

Total Synthesis of *cis*-Solamin: Exploiting the RuO₄-Catalyzed Oxidative Cyclization of Dienes[†]

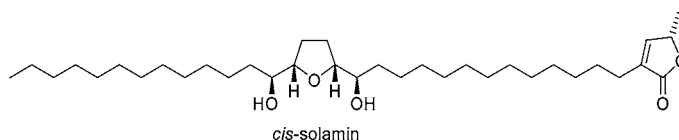
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ABSTRACT



Total synthesis: 11 steps, 7.5% overall yield

An enantioselective total synthesis of *cis*-solamin has been accomplished using a highly diastereoselective ruthenium tetroxide catalyzed oxidative cyclization as a crucial transformation. Further key steps involved an enzymatic desymmetrization, a TPAP-catalyzed oxidative terminus differentiation, and a ruthenium-catalyzed Alder-ene reaction. Thus, the total synthesis of *cis*-solamin was achieved in 11 steps with an overall yield of 7.5%.

The annonaceous acetogenins are a class of more than 400 natural products isolated exclusively from the tropical plant family *Annonaceae*.¹ This unique class of metabolites has attracted particular attention as a result of their remarkable range of biological effects. They exhibit high antitumor, antimalarial, pesticidal, and immunosuppressive activity.² Interaction with mitochondrial complex I of the respiratory chain appears to be the molecular basis for at least some of these effects.

Structurally, most acetogenins are characterized by a long unbranched fatty acid chain (C₃₂ or C₃₄) with one, two, or three central tetrahydrofuran (THF) rings and a terminal butenolide segment (Figure 1). Usually the THF core is

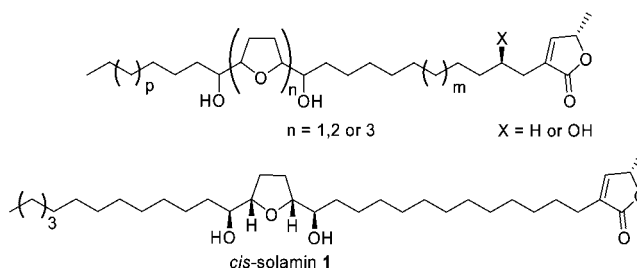


Figure 1. General structure of annonaceous acetogenins and *cis*-solamin (1).

flanked by additional hydroxy groups. Most acetogenins differ in the number of THF rings and the stereochemistry of the densely oxygenated central unit. Consequently, most synthetic efforts^{3,4} have focused on an efficient and stereoselective construction of this core.

(3) For reviews, see: (a) Hoppe, R.; Scharf, H.-D. *Synthesis* **1995**, 1447–1464. (b) Figadère, B. *Acc. Chem. Res.* **1995**, *28*, 359–365. (c) Marshall, J. A.; Hinkle, K. W.; Hagedorn, C. E. *Isr. J. Chem.* **1997**, *37*, 97–107. (d) Cassiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G.; Appendino, G. *Chemtracts: Org. Chem.* **1998**, *11*, 803–827.

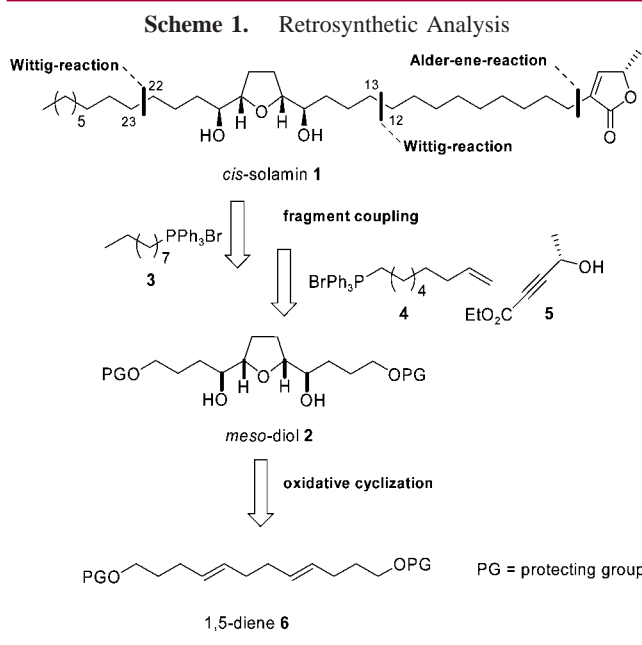
[†] Dedicated to Professor S. V. Ley on occasion of his 60th birthday.

(1) For recent reviews, see: (a) Cavé, A.; Figadère, B.; Laurens, A.; Cortes, D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds.; Springer-Verlag: Wien, 1997; Vol. 10, pp 81–288. (b) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504–540. (c) Bermejo, A.; Figadère, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269–303.

(2) (a) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K. *Nat. Prod. Rep.* **1996**, *13*, 276–306. (b) Oberlies, N. H.; Croy, V. L.; Harrison, M. L.; McLaughlin, J. L. *Cancer Lett.* **1997**, *115*, 73–79. (c) Oberlies, N. H.; Chang, C.-J.; McLaughlin, J. L. *J. Med. Chem.* **1997**, *40*, 2102–2106. See also ref 1.

As part of our interest in oxidation catalysis we have recently developed an efficient ruthenium tetroxide⁵ catalyzed oxidative cyclization of 1,5-dienes.^{6,7} We here present the first application of this method to natural product synthesis. As a target compound, *cis*-solamin, a representative mono-THF acetogenin isolated in 1998,⁸ was chosen (Figure 1). To date two total syntheses⁹ and one formal synthesis¹⁰ have been reported.¹¹

Our retrosynthetic analysis is outlined in Scheme 1. It takes advantage of the inherent symmetry of the central THF diol unit of *cis*-solamin by disconnection between C12–C13 and C22–C23. The strategy is centered on the single-step construction of the core THF unit by oxidative cyclization of an appropriate diene precursor (**6**). Crucial to the success of this approach is both the efficiency of the oxidative cyclization and the feasibility of a subsequent desymmetrization of the C_s-symmetric cyclization product.



(4) Representative acetogenin total syntheses: (a) Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1999**, *64*, 971–975. (b) Bäurle, S.; Hoppen, S.; Koert, U. *Angew. Chem.* **1999**, *111*, 1341–1344; *Angew. Chem., Int. Ed.* **1999**, *38*, 1263–1266. (c) Sinha, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 2381–2386. (d) Hoppen, S.; Bäurle, S.; Koert, U. *Chem. Eur. J.* **2000**, *6*, 2382–2396. (e) Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Angew. Chem.* **2000**, *112*, 3768–3772; *Angew. Chem., Int. Ed.* **2000**, *39*, 3622–3626. (f) Harcken, C.; Brückner, R. *New J. Chem.* **2001**, *25*, 40–54. (g) Hu, T.-S.; Yu, Q.; Wu, Y.-L.; Wu, Y. *J. Org. Chem.* **2001**, *66*, 853–861. (h) Burke, S. D.; Jiang, L. *Org. Lett.* **2001**, *3*, 1953–1955. (i) Takahashi, S.; Kubota, A.; Nakata, T. *Angew. Chem.* **2002**, *114*, 4945–4948; *Angew. Chem., Int. Ed.* **2002**, *41*, 4751–4754. (j) Zhu, L.; Mootoo, D. R. *Org. Lett.* **2003**, *5*, 3475–3478. (k) Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 36–37. (l) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790–12791. (m) Nattress, G. L.; Diez, E.; McLachlan, M. M.; Dixon, D. J.; Ley, S. V. *Angew. Chem.* **2005**, *117*, 586–590; *Angew. Chem., Int. Ed.* **2005**, *44*, 580–584. (n) Hanessian, S.; Giroux, S.; Buffat, M. *Org. Lett.* **2005**, *7*, 3989–3992. (o) Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R.-A. F.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245–4248. See also refs 9–11.

(5) For a recent review on ruthenium tetroxide catalyzed oxidations, see: Plietker, B. *Synthesis* **2005**, 2453–2472.

(6) Roth, S.; Göhler, S.; Cheng, H.; Stark, C. B. W. *Eur. J. Org. Chem.* **2005**, 4109–4118.

(7) Representative references for the oxidative cyclization of 1,5-dienes. With ruthenium tetroxide: (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938. (b) Albarella, L.; Musumeci, D.; Sica, D. *Eur. J. Org. Chem.* **2001**, 997–1003. (c) Piccialli, V.; Cavallo, N. *Tetrahedron Lett.* **2001**, *42*, 4695–4699. See also ref 6. With potassium permanganate: (d) Klein, E.; Rojahn, W. *Tetrahedron* **1965**, *21*, 2353–2358. (e) Walba, D. M.; Wand, M. D.; Wilkes, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4396–4397. (f) Baldwin, J. E.; Crossley, M. J.; Lehtonen, E.-M. *J. Chem. Soc., Chem. Commun.* **1979**, 918–920 (g) Kocienski, P. J.; Brown, R. C. D.; Pommier, A.; Procter, M.; Schmidt, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 9–39. (h) Brown, R. C. D.; Keily, J. F. *Angew. Chem.* **2001**, *113*, 4628–4630; *Angew. Chem., Int. Ed.* **2001**, *40*, 4496–4498. See also ref 9b and 9c. With osmium tetroxide: (i) de Champdoré, M.; Lasalvia, M.; Piccialli, V. *Tetrahedron Lett.* **1998**, *39*, 9781–9784. (j) Donohoe, T. J.; Butterworth, S. *Angew. Chem.* **2003**, *115*, 978–981; *Angew. Chem., Int. Ed.* **2003**, *42*, 948–951.

(8) Gleye, C.; Duret, P.; Laurens, A.; Hocquemiller, R.; Cavé, A. *J. Nat. Prod.* **1998**, *61*, 576–579.

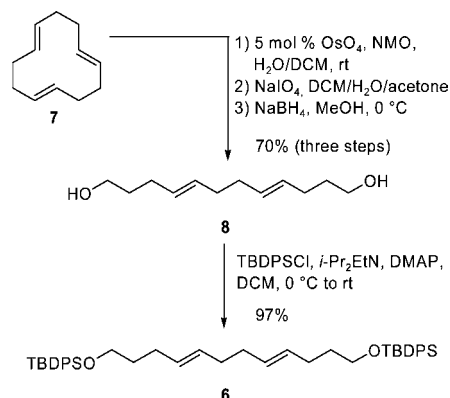
(9) (a) Makabe, H.; Hattori, Y.; Tanaka, A.; Oritani, T. *Org. Lett.* **2002**, *4*, 1083–1085. (b) Cecil, A. R. L.; Brown, R. C. D. *Org. Lett.* **2002**, *4*, 3715–3718. (c) Cecil, A. R. L.; Hu, Y. L.; Vicent, M. J.; Duncan, R.; Brown, R. C. D. *J. Org. Chem.* **2004**, *69*, 3368–3374.

(10) Donohoe, T. J.; Butterworth, S. *Angew. Chem.* **2005**, *117*, 4844–4867; *Angew. Chem., Int. Ed.* **2005**, *44*, 4766–4768.

(11) For syntheses of the natural isomer *trans*-solamin, see: (a) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891–4892. (b) Trost, B. M.; Shi, Z. P. *J. Am. Chem. Soc.* **1994**, *116*, 7459–7460. (c) Makabe, H.; Tanaka, A.; Oritani, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1975–1981. (d) Kuriyama, W.; Ishigami, K.; Kitahara, T. *Heterocycles* **1999**, *50*, 981–988. (e) Prestat, G.; Baylon, C.; Heck, M.-P.; Grasa, G. A.; Nolan, S. P.; Mioskowski, C. *J. Org. Chem.* **2004**, *69*, 5770–5773. For a semi-synthesis of *cis*- and *trans*-solamin from Diepomuricanin A, see: Gleye, C.; Franck, X.; Hocquemiller, R.; Laurens, A.; Laprevote, O.; de Barros, S.; Figadère, B. *Eur. J. Org. Chem.* **2001**, 3161–3164.

The synthesis of the cyclization precursor is summarized in Scheme 2. Commercially available (*E,E,E*)-1,5,9-cy-

Scheme 2. Synthesis of the Cyclization Precursor



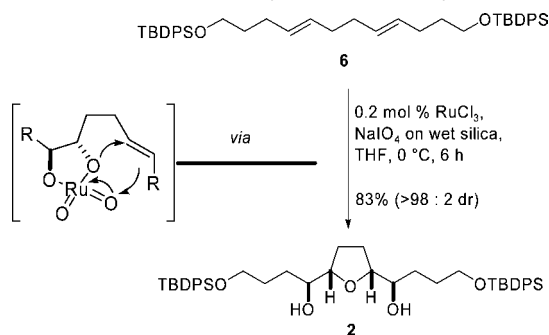
clododecatriene **7** was readily converted into diene **8** via monodihydroxylation, glycol cleavage, and subsequent borohydride reduction.¹² Standard silyl protection of diol **8** afforded the cyclization precursor **6** in excellent overall yield (65% over 4 steps). It is worth noting that these four steps can be carried out on a multigram scale without purification of intermediates.

We next turned our attention to the ruthenium tetroxide catalyzed oxidative cyclization.⁶ Treatment of diene **6** with 0.2 mol % ruthenium(III) chloride (as a precatalyst for the ruthenium tetroxide generated in situ) in the presence of sodium periodate on wet silica^{6,13} (in THF¹⁴ at 0 °C) resulted

(12) The first two steps of this sequence have previously been described, cf.: Neogi, P.; Doundoulakis, T.; Yazbak, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 11279–11284.

in a smooth conversion of the starting material. The cyclization product was obtained in high yield (83%) and as a single diastereoisomer (>98:2 dr). The excellent diastereoselectivity of this transformation is believed to result from a double *syn* specific [3 + 2]-cycloaddition with a conformationally constrained second intramolecular addition process (Scheme 3).⁶

Scheme 3. RuO₄-Catalyzed Oxidative Cyclization



For the desymmetrization of *meso*-diol **2** we envisaged enzymatic methodology.¹⁵ To avoid an additional acetylation step (followed by lipase-catalyzed hydrolysis), an enzymatic esterification was considered.^{16,17} After extensive investigation of a variety of lipases under different conditions we found that lipase Amano AK provided best results concerning both conversion and enantioselectivity. Under optimized conditions in hexane at 60 °C using vinyl acetate as the acylating agent, enantiomerically pure (>99% ee) acetate (+)-**9** was obtained in 81% yield. The absolute configuration of (+)-**9** was assigned by the use of Mosher esters. Fluoride-induced deprotection furnished triol (+)-**10** in 98% yield. It is important to note that although this compound ((+)-**10**) is enantiomerically pure, termini differentiation is required for appropriate side chain attachment. We planned to achieve this differentiation by oxidative means (Scheme 5). Pleas-

(13) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622–2624.

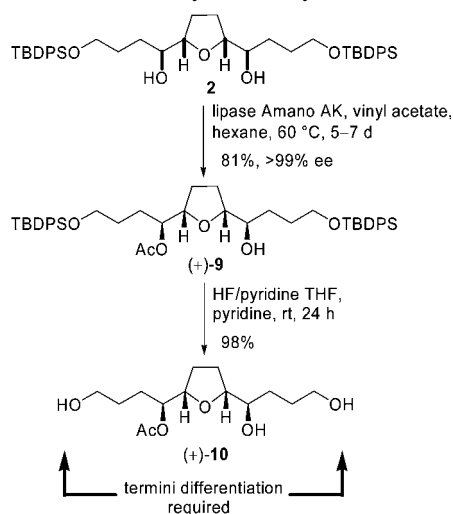
(14) In a general procedure the addition 10 vol % CH₂Cl₂ has previously been suggested to suppress unwanted overoxidation (ref 6). In the case of substrate **6** the addition of this cosolvent proved not necessary.

(15) For reviews, see: (a) Theil, F. *Chem. Rev.* **1995**, *95*, 2203–2227. (b) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769–3826. (c) Schmid, R. D.; Verger, R. *Angew. Chem.* **1998**, *110*, 1694–1720 *Angew. Chem., Int. Ed.* **1998**, *37*, 1608–1633. For a review on nonenzymatic desymmetrizations of *meso*-compounds, see: Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765–1784. For a general review on *meso*-compounds in stereoselective synthesis, see: Hoffmann, R. W. *Angew. Chem.* **2003**, *115*, 1128–1142; *Angew. Chem., Int. Ed.* **2003**, *42*, 1096–1109.

(16) Enzymatic desymmetrizations of THF diols using, e.g., *Candida antarctica*, *Candida rugosa*, and *Mucor javanicus* lipases have been reported previously (ref 17). However, in case of diol **2**, these enzymes did not provide substantial amounts of product.

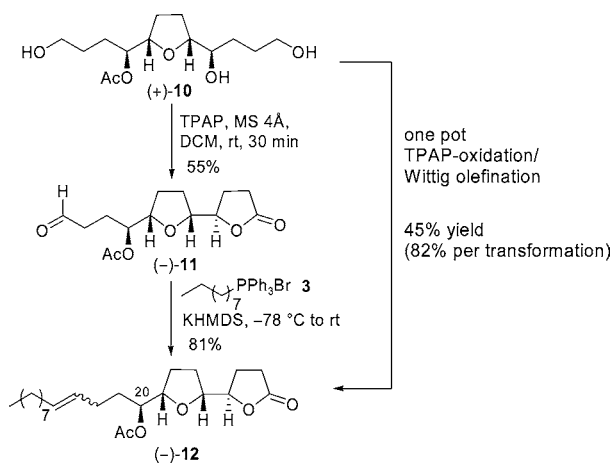
(17) For enzymatic desymmetrizations of THF diols, see: (a) Estermann, H.; Prasad, K.; Shapiro, M. *Tetrahedron Lett.* **1990**, *31*, 445–448. (b) Naemura, K.; Fukada, R.; Takahashi, N.; Konishi, M.; Hirose, Y. *Tetrahedron: Asymmetry* **1993**, *4*, 911–918. (c) Hegemann, K.; Schimanski, H.; Höweler, U.; Haufe, G. *Tetrahedron Lett.* **2003**, *44*, 2225–2229. (d) Hegemann, K.; Fröhlich, R.; Haufe, G. *Eur. J. Org. Chem.* **2004**, 2181–2192.

Scheme 4. Enzymatic Desymmetrization



ingly, TPAP (tetrapropylammonium perruthenate)¹⁸ catalyzed oxidation of triol (+)-**10** in the presence of an excess of NMO (*N*-methyl-morpholine-*N*-oxide) co-oxidant furnished the desired lactone aldehyde (–)-**11** in 55% yield (3 oxidation

Scheme 5. Termini Differentiation



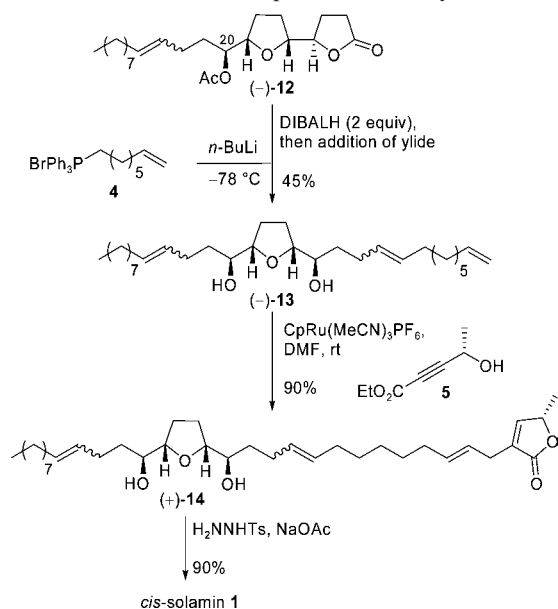
events). Through this oxidation reaction both the termini differentiation and the establishment of a functional group required for C–C bond coupling were achieved. Subsequent olefination provided the C12–C32 fragment in 81% yield. Notably, the oxidation-olefination sequence could be carried out as a one-pot procedure¹⁹ with an almost identical overall yield (Scheme 5).

The next crucial step involved the C₉-extension to introduce the C3–C11 linear carbon chain (Scheme 6). Thus,

(18) For reviews, see: (a) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666. (b) Langer, P. *J. Prakt. Chem.* **2000**, *342*, 728–730. For an early publication on the oxidative lactonization of diols using TPAP, see: Bloch, R.; Brillet, C. *Synlett* **1991**, 829–830.

(19) MacCoss, R. N.; Balskus, E. P.; Ley, S. V. *Tetrahedron Lett.* **2003**, *44*, 7779–7781.

Scheme 6. Final Steps of the Total Synthesis



lactone (–)-**12** was reduced with 1 equiv of DIBALH followed by addition of the separately generated Wittig ylide derived from phosphonium salt **4**. Under these conditions a competing reduction of the C20 acetate protecting group could not be prevented, resulting in diminished yields of the desired coupling product and a significant amount of recovered starting material. After some experimentation, it was found that addition of 2 equiv of DIBALH (at $-78\text{ }^{\circ}\text{C}$ in toluene) followed by addition of an excess of Wittig reagent yielded the coupled *and* reductively deprotected product (–)-**13** (Scheme 6). With compound (–)-**13** in hand, the final sequence for the solamin synthesis was performed as shown in Scheme 6. The butenolide segment was introduced using a ruthenium(II)-catalyzed Alder-ene reaction developed by Trost and co-workers.²⁰ Thus, treatment of an

(20) (a) Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739–7743. (b) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067–2096. (c) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem.* **2005**, *117*, 6788–6825; *Angew. Chem., Int. Ed.* **2005**, *44*, 6630–6666.

equimolar mixture of (–)-**13** and known alkyne **5**²¹ with a catalytic amount of $\text{CpRu}(\text{MeCN})_3\text{PF}_6$ afforded the coupled product with excellent chemoselectivity (in favor of the terminal olefin) and in high yield (90%). Final diimide reduction of the $\Delta^{4,11,23}$ -triene in the presence of the α,β -unsaturated lactone furnished *cis*-solamin (**1**) as a colorless powder in 90% yield. Spectroscopic data for this compound were identical to those reported for *cis*-solamin isolated from natural sources.⁸ In addition, these data²² were in accord with the absolute stereochemical assignment reported by Makabe and co-workers.^{9a}

In conclusion, our total synthesis of *cis*-solamin demonstrates the potential of ruthenium tetroxide catalyzed oxidative cyclizations. It represents the first application of this method to natural product synthesis, and four of the five stereogenic centers of *cis*-solamin were established through this pivotal transformation. Other key steps involved an enzymatic desymmetrization, a TPAP-catalyzed oxidative termini differentiation, and a ruthenium-catalyzed Alder-ene reaction. It is also worth mentioning that our strategy makes minimal use of protecting groups and exploits the inherent C_s -symmetry of the central THF diol unit. Thus, the total synthesis of *cis*-solamin was achieved in 11 steps with an overall yield of 7.5%.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (STA-634/1-1) and the Fonds der Chemischen Industrie. We thank Prof. U. T. Bornscheuer (Universität Greifswald, Germany) for valuable suggestions regarding the enzymatic desymmetrization. We are also grateful to Prof. H.-U. Reissig (Freie Universität Berlin, Germany) for helpful discussions and generous support.

Supporting Information Available: Experimental procedures for key reactions and full spectroscopic data for compounds **2**, **6**, **10**, **12**, **13**, and **1**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(21) Trost, B. M.; Müller, T. J. J.; Martinez, J. J. *Am. Chem. Soc.* **1995**, *117*, 1888–1899.

(22) Optical rotations. Synthetic *cis*-solamin **1**: $[\alpha]_D^{24} = +20.6$ ($c = 0.1$ in MeOH). Natural *cis*-solamin $[\alpha]_D = +22$ ($c = 0.55$ in MeOH); see ref 8. For details see also Supporting Information.