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Formal Synthesis of Uvaricin via Palladium-Mediated Double Cyclization

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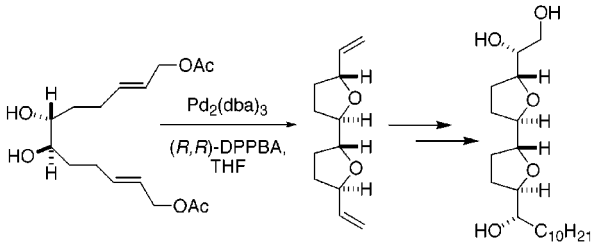
ABSTRACT



A novel palladium-mediated, ligand-controlled double cyclization is reported. The C_2-symmetric diene produced was desymmetrized via Sharpless asymmetric dihydroxylation and was further transformed into a known intermediate in the synthesis of uvaricin.

Annonaceous acetogenins constitute a new class of compounds that has shown extremely diverse biological activities including cytotoxic, antitumor, antimalarial, immunosuppressive, pesticidal, and antifeedant agents.[1] Their mechanism of action involves the inhibition of either NADH oxidase in plasma membrane or mitochondrial NADH-ubiquinone reductase. The isolation, structure elucidation, and synthesis of these compounds has been an area of active research during the past decade.[2] More than 300 compounds have been isolated; the most potent of these possess central 10-carbon fragments comprising two adjacent 2,5-disubstituted tetrahydrofuran subunits flanked by secondary carbinols.[3] One set (trans/threo/trans) of bis-THF core stereochemistries is represented in compounds **1**−**4** (Figure 1). Their structural similarity suggests that **1**−**4** could be derived from a common intermediate.

Two-directional synthesis by simultaneous chain homologation and terminus differentiation[4] has been one of our main strategies in the synthesis of complex natural products.[5] It offers not only the intrinsic efficiency in skeleton synthesis but also the possibility of higher enantio- and diastereoselectivity. One possibility involves the synthesis of a C_2-symmetric intermediate. Differentiation of the termini is simplified due to the fact that the two ends are homotopic. The local C_2 symmetry about the bis-THF core in numerous annonaceous acetogenins motivated us to adopt this approach.

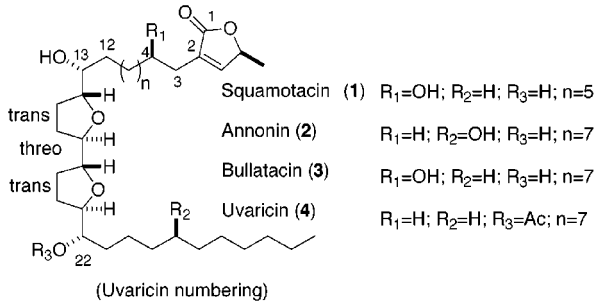


Figure 1. Representative structure.

(1) For recent reviews, see: (a) Tormo, J. R.; Gallardo, T.; Gonzalez, M. C.; Bermejo, A.; Cabedo, N.; Andreu, I.; Estornell, E. *Curr. Top. Phytochem.* **1999**, *2*, 69−90. (b) Johnson, H. A.; Oberlies, N. H.; Alali, F. Q.; Mclaughlin, J. L. *Bio. Act. Nat. Prod.* **2000**, 173−183.

(2) For recent reviews, see: (a) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G.; Appendino, G. *Chemtracts* **1998**, *11*, 803−827. (b) Zafra-Polo, M. C.; Figadere, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087−1117. (C) Marshall, J. A.; Hinkle, K. W.; Hagedorn, C. E. *Isr. J. Chem.* **1997**, *37*, 97−107.

(3) Alali, F. Q.; Liu, X.; Mclaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540.

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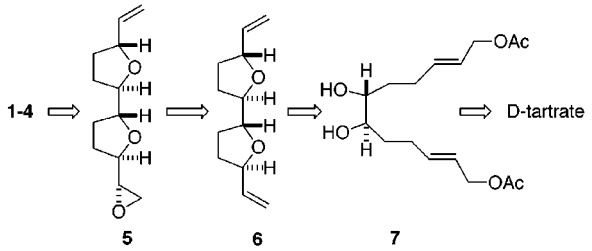
Our retrosynthetic analysis revealed epoxide **5** (Scheme 1), which should be available from C_2-symmetric diene **6**,

Scheme 1. Restrosythetic Analysis



as a common intermediate for conversion to the set of compounds in Figure 1. The double cyclization substrate **7** could potentially be derived from diethyl D-tartrate.[6]

Trost and Tenaglia have demonstrated that vicinal diol allyl acetates could be cyclized selectively to afford substituted tetrahydrofurans instead of tetrahydropyrans (Figure 2)[7] in

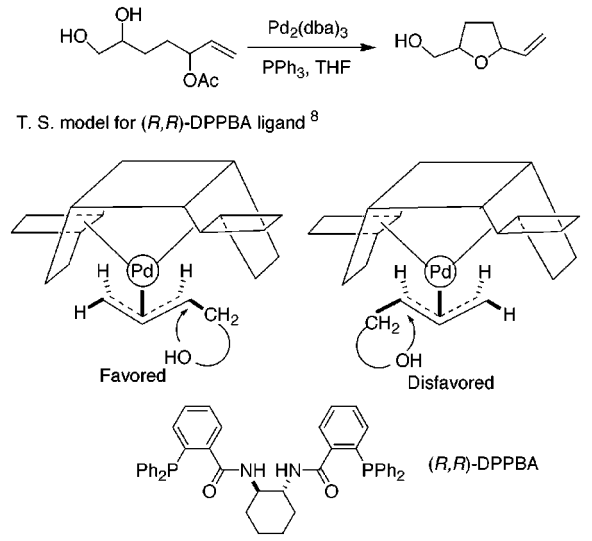
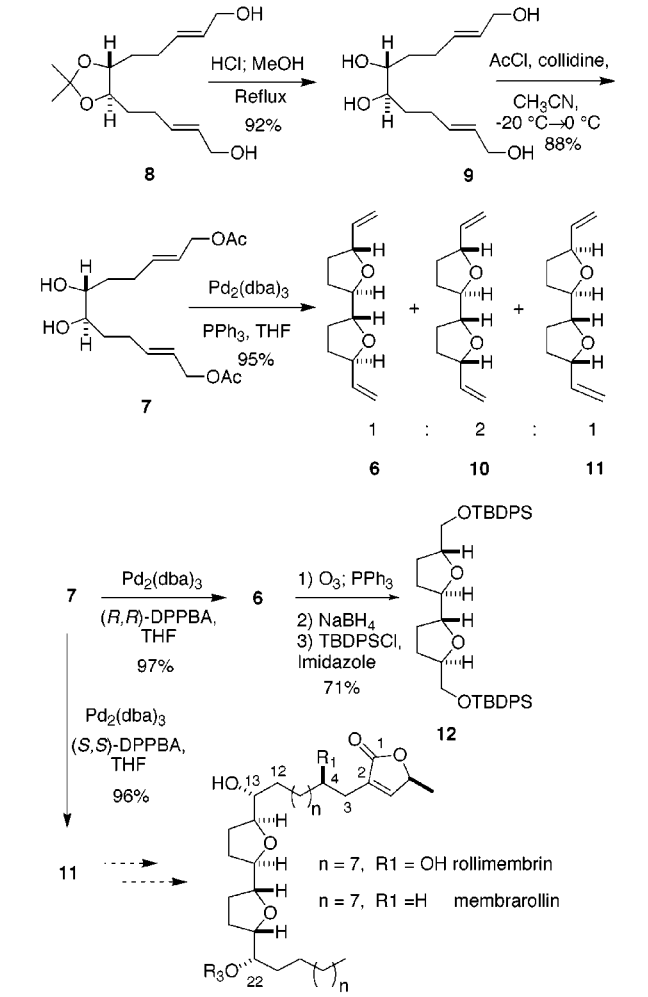


Figure 2.

excellent yield, albeit in low diastereoselectivity. The diastereoselectivity could, in principle, be controlled by utilizing Trost's chiral *N*-[2-(2′-diphenylphosphino)benzamino-cyclohexyl](2′-diphenylphosphino)benzamide (DPPBA) ligand.[8] According to the model proposed by Trost and Toste, the two faces of the alkene could be discriminated as shown in Figure 2. We envisioned that the diol bis(allylic acetate) **7** could undergo a double cyclization to afford the bis-THF core where two newly formed stereogenic centers could be selectively introduced by applying the appropriate DPPBA ligand.

Following known procedures,[9] diol **8** (Scheme 2) was

Scheme 2



synthesized from diethyl D-tartrate in five steps and 54% overall yield. Acetonide removal with aqueous HCl in refluxing methanol smoothly afforded tetraol **9**. Attempted selective acylation in CH_2Cl_2 afforded a mixture of triacylated, diacylated, and monoacylated products, probably because of the poor solubility of the tetraol. Switching the solvent to CH_3CN provided the desired diacetate **7** in good yield. The crystalline diol diacetate **7** was subjected to $Pd_2(dba)_3$-catalyzed cyclization conditions in the absence of a chiral ligand. A statistical mixture (1:2:1) of cyclized bis-THF products (trans/threo/trans **6**, trans/threo/cis **10**, and cis/

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(5) (a) Burke, S. D.; Buchanan, J. C.; Rovin, J. D. *Tetrahedron Lett.* **1991**, *32*, 3961−3964. (b) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626−8627. (c) Burke, S. D.; Austad, B. C.; Hart, A. C. *J. Org. Chem.* **1998**, *63*, 6770−6771

(6) For an early effort yielding (+)-(15,16,19,20,23,24)-hexaepiuvaricin from diethyl L-tartrate, see: Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369−9371.

(7) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2927−2930.

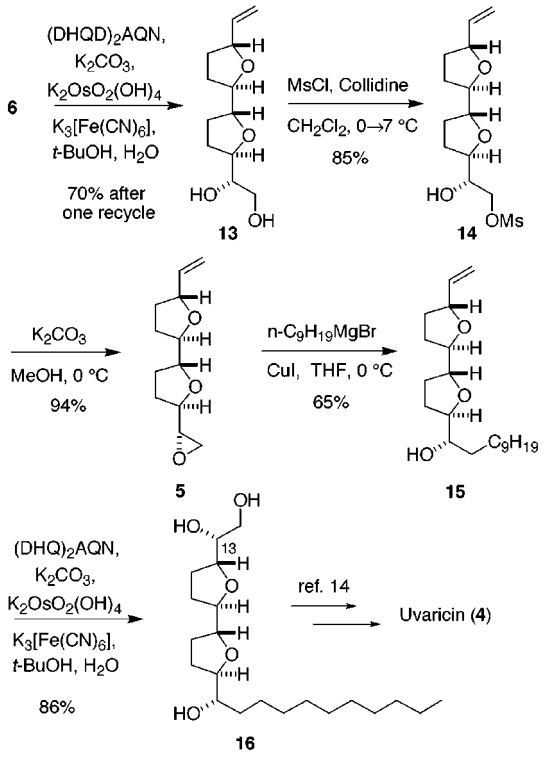
(8) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545−4554.

(9) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419−4427.

threo/cis **11**) was formed in excellent yield. Encouraged by this result, (*R*,*R*)-DPPBA was used as a chiral ligand, in conjunction with the palladium catalyst. Gratifyingly, diene **6**[10] was isolated in 97% yield as a single diastereomer (^{1}H, ^{13}C NMR), with trans disubstitution on both new THF rings. To confirm the *R*,*R* stereochemistries of newly formed asymmetric centers, diene **6** was treated with ozone and reduced to the corresponding diol, which was subsquently converted to bis(silyl ether) **12**, the enantiomer of which is known.[11] When (*S*,*S*)-DPPBA was used, the diastereomeric bis-THF product **11** was generated cleanly in excellent yield, demonstrating potential application to the synthesis of other annonaceous acetogenins such as rollimembrin and membrarollin (Scheme 2).[3]

Desymmetrization (Scheme 3) of diene **6** with AD-mix-β to set the secondary hydroxyl center gave only moderate diastereoselectivity. The $(DHQD)_2AQN$ ligand[12] provided better selectivity, giving the desired diastereomer cleanly when 4% of $(DHQD)_2AQN$ and 0.4% of $K_2OsO_4(OH)_2$ were used. The reaction was allowed to proceed to about 50% conversion, and unreacted diene (45%) was isolated and resubjected to the reaction conditions to afford diol **13** in 70% combined yield after one recycle. Selective monosulfonylation of the diol[13] gave monomesylate **14**, which was treated with K_2CO_3 to afford epoxide **5** in excellent yield. Attempted opening of the epoxide with nonylmagnesium bromide in the presence of a catalytic amount of CuBr failed. Instead, fragmentation of the top THF ring was observed, presumably through an S_N2' mechanism. After careful optimization of the reaction conditions, we found that treating epoxide **5** with 1.1 equiv of nonylmagnesium bromide and 0.5 equiv of CuI afforded alcohol **15** in 65% yield. Dihydroxylation of the remaining alkene with $(DHQ)_2AQN$ as the osmate ligand set the stereochemistry of the C13 hydroxyl group and provided the known triol **16**, which has served as an intermediate in a total synthesis of uvaricin.[14]

Scheme 3



In summary, a formal synthesis of uvaricin was realized. A palladium-mediated double cyclization allowed the selective formation of two stereocenters and two rings in a single step. The formation of the new stereocenters was controlled by the use of chiral DPPBA ligands, thus providing general access to annonaceous acetogenins containing trans/threo/trans or cis/threo/cis bis-THF core structures.

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Supporting Information Available: Experimental procedures and spectral data for compound **5**—**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) A 12:1 diastereomeric mixture of trans—trans and cis—trans dienes has been synthesized via S_N2' reactions: Li, P.; Yang, J.; Zhao, K. *J. Org. Chem.* **1999**, *64*, 2259—2263.

(11) Koert, U.; Stein, M.; Harmes, K. *Tetrahedron Lett.* **1993**, *34*, 2299—2302.

(12) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448—451.

(13) O'Donnell, C. J.; Burke, S. D. *J. Org. Chem.* **1998**, *63*, 8614—8616.

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