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Total Synthesis of *cis*-Solamin: Exploiting the RuO_4-Catalyzed Oxidative Cyclization of Dienes†

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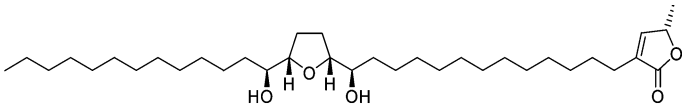
ABSTRACT



cis-solamin

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 termini 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 (C_{32} or C_{34}) with one, two, or three central tetrahydrofuran (THF) rings and a terminal butenolide segment (Figure 1). Usually the THF core is 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.

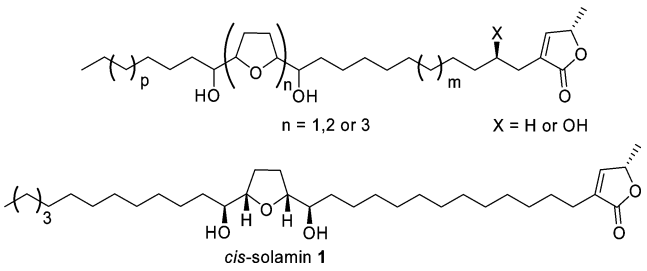


Figure 1. General structure of annonaceous acetogenins and *cis*-solamin (**1**).

† 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.

(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.

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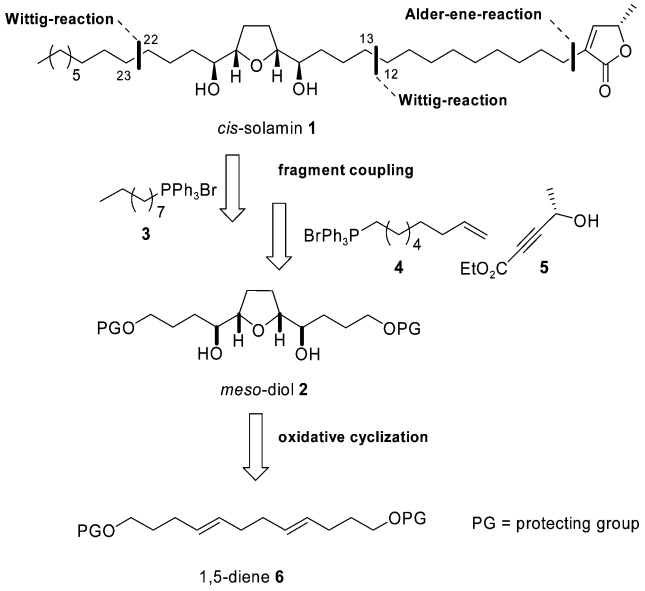
As part of our interest in oxidation catalysis we have recently developed an efficient ruthenium tetroxide[5] catalyzed oxidative cyclization of 1,5-dienes.[6,7] We here present the first application of this method to natural product synthesis. As a target compound, *cis*-solamin, a representative mono-THF acetogenin isolated in 1998,[8] was chosen (Figure 1). To date two total syntheses[9] and one formal synthesis[10] have been reported.[11]

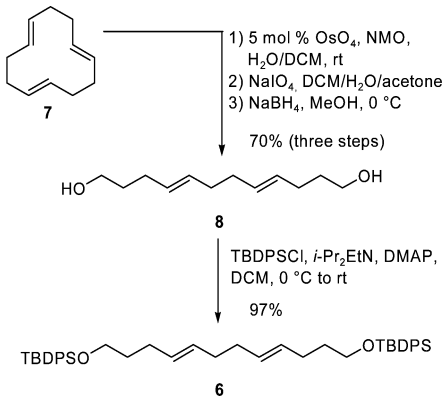
Our retrosynthetic analysis is outlined in Scheme 1. It takes advantage of the inherent symmetry of the central THF diol unit of *cis*-solamin by disconnection between C12−C13 and C22−C23. The strategy is centered on the single-step construction of the core THF unit by oxidative cyclization of an appropriate 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.

Scheme 1. Retrosynthetic Analysis



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

Scheme 2. Synthesis of the Cyclization Precursor



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 THF[14] at 0 °C) resulted

(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) Nattrass, 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. 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.

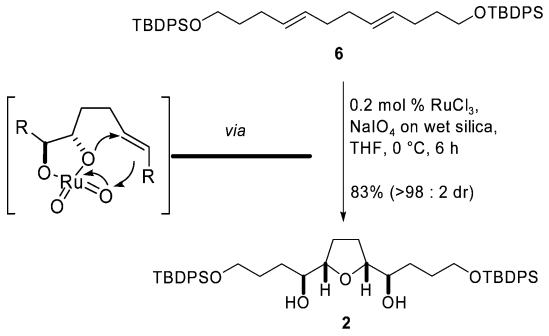
(10) Donohoe, T. J.; Butterworth: S. *Angew. Chem.* **2005**, *117*, 4844−4867; *Angew. Chem., Int. Ed.* **2005**, *44*, 4766−4768.

(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.

(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.

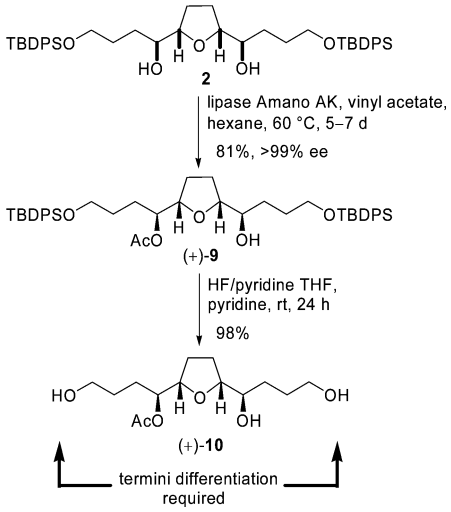
in a smooth conversion of the starting material. The cyclization product was obtained in high yield (83%) and as a single diastereoisomer (>98:2 dr). The excellent diastereoselectivity of this transformation is believed to result from a double *syn* specific [3 + 2]-cycloaddition with a conformationally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

Scheme 3. RuO_4-Catalyzed Oxidative Cyclization

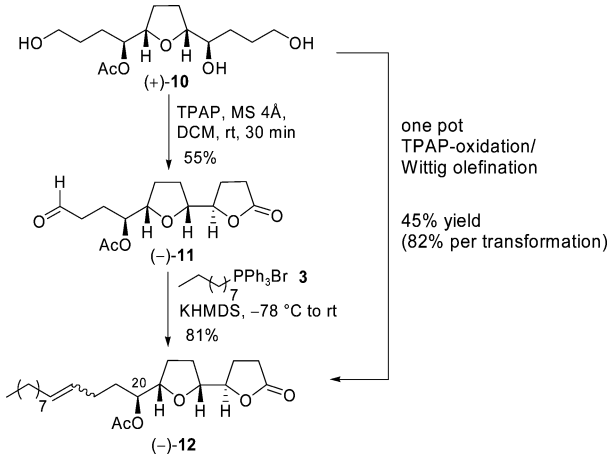


For the desymmetrization of *meso*-diol **2** we envisaged enzymatic methodology.[15] To avoid an additional acetylation step (followed by lipase-catalyzed hydrolysis), an enzymatic esterification was considered.[16,17] After extensive investigation of a variety of lipases under different conditions 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). Pleasingly, 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 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 procedure[19] with an almost identical overall yield (Scheme 5).

Scheme 4. Enzymatic Desymmetrization



Scheme 5. Termini Differentiation



The next crucial step involved the C_9-extension to introduce the C3−C11 linear carbon chain (Scheme 6). Thus,

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

(14) In a general procedure the addition 10 vol % CH_2Cl_2 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.

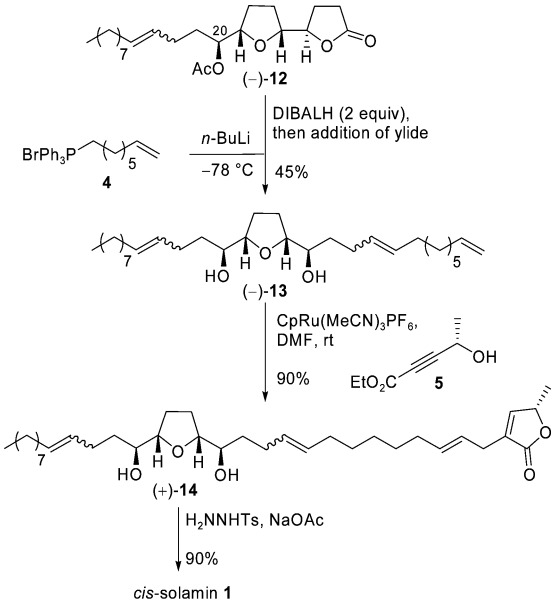
(16) Enzymatic desymmetrizations of THF diols using, e.g., *Candida antarctica*, *Candida rugosa*, and *Mucor javanicus* lipases have been reported previously (ref 17). However, in case of diol **2**, these enzymes did not provide substantial amounts of product.

(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.

(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 °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 equimolar mixture of (−)-**13** and known alkyne **5**[21] with a catalytic amount of $CpRu(MeCN)_3PF_6$ 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 data[22] 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%.

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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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(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.

(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**: $[\alpha]^{24}_D = +20.6$ (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.