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Stereochemically General Approach to Adjacent Bis(tetrahydrofuran) Cores of Annonaceous Acetogenins

Laura M. Wysocki, Matthew W. Dodge, Eric A. Voight, and Steven D. Burke*

Department of Chemistry, University of Wisconsin—Madison, 1101 University Avenue, Madison, Wisconsin 53706

burke@chem.wisc.edu

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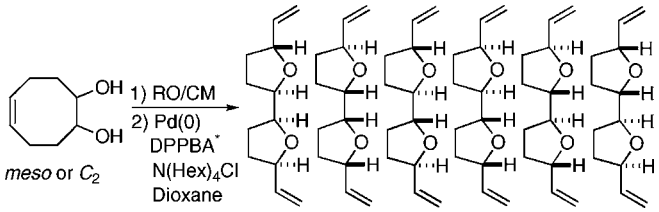
ABSTRACT



A series of six 2,5-disubstituted adjacent bis(tetrahydrofuran) stereoisomers with *trans*/*erythro*/*cis*, *trans*/*threo*/*trans*, or *cis*/*threo*/*cis* relative stereochemistry have been synthesized from known dihydroxycyclooctenes via ring opening/cross metathesis and Pd(0)-mediated asymmetric double cycloetherification. The stereochemistry of four of these isomers has been found in the biologically active annonaceous acetogenin natural products.

Annonaceous acetogenins comprise a large class of natural products isolated from the *Annonaceae*, a family of tropical and subtropical trees and shrubs.[1,2] The annonaceous acetogenins display a myriad of interesting biological properties including anthelmintic, cytotoxic, antimalarial, antimicrobial, antiprotozoal, and pesticidal activities. Annonaceous acetogenins are the most powerful known inhibitors of mitochondrial complex I (NADH/ubiquinone oxidoreductase) in mammalian and insect electron-transport systems.[3] They are also potent inhibitors of NADH oxidase in the plasma membranes of cancer cells. These actions decrease both oxidative and cytosolic ATP production, which results in apoptosis through ATP deprivation.[4] The annonaceous acetogenins have received considerable attention in the synthetic community because of their interesting structural and biological properties.[5] Figure 1 shows representative annonaceous acetogenins

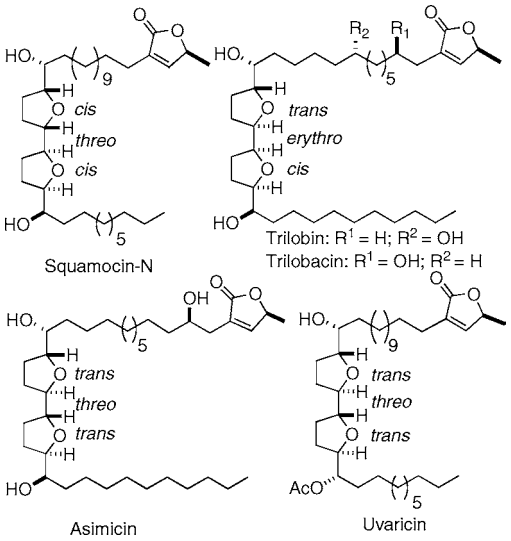


Figure 1. Representative annonaceous acetogenins.

(1) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504.

(2) Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269.

(3) (a) Tormo, J. R.; Gallardo, T.; Gonzalez, M. C.; Bermejo, A.; Cabedo, N.; Andreu, I.; Estornell, E. *Curr. Top. Phytochem.* **1999**, *2*, 69. (b) Wang, X.-W.; Xie, H. *Drugs Future* **1999**, *24*, 159.

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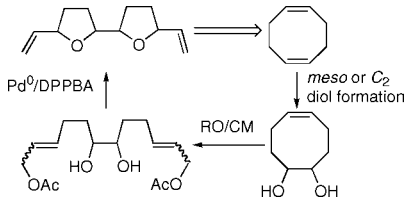
that contain bis(THF) cores with *cis*/*threo*/*cis*, *trans*/*erythro*/*cis*, and *trans*/*threo*/*trans* relative stereochemistry about the adjacent THF rings.

We initially demonstrated the utility of asymmetric double cycloetherification to construct 2,5-disubstituted bis(THF) ring systems in a formal synthesis of uvaricin.[6] In this letter, we present short, efficient syntheses of several diol bis(allylic acetate) and diol bis(allylic benzoate) cycloetherification substrates as well as a general approach to six stereoisomeric bis(THF) cores of annonaceous acetogenins and analogues thereof.

Our synthetic strategy is illustrated in Scheme 1. We envisioned using reagent control through asymmetric double

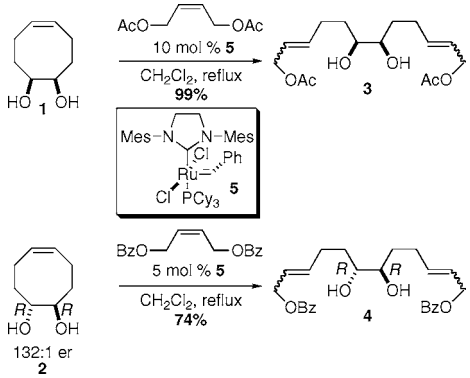
Scheme 1. Synthetic Strategy



cycloetherification of diol bis(allylic acetates) to set the outermost stereocenters of the bis(THF) cores to maintain C_2-symmetry or to break *meso*-symmetry. The requisite diol bis(allylic esters) could be accessed via ring opening/cross metathesis (RO/CM) of *meso*- or C_2-symmetric dihydroxycyclooctenes, which are available[7,8] from inexpensive cyclooctadiene (COD).

The syntheses of *meso*-diol bis(allylic acetate) **3** and C_2-symmetric diol bis(allylic benzoates) **4** and *ent*-**4** are shown in Scheme 2. Known 1,2-dihydroxycyclooctenes **1**,[7] **2**,[8] and

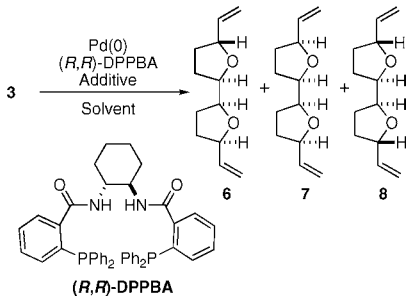
Scheme 2. Preparation of *meso*-Bis(allylic acetate) **3** and C_2-Symmetric Bis(allylic benzoates) **4** and *ent*-**4**[9]



ent-**2**[8] were subjected to RO/CM. Treatment of **1** with Grubbs' second-generation ruthenium catalyst **5** (10 mol %) and 1,4-diacetoxy-*cis*-2-butene[10] gave *meso*-diol bis(allylic acetate) **3** in excellent yield. However, RO/CM of C_2-symmetric **2** and *ent*-**2** under the same conditions gave the corresponding diol bis(allylic acetates) in low yield.[11] Substituting 1,4-dibenzoyloxy-*cis*-2-butene and using **5** (5 mol %) yielded diol bis(allylic benzoates) **4** and *ent*-**4** in good yield. In all reactions, the major product is that with all *E* double bonds, with a small amount of *E*/*Z* double bond isomers also detectable.[12] Our experience with asymmetric double cycloetherification[13] has shown the presence of *E*/*Z* isomers to be inconsequential. This independence of the cycloetherification reaction on double bond geometry was verified for five-membered ring formation (vide infra).

With the *meso*-symmetric bis(allylic acetate) and the enantiomeric C_2-symmetric bis(allylic benzoate) substrates in hand, we systematically evaluated the Pd(0)-mediated asymmetric double cycloetherification. A general representation of this reaction using (*R*,*R*)-*N*-[2,(2′-diphenylphosphino)-benzamidocyclohexyl] (2′-diphenylphosphino) benzamide ligand [(*R*,*R*)-DPPBA] and **3** is shown in Scheme 3.

Scheme 3. Double Cycloetherification of **3**



Although early attempts resulted in complete conversion to an adjacent bis(THF) core, we obtained a mixture of the desired desymmetrized product **6** and two undesired *meso*-symmetric diastereomers **7** and **8** in which stereochemical errors had occurred in one of the THF ring-forming reactions.

The configuration of the newly formed stereocenters in this Pd(0)-mediated, chiral ligand-controlled cycloetherification can be predicted using Trost's transition-state model shown in Figure 2.[14] The phenyl groups from the C_2-

(4) Chavez, D.; Mata, R.; Iglesias-Prieto, R.; Lotina-Hennsen, B. *Physiol. Plant.* **2001**, *111*, 262.

(5) For select recent examples, see: (a) Das, S.; Li, L.-S.; Abraham, S.; Chen, Z.; Sinha, S. C. *J. Org. Chem.* **2005**, *70*, 5922. (b) Mertz, E.; Tinsley, J. M.; Roush, W. R. *J. Org. Chem.* **2005**, *70*, 8035. (c) Crimmins, M. T.; Zhang, Y.; Diaz, F. A. *Org. Lett.* **2006**, *8*, 2369. (d) Marshall, J. A.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 3557. (e) Zhao, H.; Gorman, J. S .T.; Pagenkopf, B. L. *Org. Lett.* **2006**, *8*, 4379.

(6) Burke, S. D.; Jiang, L. *Org. Lett.* **2001**, *3*, 1953.

(7) Kawazoe, K.; Furusho, Y.; Nakanishi, S.; Takata, T. *Synth. Commun.* **2001**, *31*, 2107.

(8) Horikawa, T.; Norimine, Y.; Tanaka, M.; Sakai, K.; Suemune, H. *Chem. Pharm. Bull.* **1998**, *46*, 17.

(9) (*S*,*S*)-Diol *ent*-**2** affords *ent*-**4** in 73% yield.

(10) Morgan, J. P.; Morrill, C.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 67.

(11) Scherman, O. A.; Walker, R.; Grubbs, R. H. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **2003**, *44*, 952.

(12) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(13) (a) Lucas, B. S.; Burke, S. D. *Org. Lett.* **2003**, *5*, 3915. (b) Lucas, B. S.; Luther, L. M.; Burke, S. D. *Org. Lett.* **2004**, *6*, 2965. (c) Keller, V. A.; Kim, I.; Burke, S. D. *Org. Lett.* **2005**, *7*, 737.

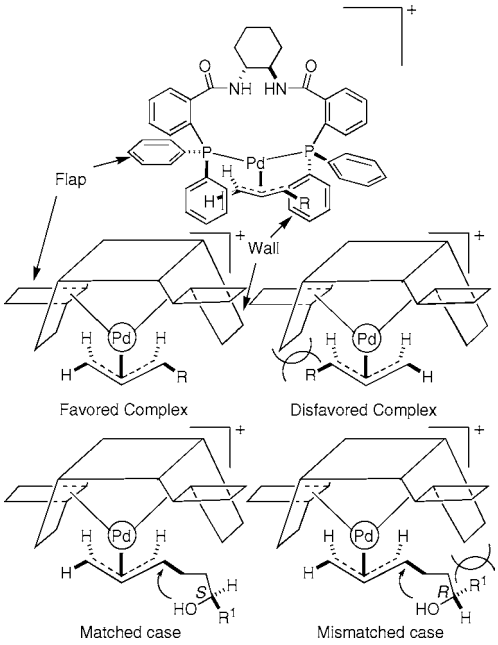


Figure 2. Transition-state model using (*R*,*R*)-DPPBA for matched and mismatched cyclizations.

symmetric bis(diphenylphosphine) ligand surround the Pd π-allyl complex in such a way that they act as a "flap" and a "wall" as shown.[15] The Pd complex can undergo $\pi-\sigma-\pi$ interconversion, allowing Pd complexation to either face of the π-allyl. The R group, representing the rest of the molecule, can therefore be positioned in open space toward a flap, which is the favored lower-energy complex, or toward a wall, which is disfavored because of steric congestion.

With our substrates in this favored complex, when the alcohol nucleophile is lined up for intramolecular attack, the rest of the molecule, R^1, will either extend away into open space in the matched case, leading to a 2,5-*cis*-disubstituted THF, or extend back toward the large Pd π-allyl complex in the mismatched case, affording a 2,5-*trans*-disubstituted THF ring.

Initial conditions for the double cycloetherification in Scheme 3 employed 4 mol % of Pd(0) in THF without any additive. As shown in Table 1, these reaction conditions led to a modest 2.12:1 diastereomeric ratio (dr) of **6** to the mixture of **7** and **8**[16] but an excellent enantiomeric ratio (er)[17] of 25.7:1 for **6** (entry 1).[18] Note that two stereochemical "errors" are required to form *ent*-**6**.

Table 1. Optimization of Double Cycloetherification of **3** with (*R*,*R*)-DPPBA*

	[Pd(0)][a]	solvent	additive	yield	dr[i]	er[l]
1	4[b]	THF	none	87%[f]	2.12:1[j]	25.7:1
2	8[b]	THF	none	74%[g]	1.85:1[k]	
3	2[b]	THF	none	58%[f]	2.88:1[j]	
4	4[b]	CH_2Cl_2	none	74%[g]	4.5:1[k]	
5	3.5[c]	dioxane	none	89%[g]	1.8:1[k]	
6	4[b]	CH_2Cl_2	NEt_3[d]	76%[f]	1.53:1[j]	
7	4[b]	THF	$N(Hex)_4Cl$[e]	50%[g,h]	9:1[k]	
8	3.5[c]	CH_2Cl_2	$N(Hex)_4Cl$[e]	78%[g]	1.3:1[k]	
9	7[c]	dioxane	$N(Hex)_4Cl$[e]	89%[g]	19.9:1[k]	>200:1

* Reactions in THF and CH_2Cl_2 were run at 0 °C to room temperature. Reactions in dioxane were run at room temperature. Legend: [a]mol % of Pd(0) source; [b]$Pd_2(dba)_3{\cdot}CHCl_3$; [c]$Pd(dba)_2$; [d]2 equiv; [e]60 mol %. [f] The sum of separately isolated yields of **6** and a mixture of **7** and **8** after extensive chromatography. [g] Yield of a mixture of **6**, **7**, and **8**. [h] Reaction did not go to completion. [i] dr is the ratio of **6** to the mixture of **7** and **8**. [j] Ratio determined by isolated yields. [k] Ratio determined by quantitative ^{13}C NMR.[21] [l] See ref 18.

Encouraged by this initial result, we examined several potential influences on the diastereoselectivity of the cyclization. As mentioned earlier, the ring opening/cross metathesis was an efficient way to access **3** but left some *E*/*Z* isomers in the product. The all-*E* analogue of **3** was synthesized[19] and subjected to the same Pd(0)/DPPBA cycloetherification conditions. No change in the diastereoselectivity was observed, so we do not believe the *E*/*Z* isomers have any effect on the selectivity. Differences in substrate geometry are no longer present in the cycloetherification transition state if geometric isomerization of the Pd π-allyl complex occurs.[15]

Changing the concentration of Pd(0) in solution can also affect the stereoselectivity of asymmetric allylic alkylation. Lloyd−Jones found that at high Pd(0) concentrations the discrete 1:1 ratio of Pd to ligand assumed thus far is in equilibrium with several oligomers that are no longer C_2-symmetric.[20]When Pd(0) concentration was increased to 8 mol % (entry 2), there was a slight decrease in diastereoselectivity from the initial experiment, and when it was decreased to 2 mol % (entry 3), there was a slight increase in diastereoselectivity. Although consistent with the precedent cited,[21] these variations in stereoselectivity were modest.

A substantial improvement in diastereoselectivity for this double cycloetherification was accomplished through the screening of several different solvents and additives. In the absence of an additive, there was a slight improvement in diastereoselectivity to 4.5:1 in CH_2Cl_2 when compared to THF and dioxane as solvents (entries 1, 4, and 5). Additives were found to change selectivity significantly. In CH_2Cl_2, the addition of NEt_3 reduced the diastereoselectivity (entry

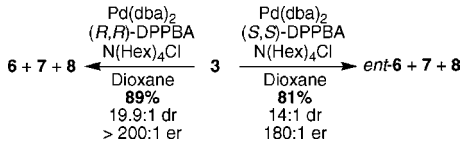
(14) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.
(15) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747−760.
(16) We found that **6** could be isolated, but **7** and **8** were inseparable from one another; so, the dr is reported as the ratio of **6** to the mixture of **7** and **8**.
(17) Gawley, R. E. *J. Org. Chem.* **2006**, *71*, 2411.
(18) The enantiomeric ratio (er) was determined by HPLC after derivatization. For all bis(THF) diene products, the terminal alkenes were ozonolytically cleaved, reduced to the primary diol with $NaBH_4$, and converted to the dibenzoate with BzCl and pyridine. Details and HPLC traces are in the Supporting Information.
(19) The synthesis of the all-*E*-**3** is shown in the Supporting Information.
(20) (a) Lloyd-Jones, G. C.; Stephen, S. C.; Fairlamb, I. J. S.; Martorell, A.; Dominguez, B.; Tomlin, P. M.; Murray, M.; Fernandez, J. M.; Jeffery, J. C.; Riis-Johannessen, T.; Guerziz, T. *Pure Appl. Chem.* **2004**, *76*, 589. (b) Fairlamb, I. J. S.; Lloyd-Jones, G. C. *Chem. Commun.* **2000**, *24*, 2447.
(21) Claridge, T. D. W. *High-Resolution NMR Techniques in Organic Chemistry*; Elsevier: Oxford, England, 1999; pp 114−116.

6), possibly due to an increase in the rate of nucleophilic attack of the alcohol,[22] decreasing the extent of interconversion of π-allyl complexes and consequently decreasing the ligand-mediated selectivity.

Addition of a chloride ion to Pd(0)-catalyzed allylic substitutions is thought to promote interconversion of π-allyl complexes by coordinating to the Pd center and facilitating σ-complex formation,[22,23] allowing more rapid $\pi-\sigma-\pi$ exchange. In this case, use of $N(Hex)_4Cl$ in dioxane led to a dramatic increase in diastereoselectivity (~20:1) and very high enantiomeric ratios (>200:1) for the major diastereomer (entry 9).

Application of these optimized conditions to **3** with the enantiomeric DPPBA ligands is summarized in Scheme 4.

Scheme 4. Cyclization of **3** to Enantiomeric *trans/erythro/cis*-Bis(THF) Cores[a]

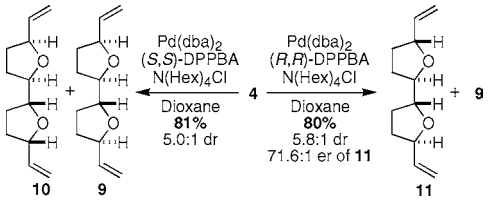


[a] Diastereomer ratios determined by quantitative ^{13}C NMR.

Cyclization using (*R*,*R*)-DPPBA resulted in an 89% yield of a mixture favoring **6** as a single enantiomer in a 19.9:1 dr. Using (*S*,*S*)-DPPBA, we observed similar results, with a mixture of 14:1 dr produced in 80% yield and an er of the desired product, *ent*-**6**, of 180:1 as determined by chiral HPLC.[18]

With the success of the chloride ion additive in dioxane, we applied these conditions to the C_2-symmetric substrates **4** and *ent*-**4**.[24] Scheme 5 shows the reaction of substrate **4** with (*S*,*S*)-DPPBA, which yielded a 5.0:1 ratio of the desired product **10** and the undesired, dissymmetric **9** in 81% yield. Double cycloetherification of **4** with (*R*,*R*)-DPPBA afforded a 5.8:1 ratio of **11** and **9** with **11** formed in 71.6:1 er.[25] Although the diastereomeric and enantiomeric ratios for the products from the C_2-symmetric substrates are not as high as in the desymmetrization of *meso*-symmetric substrate **3**, they are synthetically useful.

Scheme 5. Double Cycloetherification of **4**[a]



[a] Diastereomer ratios determined by quantitative ^{13}C NMR.

In summary, we have demonstrated a general, efficient, two-step approach to 2,5-disubstituted adjacent bis(THF) stereoisomers utilizing ring opening/cross metathesis and Pd(0)-mediated asymmetric double cycloetherification. High diastereomeric ratios (dr) and very high enantiomeric ratios (er) were observed for the reagent-controlled asymmetric double cycloetherifications in the presence of a chloride ion additive. Differentiation of the homotopic or diastereotopic terminal alkenes of these bis(THF) dienes is underway and should provide rapid access to numerous adjacent bis(THF)-containing annonaceous acetogenins.

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

OL062390L

(22) Trost, B. M.; Machacek, M. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 4693.

(23) (a) Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron: Asymmetry* **1997**, *8*, 155. (b) Cantat, T.; Génin, E.; Giroud, C.; Meyer, G.; Jutand, A. *J. Organomet. Chem.* **2003**, *687*, 365.

(24) Reactions with *ent*-**4** using $N(Hex)_4Cl$ in dioxane and (*R*,*R*)-DPPBA gave a 6.4:1 mixture of *ent*-**10** and *ent*-**9** in 79% yield. Reaction in THF with no additive produced a 5.0:1 mixture of *ent*-**10** and *ent*-**9** in 78% yield. Reaction of *ent*-**4** using $N(Hex)_4Cl$ in dioxane and (*S*,*S*)-DPPBA gave a 5.9:1 mixture of *ent*-**11** and *ent*-**9** in 75% yield. Product *ent*-**11** was obtained in an er of 55.5:1. Reaction in THF with no additive produced a 2.6:1 mixture of *ent*-**11** and *ent*-**9** in 81% yield.

(25) When the reactions were performed in THF without an additive, **4** yielded a 2.8:1 mixture of **11** and **9** in 83% yield with (*R*,*R*)-DPPBA and a 4.3:1 mixture of **10** and **9** in 74% yield using (*S*,*S*)-DPPBA.