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A [2 + 2] Photocycloaddition−Fragmentation Approach toward the Carbon Skeleton of *cis*-Fused Lycorine-type Alkaloids

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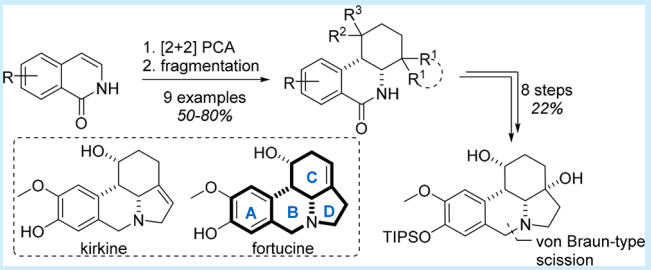
Supporting Information

ABSTRACT: Starting from isoquinolones, the *cis*-selective annulation of six-membered rings was possible employing cyclobutenes as olefin components in a [2 + 2] photocycloaddition−fragmentation approach (nine examples, 54−80% yield). The developed sequence enables a conceptually new entry to *cis*-fused lycorine-type alkaloids of the *Amaryllidaceae* family with the complete carbon skeleton being successfully assembled. A subsequent von Braun-type reaction emphasized the biological relation between lycorine- and homolycorine-type alkaloids providing a synthetic tool to access this class of natural products.



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Plants from the *Amaryllidaceae* family belong to the top 20 most widely considered medicinal plants, and their alkaloids have been frequently reported to play important pharmacological and medicinal roles.[1] In the past decades, up to 500 highly diversified alkaloids have been isolated that can be classified into 15 different skeleton types. The most common among all skeleton types is represented by lycorine-type alkaloids.[2] Usually, the pyrrolo[*d*,*e*]phenanthridine skeleton exhibits a *trans*-junction between the B and C ring, but there is a highly interesting subclass showing a unique *cis*-configuration (Figure 1). As opposed to the *trans*-fused natural products that have been the subject of extensive synthetic studies,[3] there is little known on complete synthetic approaches to their *cis*-fused counterparts. Besides γ-lycorane, which has become a popular target for illustrating the potential of new synthetic methods,[4] fortucine is the only natural product from that subclass that has been synthesized both in a racemic[5] and enantioselective[6] fashion. A compound with the putative structure of amarbellisine was synthesized in 2012, but its analytical data did not match the originally reported data.[7]

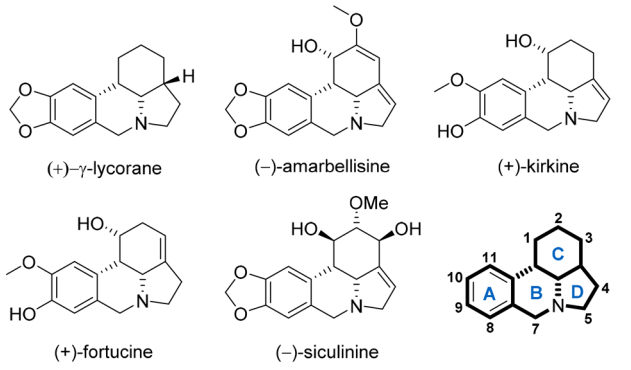
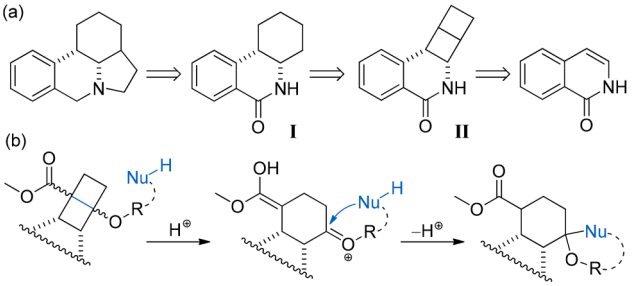


Figure 1. Representative lycorine-type alkaloids exhibiting a *cis*-junction between the B and C ring.

To study the pharmacological and structural features of this subclass in-depth, we envisioned a conceptually new entry to members of the *Amaryllidaceae* family, which gives access to a variety of *cis*-fused lycorine-type alkaloids and which is reported herein. As shown in Scheme 1a, the natural product's carbon skeleton can be derived by core modifications and introduction of the D ring from **I**. The required *cis*-fused six-membered ring can be obtained by fragmentation of tetracycle **II**. To allow for a convergent assembly process, we imagined disconnecting the tetracyclic core **II** by a [2 + 2] photocycloaddition,[8] revealing an isoquinolone and cyclobutene

Scheme 1. (a) Schematic Retrosynthesis of the Carbon Skeleton of *cis*-Fused Lycorine-type Alkaloids; (b) Envisioned Fragmentation using Appropriate Nucleophiles either Intra- or Intermolecularly



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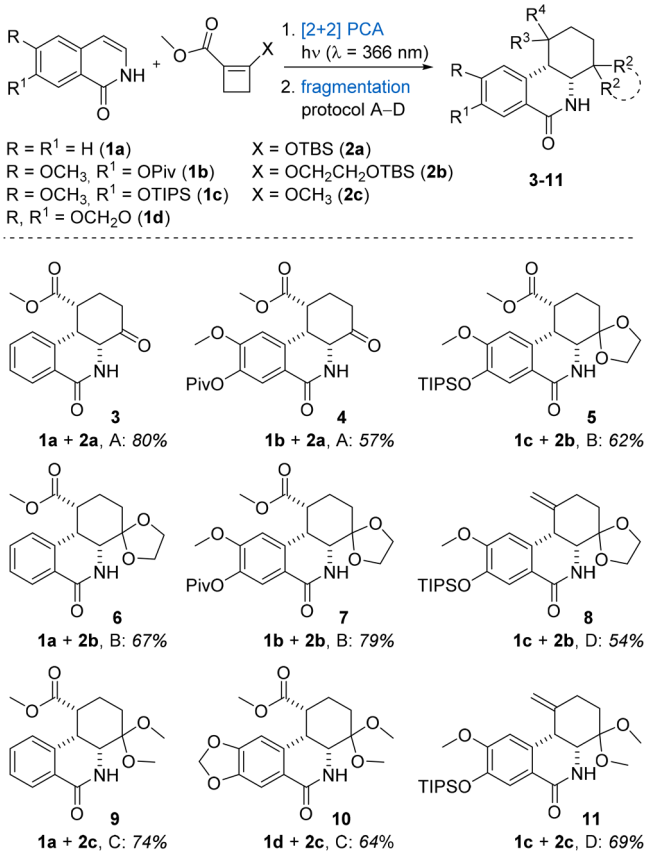
moiety. In a forward direction, the envisioned approach should include a photochemically induced [2 + 2] cycloaddition, followed by a fragmentation.[9] Acidic activation of the ester substituent at the bicyclo[2.2.0]hexane core should allow for scission of the central σ-bond forming an oxonium ion, which can be trapped by nucleophiles both intra- and intermolecularly[10] allowing access to a wide range of different substitution patterns (Scheme 1b). To the best of our knowledge, there is only one example reported using a donor−acceptor substituted cyclobutene for [2 + 2] photocycloaddition and fragmentation. In 1992, Smith and co-workers treated a dihydrofuran derivative with cyclobutene **2a** (Scheme 2) in a [2 + 2] photocycloaddition and induced follow-up fragmentation by deprotection of the newly formed tertiary alcohol using tetrabutylammonium fluoride (TBAF).[11−13]

Scheme 2. [2 + 2] Photocycloaddition−Fragmentation Sequence To Assemble *cis*-Fused Six-Membered Rings[a]



[a](A) $BF_3{\cdot}Et_2O$ (CH_2Cl_2), −40 °C. (B) TMSBr, MeOH (DMF), 0 °C → rt. (C) TMSBr *or* HCl (MeOH), 0 °C → rt. (D). (i) $LiBH_4$ (Et_2O), rt, (ii) MsCl, NEt_3, (CH_2Cl_2), 0 °C, (iii) TMSBr, (MeOH), 0 °C.

To evaluate the utility and frontiers of the envisioned [2 + 2] photocycloaddition−fragmentation sequence on isoquinolones, we chose a variety of substitution patterns of particular interest for *Amaryllidaceae* natural products (Figure 1). All alkaloids bear either a 9-OH/10-OCH_3 (**1b** or **1c**) or a 9,10-dioxolane (**1d**) entity on the aromatic core. Interestingly, the reported fragmentation conditions of Smith and co-workers[11] were not suitable for isoquinolones and required modification. The [2 + 2] photocycloaddition between cyclobutene **2a** (as for all cyclobutenes) and unsubstituted isoquinolone **1a** (as for all isoquinolones) proceeded in an extremely clean reaction with an excellent yield of 84% (see Supporting Information for more details). Inducing fragmentation using TBAF, however, led to oxidation of the product restoring the aromaticity of the isoquinolone core. Changing to $BF_3{\cdot}Et_2O$ in CH_2Cl_2 (Scheme 2, protocol A, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, Piv = pivaloyl) resulted in product **3** and the *cis*-selective assembly of the six-membered ring in an excellent yield of 80%. Similar to the parent isoquinolone **1a**, this sequence worked equally well with isoquinolone **1b**, yielding **4** in 57%. Expanding the scope to the formation of cyclic acetals upon fragmentation required an intramolecular nucleophile to trap the intermediate oxonium ion (vide supra). Cyclobutene **2b** was reacted with **1a**, **1b**, and **1c**, and fragmentation was induced following protocol B to obtain the *cis*-assembled products **6**, **7**, and **5** in 67%, 79%, and 62% yields, respectively, highlighting its robustness and reliability across several substrates. Not only was intramolecular trapping of the oxonium ion feasible, but also the introduction of external nucleophiles (protocol C) allowed for the formation of acyclic acetals **9** in 74% yield and **10** in 64%. To achieve even more versatile building blocks, the ester group was reduced to the corresponding primary alcohol and mesylated prior to ring cleavage (protocol D). Thus, a Grob fragmentation[14] became feasible creating an exocyclic double bond in a 1,4 relation to the acetal. Following this strategy, methylenecyclohexanes **8** and **11** were obtained in excellent yields of 54% and 69% over four steps, respectively, accounting for an average yield per step of 86% and 91%.

In an attempt to apply the five-membered analogue of **2a**, we envisioned extending this transformation to assemble seven-membered rings *cis*-selectively. Treatment of **1a** with methyl 2-[(*tert*-butyldimethylsilyl)oxy]cyclopent-1-ene-1-carboxylate under photochemical conditions promoted the formation of the corresponding photoproducts in an excellent yield of 97%. However, using protocol A to induce the desired fragmentation was unsuccessful and resulted in the deprotected photoproducts rather than the seven-membered ring. Hence, the high ring strain energy is crucial for this transformation as its release is a major driving force.[9] Finally, we were also interested in the significance of substitution patterns on the cyclobutene moiety. Utilizing a cyclobutene with X = H did not allow for fragmentation to form a less decorated cyclohexane unit emphasizing the strict demand for a push−pull system.

To highlight the utility of the developed procedure, we aimed to demonstrate its synthetic benefit by a conceptually new entry to the carbon skeleton of *cis*-fused lycorine-type alkaloids.[15] We first designed a synthetic route to the A−B−C tricyclic ring fragment **15** starting from isoquinolone **1c**, the [2 + 2] photocycloaddition−fragmentation sequence precursor (Scheme 3, Cp* = pentamethylcyclopentadienyl, Ac = acetyl, Vin = vinyl, Ms = mesyl). The latter was obtained from amide **12** using Raw's modification[16] of Fagnou's rhodium catalyzed redox-neutral isoquinolone synthesis.[17] Amide **12** itself was readily prepared starting from commercially available isovanillic acid in two steps and in 60% yield. As described in Scheme 2, the six-membered ring was established *cis*-selectively in 69% yield to give product **11**. The dimethoxy acetal was deprotected using $LiBF_4$ in wet acetonitrile[18] and subjected to a Grignard reaction with the reagent approaching selectively from the more accessible top face of the molecule, giving rise to the single diastereoisomer **13** in 82% yield over two steps.

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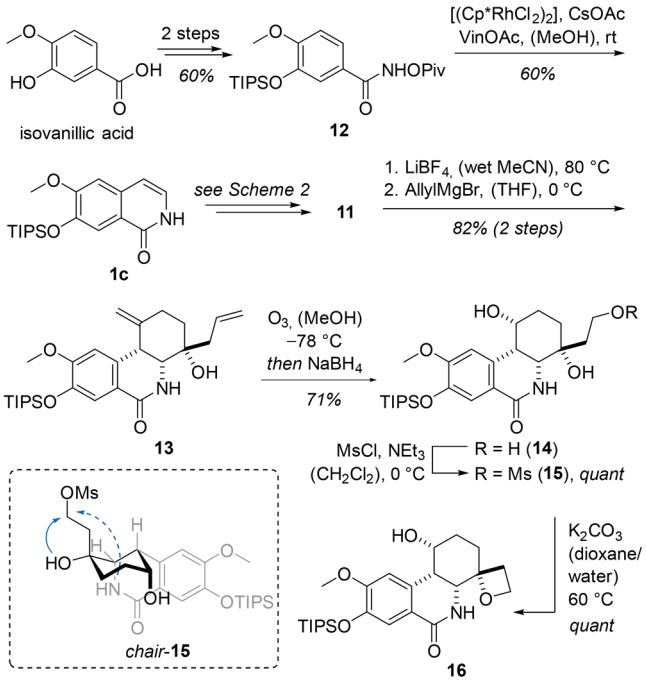
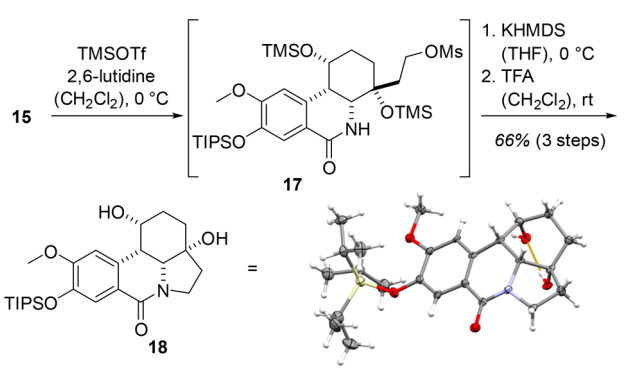
Scheme 3. Synthesis of Cyclization Precursor 15 and Attempted Formation of the Five-Membered Ring



Ozonolysis of both double bonds and reductive quenching furnished triol **14** in 71% yield. Selective mesylation of the primary alcohol was achieved in quantitative yield, forming cyclization precursor **15**. During our investigation to form the missing D ring, we found that oxetane **16** was preferentially formed under various conditions independent of the basicity of the applied reagents. With **15** adopting a chair-like conformation, spatial distance between the amide moiety and the leaving group would require a conformational flip prior to substitution. As a consequence, the latter pathway becomes less likely and oxetane formation prevails (Scheme 3). This unexpected reactivity stimulated a search for suitable protecting groups for the secondary and tertiary alcohol allowing for a single reactivity at the amide unit.

Hence, we were delighted to find that A−B−C−D tetracyclic product **18** was formed from mesylate **17** by using trimethylsilyl (TMS) as a protecting group. The structure of **18** was unambiguously confirmed by single-crystal X-ray analysis (Scheme 4, Tf = trifluoromethanesulfonyl, HMDS = hexamethyldisilazide, TFA = trifluoroacetic acid).

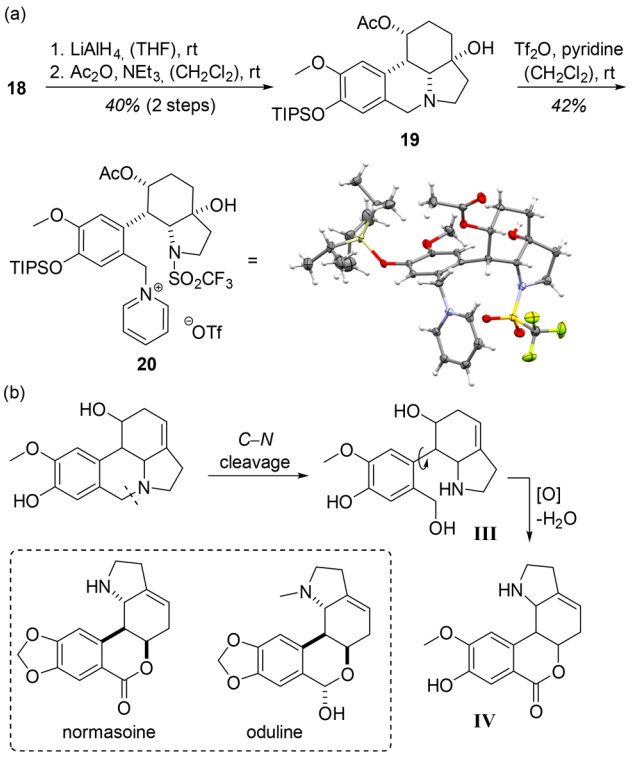
Scheme 4. Completion of the Full Carbon Skeleton and Its Crystal Structure



The crystal data also showed that the cyclohexane ring adopts a boat conformation after cyclization, which is stabilized by an intramolecular hydrogen bond between the secondary and tertiary alcohol.

Numerous attempts to directly eliminate the tertiary alcohol from amide **18** or amine **19** via carbocation formation using various acids were met with failure. The latter compound was obtained by $LiAlH_4$ reduction and acetylation in 40% over two steps (Scheme 5). Attempting a *syn* elimination to selectively

Scheme 5. (a) Synthesis of Amine 19 and Attempted Elimination; (b) Proposed Biosynthetic Pathway to Homolycorine-type Alkaloids with Two Representatives of this Class



enable the double bond in the positions required for the total syntheses of fortucine and kirkine (see Figure 1), the established methods remained unsuccessful. Likewise, various protecting groups on the secondary alcohol at either amide **18** or amine **19** did not allow for the formation of the desired alkene. After having failed to introduce the double bond by *syn* elimination, we turned our attention to procedures for *anti* elimination. Triflic anhydride and pyridine in CH_2Cl_2 at room temperature yielded a new compound after 1.5 h. Remarkably, NMR analysis indicated the incorporation of a pyridine unit into the skeleton. Further structure elucidation by single-crystal X-ray analysis revealed the formation of product **20** (Scheme 5a, counteranion omitted for clarity). Presumably the tertiary amine rather than the targeted tertiary alcohol was triflated. The quaternization allowed for a nucleophilic attack of pyridine at the benzylic position resembling a von Braun-type reaction.[19] The strained, polycyclic compound **19** is reminiscent of quinuclidine which displays—compared to triethylamine—a remarkable increase in nucleophilicity at the amino group.[20] Thus, the tertiary amine is more reactive and

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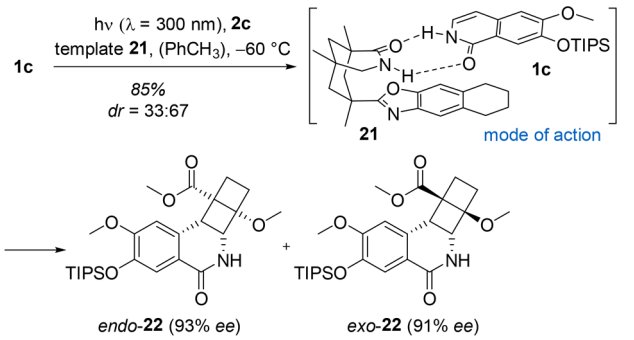
sterically less hindered than the tertiary alcohol allowing for this unusual selectivity.

In analogy to the observed von Braun-type reaction, there is a biosynthetic precedent for a C−N cleavage to form **III**, which upon rotation and oxidative cyclization generates lactone **IV**.[2] Along these lines, it is highly intriguing that lycorine-type alkaloids are intermediates in the biosynthesis of homolycorines (Scheme 5b). The synthetic importance of this von Braun-type transformation[21] to access the class of homolycorine-type alkaloids is currently being studied in more detail and might be applicable to the total synthesis of a representative member of this natural product class (Scheme 5b, dashed box).

Common to the synthetic strategies to lycorines and homolycorines is the requirement to obtain the carbon skeleton of basic structure **II** in a highly enantioselective fashion. We have previously shown that [2 + 2] photocycloaddition reactions between isoquinolones and electron deficient alkenes can be conducted enantioselectively by using a hydrogen-bonding template (**21**).[22] To our delight, the coordination of electron-rich isoquinolone **1c** and the site-differentiating attack of a donor−acceptor substituted cyclobutene works equally selective with *endo*-**22** being obtained with 93% ee and *exo*-**22** with 91% ee (Scheme 6, absolute

Scheme 6. Enantioselective Version of the [2 + 2] Photocycloaddition between Isoquinolone 1c and Cyclobutene 2c Using a Chiral Template



configuration in analogy to Coote et al.[22c]). Thus, this example highlights—on a proof of principle level—that the class of *cis*-fused lycorine-type alkaloids can be obtained not only racemically, but also enantioselectively.

In summary, a sequence of [2 + 2] photocycloaddition−fragmentation reactions using cyclobutenes as reaction partners has been demonstrated to be a versatile tool to access the skeleton of *cis*-fused lycorine type alkaloids. By considering cyclobutenes not as targets, but rather as reactive intermediates with a high ring strain energy, the *cis*-selective annulation of six-membered rings to isoquinolones has become feasible. While attempting the final elimination of the tertiary alcohol in the total synthesis of kirkine and fortucine, we discovered a tendency for a von Braun-type reaction that parallels the biosynthetic formation of homolycorine-type alkaloids from lycorine-type alkaloids. Ongoing work is now primarily devoted to the total syntheses of homolycorine-type alkaloids, but also to further extend the scope of this assembly process by introducing a wider variety of nucleophiles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03402.

Experimental procedures, analytical data for all new compounds, NMR spectra and X-ray data for **18** and **20** (PDF)

Accession Codes

CCDC 1874682−1874683 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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