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Ring-Expansion Reactions of the Biomass Derivative Cyrene via Enamine Dihalocyclopropanation

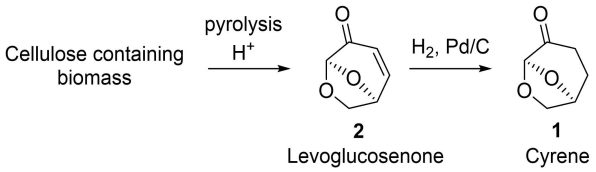
Johannes Puschnig[a] and Ben W. Greatrex*[a]

A ring-expansion process for the biomass derivative Cyrene obtained from levoglucosenone has been developed using *gem*-dihalocyclopropanes as intermediates. The process involves conversion of Cyrene to an enamine, reaction with an in situ generated dihalocarbene, and then ring-opening. Competition between endocyclic and exocyclic olefinic products was switchable using solvent and temperature, and ring-expanded alkenyl halides were obtained in 50–64% yield from Cyrene. Under extended heating, dehalogenation occurred giving homologated levoglucosenone in 25% overall yield from Cyrene in 3 steps.

Introduction

The biomass derived solvent Cyrene (**1**) is available in bulk quantities via the reduction of the cellulose pyrolysis product levoglucosenone (**2**), and it is emerging as a versatile starting material for enantioselective synthesis (Scheme 1).[1] A variety of derivatization processes have been developed giving C6 synthons from **1** following ring-opening,[2] and C5 synthons following Baeyer-Villiger reaction[3] or photochemical decarbonylation.[4] The preparation of C7 synthons is less developed, being limited to low yielding diazo insertions such as the reaction of **2** with TMS-diazomethane first investigated by Isobe's group,[5] and branched materials such as from the conjugate addition of methyl cuprate,[6] or cyclopropanation of **2** using sulfoxonium ylides.[7] A simple and high-yielding process to prepare ring-expanded products from **1** or **2** would increase the chemical space readily accessible using these biomass derived materials.

A classical approach for ring-expansion of cyclic olefins is via the ring-opening of a *gem*-dihalocyclopropane,[8] which has not been previously reported using **1**, **2** or derivatives. Following cyclopropanation, ring-opening can be promoted using a variety of bases, transition metals and heat, resulting in the formation of ring-expanded endocyclic alkenyl halides, or exocyclic haloalkenes without ring-expansion. Both *gem*-dichloro and *gem*-dibromocyclopropanes can be employed in the ring-expansion process, and the outcomes of reactions are



Scheme 1. Formation of levoglucosenone **2** and Cyrene **1**.

sensitive to the conditions used in each reaction including solvent, temperature and the nature of the reagent.[9] For example, Reissig reported yields of 40–65% in the ring-expansion of carbohydrate derived cyclic enol ethers via the *gem*-dibromocyclopropane in refluxing methanol.[10] Banwell and coworkers used the electrocyclic ring-expansion of a bicyclic *gem*-dibromocyclopropane in their total syntheses of the alkaloid (±)-haymayne,[11] and a silver promoted ring-expansion for the preparation of the hapalindole framework.[12] Hewitt and Harvey studied the ring-opening of a D-glucal derived *gem*-dibromocyclopropane and found that the exocyclic methylidene bromide was formed in protic solvents, while the ring-expanded endocyclic alkenyl bromide was preferentially formed using AgOAc in refluxing toluene.[13]

In connection with our continued interest in developing new transformations for **1** and **2**,[1a] we have investigated the ring-expansion reactions of the dioxabicyclo[3.2.1]octane ring system using *gem*-dihalocyclopropane intermediates. While both 2,3- and 3,4-olefins are accessible in the 6,8-dioxabicyclo[3.2.1]octane ring-system, the availability of enamines derived from **1** led us to investigate these readily prepared 3,4-olefinic substrates first. Cyclopropanation reactions of enamines by dihalocarbenes are known,[14] and the expected alkenyl halide ring-expansion products would be homologues of the useful 3-halolevoglucosenone that has been used in total synthesis and the preparation of pharmaceutically interesting materials.[15]

[a] *J. Puschnig, Dr. B. W. Greatrex*
Faculty of Medicine and Health
University of New England
Elm Avenue, Armidale, 2351, Australia
E-mail: ben.greatrex@une.edu.au

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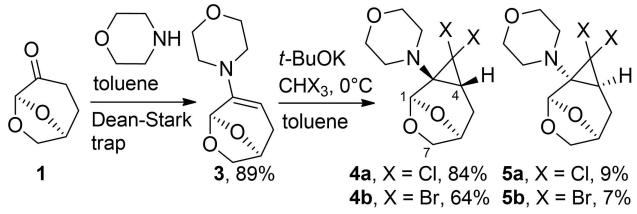
Results and Discussion

To investigate the potential ring-expansion reaction, enamine **3** was prepared from **1** in 89% yield using our previously reported approach,[16] and then the cyclopropanation to give *gem*-dichlorocyclopropanes examined (Scheme 2). The water sensitivity of enamine **3** led us to adapt the cyclopropanation conditions described by Skattebøl and Solomon.[17] Under optimized conditions, slow addition of $CHCl_3$ to a mixture of *t*-BuOK/**3** in toluene at 0 °C gave excellent yields of the cyclopropanes **4a**/**5a** as a 9:1 mixture of diastereomers (NMR of the crude reaction mixture matched the ratio of isolated products). Although readily separable by chromatography, the major isomer was most easily isolated by crystallization from the crude reaction mixture allowing for multi-gram amounts of material to be prepared. Similarly, the reaction of **3** with dibromocarbene generated from $CHBr_3$ and *t*-BuOK afforded an 85:15 ratio of diastereomers (NMR). Upon standing at ambient temperature or in solution, both the *gem*-dichlorocyclopropane mixture **4a**/**5a**, and the *gem*-dibromocyclopropane mixture **4b**/**5b** underwent ring-opening to give the exocyclic alkenylhalides **7a** or **7b**. The reaction was faster for the dibromocyclopropane mixture **4b**/**5b**, with the formation of the ring-opened products visible during NMR characterization.

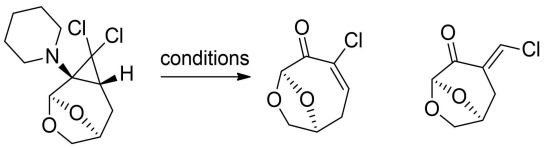


Scheme 2. Enamine formation and cyclopropanation.

Assignment of stereochemistry in the major isomer **4a** was made based on the observed interactions between the cyclopropyl H4 and the *syn*-H7 of the oxymethylene bridge in the 1D selective NOE spectrum. The reaction outcome was consistent with the facial selectivity seen in addition of nucleophiles to the carbonyl group of **1** and **2**. In the minor isomers **5a**/**5b**, the morpholine ring underwent slow rotation on the NMR timescale due to the congested environment, broadening some signals in the ^1H and ^{13}C NMR spectra.

The reaction of isolated **4a** was studied under a variety of conditions to optimize the formation of the ring-expanded product **6a**, with the outcomes followed by NMR (Table 1). Purified cyclopropane **4a** was used as a single isomer to identify favourable reaction conditions for the ring-opening, while for preparative work, mixtures of **4a**/**5a** were used following aqueous workup (entries 7 and 12). The product selectivity in the reactions were solvent dependent as previously observed in reactions of this type;[13] mixtures of the two products **6a** and **7a** were obtained in DMSO, 1,4-dioxane and toluene (entries 1,3 and 8). The exocyclic alkenyl chloride **7a** was formed with the greatest selectivity in the solvent Cyrene and was isolated in 56% yield (entry 7). In the presence of silver salts, an increase in

Table 1. Ring-opening of amino cyclopropane **4a**.



4a **6a** **7a**

Entry[a]	Solvent	Additive	*T* (°C)	T (h)	**6a**/**7a**	Yield% (conv.)[b]
1	DMSO	–	120	5	83:17	(89)
2	cycloheptane	–	120	2	–	(0)
		–		4	67:33	(100)
3	1,4-dioxane	–	120	2	52:48	(8)
		–		4	25:75	(100)
4	DMA	–	120	5	86:14	(50)
5[c]	pyridine	–	130	3	99:1	(50)
6[d]	NMP	–	120	5	–	(100)
7	Cyrene (**2**)	–	120	5	4:96	**7a** 56
8[c]	toluene	–	130	2	33:67	(33)
9	CH_3CN	$AgNO_3$	60	24	85:15	(100)
10	Acetone/H_2O	$AgClO_4$	60	24	22:78	(100)
11[f]	DMF	–	120	2	66:33	(100)
12[g]	DMF	–	140	2	95:5	**6a** 56

[a] Reactions were performed on 1 mmol **4a** at 0.2 M in a sealed tube using conventional heating unless specified. [b] % conversion was determined based on the consumption of starting material **4a** and yields calculated from enamine **3**. [c] Microwave heating was used. [d] Decomposition was observed. [e] Yield calculated from enamine **3**. [f] 0.4 M. [g] 0.08 M (atmospheric pressure, N_2), 1.0 g scale.

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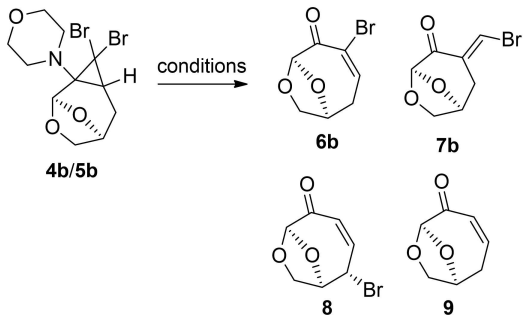
the formation of the ring-expanded product **6a** could be detected; however, the reaction mixtures were complex and so the use of silver to promote the ring-expansion was abandoned (entries 9 and 10). The formation of the ring-expanded product **6a** was selective in pyridine and wet DMF, although it was faster in DMF and **6a** could be isolated in good yield (entries 5 and 11–12). The selectivity was found to be concentration dependent, at 0.4 M there were significant amounts of the exocyclic product **7a**, while at 0.08 M the endocyclic product was obtained with only trace **7a** in the crude mixture (entries 11–12). This was attributed to the influence of the byproducts on the reaction, which was lessened at lower concentrations. The temperature and heating method also influenced the outcome for the reaction, with higher temperatures and microwave heating generally giving less complex crude reaction mixtures for the endocyclic product **6a**. The formation of gaseous decomposition products from DMF occurs at its boiling point, and so reactions of **4a** near the boiling point of DMF were performed at atmospheric pressure.

The *gem*-dibromocyclopropane mixture **4b**/**5b** was used without purification following its preparation to minimize formation of the exocyclic product **7b**, and therefore yields in the cyclopropane ring-opening were calculated from the starting enamine **3** (Table 2). Similar results to the dichlorocyclopropane **4a** were obtained, and exocyclic alkenyl bromide **7b** was isolated in 28% yield by heating crude **4b**/**5b** in toluene (entry 2). Stereochemical assignment of the bromide **7b** was confirmed by conversion to the known styrene derivative via Suzuki reaction with phenyl boronic acid.[3d] Ring-expanded ketone **6b** was formed as the major product in wet DMF at 100 °C and isolated in 72% yield. A high yield of **6b** required that the reaction was immediately cooled once the starting material **4b** was consumed. When left for longer times at elevated temperature, the endocyclic product underwent further reaction and new products were observed, initially the rearranged allylic bromide **8**, followed by the formation of the dehalogenated product **9** (homolevoglucosenone) (entries 3 and 4). Allylic bromide **8** was transient in mixtures meaning it was difficult to obtain high yields and both **6b** and **9** were always present with **8**. When the mixture of **4b**/**5b** was heated for 3.3 hours, allylic bromide **8** was totally consumed and the dehalogenated material **9** could be isolated by chromatography.

Table 2. Ring-opening of amino cyclopropane **4a**.

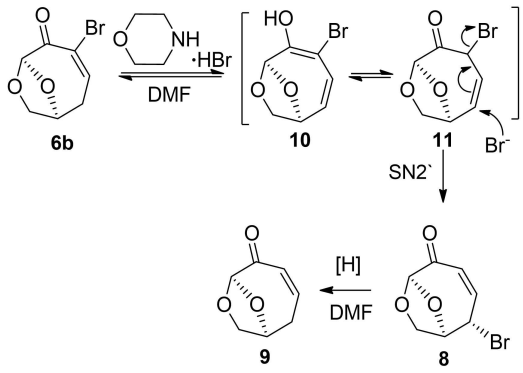


Entry[a]	Solvent	*T* (°C)	Time	Yield%[b]			
				6b	**7b**	**8**	**9**
1[c]	DMF	100	1.5 h	72	–	–	–
2	toluene	130	2 h	–	28	–	–
3	DMF	150	1 h	–	–	17	–
4	DMF	160	3.3 h	–	–	–	28
5[c]	DMF	150	3 h	–	–	–	20

[a] Reactions were performed in a sealed tube with microwave heating at 0.2 M with internal pressure monitoring. [b] Yields refer to the amount of enamine **3** assuming quantitative conversion to **4b**/**5b** and represent conditions to maximize the amount of each species. [c] Conventional heating.

Bromide **8** had a molecular ion at *m/z* 218.9649 consistent with a rearrangement of **6b**. Resonances for an α,β-unsaturated ketone were present in the ^{1}H NMR spectrum of **8** at δ 6.45 and 5.96 ppm, and in the ^{13}C NMR spectrum at δ 194.1, 137.3 and 128.2 ppm. The bromo substituent was established as *exo* on the basis of a NOE interaction between the attached methine proton at δ 4.73 and the *syn* proton on the oxymethylene bridge at δ 3.87.

The formation of the rearranged product **8** and dehalogenated **9** were surprising, and so the mechanism was probed following the isolation of the intermediates. Heating alkenyl bromide **6b** in DMF gave an unidentified mixture; however, heating with morpholine hydrobromide in DMF generated **8** and **9**. When the endocyclic product **8** was heated in DMF in the presence of morpholine hydrobromide, the formation of **9** was also observed, demonstrating that the three materials **6b**, **8** and **9** are part of the same manifold and **9** is not formed from some alternate process starting with **6b**. These results allowed the mechanism shown in Scheme 3 to be proposed. Functionalization of the δ-carbon could occur via a dienolate to give enol **10**, then a tautomerization to allylic bromide **11**, followed by an S_N2' reaction giving intermediate **8**. An S_N2' mechanism for the formation of **8** is supported by the observation that morpholine hydrobromide was required for the formation of **8** from **6b** to catalyze the enolization. The reductive dehalogenation was only observed in DMF, and the exact nature of the reducing species remains unclear. Partali and coworkers have previously demonstrated via ESR that the reaction of potassium hydroxide and DMF produces carbon centered radicals at room temperature.[18]



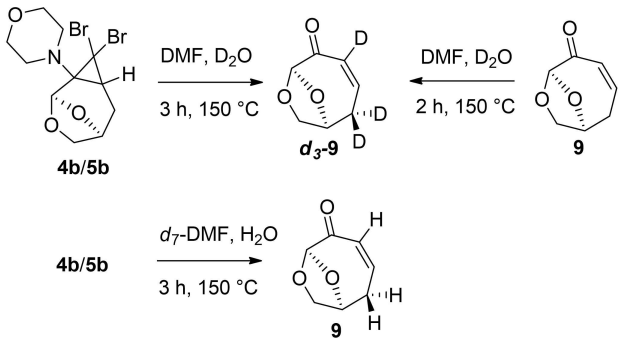
Scheme 3. Plausible mechanism for the formation of **9** from **6b**.

These radicals have since been exploited in metal-free coupling and reduction reactions of aryl iodides.[19] The formation of reducing species from DMF at elevated temperature has also been demonstrated.[20]

To examine the viability of the processes shown in Scheme 3, a series of deuterium incorporation experiments were performed. Including D_2O in the rearrangement of **4b/5b** gave the dehalogenated product **9** with deuterium incorporation at H4 (25%) and at H2/H2′ (10%) (Scheme 4). To test whether the deuterium was incorporated during the reaction or from the product, the product **9** was also heated at 150 °C with D_2O in DMF. Under these conditions, the olefinic H4 exchanged with deuterium giving 30% incorporation, and one of the methylenes (H2) gave 5% incorporation of deuterium. When morpholine was included to catalyze the reaction, the deuterium exchange was complete after 2 hours. Deuterium incorporation on the olefin at C3 presumably occurred via a conjugate addition with D_2O or morpholine, deuteration of the enolate, followed by elimination, while the deuteration of the methylene at C2 proceeds through extended enol **10**. The higher deuterium incorporation at H4 indicates that a reversible conjugate addition of water or DMF occurs more readily than the remote enolization. No deuterium incorporation was observed when d_7-DMF was used as the solvent. It was unclear at what point in the sequence deuterium was incorporated when D_2O was included in the rearrangement of **4b/5b** to **9**, although these observations demonstrate that formation of extended enols such as **10** in the 7,9-dioxabicyclo[4.3.1]nonan-5-one ring system is a facile process. These deuterium incorporation experiments support the possibility of an S_N2' mechanism leading to **8** through enol **10** and allylic bromide **11** (Scheme 3).

Conclusions

This work has demonstrated a short and high yielding approach for the ring-expansion of the biomass derived platform molecule Cyrene via amino-substituted *gem*-dihalocyclopropanes. Solvent effects allow for switching the selectivity between the exocyclic alkenyl halide and ring-expanded products. The reaction sequence gives access to the ring-expanded alkenyl bromide or chloride, both of which have potential for further reactions via transition metal mediated coupling processes. The dehalogenation provides **9**, a compound we term homolevoglucosenone in 25% over three steps, which we envisage will be a useful material for enantioselective synthesis.



Scheme 4. Deuterium incorporation reactions starting with **4b/5b**.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are openly available in Mendeley Data at https://doi.org/10.17632/bj2vwsds2z.1.

Keywords: ring expansion · green chemistry · oxygen heterocycles · levoglucosenone · cyrene

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