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A Photocycloaddition/Fragmentation Approach toward the 3,12-Dioxatricyclo[8.2.1.0^{6,13}]tridecane Skeleton of Terpenoid Natural Products

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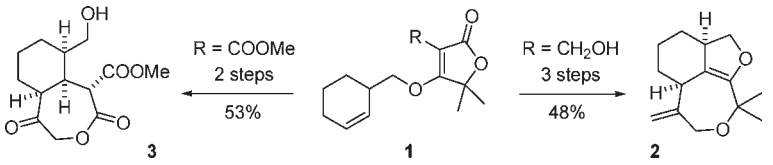
ABSTRACT



Starting from tetronate 1 (R = CH_2OH), a short photochemical access to the 3,12-dioxatricyclo[8.2.1.0^{6,13}]tridecane-skeleton 2 of briarellin and asbestinin diterpenes has been explored. In the course of these studies, a number of surprising observations were made. For example, a two-step reaction pathway to the bicyclic ketolactone 3 was discovered, which is based on tetronate 1 (R = COOMe).

One of the big advantages of synthetic photochemical methods is their potential to generate strained ring systems in good yields and with high stereoselectivity.[1] The energy of the activation by light is, at least partially, conserved in the ring strain of the product molecules. Many applications of photochemical procedures in natural product synthesis[2] make elegant use of this feature, either by forming directly complex natural products with a strained scaffold or by accessing natural products through selective cyclobutane cleavage reactions of a strained skeleton. These reactions are particularly useful for the formation of seven- to twelve-membered rings. The prototypical example for a [2 + 2]-photocycloaddition/fragmentation sequence is the widely used de Mayo reaction,[3] in which a [2 + 2]-photocycloaddition is combined with a retro-aldol reaction. Free radical fragmentations represent a second class of important cleavage reactions, which enjoy great popularity in synthesis.[4]

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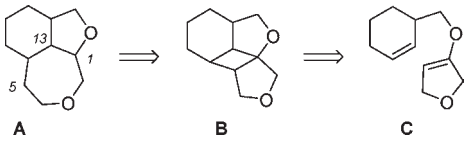
In the context of a project that is directed toward the synthesis of diterpenoid natural products of the briarellin and asbestinin family,[5] we wondered if the central core **A** of these compounds may be formed via intermediate **B**, which in turn could be obtained by an intramolecular [2 + 2]-photocycloaddition (Scheme 1).[6] This letter reveals preliminary results of our studies, in the course of which two unexpected ionic ring expansion reactions of cyclobutanes[7] were discovered.

Scheme 1. Retrosynthetic Consideration for the Synthesis of Dioxatricyclo[8.2.1.0^{6,13}]tridecane Scaffold **A** via Cyclobutane **B**



Tetronates appeared to be particularly useful synthetic equivalents for the precursor **C** depicted in Scheme 1. They have been described as versatile, robust substrates for [2 + 2]-photocycloaddition reactions,[8] and they have previously been applied in natural product synthesis.[9] As the skeleton **A** of the briarellins and asbestinins exhibits a methyl group at position C5, it appeared sensible to introduce this C_1-unit as part of the tetronate. Thus, we focused our studies on [2 + 2]-photocycloadditions of α-substituted tetronates. Apart from that, a disubstituted γ-position was to be included in the model substrate in order to mimic the quarternary carbon atom at the respective position of the natural products. The synthesis of the [2 + 2]-photocycloaddition substrates (cf. Supporting Information) commenced with the known primary alcohol **1**, which is accessible from cyclohexene in one step (Figure 1).[10]

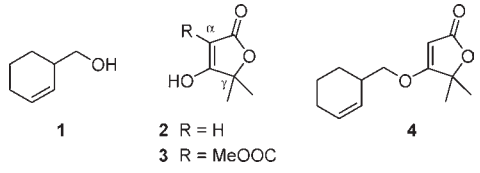
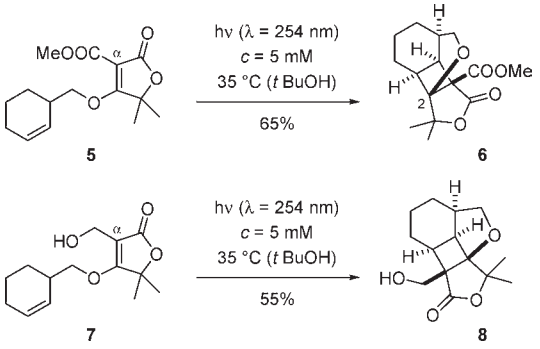


Figure 1. Structures of starting materials **1**−**4**.

Tetronic acid **3**[11] and the parent compound **2**[12] are literature known and can be prepared from α-hydroxy-*iso*-butyric acid. The coupling of the tetronic acids with alcohol **1** was accomplished by a Mitsunobu reaction.[13] Starting from tetronic acid **2**, product **4** was obtained in 93% yield, and starting from tetronic acid **3**, substrate **5** was formed (90% yield), which features a methoxycarbonyl group in the α-position (Scheme 2). In the intramolecular [2 + 2]-photocycloaddition of the latter compound, the crossed product **6** was generated exclusively. This violation of the 'rule of five'[14,15] (preference of five-membered ring formation during the [2 + 2]-photocycloaddition) is remarkable, in particular because the formal reduction product of the ester **5**, the α-tetronate **7**, which was formed by hydroxymethylation[16] of tetronate **4**, gave exclusively the straight photocycloaddition product **8** (Scheme 2).

Scheme 2. [2 + 2]-Photocycloaddition of Tetronate **5** To Afford Crossed Product **6** and of Tetronate **7** To Afford Straight Product **8**



Studies to shed light on the unexpected regioselectivity in the reaction **5** → **6** are in progress. The trivial explanation that the high stability of the radical at the former α-position of the tetronate (stabilized by two carbonyl groups) is responsible for an initial formation of a six-membered ring cannot hold true because the simple but-3-

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enyl-substituted analogue of **5** afforded predominantly (regioisomeric ratio r.r. = 90/10) the straight product. The assignment of the regiosomers is based on extensive one- and two-dimensional NMR experiments (cf. Supporting Information). Furthermore, the structure of the crossed photoproduct **6** was unambiguously proven by a crystal structure analysis (Figure 2, see Supporting Information, CCDC 813562).

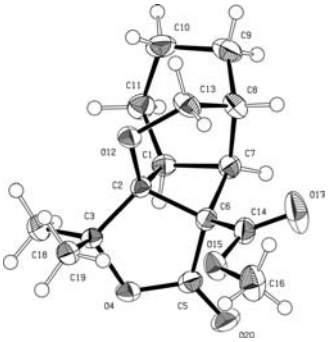
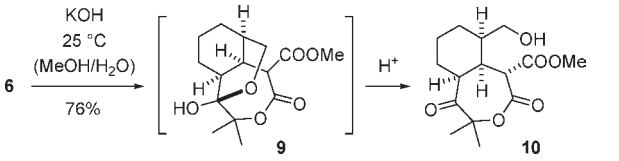


Figure 2. Proof of structure and relative configuration of the crossed product **6** by crystal structure analysis.

Both products **6** and **8** were formed as single diastereoisomers; i.e. all four newly formed stereogenic centers were generated with perfect control of the facial and simple diastereoselectivity. Diethylether and *tert*-butanol were found to be the preferred solvents for the [2 + 2]-photocycloaddition of **5** and **7**. It is noteworthy that the reaction of the methoxycarbonyl-substituted tetronate **5** was considerably faster than the reaction of **7**. While the photocycloaddition of the former substrate was complete after 30 min, an irradiation time of 8 h was required for full conversion of the latter tetronate. The rate increase is attributed to the greater absorption of tetronate **5** at the irradiation wavelength $\lambda = 254$ nm.

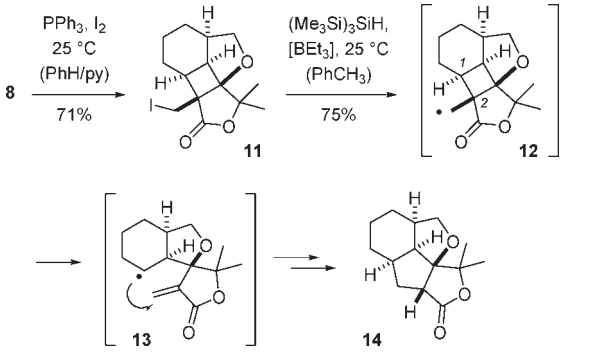
Another proof for the structure of the crossed product **6** is based on an enormously facile ionic ring expansion, which took place upon treatment with KOH in aqueous MeOH (Scheme 3). The seven-membered ketolactone **10** was formed in very good yield via the tricyclic hemiacetal **9** as an intermediate. Apparently, the ring strain facilitates a nucleophilic substitution of a malonate unit by a hydroxide ion at position C2 of the tetracyclic substrate **6** under these conditions.[17] The lability of bond C2−C6 of **6** is already apparent from its unusually long bond length of 1.575(2) Å as determined by X-ray crystallography (Figure 2).[18]

Scheme 3. Ionic Ring Expansion of [2 + 2]-Photocycloaddition Product **6** via Hemiacetal **9** To Afford Ketolactone **10**



The high propensity toward ring cleavage reactions of tetronate photocycloaddition products was confirmed in other reactions, which are not mentioned here in detail but which encouraged us to approach the planned radical fragmentation of product **8**. Accordingly, the primary alcohol **8** was converted into iodide **11**, which in turn was treated with an initiator and a reducing agent [Bu_3SnH or $(Me_3Si)_3SiH$[19]]. Surprisingly, these reactions led preferably to product **14** (Scheme 4).

Scheme 4. Transformation of the [2 + 2]-Photocycloaddition Product **8** into a Precursor of a Radical Fragmentation and Formation of Tetracycle **14** by a Radical Domino Reaction



Unexpectedly, the anticipated fragmentation toward a 3,12-dioxatricyclo[8.2.1.$0^{6,13}$]tridecane skeleton is clearly disfavored compared to the fragmentation that affords a spirocyclic dioxatridecane framework.[20] Presumably, the radical **12** was formed, followed by cyclobutane cleavage to generate the secondary radical **13**. The consecutive 5-*endo*-cyclization was fast, so that the direct reduction product of radical **13** was not observed. The conditions shown in Scheme 4 employing $(Me_3Si)_3SiH$ as the reducing agent afforded the best yield of product **14**. Attempts to induce the desired ring expansion by applying reductive conditions (SmI_2)[21] to the aldehyde that is derived from

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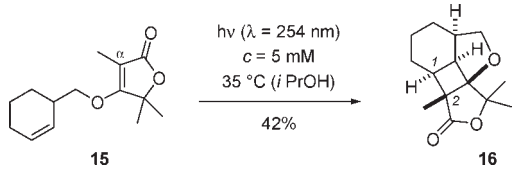
alcohol **8** delivered products, which are formed by the same reaction pathway. In this case, a 2,12-dioxatetracyclo-[6.5.1.$0^{1,10}$0^{4,14}]tetradecane was formed by a similar domino process.[22]

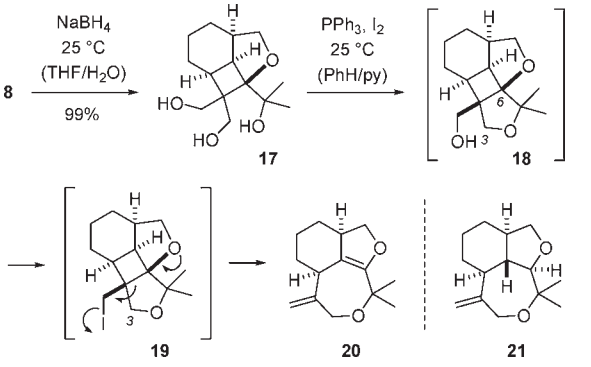
Since the extended carbon−carbon bond length in cyclobutane **6** (Figure 2) had given an indication for the regioselectivity of its ring fission (Scheme 3), we were curious whether similar structural information would give a hint as to the regioselectivity in the fragmentation of cyclobutylcarbinyl radical **12**. Iodide **11** was unstable, and we therefore prepared cyclobutane **16** (Scheme 5) as a model to elucidate the structural properties of radical **12**. Cyclobutane **16** was obtained by the [2 + 2]-photocycloaddition of tetronate **15**, which in turn was prepared from trimethyltetronic acid[23] and alcohol **1** by a Mitsunobu reaction.[13] A crystal structure analysis of **16** (cf. Supporting Information, CCDC 813563) uncovered a C1−C2 bond length of 1.579(2) Å, which is considerably longer than the remaining three cyclobutane C−C bonds.[18] Quite clearly, the preferred fragmentation of the bond between C1 and C2 in radical **12** is indeed facilitated by the intrinsic molecular strain.

Scheme 5. [2 + 2]-Photocycloaddition of Tetronate **15**



The bond cleavage to the desired scaffold **A** (Scheme 1) was eventually achieved while trying to form the respective iodomethyl-substituted tetrahydrofuran after reduction of the γ-lactone. Subjecting lactone **8** to a reduction with $NaBH_4$ resulted in the formation of triol **17**, which was to be converted into iodide **19**, i.e. the C3-deoxygenated analogue of compound **11**. Gratifyingly, although somewhat to our surprise, this reaction afforded the depicted product **20** (Scheme 6). We assume that the iodide **19** is indeed formed via alcohol **18**. However, due to the presence of an electron-donating substituent at the cyclobutane carbon atom C6, the intermediately formed iodide undergoes a 1,2-elimination resulting in a Grob fragmentation.[24,25] After deprotonation of the intermediate onium ion, product **20** is obtained.

Scheme 6. Fragmentation of Triol **17** Induced by Reaction with PPh_3 and I_2 and Putative Mechanism of the Fragmentation



The reduction of 3,12-dioxatricyclo[8.2.1.$0^{6,13}$]tridecane **20** to the saturated scaffold was readily achieved. For example, Et_3SiH in the presence of TFA resulted in being a suitable reductant in preliminary studies. Under these conditions, product **21** was obtained in a not yet optimized yield of 66%. However, rather than optimizing conditions on model systems, current work in our group is directed toward the application of the fragmentation to advanced intermediates en route to briarellin diterpenes. We feel that the other cyclobutane ring cleavage and domino reactions presented in this letter represent useful extensions to the organic toolkit, as they open expedient synthetic routes toward complex structural frameworks. Commencing with simple starting materials, the products are accessible in less than five steps in good yields.

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Supporting Information Available. Representative experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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