Total Synthesis of Naturally Occurring Acetogenins: Solamin and Reticulatacin

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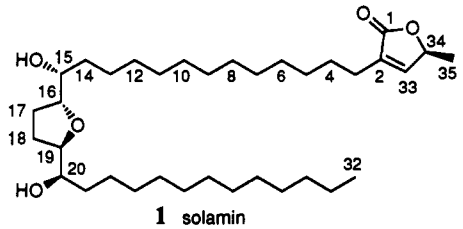
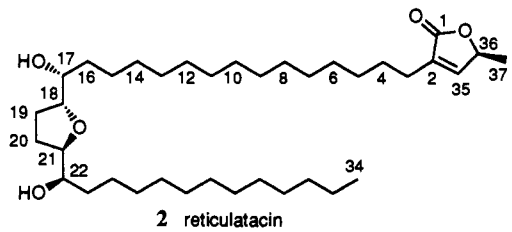
The rapidly growing class of naturally occurring acetogenins has attracted increasing interest attributed to their broad spectrum of biological activities. Many of these polyketide-derived fatty acid derivatives isolated from a number of plants in the Annonaceae have shown cytotoxic, antitumoral, antimalarial, immunosuppressive, pesticidal, or antifeedant activities.[1] Although more than 50 members of this family are now known, none of them has been synthesized, probably due to the limited information concerning their absolute configuration.[2] So far, a non-natural diastereomer of uvaricin,[3] a diastereomer of dihydro-4-oxomurisolin,[4] and a few chiral building blocks leading to the acetogenins[5] have been synthesized using enantiomerically pure natural products, such as L-diethyl tartrate, L-glutamic acid, and D-glucose. Here we report the first total synthesis of natural solamin, **1**,[6] and reticulatacin, **2**.[7]



1 solamin



2 reticulatacin

The crucial part in the synthesis of both natural products is the substituted tetrahydrofuran ring with four stereogenic carbinol centers in a *threo–trans–threo* relationship (C_{15}–C_{20} in **1** and C_{17}–C_{22} in **2**). We anticipated that conversion of an appropriately substituted (*E,E*)-1,5-diene, such as **3**, into a *threo,threo* tetraol with high enantiomeric purity and predictable absolute configuration, using the Sharpless asymmetric dihydroxylation reaction,[8] would provide us with all four asymmetric centers in one step. For example, in the case of **1**, where the 15*R*,16*R*,19*R*,20*R* configuration is required,[9] the reagent of choice would be AD-mix-β (Aldrich No. 39,276-6).[8] In addition, the requirement to transform the tetraol into a tetrahydrofuran ring with overall retention of configuration at all centers dictated a strategy that involves double inversion at either C_{16} or C_{19}.

Thus, treatment of the bis unsaturated ester **3**[10] with AD-mix-β (2.8 g/mmol) at 0 °C in *tert*-butyl alcohol/water (1:1) containing methanesulfonamide (190 mg/mmol) for 16 h[8] afforded lactone **4** contaminated with ethyl 4,5,8,9-tetrahydroxyheneicosanoate. In order for the lactonization to go to completion, this mixture was hydrolyzed to the free acid using aqueous NaOH, acidified with 3 N HCl, and then treated with *p*-toluenesulfonic acid (TsOH) in CH_2Cl_2. Recrystallization of the crude product from ethyl acetate afforded enantiomerically pure lactone **4** in 66% yield.[11] The vicinal diol in **4** was converted to acetonide **5**[12] ($[\alpha]_D$ +8.69° (c = 2.69, $CHCl_3$)) using 2,2-dimethoxypropane/acetone (1:1) and catalytic amounts of TsOH (0–25 °C, 1 h). Reaction with *p*-toluenesulfonyl chloride in CH_2Cl_2 and triethylamine with catalytic amounts of 4-(dimethylamino)pyridine at room temperature for 2 days afforded tosylate **6**.[13] The latter was converted to epoxide **7**[14] upon treatment with methanolic K_2CO_3 at room temperature for 1 h. Acid-catalyzed (BF_3·Et_2O in CH_2Cl_2) acetonide removal within **7** simultaneously opened the epoxide with concomitant lactonization to produce the substituted tetrahydrofuran **8** in 75% yield with the desired *threo–trans–threo* configuration.[15] Compound **8** represents a useful chiral building block for future synthesis of other acetogenins.

Reduction of the lactone **8** with diisobutylaluminum hydride (2.2 equiv, THF, –50 °C, 1 h) afforded the corresponding lactol. The latter was reacted at –78 °C with (bromomethylene)triphenylphosphorane to give a mixture of (*E*)- and (*Z*)-bromoalkene

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(1) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237.

(2) The absolute configuration of a broad variety of acetogenins has been determined very recently on the basis of the NMR data of their Mosher ester derivatives: Rieser, M. J.; Hui, Y.-H.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203.

(3) Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369.

(4) Figadere, B.; Harmange, J.-C.; Hai, L. X.; Cave, A. *Tetrahedron Lett.* **1992**, *36*, 5189.

(5) (a) Bertrand, P.; Gesson, J.-P. *Tetrahedron Lett.* **1992**, *36*, 5177. (b) Harmange, J.-C.; Figadere, B.; Cave, A. *Tetrahedron Lett.* **1992**, *36*, 5749. (c) Harmange, J.-C.; Figadere, B.; Hocquemiller, R. *Tetrahedron: Asymmetry* **1991**, *2*, 347.

(6) Myint, S. H.; Cortes, D.; Laurens, A.; Hocquemiller, R.; Leboeuf, M.; Cave, A.; Cotte, J.; Quero, A.-M. *Phytochemistry* **1991**, *30*, 3335.

(7) Saad, J. M.; Hui, Y.-H.; Rupprecht, J. K.; Anderson, J. E.; Kozlowsky, J. F.; Zhao, G.-X.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron*, **1991**, *47*, 2751.

(8) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org.Chem.* **1992**, *57*, 2768.

(9) On the basis of the very similar optical rotation of **1** and **2** and because the absolute configuration of **2** has been assigned as (17*R*,18*R*,21*R*,22*R*) (ref 2), we assumed that both compounds possess the same configuration. The configuration at the methyl carbinol (34*S* and 36*S*, respectively) was anticipated on the basis of possible analogy to other acetogenins (ref 2).

(10) Ethyl (*E,E*)-heneicosa-4,8-dienoate, **3**, was prepared in 65% yield from ethyl (*E*)-heptadec-4-enoate (Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B.; Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, 33, 6407) as follows: Reduction with $LiAlH_4$, followed by oxidation to aldehyde with pyridinium chlorochromate in CH_2Cl_2 and then reaction with vinylmagnesium bromide, afforded (*E*)-nonadeca-1,6-dien-3-ol. The latter was converted to **3** by the Johnson–Claisen rearrangement (Trust, R. I.; Ireland, R. E. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 606.) using triethyl orthoacetate and catalytic amounts of propionic acid. ^{1}H NMR of **3**: δ 5.42 (m, 4H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.32 (m, 4H), 2.10–1.90 (m, 6H), 1.26 (br, 23H), 0.88 (t, *J* = 6.4 Hz, 3H).

(11) Compound **4**: mp 105–106 °C, $[\alpha]_D$ +4.18° (*c* = 1.00, MeOH). Anal. Calcd for $C_{21}H_{40}O_5$: C, 67.70; H, 10.82. *Found*: C, 67.70; H, 10.89. ^{1}H NMR: δ 4.44 (dt, *J* = 7.2, 4.6 Hz, 1H), 3.66 (m, 1H), 3.45 (m, 2H), 3.00 (br, 1H), 2.66 (ddd, *J* = 17.2, 10.0, 5.2 Hz, 1H), 2.55 (ddd, *J* = 17.2, 9.7, 8.4 Hz, 1H), 1.80–1.20 (m, 30H), 0.88 (t, *J* = 7.2 Hz, 3H). Generally, AD reaction of *E*-disubstituted alkenes proceeds with more than 96% ee (ref 8). Accordingly, the crude product **4** contained approximately 5% of other diastereomers.

(12) Satisfactory analytical and spectroscopic data were obtained for all compounds reported in the paper.

(13) Compound **6**: HRMS calcd for $C_{31}H_{55}O_7SCs$ (M + Cs^+) 699.2332, found 699.2311.

(14) Compound **7**: oil, $[\alpha]_D$ +18.96° (*c* = 2.83, $CHCl_3$). Anal. Calcd for $C_{25}H_{46}O_5$: C, 70.38; H, 10.87. Found: C, 70.31; H, 10.87. ^{1}H NMR: 3.70 (s, 3H), 3.60 (m, 2H), 2.98 (m, 2H), 2.50 (m, 2H), 2.00–1.40 (m, 9H), 1.38 (s, 6H), 1.36–1.20 (br, 19H), 0.88 (t, *J* = 6.8 Hz, 3H).

(15) Somewhat lower yields (61%) of **8** were achieved with Amberlyst-15 in methanol instead of BF_3·Et_2O. Compound **8**: mp 95–96 °C, $[\alpha]_D$ –7.36° (*c* = 1.44, $CHCl_3$). Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found: C, 70.98; H, 10.83. ^{1}H NMR ($CDCl_3$): 4.47 (ddd, *J* = 8.0, 5.4, 3.0 Hz, 1H), 4.06 (dt, *J* = 7.7, 3.0 Hz, 1H), 3.83 (dt, *J* = 8.1, 5.8 Hz, 1H), 3.38 (m, 1H), 2.65 (ddd, *J* = 17.0, 10.0, 7.0 Hz, 1H), 2.47 (ddd, *J* = 17.0, 10.0, 6.5 Hz, 1H), 2.25 (m, 3H), 2.00 (m, 3H), 1.71 (m, 1H) 1.53–1.18 (br, 22 H), 0.88 (t, *J* = 6.8 Hz, 3H).

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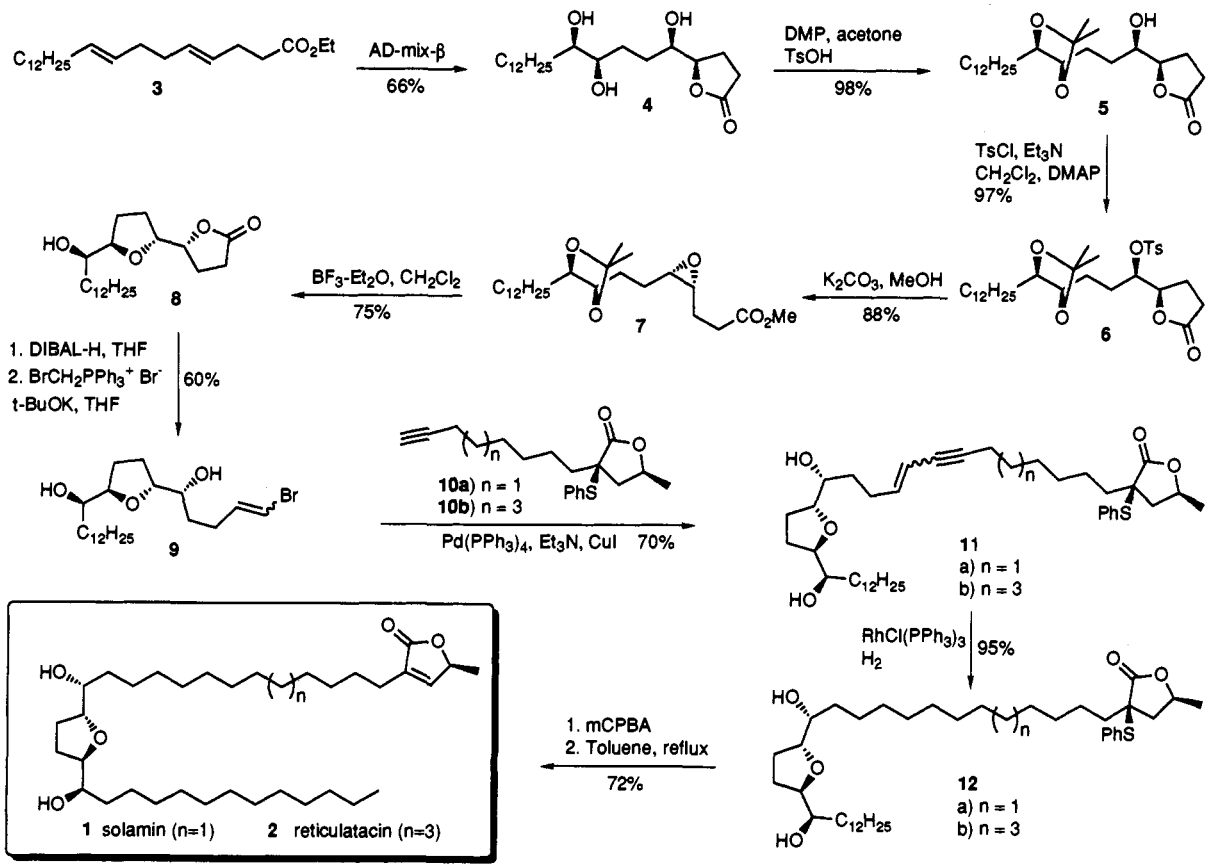
Scheme I



9.[16] Completion of the carbon skeletons to give enynes **11a** and **11b** was achieved through a Pd(0)-catalyzed cross-coupling reaction ($Pd(PPh_3)_4$, CuI, Et_3N in THF, 50 °C, 2 h) of **9** with either **10a** or **10b**, both having the appropriate *S* configuration at the position α to the lactone carbonyl.[17] Catalytic hydrogenation of **11** using Wilkinson's catalyst in benzene/acetone (2:3) under hydrogen (1 atm, 16 h) afforded the saturated compounds **12a** and **12b**.[18] Finally, oxidation of the sulfide to sulfoxide with *m*-chloroperbenzoic acid in CH_2Cl_2 (15 min at 0 °C), followed by thermal elimination in refluxing toluene (1 h), afforded either solamin, **1**, or reticulatacin, **2**, in the form of white solids. Both were recrystallized from hexane to give colorless needles.

Our synthetic **1** (mp 76–77 °C, $[\alpha]_D$ = +22.0° (*c* = 0.2, MeOH); lit.[6] mp 64–68°C, $[\alpha]_D$ = +21.2° (*c* = 0.16, MeOH)) and **2** (mp 80–81 °C, $[\alpha]_D$ = +25.6° (*c* = 0.5, $CHCl_3$); lit.[7] mp 80–80.5 °C, $[\alpha]_D$ = +26° (*c* = 0.5, $CHCl_3$)) were found by ^1H NMR, ^{13}C NMR, IR, and MS to be identical to the naturally occurring compounds.[6,7]

Using the sulforhodamine B assay,[19] the cytotoxicities of **1** and **2** were evaluated against a broad spectrum of tumor cell lines as well as normal cells for comparison.[20] On the average, solamin, **1**, exhibited IC_{50} values at micromolar concentrations, in agreement with the previously reported cytotoxicities for the natural solamin using epidermoid carcinoma (KB) cell line.[6] Interestingly, reticulatacin, **2**, was found to be approximately 10–100-fold less cytotoxic to tumor cells than solamin, in agreement with the previously reported data for natural reticulatacin using three tumor cell lines.[7]

In conclusion, the first synthesis of two naturally occurring acetogenins has been achieved, thus confirming their absolute configuration, previously determined on the basis of NMR data.[2] Our approach to solamin and reticulatacin represents a convenient entry into other members of this class of biologically active compounds, many of which are currently being prepared for cytotoxicity evaluation.

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Supplementary Material Available: Table of cytotoxicities of **1** and **2** against a panel of 14 tumor cell lines and four normal cell lines (1 page). Ordering information is given on any current masthead page.

(16) The Wittig reagent was prepared by treatment of (bromomethyl)-triphenylphosphonium bromide (Aldrich) with potassium *tert*-butoxide (1 equiv) in THF at −78 °C for 1 h (Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021). The lactol was then added, and the mixture was stirred at −78 °C for 1 h, warmed to −20 °C and quenched with saturated aqueous NH_4Cl. Compound **9**: oil; HRMS calcd for $C_{22}H_{41}O_3BrCs$ (M + Cs^+) 565.1293, found 565.1293.

(17) To prepare **10a**, a mixture of (2*R*,4*S*)- and (2*S*,4*S*)-4-methyl-2-(phenylthio)-γ-butyrolactone (Iwai, K.; Kosugi, H.; Uda, H.; Kawai, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 242) was treated with potassium hexamethyldisilazide (1 equiv) in THF at 0 °C. 8-Iodooct-1-yne was added at the same temperature, and the mixture was then refluxed for 2 h (as described by Hoye et al.[3]) to give a 4:1 mixture of **10a** and 2-*epi*-**10a**, respectively, in 70% yield. The major diastereomer, **10a**, was easily purified by column chromatography (silica gel, 1:9 ethyl acetate/hexane). Using the same procedure with 10-iododec-1-yne afforded **10b**.

(18) Compound **12a**: HRMS calcd for $C_{41}H_{70}O_5SCs$ (M + Cs^+), 807.3977, found 807.3977. ^1H NMR ($CDCl_3$): 7.56 (m, 2H), 7.38 (m, 3H), 4.49 (m, 1H), 3.80 (q, *J* = 6.4 Hz, 1H), 3.41 (br, 1H), 2.51 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.42 (br, 2H), 1.97 (m, 4H), 1.78–1.22 (br, 49 H), 1.18 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 6.4 Hz, 3H). Compound **12b**: HRMS calcd for $C_{43}H_{74}O_5SCs$ (M + Cs^+), 835.4311, found 835.4309. ^1H NMR ($CDCl_3$): 7.55 (m, 2H), 7.37 (m, 3H), 4.49 (m, 1H), 3.80 (q, *J* = 6.8 Hz, 1H), 3.41 (br, 1H), 2.52 (dd, *J* = 14.0, 6.4 Hz, 1H), 2.45 (br, 2H), 1.99 (m, 4H), 1.82–1.22 (br, 53 H), 1.18 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 6.4 Hz, 3H).

(19) Skehan, P.; et al. *J. Natl. Cancer Inst.* **1990**, *82*, 1107.

(20) Representative cytotoxicity data (cell line, cell type, IC_{50} [M] of **1**, IC_{50} [M] of **2**): SK-Mel-28, melanoma, 5.1×10^{-6}, 1.8×10^{-5}; HT-29, colon carcinoma, 2.1×10^{-6}, 1.5×10^{-5}; Ovcar-3, ovarian carcinoma, 1.1×10^{-6}, 1.5×10^{-5}; BT-549, breast carcinoma, 3.4×10^{-6}, 8.6×10^{-6}; UCLA P-3, lung carcinoma, 1.3×10^{-6}, 7.4×10^{-5}; HL-60, promyeocytic leukemia, 8.9×10^{-8}, 2.6×10^{-5}; MCF-7, breast carcinoma, 3.4×10^{-6}, 1.9×10^{-5}; PC-3, prostate carcinoma, 1.2×10^{-5}, 5.9×10^{-5}; 786-O, renal cell carcinoma, 3.0×10^{-6}, 8.9×10^{-6}; Molt-4, T-cell leukemia, 4.1×10^{-6}, 2.1×10^{-5}; NHDF, normal human dermal fibroblast, 8.8×10^{-5}, 2.4×10^{-5}; RPMI-7666, normal human PBLs, 2.1×10^{-5}, 2.5×10^{-5}.