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Enantioselective Synthesis of a *trans*-7,8-Dimethoxycalamenene

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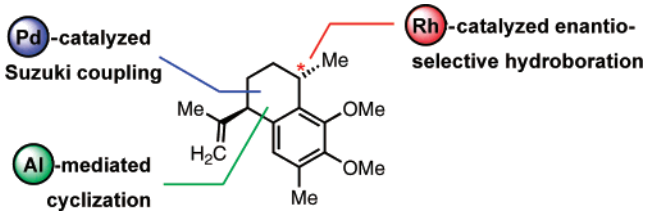
ABSTRACT



***trans*-7,8-Dimethoxy-11,12-dehydrocalamenene, a projected intermediate for the total synthesis of marine serrulatane and amphilectane diterpenes, was efficiently synthesized. Starting from a styrene, asymmetric Rh-catalyzed hydroboration using a novel chiral *P*,*P*-bidentate ligand afforded an organoboron intermediate (93% ee) which was directly used for C–C bond formation (double homologation, Suzuki coupling). The 1,4-trans-disubstituted tetralin skeleton was selectively formed by a Friedel–Crafts-type cationic cyclization under strictly aprotic conditions (Me_2AlCl) to suppress a remarkable proton-catalyzed disproportionation via diastereoselective hydride transfer.**

Over the past 20 years, several aromatic diterpenes with an amphilectane or serrulatane skeleton were identified as bioactive metabolites from marine soft corals, especially *Pseudopterogorgia elisabethae*.[1] Prominent representatives of such compounds (Figure 1) are the anti-inflammatory

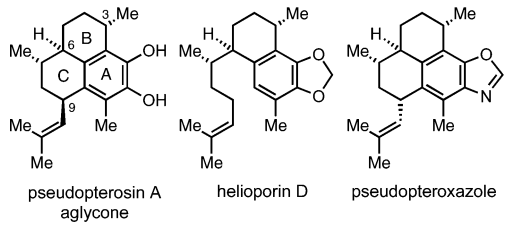


Figure 1. Structures of some amphilectane diterpenoids.

pseudopterosins,[2] the antiviral and cytotoxic helioporins,[3] and the pseudopteroxazoles,[4] the latter exhibiting promising antibiotic activities against *Mycobacterium tuberculosis* H37Rv.

All of these compounds possess a tetralin substructure formed by rings A and B with the same relative (*trans*) configuration of the benzylic substituents (stereocenters C-3 and C-6)—as a consequence of a 1,4-trans-disubstituted

(1) For reviews, see: (a) Heckrodt, T. J.; Mulzer, J. *Top. Curr. Chem.* **2005**, *244*, 1−41. (b) Rodriguez, A. D. *Tetrahedron* **1995**, *51*, 4571−4618. For additional leading references, see: (c) Rodriguez, I. I.; Shi, Y.-P.; Garcia, O. J.; Rodriguez, A. D.; Mayer, A. M. S.; Sanchez, J. A.; Ortega-Barria, E.; Gonzalez, J. *J. Nat. Prod.* **2004**, *67*, 1672−1680. (d) Ata, A.; Win, H. Y.; Holt, D.; Holloway, P.; Segstro, E. P.; Jayatilake, G. S. *Helv. Chim. Acta* **2004**, *87*, 1090−1098.

(2) (a) Look, S. A.; Fenical, W.; Jacobs, R. S.; Clardy, J. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 6238−6240. (b) Look, S. A.; Fenical, W.; Matsumoto, G. K.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5140−5145. For enantioselective syntheses, see: (c) Broka, C. A.; Chan, S.; Peterson, B. *J. Org. Chem.* **1988**, *53*, 1584−1586. (d) Corey, E. J.; Carpino, P. *J. Am. Chem. Soc.* **1989**, *111*, 5472−5474. (e) Majdalani, A.; Schmalz, H.-G. *Synlett* **1997**, 1303−1305. (f) Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 12777−12782. (g) Kocienski, P. J.; Pontiroli, A.; Qun, L. *J. Chem. Soc. Perkin Trans. 1*, **2001**, 2356−2366.

(3) (a) Tanaka, J.; Ogawa, N.; Liang, J.; Higa, T.; Gravalos, D. G. *Tetrahedron* **1993**, *49*, 811−822. For syntheses and stereostructural revision, see: (b) Geller, T.; Jakupovic, J.; Schmalz, H. G. *Tetrahedron Lett.* **1998**, *39*, 1541−1544. (c) Lazerwith, S. E.; Johnson, T. W.; Corey, E. J. *Org. Lett.* **2000**, *2*, 2389−2392.

(4) (a) Rodriguez, A. D.; Ramirez, C.; Rodriguez, I. I.; Gonzalez, E. *Org. Lett.* **1999**, *1*, 527−530. For syntheses and stereostructural revision, see: (b) Davidson, J. P.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 13486−13489. (c) Harmata, M.; Hong, X. C. *Org. Lett.* **2005**, *7*, 3581−3583.

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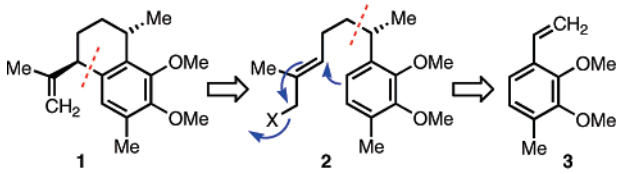
tetralin derivative (erogorgiaene) serving as a common biosynthetic intermediate.[1a,5]

We describe here an efficient and highly stereoselective synthetic entry to the calamenene **1**, a *trans*-1,4-disubstituted tetralin derivative representing a promising precursor for the synthesis of the marine diterpenes mentioned above.[6] Also, the bis-*O*-demethylated compound corresponding to **1** is a known anti-infective constituent of the plant *Guardiola platyphylla*.[7]

According to the retrosynthetic analysis sketched in Scheme 1, we optimistically planned to build up the *trans*-

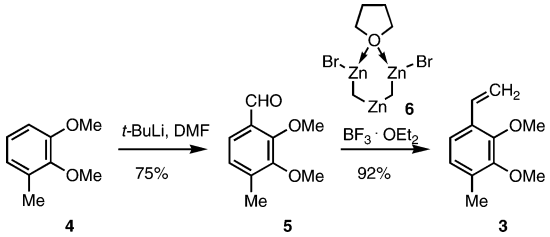
Scheme 1. Retrosynthetic Analysis



tetralin through a diastereoselective cyclization[8] from a precursor of type **2**. This compound in turn might be derived from the styrene derivative **3** by means of enantioselective hydroboration[9] and subsequent coupling reactions of the organoboron intermediates.

Building block **3**, needed as a substrate for the planned hydroboration, was prepared from commercially available 2,3-dimethoxytoluene (**4**) by directed ortho-metalation/formylation and subsequent methylenation of the aldehyde **5** employing Nysted reagent (**6**)[10] in the presence of BF_3 etherate (Scheme 2). Noteworthy, much lower yields were

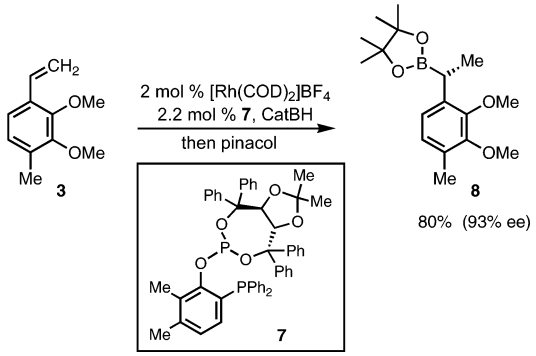
Scheme 2. Preparation of the Styrene **3**



obtained in the latter transformation under conventional Wittig conditions.

Using **3** as a substrate, we next studied its asymmetric Rh-catalyzed hydroboration to establish the first (benzylic) stereocenter. Initially, we performed the reaction according to Hayashi[9b] using catecholborane and a catalyst prepared in situ from $[Rh(COD)_2]BF_4$ and (*R*)-BINAP in DME as a solvent at −78 °C. However, after addition of pinacol,[11] the boronate **8** was obtained with an enantiomeric purity of only 63% ee,[12] a rather low value as compared to 96% ee obtained for the hydroboration of simple styrene under the same conditions.[9b] By screening a library of chiral phosphite−phosphane ligands developed in our laboratory,[13] we identified the TADDOL[14]-derived ligand **7** as particularly well suited. Under optimized conditions, the enantioselective hydroboration of **3** proceeded smoothly on a multigram scale to afford pure **8** in 93% ee and 80% isolated yield after chromatography (Scheme 3).[15]

Scheme 3. Enantioselective Hydroboration of **3**



The absolute configuration of the hydroboration product **8**[16] was proven by X-ray crystal structure analysis of its tricarbonylchromium complex (Figure 2).

(5) (a) Kerr, R. G.; Kohl, A. C.; Ferns, T. A. *J. Industr. Microbiol. Biotech.* **2006**, *33*, 532−538. (b) Ferns, T. A.; Kerr, R. G. *J. Org. Chem.* **2005**, *70*, 6152−6157.

(6) We had previously reported an enantioselective synthesis of *cis*-calamenenes related to **1** exploiting arene−$Cr(CO)_3$ complexes: (a) Schmalz, H.-G.; Arnold, M.; Hollander, J.; Bats, J. W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 109−111. (b) Schmalz, H.-G.; Hollander, J.; Arnold, M.; Dürner, G. *Tetrahedron Lett.* **1993**, *34*, 6259−6262. For a review, see: (c) Schmalz, H.-G.; Gotov, B.; Böttcher, A. In *Arene Metal Complexes*; Kündig, E. P., Ed. *Top. Organomet. Chem.* **2004**, *7*, 157−179.

(7) Wahyouno, S.; Hoffmann, J. J.; Bates, R. B.; McLaughlin, S. P. *Phytochemistry* **1991**, *30*, 2175−2182.

(8) Only few and little convincing examples exist for the diastereoselective synthesis of tetralins through cationic cyclization: (a) Appelbe, R.; Casey, M.; Dunne, A.; Pascarella, E. *Tetrahedron Lett.* **2003**, *44*, 7641−7644. For an exceptional case employing a $Co_2(CO)_6$-complexed propargylic cation, see: Jackson, S. R.; Johnson, M. G.; Mikami; M.; Shiokawa, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2694−2697.

(9) (a) Burgess, K.; Ohlmeyer, M. J. *J. Org. Chem.* **1988**, *53*, 5178−5179. (b) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426−3428. For leading reviews, see: (c) Hayashi, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg 1999; Vol. 1, pp 351−364. (d) Crudden, C. M., Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695−4712. (e) Carroll, A. M.; O'Sullivan, T. P.; Guiry, P. J. *Adv. Syn. Catal.* **2005**, *347*, 609−631.

(10) Matsubara, S.; Sugihara, M.; Utimoto, K. *Synlett* **1998**, 313−315.

(11) Chen, A. C.; Ren, L.; Crudden C. M. *Chem. Commun.* **1999**, 611−612.

(12) The enantiomeric excess of **8** was determined by means of GC using a chiral stationary phase (6T-2,3-methyl-β-cyclodextrin) after oxidation of **8** to the corresponding phenylethanol derivative (H_2O_2, NaOH, H_2O/MeOH).

(13) (a) Kranich, R.; Eis, K.; Geis, O.; Mühle, S.; Bats, J. W.; Schmalz, H.-G. *Chem. Eur. J.* **2000**, *6*, 2874−2894. (b) Blume, F.; Zemolka, S.; Fey, T.; Kranich, R.; Schmalz, H.-G. *Adv. Synth. Catal.* **2002**, *344*, 868−883. (c) Velder, J.; Weidner, I.; Schmalz, H.-G. Unpublished results.

(14) For, a review see: Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92−138.

(15) Small amounts of the nonbranched isomer of **8** were also isolated, the regioisomeric ratio being 87:13 as determined by NMR from the crude product mixture prior to chromatography.

(16) A pure sample of **8**−$Cr(CO)_3$ was obtained by refluxing **8** with $Cr(CO)_6$ under argon in Bu_2O/THF (6:1) for 18 h, followed by chromatographic purification and crystallization from heptane.

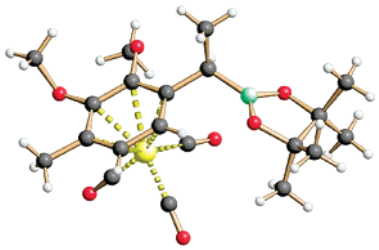
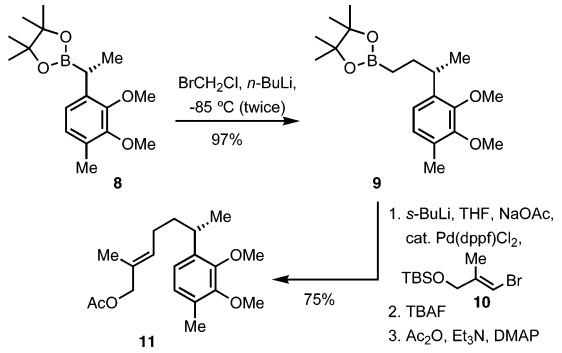


Figure 2. Structure of **8**−$Cr(CO)_3$ in the crystalline state.

The conversion of **8** into the cyclization precursor **11** was achieved as shown in Scheme 4. To prepare for the side chain

Scheme 4. Preparation of the Cyclization Precursor **11**



elongation by means of an sp^2-sp^3 Suzuki cross coupling,[17] **8** was first double homologated through two subsequent treatments with bromochloromethane and *n*-butyllithium under in situ quench conditions at low temperature.[11,18] The boronate **9**, thus obtained in high yield (under optimized conditions), was then first activated by addition of *sec*-butyllithium[19] before it was reacted with the substituted vinyl bromide **10**[20] in the presence of 5 mol % of $Pd(dppf)Cl_2$. Fluoride-induced cleavage of the TBS-ether and *O*-acetylation finally afforded the desired allylic acetate **11** in good overall yield.

We next investigated the projected cationic (Friedel−Crafts-type) cyclization of **11** (see Scheme 1). In a first experiment, a solution of the acetate **11** in a 3:1 mixture of trifluoroacetic acid and acetic acid was stirred for 5 days at 20 °C, according to the protocol of Ma and Zhang.[21]

Surprisingly, GC−MS analysis of the crude product (Figure 3) revealed the formation of a 1:1 mixture of two products

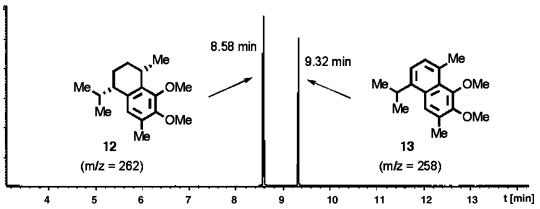
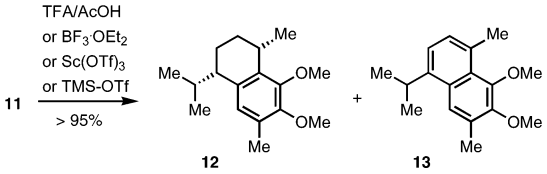


Figure 3. GC−MS of the crude product resulting from the cyclization of **11** according to Scheme 5.

(with $m/z = 258$ and 262, respectively), none of them showing the molecular weight of the expected cyclization product **1** ($m/z = 260$). Repetition of the cyclization reaction in dichloromethane (0 to 20 °C) in the presence of different common Lewis acids such as BF_3•etherate (1.0 equiv, 1 h), scandium triflate (1.1 equiv, 40 min), TMS-triflate (0.75 equiv, 1 h), or $AlMe_3$ (0.3 equiv, 12 h) gave more or less identical results (Scheme 5).

Scheme 5. Cyclization of **11** under "Protic" Conditions



The two reaction products, which obviously result from an unexpected disproportionation process, were identified as the *cis*-calamenene **12** and the naphthalene derivative **13** by means of NMR spectroscopy.[22,23]

While, according to TLC analysis, the conversion of **11** accordant to Scheme 5 was quantitative in all cases within a few minutes once the temperature had reached a critical value (ca. 0 °C), a more careful monitoring of the BF_3-mediated reaction (using initially only 0.3 equiv) revealed the occurrence of three major transient species with the (desired) mass of $m/z = 260$.

We therefore reasoned that the formation of **12** and **13** might result from a proton-catalyzed secondary process. To probe this hypothesis, we reacted the cyclization precursor **11** again, however under strictly aprotic conditions by

(17) Selected reviews: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168.

(18) (a) Sadhu, K. M.; Matteson, D. S. *Organometallics.* **1985**, *4*, 1687−1689. (b) Chen, A. C.; Ren, L.; Crudden, C. M. *J. Org. Chem.* **1999**, *64*, 9704−9710. (c) Ren, L.; Crudden, C. M. *Chem. Commun.* **2000**, 721−722. For a first example of a high-yield sequential double CH_2-insertion, see: (d) Fey, T. Dissertation, University of Cologne, Germany, 2005.

(19) Zou, G.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 5817−5819.

(20) Compound **10** was prepared in 71% yield from methyl (*E*)-3-bromometacrylate (Aberhart, D. J.; Tann, C.-H. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 939−942) by reduction (DIBAH, DCM) and *O*-protection (TBS-Cl, imidazole, DMF).

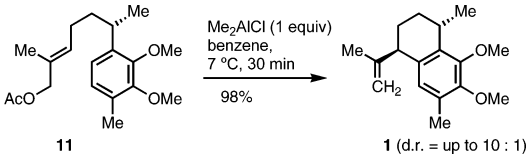
(21) Ma, S.; Zhang, J. *Tetrahedron* **2003**, *59*, 6273−6283.

(22) From the NMR spectra of the mixture, the signals of compounds **12** and *cis*-**1** could be unambiguously assigned by comparision with the spectrum of authentic samples of the pure cis isomers obtained in this laboratory by stereo-rational synthesis; see refs 6a and 6b as well as: Arnold, M. Dissertation, Universität Frankfurt 1994.

(23) After completion of our experimental work, Kraus and Jeon independently reported the related observation that the TFA-mediated (ref 20) cyclization of compound *rac*-**11**, prepared by a different route, leads to disproportionation to afford a mixture of two products, one of them being a *cis*-calamenene; see: Kraus, G. A.; Jeon, I. *Org. Lett.* **2006**, *8*, 5315−5316.

employing Me_2AlCl (1 equiv) as a "proton-scavenging" Lewis acid (Scheme 6).[24]

Scheme 6. Cyclization of **11** under "Aprotic" Conditions

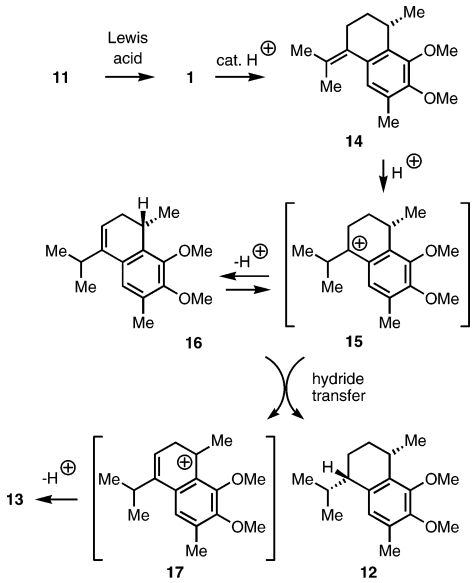


Much to our satisfaction, the envisioned *trans*-dehydrocalamenene **1** was formed under these conditions in almost quantitative yield and with very good diastereoselectivity (up to 10:1), if benzene was used as a solvent.[25] In dichloromethane or 1,2-dichloroethane somewhat lower trans/cis selectivities were obtained (3:1 and 5:1, respectively).

The trans configuration of the main product (**1**) was unambiguously proven by comparing its NMR data with those reported by Wahyouno.[7] In addition, a spectrum of an authentic sample of *cis*-**1**[6a,22] allowed its reliable identification as the minor isomer in the mixture. As a most characteristic feature, the signals of the two olefinic protons (isopropenyl side chain) are strongly split in the trans isomer (4.21 and 4.83 ppm) while they are virtually isochronic (4.92 ppm) in the cis isomer.

The surprising formation of **12** and **13** from **11** can be rationalized in terms of the mechanistic picture given in Scheme 7. At first, proton-catalyzed double bond migration

Scheme 7. Suggested Mechanism of the Formation of Compounds **12** and **13** from **11**



leads from the primary cyclization product (**1**) to its isomers **14** and **16**. In the key disproportionation step, the benzylic cation **15** formed by protonation of either **14** or **16** now abstracts a hydride[26] from **16** to give rise to **12** and a new benzylic cation (**17**), from which the naphthalene **13** is generated by proton loss.

While the cis diastereoselectivity of the formation of **12** certainly results from the hydride donor **16** to approaching the cation **15** from the less hindered face (Figure 4), the

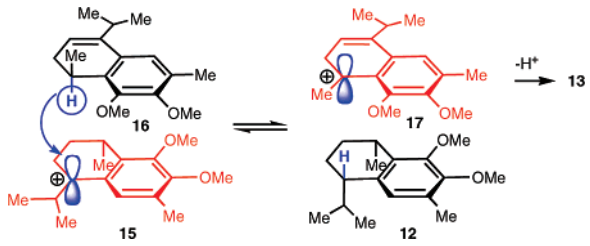


Figure 4. Diastereoselective hydride transfer between a dihydronaphthalene and a benzylic cation (red).

preferred formation of the trans-configurated product **1** in the Me_2AlCl-mediated cyclization of **11** is not easily explained. Actually, the stereochemical outcome contradicts the prediction of Kraus[23] that the cationic cyclization should proceed via a chairlike transition state (with the benzylic methyl group taking a pseudoaxial position to avoid allylic strain) to give a cis product.

In conclusion, we have elaborated a stereoselective synthetic route to the nonracemic *trans*-calamenene **1** (6 linear steps and 57% overall yield starting from **3**). The novel combination of (1) catalytic asymmetric hydroboration, (2) double homologation, and (3) Suzuki coupling may prove of value for other applications, as does the new chiral *P*,*P*-ligand **7**. Moreover, a remarkable trans-selective cationic cyclization was achieved, and important insight into the chemical and stereochemical aspects of the proton-catalyzed disproportionation process[23] was gained.

Acknowledgment. This work was supported by the European Commission (Ligbank) and the Fonds der Chemischen Industrie. We thank Ingo Weidner and Janna Velder, University of Cologne, for preparing and providing ligand **7**.

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

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(24) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927−3934.

(25) The quality of the Me_2AlCl (1 M in hexanes or 0.9 M in heptane) is very important. At least 1 equiv of active reagent seems to be necessary to achieve full conversion. An excess of reagent usually leads to lower selectivity. Also, reagent taken from a freshly opened bottle gave the product with a diastereomeric ratio of only 6:1.

(26) For a recent treatment of hydride transfer reactions between carbocations and unsaturated organic compounds, see: (a) Mayr, H.; Lang, G.; Ofial, A. R. *J. Am. Chem. Soc.* **2002**, *124*, 4076−4083. (b) Würthwein, E.-U.; Lang, G.; Schappele, L. H.; Mayr, H. *J. Am. Chem. Soc.* **2002**, *124*, 4084−4092.