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From Stereodefined Cyclobutenes to Dienes: Total Syntheses of Ieodomycin D and the Southern Fragment of Macrolactin A

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Supporting Information

ABSTRACT: A copper-promoted flexible synthesis of cyclobutenes carrying simple alkyl chains, enabling even the most hindered nucleophiles to be employed, has been developed. The versatility of this approach was exemplified by a short total synthesis of ieodomycin D and a straightforward preparation of the southeastern fragment of macrolactin A. The latter features a late-stage, double cyclobutene electrocyclic ring opening that directly delivers a bis-diene of defined geometry.

Polyene motifs are widely represented in the skeleton of biologically active compounds such as the eicosanoids,[1] the retinoids,[2] and the macrolides,[3] a large group comprising over 200 members. To date, despite significant efforts from the synthetic community in the area of diene synthesis, the stereoselective preparation of substituted 1,3-butadienes remains a challenge.[4] Nature decorates these polyenes in a variety of fascinating patterns, among which 1,3-butadienoic carboxylates and diene carbinol fragments represent an important subset of structural units. The latter find representation in natural products of varying size and molecular weight (Figure 1). In particular, the ieodomycins are extracted

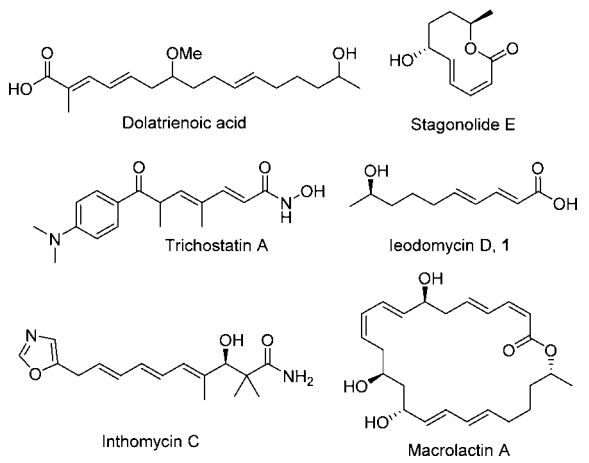
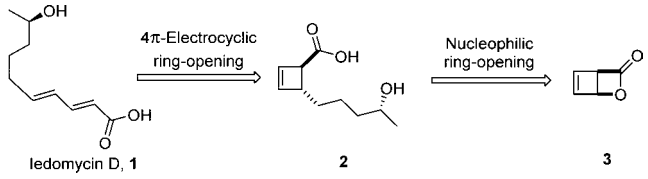


Figure 1. Diene containing natural products.

from marine bacteria of the *Bacillus* species,[5] ubiquitous and abundant microorganisms in the marine ecosystem. They were isolated in 2011 by the group of Shin, who additionally determined their absolute configuration and identified their biological targets.[5] One total synthesis of this natural product has been reported, delivering ieodomycin D **1** in five linear steps.[6] We were drawn toward this natural product following our initial studies on the stereoselective synthesis of dienes by 4π-electrocyclic ring opening of preformed cyclobutenes of defined stereochemistry[7] and, thus, proposed that *trans*-cyclobutene **2** might be the direct precursor of **1**. In the retrosynthetic sense, we further speculated that a nucleophilic ring opening of the bicyclolactone **3** with a properly functionalized (and enantiopure) nucleophile might directly afford the requisite *trans*-substituted cyclobutene **2** (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Ieodomycin D Featuring a 4π-Electrocyclic Ring-Opening Event



Our group has previously explored catalytic nucleophilic ring opening of **3** employing allylic alkylation reactions with stabilized nucleophiles,[8] allylborane derivatives,[9a] and dialkyl zinc reagents.[9b] However, none of those methods is suitable for the direct introduction of a long alkyl chain such as the one required for expeditious conversion of **3** into **2**. We thus turned our attention to the potential use of organocopper reagents.[10] Although the considerable reactivity of both such reagents and the highly strained lactone **3** could conceivably lead to an unselective reaction, our preliminary experiments met with encouraging results.

As shown in Scheme 2, simple exposure of lactone **3** to the combined action of EtMgBr, CuCN, and LiCl smoothly delivered the ethyl-substituted product **4**. Importantly, **4** was

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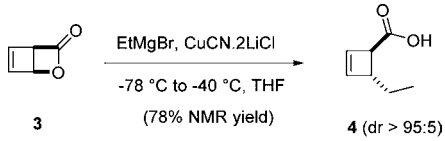
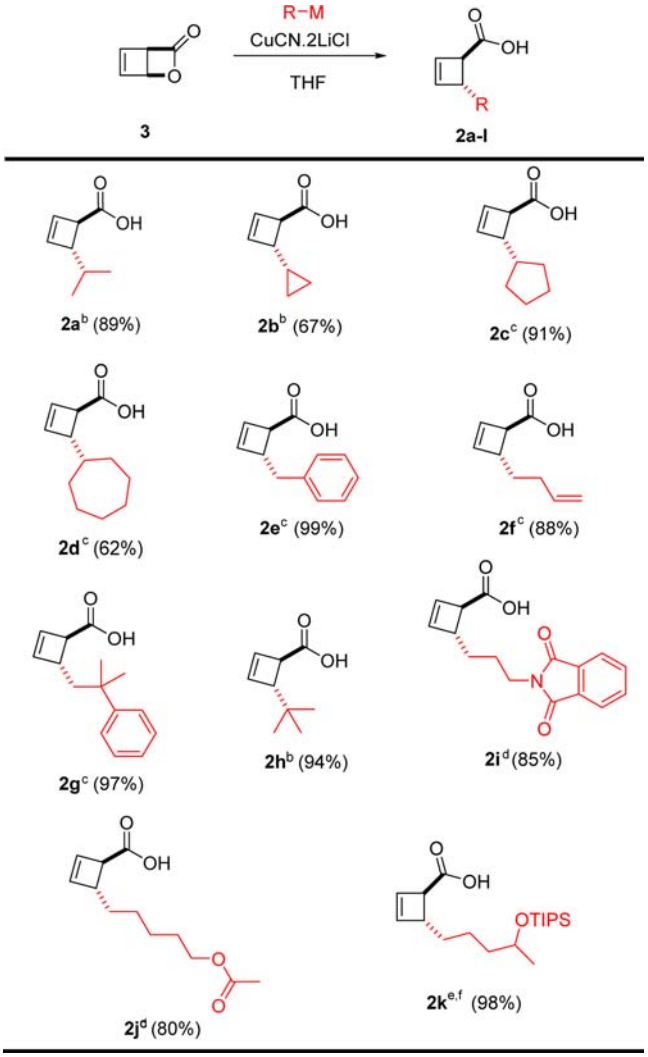
Scheme 2. Preliminary Result for the Alkylation of Lactone 3 with an Organocopper Reagent



formed as a single, *trans*-configured diastereoisomer (as ascertained by crude ^{1}H NMR analysis) in high yield.

Spurred by this initial success, we proceeded to examine the scope of the transformation. As shown in Table 1, organocopper reagents appear to constitute very valuable tools to achieve the straightforward appendage of varied alkyl and cycloalkyl functionalities to the cyclobutene ring. Remarkably, very congested tertiary alkyl groups could be introduced (cf. **2g/h**); the successful use of *t*-BuMgCl in a nucleophilic C−C bond forming event is especially noteworthy.[11] Furthermore, this process is compatible with functionalized heteroatom substituents based on oxygen or nitrogen (cf. **2i−k**), delivering functionalities ripe for further synthetic elaboration. The exclusive formation of the *trans*-disubstituted cyclobutene products can be assumed to result from a nucleophilic attack on lactone **3** from the face opposite to the carboxylate leaving group.[12]

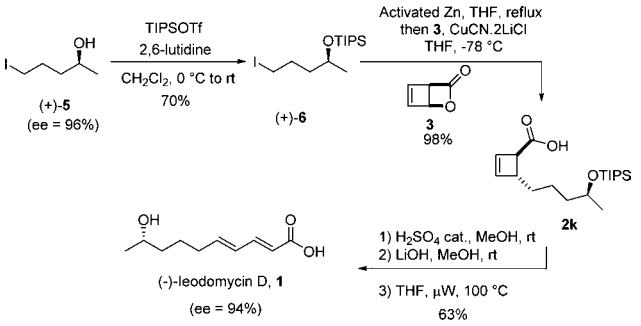
Table 1. Substrate Scope of the Diastereoselective Cuprate Alkylations[a]



[a]All products were isolated and characterized as the corresponding benzylamides. dr >95:5 for **2a−2j** as determined by crude ^{1}H NMR analysis. **2b** was isolated as an inseparable 3:1 mixture with the corresponding diene. For detailed reaction conditions, see the Supporting Information. [b]RMgCl. [c]RMgBr. [d]RZnBr. [e]RZnI. [f]1:1 mixture of diastereomers.

With this methodology in hand, we validated our original blueprint for the synthesis of ieodomycin D, **1**. As shown in Scheme 3, alkylation of lactone **3** with the organometallic

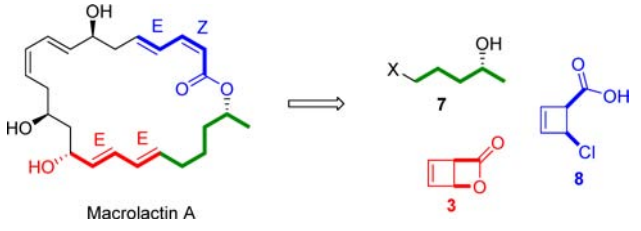
Scheme 3. Asymmetric Synthesis of (−)-Ieodomycin D, 1



reagent obtained by successive zincation and copper transmetalation of (+)-**6** delivered **2k** in 98% yield. Further removal of the TIPS protecting group under mild acidic conditions in methanol eventually led to concomitant esterification of the carboxylic acid moiety. (−)-Ieodomycin D was finally obtained after hydrolysis of the methyl ester and thermolysis of the cyclobutene moiety. This expeditious route delivered (−)-**1** in only five steps from readily available alcohol (+)-**5**[13] and 43% overall yield.

An interesting observation is that ieodomycin D bears an alkyl chain identical to the one encompassed in the southern fragment of the macrolactins.[14] Aware of this, we hypothesized that a strategy related to that depicted in Scheme 3 might be employed for the preparation of the southeastern fragment of macrolactin A. This led us to the generic plan outlined in Scheme 4.

Scheme 4. Approach to Macrolactin A (southeastern fragment highlighted)



Our approach relies on the recognition of two differently configured diene moieties, which accordingly require different strategies for their synthesis. The (*E*,*E*)-diene carbinol fragment would arise through electrocyclic ring opening of a *trans*-substituted cyclobutene (derived from lactone **3**). For the challenging (*Z*,*E*)-dienoic portion we anticipated the use of *cis*-chlorocarboxylic acid **8**.[7]

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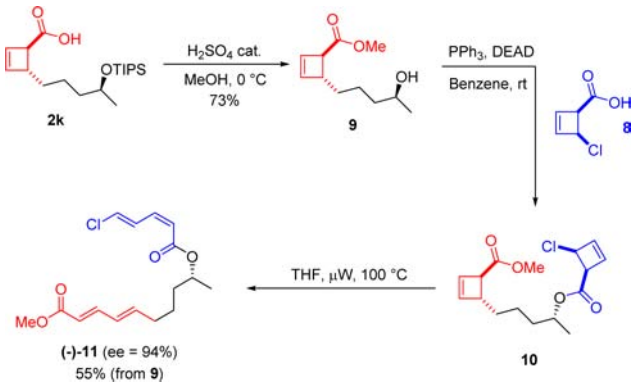
The synthesis, depicted in Scheme 5, begins with the alkylation product **2k**. As before, unravelling of the TIPS protecting group in acidic methanol simultaneously achieves esterification of the carboxylic acid moiety, leading to **9** in 73% yield. Taking advantage of the free alcohol, coupling with the aforementioned *cis*-chlorocyclobutene **8** could now be attempted. In the event, the use of common activating reagents for ester formation, such as EDCI (HOBt, DMAP),[14] proved to be inefficient in this reaction and only starting material was recovered. On the other hand, *N,N′*-dicyclohexylcarbodiimide (DCC) together with 10 mol % of 4-dimethylaminopyridine (DMAP)[15] allowed the formation of the desired product, although in less than 10% yield. We next turned our attention to the use of Yamaguchi's reagent for coupling.[16] Nevertheless, while delivering the desired ester in moderate to good yields, these reaction conditions led to extensive epimerization of the α-center, generating a mixture of *cis*-cyclobutene **10** and its thermodynamically more stable *trans*-isomer (not shown). It should be emphasized that the *cis*-configuration that is encoded in **8** is a crucial prerequisite for being able to access a (*Z,E*)-dienyl carboxylate by thermal, conrotatory electrocyclic ring opening.

Scheme 5. Synthesis of the Southeastern Fragment of Macrolactin A



Realizing that protocols relying on acid activation were inevitably prone to some degree of deleterious epimerization, we considered the use of an esterification procedure where the *alcohol* moiety undergoes activation. We thus turned our attention to the use of a Mitsunobu-type esterification[17] and, to our delight, observed that the desired isomer **10** was exclusively produced under these reaction conditions when benzene was used as solvent.[18]

Compound **10** interestingly carries two disubstituted cyclobutene moieties, one with a *cis*-arrangement (blue in the Scheme) and the other with a *trans*-configuration (red in the Scheme). Their structural assignment was supported by *J* coupling analysis.[18] It was anticipated that electrocyclic ring opening of intermediate **10** would simultaneously deliver two diene moieties of differing olefinic geometry. In the event, thermolysis of **10** smoothly delivered product **11**, embodying the entire southeastern region of macrolactin A, in 55% yield over two steps and 94% ee. The striking conciseness of this strategy bodes well for future synthetic endeavors.

In summary, we have developed the addition of organocopper reagents to lactone **3** as a tool enabling the expeditious preparation of cyclobutenes carrying simple alkyl chains. In this process, even the most hindered organocopper reagents are competent nucleophiles, as exemplified by the successful application of *t*BuMgCl in that role. The versatility of this approach was then exemplified by two synthesis case studies. In the first, ieodomycin D was prepared in a short sequence involving the use of a functionalized, optically pure organocopper reagent. That route could be further capitalized for the straightforward preparation of the southeastern fragment of macrolactin A, featuring a late-stage, double cyclobutene electrocyclic ring opening that directly delivers a bis-diene of defined geometry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02149.

General procedures; NMR spectra and GC/HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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