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Catalyst-Controlled Inverse-Electron-Demand Hetero-Diels–Alder Reactions in the Enantio- and Diastereoselective Synthesis of Iridoid Natural Products

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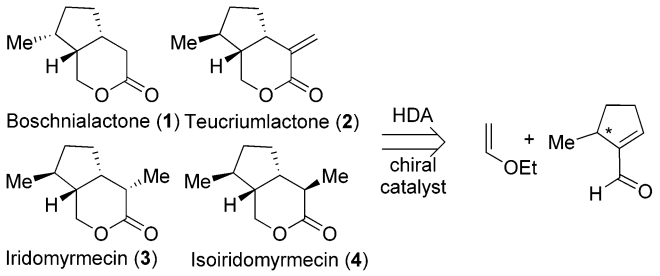
ABSTRACT



Iridoid natural products 1–4 are accessed stereoselectively by means of tridentate (Schiff base)Cr(III)-catalyzed hetero-Diels–Alder reactions between ethyl vinyl ether and enantioenriched 5-methyl-1-cyclopentene-1-carboxaldehyde. An efficient route to the aldehyde from citronellal is afforded by the ring-closing metathesis reaction.

The inverse electron-demand hetero-Diels−Alder (HDA) reaction represents an efficient strategy for the preparation of pyran derivatives, structural components in a wide variety of natural products.[1] For example, the HDA reaction between a vinyl ether and 1-cyclopentene carboxaldehyde derivatives would provide direct access to the fused cyclopenta[*c*]pyran bicyclic ring system characteristic of iridoids (eq 1), an important class of naturally occurring compounds.[2] The only

(1)

two reports to date of inverse-demand HDA approaches to the synthesis of iridoids have described high-temperature thermal cycloadditions to afford racemic products.[3] Recently, we reported efficient asymmetric catalysis of inverse electron demand HDA reactions between a variety of simple α,β-unsaturated aldehydes and ethyl vinyl ether using the tridentate (Schiff base)Cr(III) complex **5** (Scheme 1).[4] This methodology was extended to reactions of α-substituted α,β-

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(2) For reviews on iridoid natural products, see: (a) Nangia, A.; Prasuna, G.; Rao, P. B. *Tetrahedron* **1997**, *53*, 14507. (b) Thomas A. F.; Bessiere, Y. In *Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1988; Vol. 7, pp 275−454.

(3) (a) Korte, F.; Buchel, K. H.; Zschocke, A. *Chem. Ber.* **1961**, *94*, 1952. (b) Tietze, L.-F. *Chem. Ber.* **1974**, *107*, 2491.

(4) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3059. As described in this study, complex **5** is isolated as a μ-aquo dimer. However, we report catalyst loadings in terms of the amount of chromium employed, assuming the structure depicted in Scheme 1.

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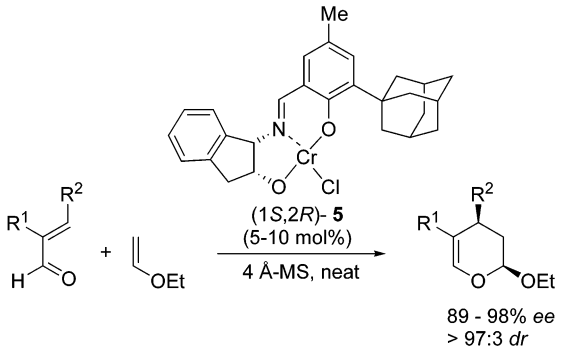
Scheme 1



unsaturated aldehydes ($R^1 \neq H$), raising the possibility of application to the stereoselective construction of bicyclic pyran ring systems. We describe here the successful execution of this strategy and the formal total synthesis of a series of stereochemically diverse iridoid natural products.

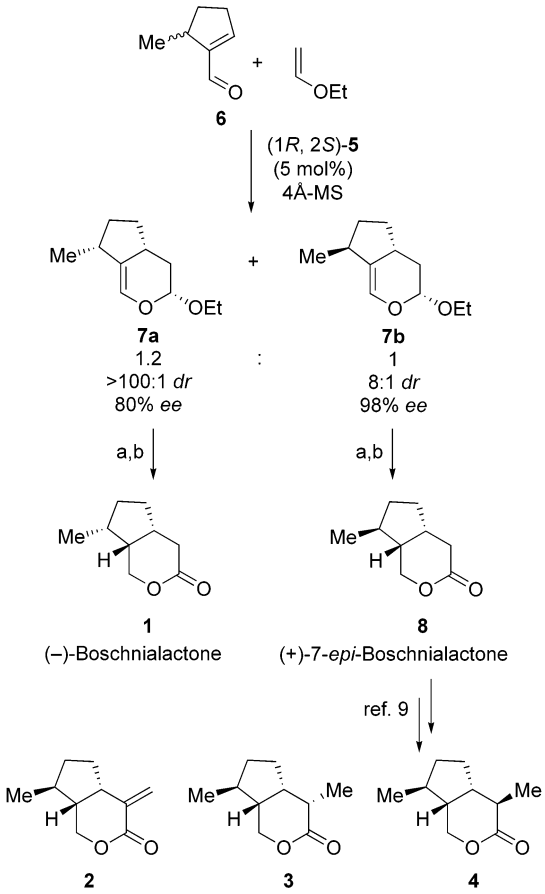
The model reaction of 1-cyclopentene-1-carboxaldehyde and ethyl vinyl ether (eq 1) was catalyzed by **5** (5 mol %) at room temperature to afford the desired cycloadduct with excellent endo diastereoselectivity (>97:3 dr) and good enantioselectivity (87% ee). With this promising result in hand, we turned our attention toward the use of substituted cyclopentenecarboxaldehydes such as those that would be required for the synthesis of iridoid natural products. For example, the use of 5-methyl-1-cyclopentene-1-carboxaldehyde (**6**) in the inverse-demand HDA reaction would provide efficient access to targets such as boschnialactone (**1**),[5] teucriumlactone (**2**), iridomyrmecin (**2**), and isoiridomyrmecin (**4**) (Scheme 2). Interestingly, both absolute stereochemistries at the methyl-bearing stereocenters are displayed in the natural products.

Initially, we evaluated a kinetic resolution approach to the synthesis of **1**−**4** using racemic **6**. The requisite aldehyde was prepared from 2-methylcyclopentanone according to a literature procedure, which involves tosyl hydrazone formation, subsequent vinyl anion formation (Shapiro reaction), and trapping with dimethylformamide.[6] Racemic **6** underwent cycloaddition in the presence of **5** and ethyl vinyl ether within 2 days at room temperature to afford a 1.2:1 ratio of diastereomers with complete conversion of the aldehyde (Scheme 2). Chiral GC analysis revealed that the major diastereomer (**7a**) was generated in 80% ee, while the minor diastereomer (**7b**) was produced in 98% ee. Thus, the "matched" aldehyde enantiomer had undergone reaction with >100:1 dr, while the mismatched aldehyde enantiomer afforded the diastereomeric cycloadduct with 8:1 dr. This represents an interesting example of a selective parallel kinetic resolution process.[7]

The cycloadducts were not readily separated, but hydrogenation of the 1.2:1 mixture of diastereomers with H_2/PtO_2 led to exclusive formation of two diastereomeric reduction products that were separable by column chromatography. Each diastereomer was subsequently hydrolyzed and the resulting lactols oxidized to afford (−)-boschnialactone (**1**)[8] from the matched aldehyde and (+)-7-*epi*-boschnialactone (**8**)[9,10] from the mismatched aldehyde. Thus, the absolute and relative stereochemistry of each cycloadduct was established, and the facial selectivity induced by the catalyst was demonstrated to be consistent with previous results obtained with prochiral substrates (Scheme 1).[4] In addition, the hydrogenation was determined to have yielded the *cis*-cyclopenta[*c*]pyran for both diastereomers.

Although the parallel kinetic resolution provided a straightforward route to enantioenriched iridoids **1**−**4**, the enantio-

Scheme 2. Parallel Kinetic Resolution of **6** with Ethyl Vinyl Ether and Catalyst **5**[a]



[a] Key: (a) H_2, PtO_2, EtOAc, 12 h, quant; (b) (i) cat. *p*-toluenesulfonic acid, acetone/H_2O (1:1), 24 h, (ii) PCC, CH_2Cl_2, 16 h, 80% over three steps.

(5) For a synthesis of *ent*-**1** involving a catalytic, enantioselective iodocarbocyclization, see: Inoue, T.; Kitagawa, O.; Saito, A.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7384.

(6) Barker, A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1901.

(7) For reviews on the topic of parallel kinetic resolution, see: (a) Kagan, H. *Croat. Chem. Acta* **1996**, *69*, 669. (b) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584. (c) Eames, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 885.

(8) Sakan, T.; Murai, Y.; Hayashi, Y.; Honda, Y.; Shono, T.; Nakajima, M.; Kato, M. *Tetrahedron* **1967**, *23*, 4635.

(9) Nangia, A.; Prasuna, G.; Rao, P. B. *Tetrahedron Lett.* **1994**, *35*, 3755.

(10) Compound **8** has been converted previously into **2**, **3** and **4**. This work thus constitutes a formal total synthesis of these irodoids. (a) Schaffner, K.; Demuth, M. *Chimia* **1981**, *35*, 437. (b) Demuth, M.; Schaffner, K. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 820.

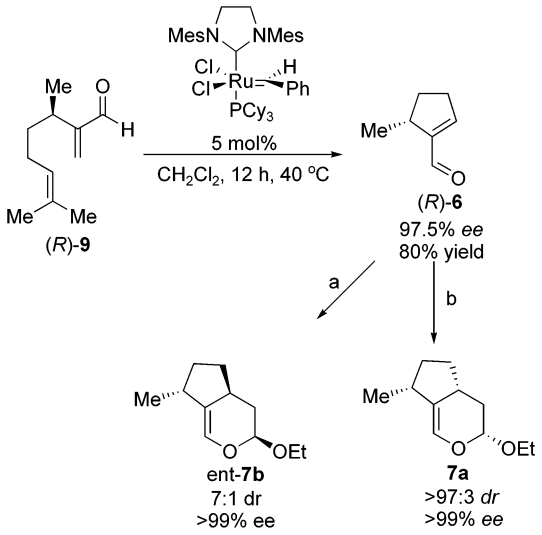
purity of the major diastereomer **7a** was only modest (80%) due to the lower diastereoselectivity of the cycloaddition for the mismatched aldehyde. To overcome this practical limitation, we investigated the use of enantioenriched **6** in the cycloaddition.

An efficient route to enantioenriched **6**[11] was envisioned based on the ring-closing metathesis of aldehyde **9**, available in a single step from commercially available citronellal (Eschenmoser's salt, TEA, CH_2Cl_2).[12] The second-generation Grubbs catalyst has been applied successfully to cross metatheses to generate isoprenyl units[13] and very recently in a single example of a ring-closing metathesis using an isoprenyl coupling partner.[14] We found that subjection of (*R*)-**9** to 5 mol % of the Grubbs catalyst in refluxing CH_2Cl_2 for 12 h resulted in complete conversion to product. Purification provided an 80% isolated yield of enantioenriched **6** (Scheme 3). Since both enantiomers of citronellal are produced commercially in a highly efficient asymmetric catalytic process,[15] this represents a practical route to either enantiomer of **6**.

Aldehyde (*R*)-**6** underwent reaction with ethyl vinyl ether in the presence of the matched (1*R*,2*S*)-**5** catalyst to afford cycloadduct **7a** in >97:3 dr and >99% ee. The reaction employing the mismatched catalyst (1*S*,2*R*)-**5** provided **7b** selectively in 7:1 dr and >99% ee (Scheme 3).

We have demonstrated the application of inverse-demand HDA reactions catalyzed by tridentate (Schiff base)Cr(III) complex **5** in the efficient and stereoselective synthesis of iridoid natural products. We anticipate that the attainment of high levels of catalyst control in cycloadditions of chiral substrates with these catalyst systems[16] will facilitate access to a wide range of other structurally and biologically interesting targets as well.

Scheme 3. Preparation and HDA Reactions of Enantioenriched **6**[a]



[a] Key: (a) ethyl vinyl ether, (1*S*,2*R*)-**5** (5 mol %), 4 Å MS, 2 d, 85%; (b) ethyl vinyl ether, (1*R*,2*S*)-**5**, 4 Å MS, 2 d, 85%.

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Supporting Information Available: Complete experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034883L

(11) The only previously reported synthesis of enantioenriched (*R*)-**6** was as a minor side-product in the preparation of methylcyclopentanoids: Becicka, B. T.; Koerwitz, F. L.; Drtina, G. J.; Baenziger, N. C.; Wiemer, D. F. *J. Org. Chem.* **1990**, *55*, 5613.

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(16) See also: Joly, G. D.; Jacobsen, E. N. *Org. Lett.* **2002**, *4*, 1795.