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Toward Chromanes by de Novo Construction of the Benzene Ring

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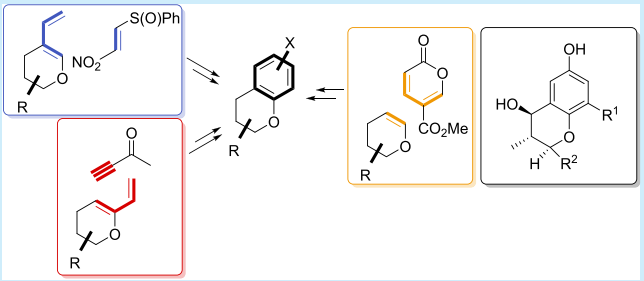
Supporting Information

ABSTRACT: The work describes three principal Diels−Alder cycloaddition approaches toward chromanes that are designed for the de novo construction of the benzene ring. This study specifically focuses on the potential exploitation in the total synthesis of chromane-bearing natural products such as cebulactam A.



Chromanes and derivates, such as coumarins,[1] chromenes, or chromane spiroketals,[2] are building blocks that are widely found in bioactive natural products. They constitute the core structures of tocopherols, flavonoids, cannabinoids, as well as many bioactive unnatural products, making them indispensable for medicinal chemistry (structures **1**−**7**, Figure 1).

The common synthetic approach toward these kind of structural motifs includes an aromatic starting material, which is functionalized and cyclized to the chromane backbone, whereas strategies that rely on the de novo syntheses of the aromatic core are, except for the Bergman cyclization[3] and the tetra/hexa-dehydro Diels−Alder reaction, rare.[4] When considering Diels−Alder approaches, one can suggest three viable retrosynthetic disconnections for the benzene moiety (Scheme 1). Strategy **A** positions the oxygen functionality at the terminus of the diene system **8**. Here an electron-deficient acetylene derivative or synthetic equivalent **9** can be chosen as a dienophile. Strategy **B** relies on diene **11**, in which the

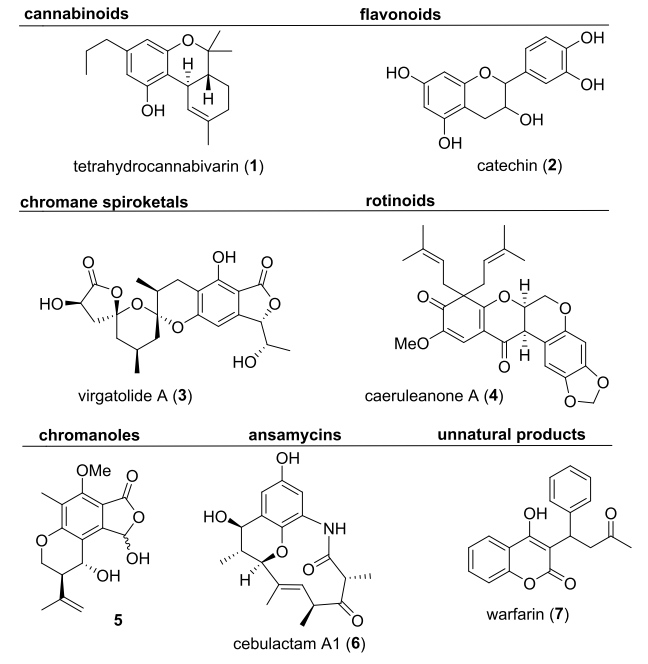
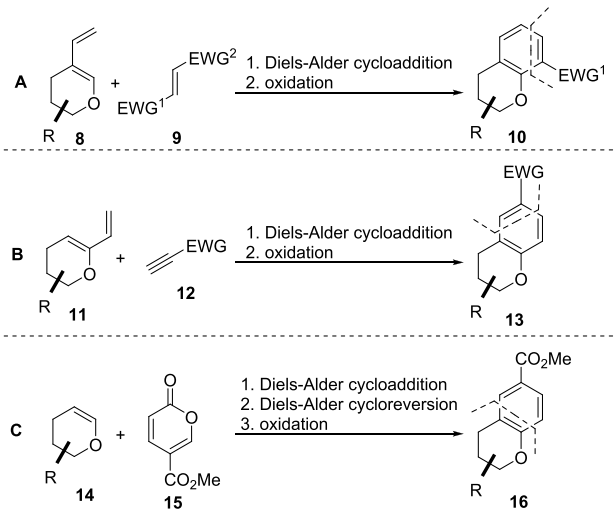


Figure 1. Structures of selected classes of chromane containing natural products **1**−**7**.

Scheme 1. Concepts A−C for the de Novo Preparation of the Aromatic Moiety in Chromanes[a]



[a]EWG, electron-withdrawing group.

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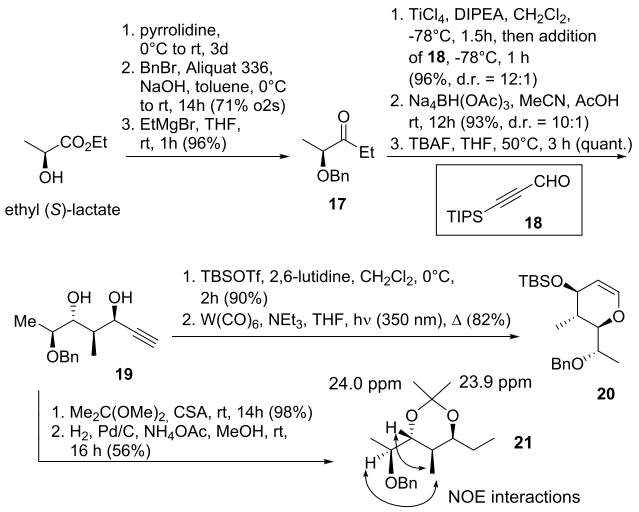
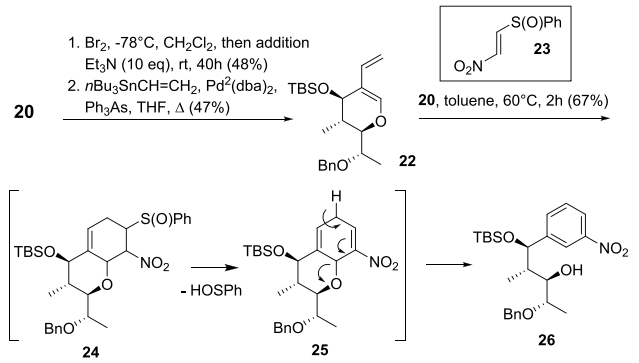
Scheme 2. Preparation of Tetrahydropyran 20 and Acetonide Derivative 21 for Determining the Relative Stereochemistry by NMR Spectroscopy[a]



[a]DIPEA, diisopropylethyl amine; TBAF, tetra-*n*-butylammonium fluoride; TBS, *tert*-butyldimethylsilyl; CSA, camphorsulfonic acid.

Scheme 3. Diels–Alder Strategy A[a]



[a]dba, dibenzylideneacetone.

oxygen substituent is positioned at C2, whereas alkyne **12** serves as dienophile.

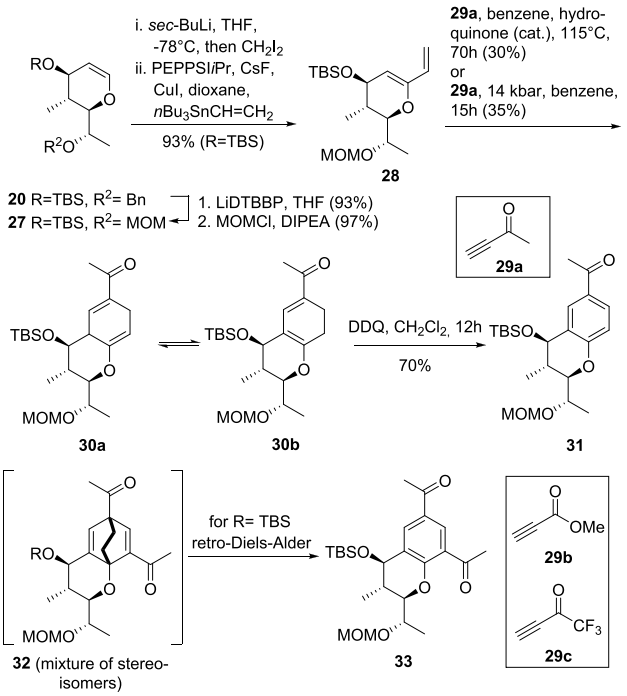
In contrast, strategy **C** utilizes enol ether **14** as dienophile in the reaction with an electron-deficient δ-lacton **15**. In this case, cycloaddition followed by a retro-Diels–Alder reaction yields the cyclohexane ring.

All strategies initially yield functionalized 2,4-cyclohexadienes that need to be oxidized to form the aromatic ring system, as depicted for benzenes **10**, **13**, and **16**, respectively.

In this work, we investigate all three options for the de novo synthesis of the chromane backbone with the ultimate goal of synthetically accessing ansamycin antibiotic cebulactam A1 (**6**),[5] a macromlactam antibiotic that belongs to the class of polyketide-derived ansamycins.[6]

To evaluate the feasibility of all three strategies for the synthesis of cebulactam A1 (**6**), we chose the complex, highly substituted dihydropyran **20** to serve as general precursor. Its synthesis commenced by transforming ethyl (*S*)-lactate into ketone **17** via the corresponding pyrrolidine amide (Scheme 2). Next, the titanium-mediated aldol reaction with aldehyde **18** yielded the aldol product with 1,4-syn stereochemistry. This underwent a 1,3-anti reduction and established the stereo-

Scheme 4. Diels–Alder Strategy B[a]



[a]DTBBP, 4,4′-di-*tert*-butylbiphenyl; MOM, methoxymethyl; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

tetrade in diol **19**. *O*-Benzyl protection in ketone **17** is crucial for achieving the desired 1,4-syn stereorelationship with very good diastereomeric excess, as judged after the derivatization of diol **19** and the formation of acetonide **21**.[7]

McDonald and coworkers reported on the photolysis of $W(CO)_6$ in the presence of alkynyl alcohols, which induces a cycloisomerization to endocyclic enol ethers.[8] In the present case, we exploited this method but had to silylate the propargylic alcohol first to achieve cyclization. Excellent regioselectivity was achieved by the slow addition of TBSOTf at 0 °C. Gratifyingly, the cycloisomerization yielded enol ether **20** in very good yield.

For realizing strategy **A**, a vinyl group was installed in the β-position of the enol ether group (Scheme 3). This was achieved by bromination through an addition/elimination mechanism, followed by a Stille cross-coupling reaction. To achieve acceptable yields, the presence of the ligand $AsPh_3$ was essential.[9] The resulting diene was subjected to Diels–Alder cycloaddition conditions using β-sulfinylnitro ethylene **23** (equals **9** in Scheme 1), a nitroacetylene equivalent reported by Ono et al.[10] After the cycloaddition and formation of cycloadduct **24**, the elimination of sulfenic acid occurs to afford 1-nitro-1,4-cyclohexadiene **25**. It was planned to form the bicyclic coumarin ring system **10** upon oxidative aromatization, but rather we found nitrobenzene **26** upon purification. Obviously, intermediate **25** undergoes a vinylogous elimination that ring-opens the pyran ring.[11] Nevertheless, this approach is principally feasible for the de novo construction of substituted benzene rings in natural product synthesis.

In contrast, the second strategy **B** cannot yield a dihydrobenzene that would be prone to aromatization through Grob-type elimination. Consequently, we prepared diene **28** from enol ether **27**, which itself was obtained from the central

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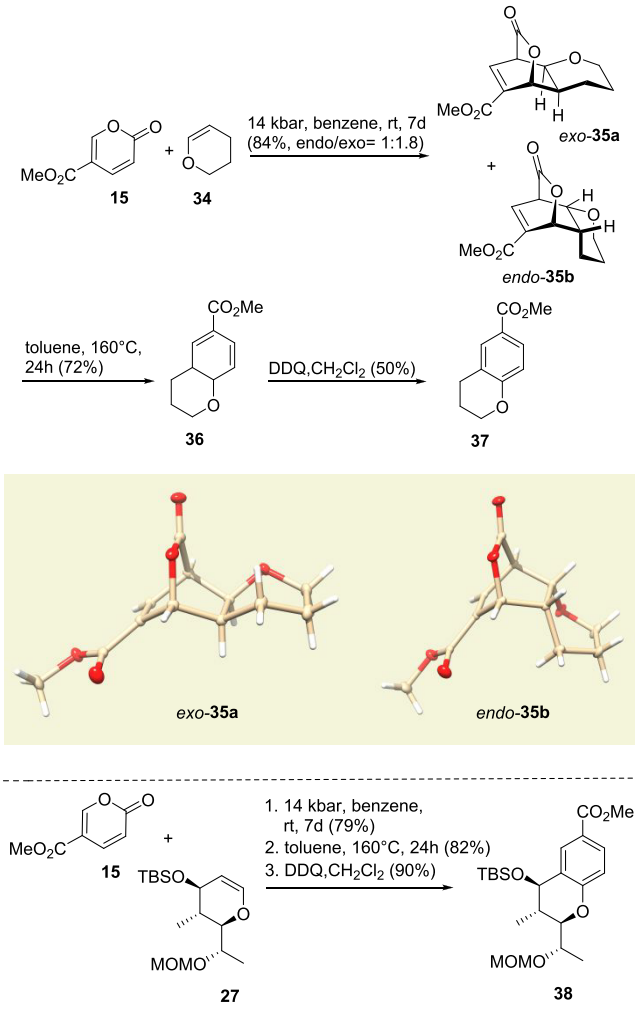
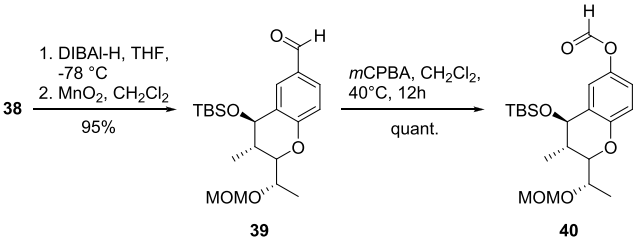
Scheme 5. Diels–Alder Strategy C



Scheme 6. Transformation of Diels–Alder Adduct 38 to Hydroquinone Derivative 40



precursor **20** (Scheme 4). The exchange of the benzyl by the MOM group was required to obtain clean lithiation in the following. It has to be noted that DIPEA is the solvent of choice for efficient MOM protection. Next, the vinyl group was introduced to yield diene **28**, which was achieved by α-lithiation of the enol ether, followed by iodination that paved the way for the Stille cross-coupling reaction with vinyl stannane. The reversal of the coupling steps (vinyl iodide with an 1-stannylated enol ether) provided diene **28** in only low yield. With the cycloaddition precursor **28** in hand, we engaged in the Diels–Alder reaction. On the basis of the work of Wada and coworkers,[12] we first envisaged a thermal protocol. Accordingly, but-3-yn-2-one **29a** was heated with diene **28** in benzene in the presence of a catalytic amount of hydroquinone to yield the desired dehydrobenzene **30a** along with the diene isomer **30b**. Gratifyingly, both dehydrobenzenes **30** could be oxidized to the desired benzene **31** using DDQ as the oxidant. The control of conditions is essential because the use of an excess of DDQ can lead to the cleavage of the silyl ether, and this is followed by the oxidation to the corresponding acetophenone derivative.

This cycloaddition protocol did not provide preparatively acceptable yields, which also included the use of other dienophiles such as methyl propiolate **29b**[13] and trifluorobut-3-yn-2-one **29c**.[14] Therefore, we searched for Lewis acids to promote the cycloaddition.[15] Among $AlCl_3$, Et_2AlCl, $AlMe_3$, BF_3OEt_2, $LiClO_4$, $MgBr_2$, $SnCl_4$, $ScOTf_3$, $TiCl_4$, $Ti(OiPr)_3Cl$, $Ti(OiPr)_4$, and $ZnCl_2$, only the use of Et_2AlCl provided the cycloaddition product **30** in low yield, especially when the TBS protecting group in enolether **28** was exchanged for the triisopropylsilyl (TIPS) group. (See the SI.) Finally, the cycloaddition under high-pressure conditions was investigated.[16] Indeed, pressurizing a solution of alkyne **29a** and diene **28** at 14 kbar over a period of 15 h using a hydraulic press furnished the desired dehydrobenzenes **30**. This time, the formation of the byproduct diacetylchromane **33** could unequivocally be identified. This product is derived from the tricyclic product **32** that itself arises from a second Diels–Alder reaction of the isomerized dehydrobenzene **30b** with acetylene **29a**. Under the given conditions, the extrusion of ethylene must have taken place, which is accompanied by rearomatization by means of a retro Diels–Alder reaction. The formation of these byproducts could not be suppressed when varying the pressure and reaction time. In fact, when instead of a TBS group the TIPS-protecting group was installed in chromane **31**, intermediate **32** (R = TIPS) could be isolated and fully characterized. (See the SI.) Because of these side reactions, the combined yields of cycloaddition and oxidation were preparatively not satisfactory.

Consequently, we pursued strategy **C** utilizing dehydropyran of type **14** as dienophile and methyl 2-oxo-2*H*-pyran-5-carboxylate **15** as diene to construct a highly substituted chromane core by utilizing a cycloaddition/cycloreversion sequence followed by oxidation (Scheme 5).

Thus the simplest dihydropyran **34** was converted into the tricyclic exo- and endo-cyclization products **35a,b** under high-pressure conditions. After substantial optimization, we found that it is only possible to initiate cycloaddition under high-pressure conditions at room temperature over an extended time. In this first case, both crystalline cycloaddition products **35a,b** were separated and structurally characterized by X-ray analysis. Next, both diastereomers underwent a retro Diels–Alder reaction with the extrusion of carbon dioxide under thermal conditions, which provided dehydrobenzene **36**, which was dehydrogenated to yield chromane derivative **37** using DDQ as an oxidant.[17] This three-step protocol also works for the complex dihydropyran **27** and provided chromane derivative **38**, which can principally serve as a precursor for the synthesis of cebulactam A1 (**6**).

This would require the transformation of the methyl benzoate group into the corresponding hydroquinone derivative. This was achieved after the reduction/oxidation of ester **38** to the corresponding benzaldehyde **39** (Scheme 6). Dakin oxidation with 3-chloroperbenzoic acid smoothly yielded formiate **40** in quantitative yield.[18]

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Overall, we provided three unconventional approaches embedded in a natural-product-like environment that disclose new synthetic avenues toward substituted chromane backbones. In particular, the last strategy has the potential to be broadly applied in natural product synthesis, especially of the chromanes listed in Figure 1. It will be a versatile addition to known de novo strategies.[3,4,19]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03209.

Detailed experimental procedures and spectral data (PDF)

Accession Codes

CCDC 1948955 and 1949004 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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