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Stereoselective Synthesis of Dienyl-Carboxylate Building Blocks: Formal Synthesis of Inthomycin C

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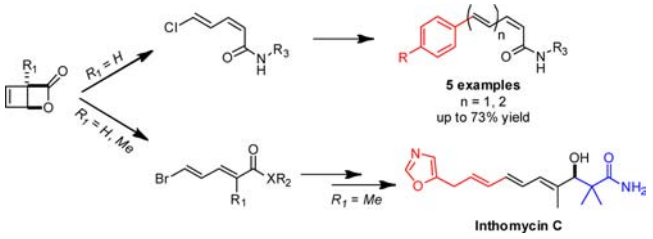
ABSTRACT



A direct synthesis of stereodefined halodienes is reported. Those key building blocks enable a concise access to polyenic products, as demonstrated in a modular synthesis of Inthomycin C.

Dienyl carboxylate and carbinol subunits are fundamental structural scaffolds present in various natural products[1] (Figure 1). Through simple modifications in the diene substitution pattern and olefin geometry, Nature is able to access remarkable structural diversity. Such functionalized conjugated dienes are conventionally built from simple mono-olefinic fragments[2] through, e.g., cross-coupling,[3,4] metathesis,[5] or olefination reactions.[6] Controlling the configuration of the double bond arrays generated during such transformations represents a major challenge.

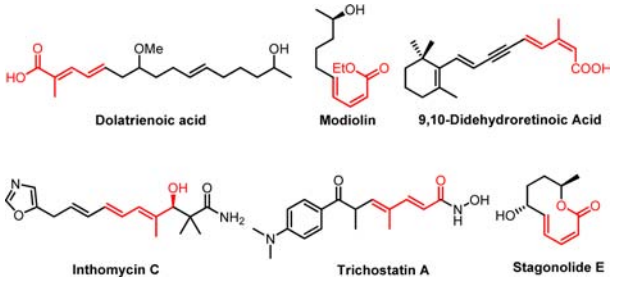


Figure 1. Examples of natural products containing a dienyl-carboxylate or -carbinol moiety.

The use of stereodefined mono-olefinic fragments as building blocks for cross-coupling reactions leading to the di- or polyenyl frameworks of interest is a strategy that has gained prominence.[7] An elegant example of such a tactic is the development by Burke of an assembly of so-called

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(5) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003.
(6) *Modern Carbonyl Olefination: Methods and Applications*; Takeda, T., Ed.; Wiley-VCH: Weinheim, 2004.

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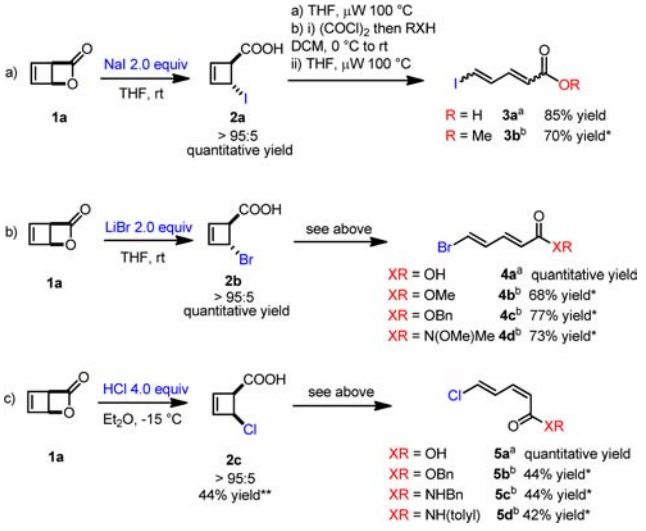
MIDA-boronate building blocks that allow the deployment of iterative cross-couplings en route to polyenic natural products.[8] Nevertheless, the syntheses of the basic mono-olefinic fragments are typically multistep and mandate the introduction of a halide and organometallic residue in each fragment. We report herein a strategy for the direct preparation of dienyl carboxylate building blocks that significantly streamlines the total synthesis of polyene natural products.[9−11]

Scheme 1. Direct Synthesis of Halocyclobutenes and Their Ring-Opening Reactions[a]



[a] * Overall isolated yield from lactone **1a**. ** Isolated yield after recrystallization.

During our studies on allylic alkylation of lactone **1a**,[12] we have discovered an unexpected halide ring opening relying on the use of alkali halide salts. As shown in Scheme 1a−b, clean ring opening of lactone **1a** with either NaI or LiBr provides almost exclusively *trans*-halocyclobutenes **2a**−**b** in quantitative yields. Furthermore, nucleophilic chlorination of **1a** with HCl selectively affords *cis*-chlorocyclobutene **2c** with similar efficiency (Scheme 1c).

These thermally stable halocyclobutenes and their ester or amide derivatives are prone to 4π-electrocyclic conrotatory ring opening[13,14] upon heating. Surprisingly, the iodocyclobutene **2a** and derivatives undergo productive ring opening leading to a mixture of diene geometrical isomers.[15,16] In contrast, **2b** and the brominated carboxylate analogues thereof afford the (*E*,*E*)-halodienes **4a**−**d** cleanly upon refluxing in THF.[17] In a complementary fashion, the *cis*-4-chlorocyclobut-2-ene carboxylic acid **2c**[18] can be readily derivatized and unravelled to deliver the (*Z*,*E*)-dienyl carboxylates **5a**−**d** (Scheme 1c).

In order to determine the factors controlling the reactivity and stereoselectivity of the ring openings of **2a**−**c**, we modeled these 4π-electrocyclic ring-opening reactions computationally.[19] Computations indicate that the electrocyclic ring-opening reactions of the disubstituted cyclobutenes **2a**−**c** are all exergonic and thus irreversible with a ΔG_{rxn} ranging from −11 kcal/mol for **2b** and **2c** to −14 kcal/mol for **2a**. The high temperatures required for the ring openings of **2a**−**c** are consistent with the computed free energy barriers (~30 kcal/mol). The transition structures for the ring opening of **2a**, **2b**, and **2c** are shown in Figure 2.[20]

Donors such as iodide stabilize the transition state by interacting with the transition state LUMO.[21] The iodide substituent is a weaker donor than chloride or bromide, explaining a 10-fold difference in the rate of reaction of **2a** and **2b**.

The stereochemical outcomes of the electrocyclic reactions of **2b**−**c** are in agreement with the model regarding

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(10) For previous syntheses of (2*E*,4*E*)-5-bromo-2,4-dienoic esters, see: (a) Macdonald, G.; Alcaraz, L.; Wei, X. D.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron* **1998**, *54*, 9823. (b) Zeng, F. X.; Negishi, E. *Org. Lett.* **2002**, *4*, 703. (c) Crombie, L.; Horsham, M. A.; Jarrett, S. R. M. *Tetrahedron Lett.* **1989**, *30*, 4299. (d) Wei, X. D.; Taylor, R. J. K. *Tettrahedron Lett.* **1998**, *39*, 3815. (e) Wei, X. D.; Taylor, R. J. K. *J. Org. Chem.* **2000**, *65*, 616.

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(16) For comparison with (2*E*,4*Z*)-5-iodo-2,4-dienoic ester and (2*Z*,4*E*)-5-iodo-2,4-dienoic ester, see: Wang, G. W.; Mohan, S.; Negishi, E. I. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 11344. See SI for details.

(17) A larger scale reaction afforded 2.5 g of diene **4b** in 95% yield from the lactone **1a**.

(18) Pirkle, W. H.; Mckendry, L. H. *J. Am. Chem. Soc.* **1969**, *91*, 1179. See also ref 12d.

(19) Computational experiments were carried out using the M06−2X/6-31+G(d,p) model chemistry with Gaussian 09. For the reaction of **2c**, the core electrons of iodine were modelled using the LAN2LDZ pseudopotential. Additional details regarding the computational methods employed as well as the full citation for Gaussian are provided in the Supporting Information.

(20) Comparing the barriers of **2a** and **2b**, we found that ring opening of **2a** proceeds with a $\Delta G^{\ddagger}$ of 29.8 kcal/mol, whereas the reaction of **2b** has a $\Delta G^{\ddagger}$ of 28.7. This 1.1 kcal/mol difference leads to a 10-fold greater reaction rate for **2b** compared to its iodo-analogue **2a**.

(21) Dolbier, W.; Koroniak, H.; Houk, K.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471.

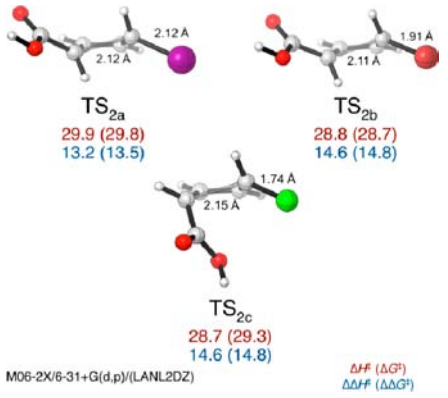


Figure 2. Lowest energy conrotatory transition structures for the ring opening of **2a**, **2b**, and **2c**. $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ are given in red below the corresponding transition structure. The enthalpy and free energy values in blue are the differences between the disfavored (not shown) and preferred transition states. Energies are given in kcal/mol.

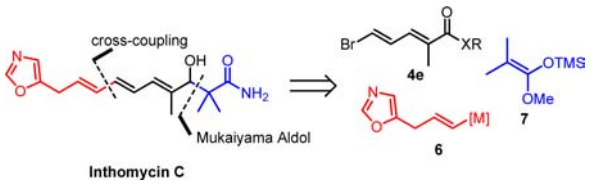
the torquoselectivity of the 4π-electrocyclic ring opening of cyclobutenes.[21] In the ring opening of halocyclobutenes, strong *n* donors rotate outward in order to maximize orbital overlap between the high energy, nonbonding orbital of the donor, and the transition state LUMO (σ^*).[22] Indeed, computations show that the conrotatory transition state of ring opening in which the halide rotates outward is 13−14 kcal/mol lower in energy than the alternative where the halide rotates inward (Figure 2). Conversely, strong acceptors, such as aldehydes, tend to rotate inward in order to maximize the overlap of their relatively low energy acceptor orbital with the transition state HOMO (σ).

The $\Delta\Delta G^{\ddagger}$ values of *trans*-substituted cyclobutenes **2a**−**c** (13−15 kcal/mol) demonstrate the clear preference of the halide substituent for outward rotation. In the ring opening of *trans*-disubstituted **2a**−**b**, both the acid[23] and the halide rotate outward, whereas in the ring opening of *cis*-isomer **2c** the acid is forced to rotate inward in the presence of the strong chloride donor. The similarity in the barriers of the *trans*- and *cis*-disubstituted cyclobutene ring openings are in agreement with prior computational work which indicates that the acid has only a small preference for outward rotation.[23]

While the formation of the (*E,E*)-iododiene via electrocyclic reaction of **2a** follows the explanation provided above, the (*E,Z*)-iododiene cannot be formed under thermal conditions via a pericyclic mechanism, as the reaction would have to proceed through a forbidden, disrotatory transition state.[13] Such a transition state is inaccessible due to its prohibitively high energy. Instead, this (*E,Z*) isomer is likely formed by subsequent isomerization of the allowed (*E,E*) product.

We next sought to demonstrate the synthetic utility of these dienyl-carboxylates.[24] Inthomycin C (Scheme 2), isolated in 1991,[25] was shown to reduce prostate cancer cell growth as well as to possess selective *in vitro* antimicrobial activity. Our retrosynthetic analysis is shown in Scheme 2, breaking the natural product down to three simple fragments **4e**, **6**, and **7**. We envisioned that the bromo diene **4e** would undergo cross-coupling with a suitable organometallic partner **6** delivering a triene. Further functional group interconversion and Mukaiyama aldol reaction with silylketene acetal **7** would ultimately allow the preparation of Inthomycin C.

Scheme 2. Retrosynthetic Strategy towards Inthomycin C



In order to obtain validation for the strategy outlined in Scheme 2, we briefly evaluated the reactivity of the stereodefined diene building blocks in cross-coupling reactions (Scheme 3).[26] For instance, Suzuki couplings employing aryl and vinyl boronic acids proceeded to deliver the corresponding substituted dienoic esters **8a**−**c**. Sonogashira reactions could be performed in good yields with silyl-, alkyl-, and aryl-substituted terminal alkynes, and various Stille cross-couplings were also successful.[27] Similarly, cross-coupling onto the (*Z,E*)-chloro-dienes **5c**−**d** took place without loss of the diene geometrical configuration (Scheme 4), an important observation.[28] To the best of our knowledge, this is an unprecedented use of doubly vinylogous chloride esters in cross-coupling reactions.

Armed with this knowledge, we could then confidently complete the synthesis of Inthomycin C (Scheme 5). As shown, lithium bromide smoothly opened the methyl substituted lactone **1b**. As before, a single *trans*-cyclobutenyl

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(29) Henaff, N.; Whiting, A. *Org. Lett.* **1999**, *1*, 1137.
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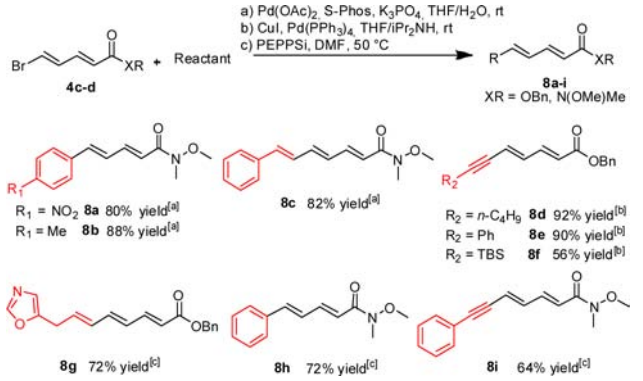
Scheme 3. Scope of Cross-Coupling Reactions of (2*E*,4*E*)-5-Bromo-2,4-dienoic Derivatives **4c**–**d**

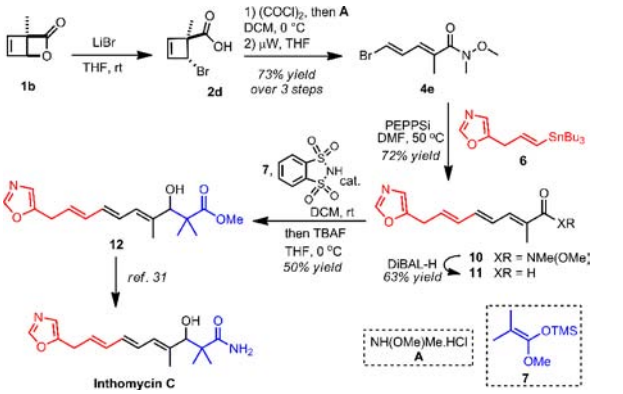


Scheme 4. Suzuki Cross-Coupling of (2*Z*,4*E*)-5-Chloro-dienoic Derivatives **5c**–**d**

bromide **2d** was obtained. Further amide coupling and 4π electrocyclic ring opening afforded 2-methyl-5-bromodienoic amide **4e** as a single geometrical isomer. Stille cross-coupling with vinyl stannane **6**,[29] followed by reduction to the aldehyde **11** and organocatalytic Mukaiyama aldol reaction with silylketene acetal **7**, then led to product **12** in 50% yield.[30] The conversion of **12** to Inthomycin C has been previously reported.[31] This modular assembly of substituents around dienes such as **4e** allows considerable flexibility in the context of total synthesis.

In summary, we have reported herein a direct route to functionalized and stereodefined halodiene carboxylate building blocks, which proceeds through electrocyclic ring opening of readily available halocyclobutene precursors. Appropriate control of stereochemical information at the cyclobutene level ensures access to a suitably configured

Scheme 5. Modular Formal Synthesis of Inthomycin C



diene fragment upon ring opening. Cross-coupling onto these subunits allows ready access to natural product-like polyene substructures without erosion of the geometrical purity. The utility of this strategy is showcased by a modular short formal synthesis of Inthomycin C. We are currently pursuing the application of these and related approaches to the total syntheses of diverse polyene natural products.

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Supporting Information Available. Experimental procedures and spectroscopic data for new compounds, computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.