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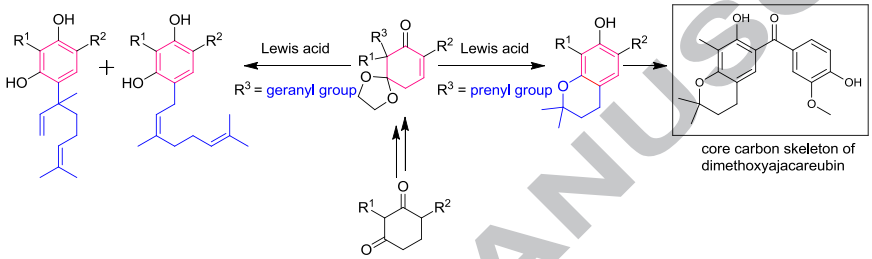

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An unexpected acid mediated rearrangement of monoethylene ketal of 2-methyl-2-(3-methylbut-2-en-1-yl)cyclohex-4-ene-1,3-diones to chromane

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ABSTRACT

We herein report a serendipitously observed acid mediated rearrangement of monoethylene ketal of 2-methyl-2-(3-methylbut-2-en-1-yl)cyclohex-4-ene-1,3-diones to Dihydrobenzopyran and demonstrated the application of this methodology in the construction of core carbon scaffolds of dimethoxyajacareubin, cariphenone-A and crotamadine.

1. Introduction

Dihydrobenzopyran and monoterpene substituted resorcinol derivatives are ubiquitous in both natural products and pharmaceutically important substances.[1] These compounds are well known to show a variety of biological activities such as anti-HIV,[2] anti-inflammatory, antimicrobial, cytotoxic,[3] tyrosinase inhibitors,[4] antioxidative,[5] plant growth inhibitory and known to control the anticholesteremic level in blood and liver.[6] Some of the biologically important natural products are shown in Figure 1.[7-12] Because of this importance, various notable approaches have been reported in the literature for their synthesis.

The dihydrobenzopyran framework has been traditionally synthesized from Claisen rearrangement of O-allylated phenol derivatives followed by acid-catalyzed cyclization.[13] Another convenient procedure is condensation of phenols with 1,3-dienes or allylic alcohols.[14] A tandem C-C and C-O bond forming reaction between various phenols and allylic alcohols mediated by recyclable mesoporous catalyst furnished dihydrobenzopyrans.[15] Several catalytic methods have been developed from phenols and allylic derivatives leading to dihydrobenzopyrans.[16] Herein, we report an unexpected acid induced tandem method for the synthesis of dihydrobenzopyrans from monoethylene ketal of 2-methyl-2-(3-methylbut-2-en-1-yl)cyclohex-4-ene-1,3-dione derivatives.

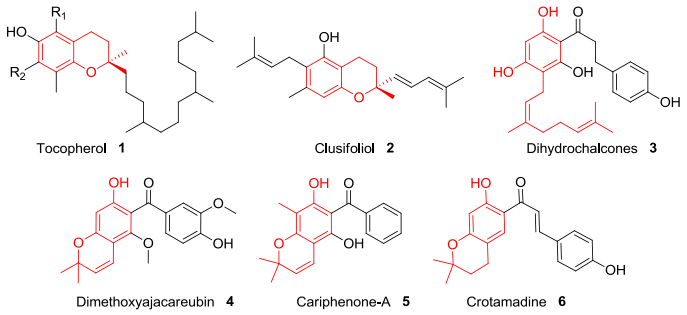

Figure 1. Naturally occurring biologically important compounds

In connection with an ongoing project, we prepared 2-prenyl substituted monoethylene ketal of 2,4-dimethylcyclohex-4-ene-1,3-dione. In our efforts to hydrolyze the monoethylene ketal moiety in **10a** under the usual hydrolytic conditions (Table 1, entry 1), we observed the formation of three chromatographically separable products. Isolation and detailed NMR spectroscopic analysis confirmed the formation of **11**, **12**, and **13** in 8%, 41% and 24% yield, respectively (73% overall). Prompted by this interesting observation, we investigated the reaction in order to optimize to get dihydrobenzopyrans as the main product. Table 1 depicts the results.

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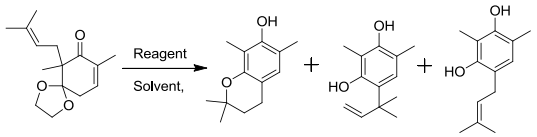
* Corresponding author. Tel.: +91 (040)23016084; e-mail: faiz@iith.ac.in (F.A. Khan).

Table 1. Optimization table for acid mediated tandem reaction for synthesis of **11**[a,b,c]



10a 11 12 13

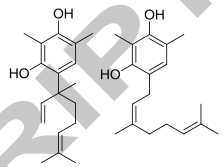
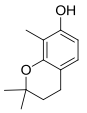
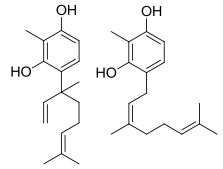
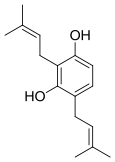
Entry	Reagent	Temp.	Solvent	11 [d] (%)	12 (%)	13 (%)
1	6N HCl	RT	Acetone:H_2O	8	41	24
2	3% HCl	0 °C to RT	Acetone:H_2O	Trace	24	12
3	6% HCl	RT	Acetonitrile	8	28	-
4	10% H_2SO_4	RT	THF	-	1 6	-
5	TFA	RT	Acetone:H_2O	Trace	24	-
6	PTSA	60 °C	THF:H_2O	8	32	12
7	PPTS	60 °C	THF:H_2O	Trace	24	-
8	$AlCl_3$	RT	Acetone:H_2O	-	21	-
9	CAN	RT	CH_3CN:H_2O	Trace	15	Trace
10	Amberlyst	72 °C	Acetone:H_2O	41	41	-
11	**$Bi(OTf)_3$**	**72 °C**	**Acetone:H_2O**	**79**	-	-
12	$Zn(OTf)_2$	72 °C	Acetone:H_2O	12	41	16
13	$La(OTf)_3$	72 °C	Acetone:H_2O	61	-	-
14	$In(OTf)_3$	72 °C	Acetone:H_2O	76	-	-
15	$InCl_3$	72 °C	Acetone:H_2O	30	24	-
16	$RuCl_3$	72 °C	Acetone:H_2O	15	25	-
17	$PdCl_2$	72 °C	Acetone:H_2O	18	-	-
18	BF_3-OEt_2	rt to 70 °C	1,4-dioxane	5	-	-
19[b]	BF_3-OEt_2	rt to 70 °C	Acetone:H_2O	-	30	40
20[c]	BF_3-OEt_2	rt to 70 °C	Acetone:H_2O	60	8	10

[a]Reaction conditions: compound **10a** (1 mmol), reagent (1.3 mmol), in solvent (1mL) at mentioned temperature. [b]BF_3-OEt_2 (1.2 eq). [c]BF_3-OEt_2 (5 eq). [d]Yields are after column chromatography.

Furthermore, various Bronsted acids such as sulfuric acid, trifluoroacetic acid, and *p*-toluenesulfonic acid (PTSA) promoted the reaction to give mainly **12**, albeit in low yield (Table 1, entries 4-9). Subsequently, we investigated Lewis acidic $InCl_3$, $RuCl_3$, and $PdCl_2$, which though yielded the desired dihydrobenzopyran along with **12** but with low efficiency (Table 1, entries 15-17). Amberlyst-15 in acetone and water at 72 °C furnished 1:1 ratio of **11** and **12** with overall 82% yield (Table 1, entry 10). Use of BF_3-OEt_2 (Table 1, entries 18-20) did not improve the reaction outcome significantly.

We then turned our attention to metal triflates due to their well known reactivity and selectivity as Lewis acids. Among the triflates that we explored, $Zn(OTf)_2$ was not selective and $La(OTf)_3$ gave a single, desired product in moderate yield (Table 1, entries 12 and 13). While $Bi(OTf)_3$ and $In(OTf)_3$ (Table 1, entries 11 and 14) afforded selectively single product with very good yield. The results depicted in Table 1 shows that $Bi(OTf)_3$ and $In(OTf)_3$ in acetone and water at 72 °C furnished with good yield (79%) and selectively single cyclized product **11**. The compound **11** was further confirmed by single crystal x-ray diffraction analysis (Figure 2).

Table 2. Lewis acid promoted rearrangement reaction on **10**[a]

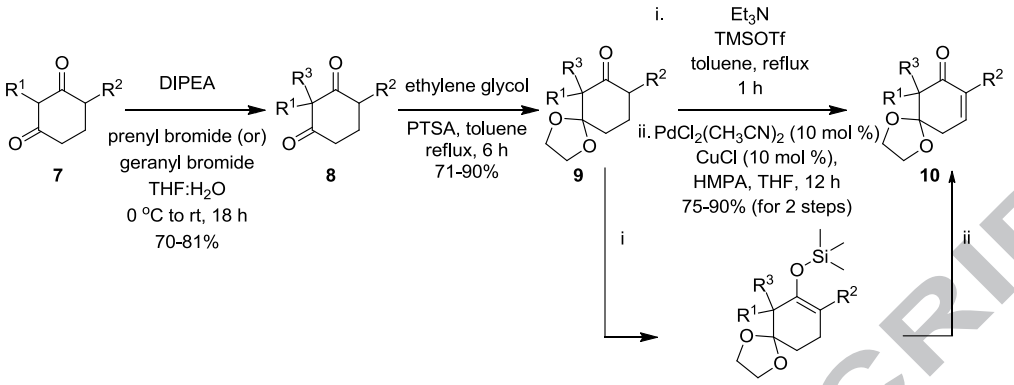
Entry	Compound	Time	Products
1[b]	**10b**	15 h	 32% **14a** 52% **14b**
2[a]	**10c**	6 h	 79% **15a**
3[b]	**10d**	15 h	 23% **16a** 60% **16b**
4[b]	**10e**	15 h	 48% **17**

[a]Reaction conditions: a) compound **10** (1 mmol), $Bi(OTf)_3$ (1.3 mmol), solvent acetone:H_2O 1 mL per 1 mmol, 72 °C, 6 h; b) compound (1 mmol), reagent (1.3 mmol), solvent acetone:H_2O 1 mL per 1 mmol, 50 °C, 15 h.

Having optimized reaction condition in hand, the scope of reaction with respect to the cyclohexenone derivatives **10a-e** was examined (Table 2). These cyclohexenone derivatives were prepared from cyclohexane-1,3-dione as shown in Scheme 1. Cyclohexane-1,3-diones **7a-c** were prenylated or geranylated according to literature procedure by using diisopropylethyl amine, at 0 °C to room temperature[17] and the resulting products (**8a-e)** were further functionalized as a monoethylene ketals **9a-e** in the presence of *p*-toluenesulfonic acid. Conversion of **9a-e** to the enones **10a-e** was accomplished via silyl enol ethers using trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of triethyl amine[18] followed by Wacker-Tsuji oxidation of the crude silyl enol ethers, filtered through a short silica gel pad, in good yield (Scheme 1).[19]

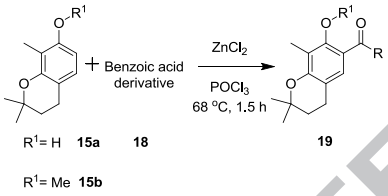
Reaction of these differently substituted cyclohexenone derivatives (**10b-e**) were examined under conditions optimized for **10a** (Table 1). The geranyl substituted cyclohexenone derivatives **10b** and **10d** gave a complex mixture under these conditions. However, when **10b**, was treated with $Bi(OTf)_3$, in acetone and water at 50 °C for 15 h, it furnished interesting structural motifs **14a**, **14b** in 32%, 52% yield respectively (84% overall, Table 2, entry 1). Similarly, **10d** gave **16a**, **16b** in 23%, 60% yield respectively (83% overall, Table 2, entry 3). Moreover, diprenyl substituted cyclohexenone derivative **10e** provided the diprenyl substituted resorcinol derivative **17** in moderate (48%) yield (Table 2, entry 4). As expected, **10c** which is similar to **10a** sans an α-methyl group, afforded corresponding chromane derivative **15a** in 79% yield (Table 2, entry 2).

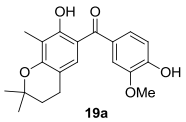
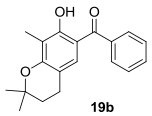
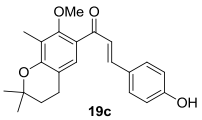
Scheme 1. Synthesis of the cyclohexenone derivatives (**10a-e**).



	R^1	R^2		R^1	R^2	R^3		R^1	R^2	R^3		R^1	R^2	R^3
7a	Me	Me	**8a**	Me	Me	prenyl	**9a**	Me	Me	prenyl	**10a**	Me	Me	prenyl
7b	Me	H	**8b**	Me	Me	geranyl	**9b**	Me	Me	geranyl	**10b**	Me	Me	geranyl
7c	H	H	**8c**	Me	H	prenyl	**9c**	Me	H	prenyl	**10c**	Me	H	prenyl
			8d	Me	H	geranyl	**9d**	Me	H	geranyl	**10d**	Me	H	geranyl
			8e	prenyl	H	prenyl	**9e**	prenyl	H	prenyl	**10e**	prenyl	H	prenyl

Scheme 2. Synthesis of natural product core structures **19**[a]

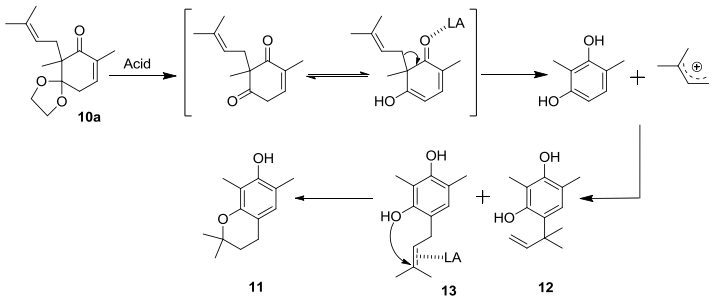


Entry	Compound	18	Yield[b]	Products
1	**15a**	Vanillic acid (**18a**)	83%	 **19a**
2	**15a**	Benzoic acid (**18b**)	65%	 **19b**
3	**15b**	4-Hydroxycinnamic acid (**18c**)	41%	 **19c**

[a]Reaction condition: Compound **15** (0.1 mmol), **18** (0.1 mmol), $ZnCl_2$ (0.3 mmol), $POCl_3$ (0.8 mL), at 68 ^{0}C. [b]Yields are after column chromatography.

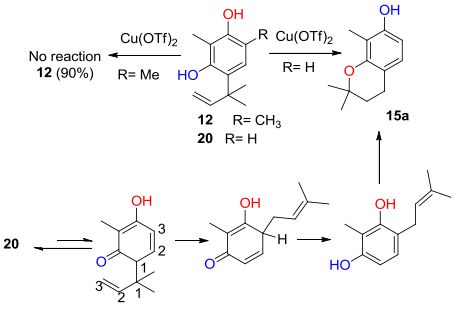
To demonstrate a synthetic application of this tandem cyclization reaction, construction of core carbon scaffolds of some related biologically active natural products such as dimethoxyajacareubin **4**, cariphenone-A **5**, crotamadine **6**, from chromane derivatives **15a-b** was achieved. Dimethoxyajacareubin **4** and cariphenone-A **5** exhibited strong antioxidative property.[10,11] Crotamadine **6** showed antifungal activity against trichophyton mentagrophytes.[12] We envisaged that a straightforward Friedel-Crafts acylation of **15a** or its methyl ether derivative **15b** using appropriately substituted benzoic or cinnamic acids **18a-c** would lead to the core skeletons. Accordingly, acylation was carried out by generating the acid chloride *in-situ* using $ZnCl_2/POCl_3$ at 68 ^{o}C for 1.5 h[20] to obtain the desired core structures **19a-c** selectively in moderate to good yield (Scheme 2).

Scheme 3. A plausible mechanism for the formation of 2,2-dimethyl-3,4-dihydrobenzopyran (**11**).



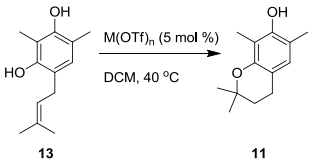
Based on isolated intermediates **12** and **13** enroute to **11**, a plausible mechanism as depicted in Scheme 3 is proposed. Hydrolysis followed by dienone-dienol tautomerization provides the driving force for the C-C bond cleavage through formation of aromatic species along with a relatively stable prenyl cation.[21] This proposal is corroborated by the isolation and characterization (^{1}H and ^{13}C NMR) of trace amount of 2,4-dimethylbenzene-1,3-diol. Recombination of 2,4-dimethylbenzene-1,3-diol and prenyl cation leads to **12** and **13**. Only **13** got converted to **11** under the reaction conditions, leaving behind unreacted **12**.

Scheme 4. Cyclization of **20** *via* [3,3]-sigmatropic rearrangement.



When the compound **12** was separately subjected to Lewis acid mediated cyclization, the cyclized product was not observed. Interestingly, when the *para*-position to the cyclizing OH group (shown in blue color) is unsubstituted (R = H, **20**) efficient cyclization occurred to give unexpected **15a** in 87% yield. This was possible through a sequence of transformations involving keto-enol tautomerization, [3,3]-sigmatropic shift and cyclization with other OH (shown in red color), leading to **15a** as outlined in Scheme 4. Having isolated **13**, it was separately subjected to cyclization using different Lewis acids (Table 3). Among them $Bi(OTf)_3$, $In(OTf)_3$, and $Cu(OTf)_2$ afforded excellent yields (Table 3, entries 3, 4, 5). Similarly, **17** was subjected to $Cu(OTf)_2$ and BF_3-OEt_2 mediated bis-cyclization to obtain **21** (Scheme 5).

Table 3. Lewis acids catalyzed cyclization reaction of **13**[a].



13 11

Entry	Catalyst[b]	Time (h)	Yield (%)
1	$Zn(OTf)_2$	4	53
2	$La(OTf)_3$	4	60
3	$Bi(OTf)_3$	2	87
4	$In(OTf)_3$	2	86
5	$Cu(OTf)_2$	4	92

[a]Reaction condition: Compound **13** (1 mmol), Catalyst[b] (0.05 mmol).

Scheme 5. BF_3-OEt_2 mediated cyclization of **17**

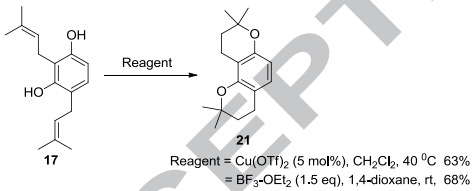
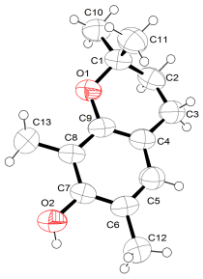


Figure 2. Solid state structure of compound **11**, as confirmed by X-ray diffraction analysis.



In conclusion, we have reported an unprecedented acid induced tandem method for the synthesis of dihydrobenzopyrans from cyclohexenone derivatives *via* C-C bond cleavage. Additionally, we prepared the core carbon scaffolds of dimethoxyajacareubin, cariphenone-A, crotamadine, from dihydrobenzopyran derivatives by Friedel-Crafts acylation with appropriately substituted benzoic or cinnamic acids. Moreover, we have detailed a mechanistic proposal supported by isolation of key resorcinol intermediate.

Acknowledgments

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Supplementary material

The detailed experimental procedures and spectroscopic data are available in supporting information at.

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22. CCDC 1557982 (**11**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Highlights:

- An acid mediated serendipitous rearrangement to dihydrobenzopyran is reported.
- A crucial C-C bond cleavage is responsible for the formation dihydrobenzopyran.
- Core scaffolds of dimethoxyajacareubin, cariphenone-A, crotamadine synthesized.