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Synthesis of 1,7-epoxycyclononanes and 1,8-epoxycyclodecanes by β-fragmentation reactions using LTA and I_2

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Abstract—The reaction of derivatives on C3 of 6-hydroxy-2,7-dimethyl-11-oxatricyclo[6.2.1.$0^{2,6}$]undecan-4-one with lead tetraacetate and iodine, gave, in a good yield, 1,7-epoxycyclononanes. These compounds are the result of a β-fragmentation at the level of C2–C6 respect to the tertiary hydroxyl group on C6, with an unexpected contraction from a ten to a nine-membered ring system, via a radical addition to the carbonyl group on C4. The treatment of precursors (non-functionalized on C3) with LTA and iodine produced again a β-fragmentation without any structural rearrangement, affording a typical 1,8-epoxycyclodecane system. The transformation of the carbonyl group on C4 into acetate avoided radical additions and rearrangements affording, in high yield, the corresponding cyclodecanes. By this methodology, either 1,7-epoxy-cyclononane or 1,8-epoxycyclodecane could be synthesized, in a good yield, from the same versatile precursor.

Medium-sized cyclic molecules, in particular, the 1,8-epoxycyclodecane systems are structural units which are present in a wide range of oxygen-bridged terpenoids. Some of these natural products present interesting pharmacological activities like the well-known eleutherobin[1] (Fig. 1), which possesses antitumour properties closely related to those of taxol. Bioactive products containing the 1,8-epoxycyclodecane framework have led to a growing interest among the synthetic chemists and different total syntheses of them have been described.[2]

The 1,7-epoxycyclononane system, however, is considerably less widespread than its homologue among natural products, nevertheless a few examples appear in the literature.[3] In this context, only a reduced number of protocols,[4–7] restricted to a few specific products, have been developed for the synthesis of these macrocyclic subunits with potential biological interest.

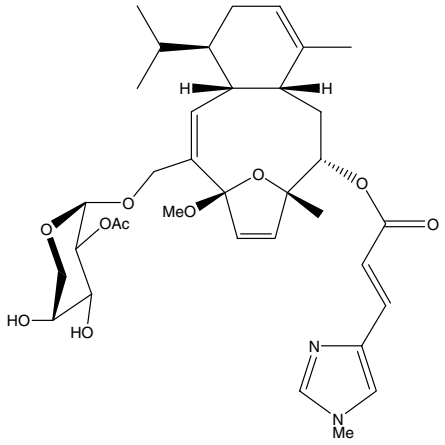

Figure 1. Eleutherobin structure.

In this letter a new way to synthesize 1,7-epoxycyclononane systems is reported, including interesting structural and mechanistic aspects involving the contraction of a 10-membered ring into a nine-membered ring, via an intramolecular radical addition to a carbonyl group. Also, it is reported how the modification of the substrate by the carbonyl group transformation into a protected alcohol (in order to avoid radical additions and rear-

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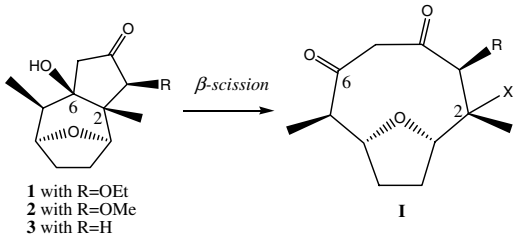
rangements) afforded, in high yield, the corresponding 1,8-epoxycyclodecanes. By this methodology, either 1,7-epoxycyclononane or 1,8-epoxycyclodecane could be synthesized in a good yield from a versatile precursor.

The initial objective of the present synthetic work was to generate a selected library of potential antitumour compounds, analogues of eleutherobin, containing the 1,8-epoxycyclodecane framework in order to carry out structure–activity relationship studies.

From the retrosynthetic point of view, to get the target molecule **I** versatile precursors (**1**, **2** and/or **3**) were considered. These precursors were previously synthesized, in an enantiomerically pure form, by the authors.[8,9] In a first approach, these oxatricyclic starting materials **1**–**3** could be transformed into the desired cyclodecanes by a β-fragmentation of the C2–C6 bond (Scheme 1).

A number of references could be found in the literature[10–15] describing the desired C–C fragmentation by using several oxidizing agents such as cerium ammonium nitrate (CAN), lead tetraacetate (LTA) or by the use of the hypoiodite reaction[16] conditions in the presence of the tandem reagents: HgO/I_2 and/or LTA/I_2 among others.[16a,c] All the aforementioned reagents were evaluated under several reaction conditions and the system LTA/I_2 showed to be the most efficient one for our substrates, resulting in shorter reaction times and higher yields than for the other alternatives. Thus, substrates **1** and/or **2** were dissolved in anhydrous benzene and reacted with LTA and iodine in a 3:1 molar ratio, submitting the mixture to irradiation with two 100 W lamps. After work-up, the crude mixture was fractioned by column chromatography on silica gel and four compounds were separated, which were physically and spectroscopically characterized (^1H NMR, ^{13}C NMR, DEPT, COSY, HETCOR , IR, MS and EA). From substrate **1** two pairs of reaction products were isolated and identified: the iodinated compounds **1a** and **1b**, epimers to each other, and the non-iodinated products **1c** and **1d**, which are also epimers to each other at the asymmetric acetalic carbon. In a similar way, from substrate **2** four compounds were isolated: the iodinated epimers **2a** and **2b** and the non-halogenated epimers **2c** and **2d** (Scheme 2). The stereochemistry of these compounds was established by a careful correlation of NMR data and it was confirmed in the case of **1a** by the X-ray diffraction analysis on single crystals.

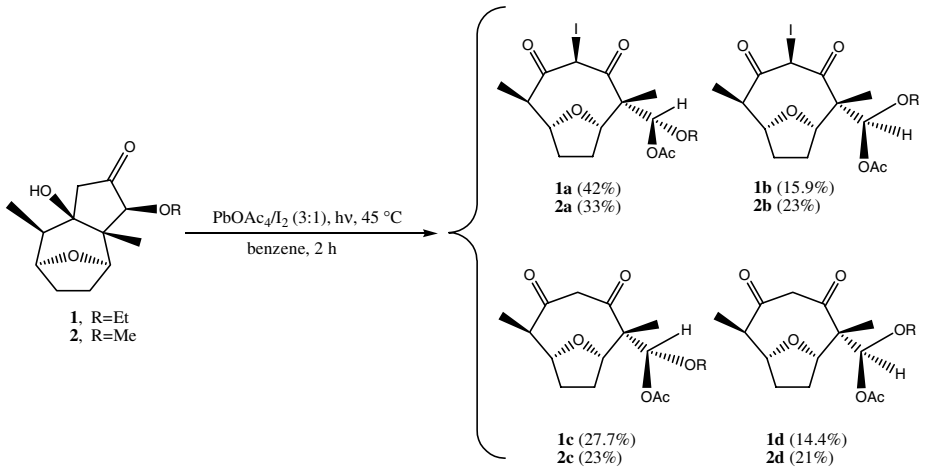


Scheme 1. Formal β-scission of oxatricyclic precursors **1**–**3** to generate cyclodecanes.

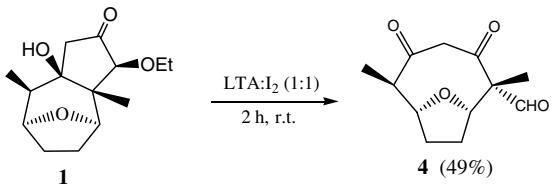
Products **1a**–**d** and **2a**–**d** are stable under standard operating conditions and they can be handled in the open air and submitted to column chromatography without decomposition.

When substrate **1** was reacted with LTA/I_2 under milder conditions (using a 1:1:1 molar ratio of substrate: $LTA:I_2$) at room temperature (without 100 W lamp irradiation) for 2 h, the non-iodinated aldehyde **4** was isolated as a major product, in a 49% yield (Scheme 3). Compound **4** was characterized and its structure confirmed by X-ray analysis.

On the basis of these results, the reactivity of **3** was studied by performing different trials in which the following experimental conditions were modified: reaction temperature and time, use or not of two 100 W lamps (to induce radical formation) and the number of equivalents of LTA and iodine (Table 1). The first three trials were performed using low amounts of **3** (100 mg), however, trials 4 and 5 were made on a higher scale (200 mg) in order to know the influence of the scale-up in the outcome and yield of the reaction.



Scheme 2. β-Fragmentation products obtained from **1** and/or **2**.



Scheme 3. Formation of aldehyde **4** in the reaction of **1** with LTA/I_2 under mild reaction conditions.

The results and conditions of the reactions are quoted in Table 1.

The first interesting observation from Table 1 was that in all products **5a**,**b**,**a**′,**b**′ a 1,8-epoxycyclodecane skeleton was present (Scheme 4). On the other hand, the use of high molar ratios of LTA gave low yields of the desired products. Moreover, in order to get a good selectivity it was preferable to work under milder conditions, even though the conversion was not complete, because the starting material could be recovered (Table 1, trials 3–5). Increasing the scale of work slightly increased the yield, and shorter reaction times propitiated the formation of a higher proportion of epimer **5a** versus **5b** (Table 1, entries 3, 4 vs 1, 2 and 5). Only in trial 1, performed at high molar ratio of oxidizing agent, with heating and simultaneous irradiation with two 100 W lamps, it was possible to observe the formation of a pair of epimeric acetoxy derivatives **5a**′,**b**′ (Scheme 4) together with the analogous iodinated cyclodecane products **5a**,**b**. The skeleton and stereochemistry of all these compounds were established by a careful study and a correlation of the spectroscopic data (^{1}H NMR, ^{13}C NMR, DEPT, COSY, HETCOR, IR and MS). These structures present a characteristic diagnostic signal in ^{1}H NMR: one singlet at 1.99 ppm (in **5a**) or at 2.34 ppm (in **5b**), which integrates for three hydrogens (corresponding to the methyl group on C7). The fact that this singlet undergoes such a high deshielding effect can only be explained by the presence of an iodine atom in the C7 position.

The above-mentioned results could be interpreted by the hypoiodite reaction[16] mechanism in which the free tertiary alcohol of **3** reacts with an iodonium cation, generated in situ from LTA and iodine, and forms the corresponding hypoiodite **A** (Scheme 5). Subsequently, with the help of light and/or heating, the molecule undergoes a homolytic breakdown of the O–I bond, forming an alkoxy radical and releasing an iodine atom. This alkoxy radical undergoes a β-fragmentation[12] by a homolytic scission of the C_2–C_6 bond and a new carbon radical on position C7 of intermediate **C** is formed. This last secondary radical reacts, by a radicalary termination reaction, with the previously released iodine radical to generate the neutral epimeric compounds **5a** and **5b** (Scheme 5, path b), in a stereoselective manner, depending on the reaction time (Table 1). In a similar way (path b), the acetoxy derivatives **5a**′ and **5b**′ could be formed (Table 1, entry 1).

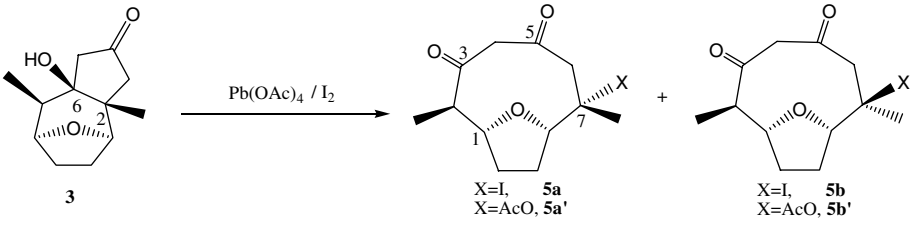
When observing these results, one question could be arisen: why such a difference in reactivity between substrates **1**, **2** and **3**? The only structural difference between these compounds is the absence of the alkoxy substituent in compound **3**.

All the obtained results clearly show that precursors **1** and **2**, when reacted with LTA and I_2 in a 3:1 ratio or in a 1:1 ratio, undergo a β-fragmentation with a structural rearrangement to a nine membered ring system. On the contrary, when compound **3** was treated with LTA and I_2 in a 1:1 or 3:1 molar ratio, the expected 10-membered ring was generated in a good yield. To explain the ring contraction undergone by the substrates **1**

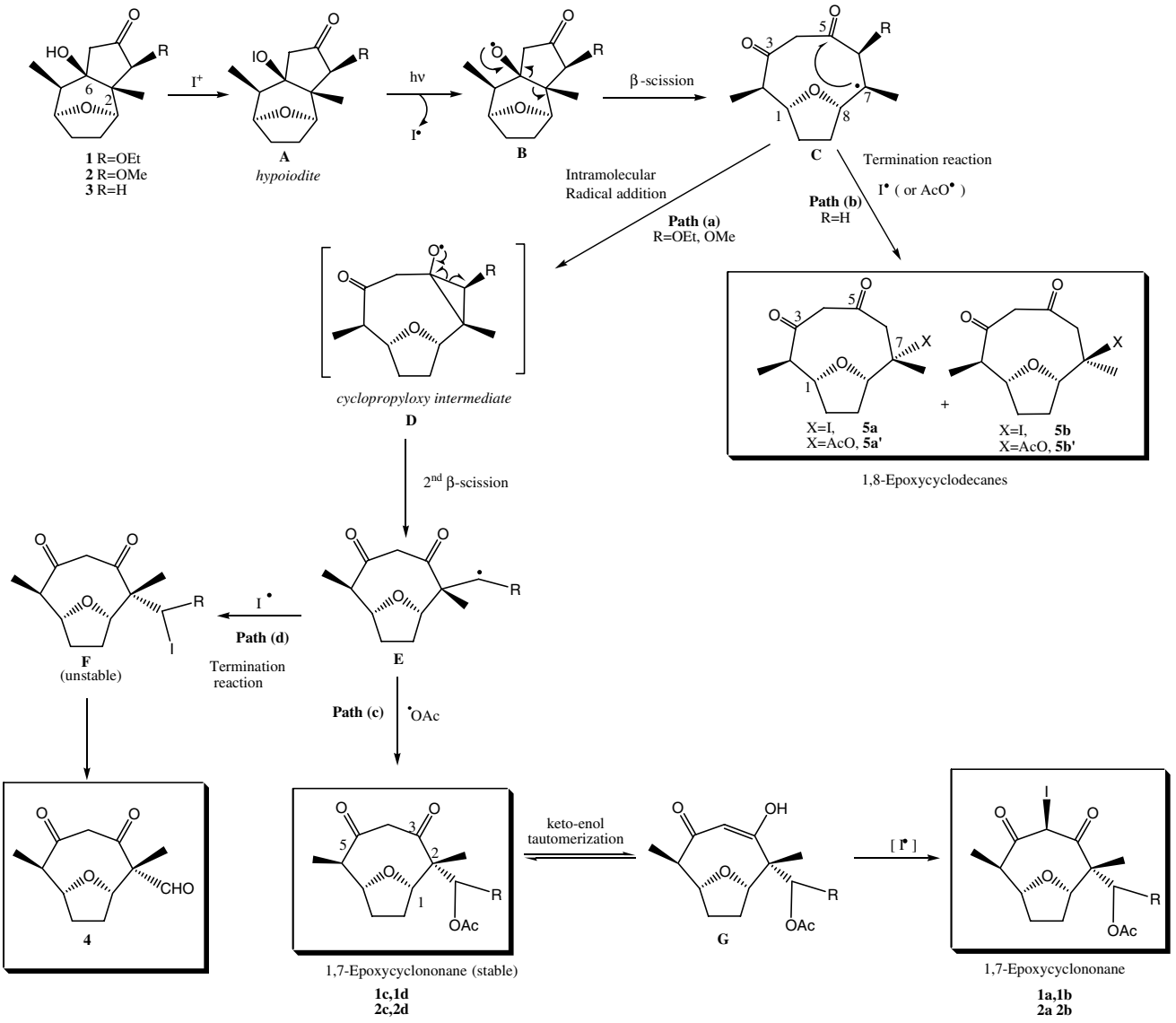
Table 1. Reactivity of precursor **3** under different reaction conditions

Trial	Molar ratio substrate:LTA:I_2	Scale (mg)	hν[a]	*T* (°C)	*t* (h)	Y[b] (%)	C[c] (%)	Product ratio I: acetate derivatives **5a**,**b**:**5a**′,**b**′	Product ratio **5a**:**5b**
1	1:3:1	100	Yes	45	1	41	100	43:57	1:1
2	1:3:1	100	No	20	1	50	84	100:0	1:1
3	1:1:1	100	No	20	0.5	67	82	100:0	7:3
4	1:1:1	200	No	20	0.5	76	82	100:0	7:3
5	1:1:1	200	No	20	1	68	83	100:0	45:55

[a] Irradiation with two 100 W lamps.
[b] Yield.
[c] Conversion.



Scheme 4. Reaction of non-alkoxylated substrate **3** with LTA/I_2 to afford 1,8-epoxycyclodecanes **5**.

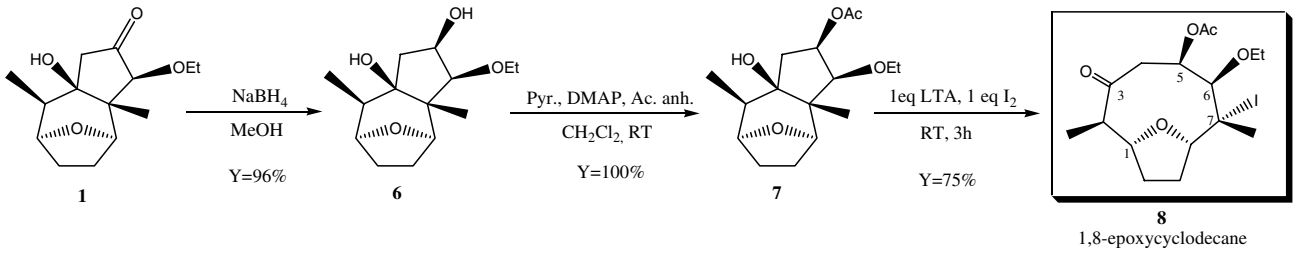


Scheme 5. Proposal of the formation mechanism of 1,7-epoxycyclononanes and 1,8-epoxycyclodecanes from substrates **1**–**3**.

and **2**, it seems reasonable to suggest that the formation of the free radical **C** on C7 should be followed by its attack and addition to the ketone carbonyl at C5 (Scheme 5, path a).[17] The intermediate cyclopropyloxy free radical **D** then undergoes a β-scission to afford the cyclononane ring. The new secondary radical **E** (Scheme 5) could subsequently react with an acetoxyl free radical, generated from the photodecomposition of LTA, following path (c) to give the non-iodinated diketone (**1c**, **1d**, **2c**, **2d**). The iodo derivatives (**1a**, **1b**, **2a**, **2b**) probably form via a keto-enol tautomerization and the subsequent attack of iodine to the double bond of the corresponding enol **G**. This unusual kind of structural rearrangement involving the contraction from a ten- to a nine-membered ring has been reported only in two previous examples.[18]

In this reaction pathway, the alkoxy group could play several roles:[17,18c] it facilitates the radical addition to the ketone on C4, by activating the carbonyl group, and it assists in the ring opening of the intermediate cyclopropyloxy free radical by stabilizing the resulting free radical in E (Scheme 5). These could be the reasons that justify the different behaviour of substrate **3** (vs **1** and/or **2**) in front of LTA/I_2. These aspects are now being studied in our laboratory, by introducing substituents different from OEt or OMe in alpha with respect to the ketone in precursors **1** or **2**. The results when available will be published at due course.

To demonstrate such a mechanism, the ketone group at C4 in **1** was reduced in order to avoid an intramolecular free radical addition to that position. The ketone group was reduced by $NaBH_4$ in a high yield and in a diastereospecific manner (Scheme 6) and the resulting alcohol **6** was quantitatively acetylated to obtain compound **7**. The obtained acetylated product was reacted with LTA/I_2 (molar ratio 1:1:1, at room temperature for 3 h) obtaining cyclodecane **8** in a 75% yield and complete stereoselectivity regarding the insertion of iodine atom into the newly formed stereocenter at C7 (no other stereoisomers of **8** were detected). The stereoselectivity



Scheme 6. Reduction, acetylation and β-fragmentation of **1** to generate **8**.

in the formation of **8** could be explained by the high steric demand of iodine atom which in the epimer of **8** would strongly interact with hydrogen atoms on C9 and C10 and with the ethoxy group on C6. The stereochemistry of **8** has been confirmed by X-ray diffraction analysis.

It is worth noting that when working under mild reaction conditions (rt and no irradiation with artificial light), no matter of the molar ratio of substrate/LTA/I_2 (1:1:1 or 1:3:1), the formation of iodinated products was preferred to the formation of the acetoxylated ones. Thus, when substrates **1** and/or **2** were reacted under these mild conditions aldehyde **4** was isolated as the major product due to the reaction mechanism following the proposed path (d) instead of path (c) (Scheme 5). The aldehyde formation could be understood by considering the formation of an unstable iodinated intermediate **F** (instead of the stable acetals **1c**,**d** or **2c**,**d**) which could be easily hydrolyzed,[19] during work-up, to afford the formyl group. The reason for the preference of path (d) over the path (c) could be justified by the low concentration of acetoxyl free radicals present in the reaction medium due to $Pb(OAc)_4$ does not decompose into $Pb(OAc)_2$ and $AcO^{\cdot}$ under thermal and/or photolytic conditions, processes that do not take place under mild reaction conditions. For this same reason, when**3** was reacted with LTA/I_2 under mild conditions (Table 1), only iodinated products **5a**,**b** were isolated. Moreover, when compound **7** was submitted to the before-mentioned reaction conditions, the iodinated product **8** was formed as the unique product and no acetoxy derivatives were detected in the reaction crude.

To conclude, a versatile methodology has been developed to synthesize either 1,7-epoxycyclononanes or 1,8-epoxycyclodecanes with a high level of functionalization, starting from the same tricyclic precursor, which could be available, in a good yield and in enantiomerically pure form, by a procedure previously described by the authors.[8,9] Also, a possible mechanism to explain the ring contraction has been proposed, demonstrating the implication of a free radical addition to the ketone on C5 of intermediate **C** by reducing the corresponding carbonyl group in substrate **1** and protecting the resultant alcohol.

Herein all mentioned products have been purified and physically and spectroscopically characterized. The stereochemistry has been assigned by 1D and 2D NMR correlation experiments and confirmed by X-ray diffraction analysis on single crystals in the case of compounds **1**, **1a**, **4** and **8**.

Acknowledgements

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