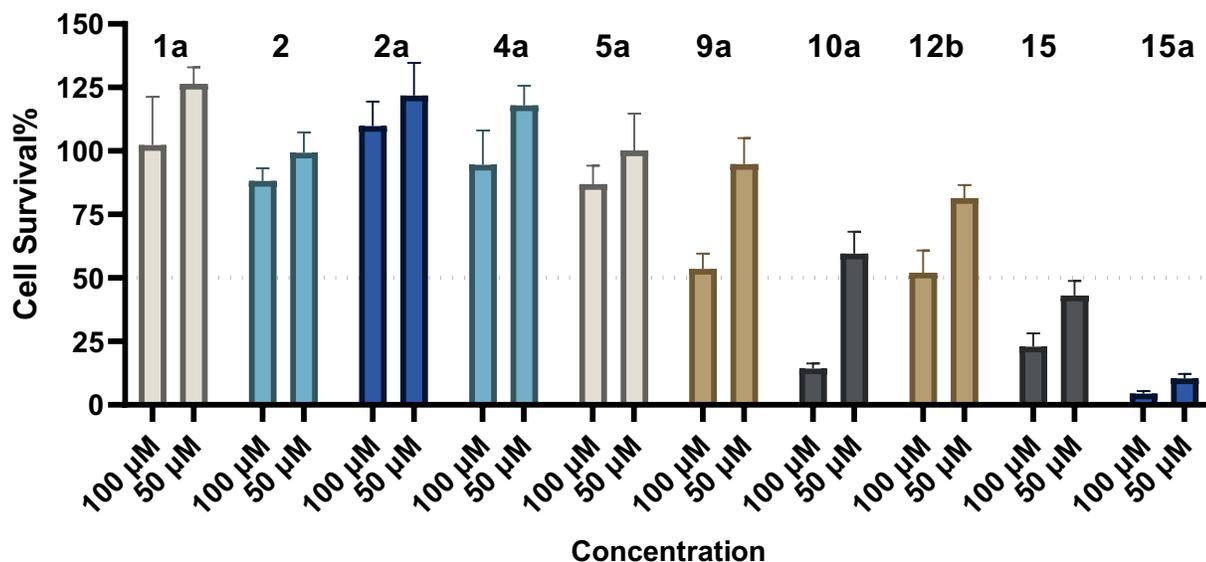
Figure 4. Effect of selected compounds at 100 and 50 µM on cell survival of MDA-MB-468 triple negative breast cancer cells after 72-hour treatment. Values are mean of n=4 experiments ±S.D.

In conclusion, we have identified a synthetically simple, single step route for the synthesis of previously unreported highly strained tricyclic ketals based around the bioactive coumarin ring structure. Substrate scope at the 4-position tolerates both electron withdrawing and donating groups, at the 6-position alkyl electron donating and withdrawing groups are tolerated. However, 6-methoxy does not form the tricyclic ketals. Similarly, substitution at the 5-position and full saturation fails to afford the tricyclic ketal product. We propose a plausible mechanism of formation involving intermolecular rearrangement of the cyclopropyl *cis* ketone. While the products are formed in low to moderate (10-40%) yield, the single step is synthetically advantageous when compared to the multistep route likely needed to access these types of complex structures. While the tricyclic ketals are not highly active antineoplastic agents, they do possess some effect suggesting that further derivatization may afford more active compounds.

Associated Content

SUPPORTING INFORMATION

Experimental procedures, characterization data, X-ray crystal data, NMR spectra (PDF).

AUTHOR INFORMATION

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ACKNOWLEDGEMENTS

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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Table of Contents Graphic

R—[benzene ring]—C(=O)OEt, X=O, with C=O (X position)
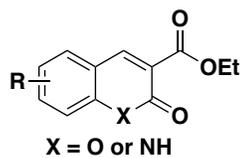
X = O or NH

→ *Chloroacetone, K₂CO₃, ACN 80 °C, Overnight*

$$X = O \text{ or NH}$$

Chloroacetone,
K$_2$CO$_3$, ACN
80 ^{o}C, Overnight
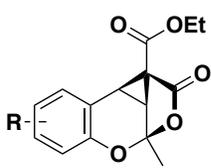
9 Examples
Sole Product with
R = 4-CH$_3$, 4-F, 4-Cl, 4-NO$_2$
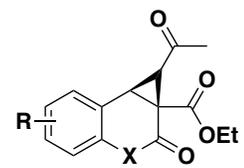
10 Examples
X = O or NH
Sole Product with
R = 5-Substitution, H, 4-OMe
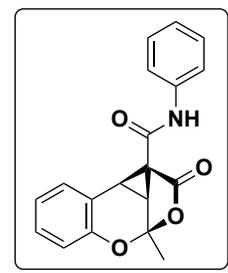
Sole Product from
Appropriatly Substituted
Coumarin