

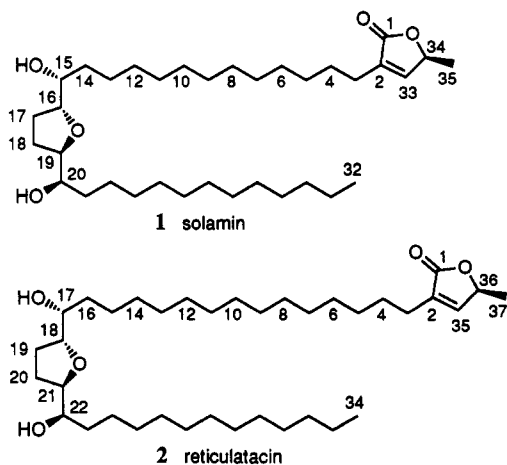
## Total Synthesis of Naturally Occurring Acetogenins: Solamin and Reticulatacin

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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.<sup>1</sup> 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.<sup>2</sup> So far, a non-natural diastereomer of uvaricin,<sup>3</sup> a diastereomer of dihydro-4-oxomurisolin,<sup>4</sup> and a few chiral building blocks leading to the acetogenins<sup>5</sup> 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**,<sup>6</sup> and reticulatacin, **2**.<sup>7</sup>



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<sub>15</sub>–C<sub>20</sub> in **1** and C<sub>17</sub>–C<sub>22</sub> 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 config-

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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.; Kozlowski, J. F.; Zhao, G.-X.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron*, **1991**, *47*, 2751.

uration, using the Sharpless asymmetric dihydroxylation reaction,<sup>8</sup> 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,<sup>9</sup> the reagent of choice would be AD-mix-β (Aldrich No. 39,276-6).<sup>8</sup> 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<sub>16</sub> or C<sub>19</sub>.

Thus, treatment of the bis unsaturated ester **3**<sup>10</sup> 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<sup>8</sup> 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<sub>2</sub>Cl<sub>2</sub>. Recrystallization of the crude product from ethyl acetate afforded enantiomerically pure lactone **4** in 66% yield.<sup>11</sup> The vicinal diol in **4** was converted to acetone **5**<sup>12</sup> ([α]<sub>D</sub> +8.69° (c = 2.69, CHCl<sub>3</sub>)) using 2,2-dimethoxypropane/acetone (1:1) and catalytic amounts of TsOH (0–25 °C, 1 h). Reaction with *p*-toluenesulfonyl chloride in CH<sub>2</sub>Cl<sub>2</sub> and triethylamine with catalytic amounts of 4-(dimethylamino)pyridine at room temperature for 2 days afforded tosylate **6**.<sup>13</sup> The latter was converted to epoxide **7**<sup>14</sup> upon treatment with methanolic K<sub>2</sub>CO<sub>3</sub> at room temperature for 1 h. Acid-catalyzed (BF<sub>3</sub>·Et<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub>) acetonide removal within **7** simultaneously opened the epoxide with concomitant lactonization to produce the substituted tetrahydrofuran **8** in 75% yield with the desired *threo-threo* configuration.<sup>15</sup> 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

(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<sub>4</sub>, followed by oxidation to aldehyde with pyridinium chlorochromate in CH<sub>2</sub>Cl<sub>2</sub> 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. <sup>1</sup>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, [α]<sub>D</sub> +4.18° (c = 1.00, MeOH). Anal. Calcd for C<sub>21</sub>H<sub>40</sub>O<sub>5</sub>: C, 67.70; H, 10.82. Found: C, 67.70; H, 10.89. <sup>1</sup>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.

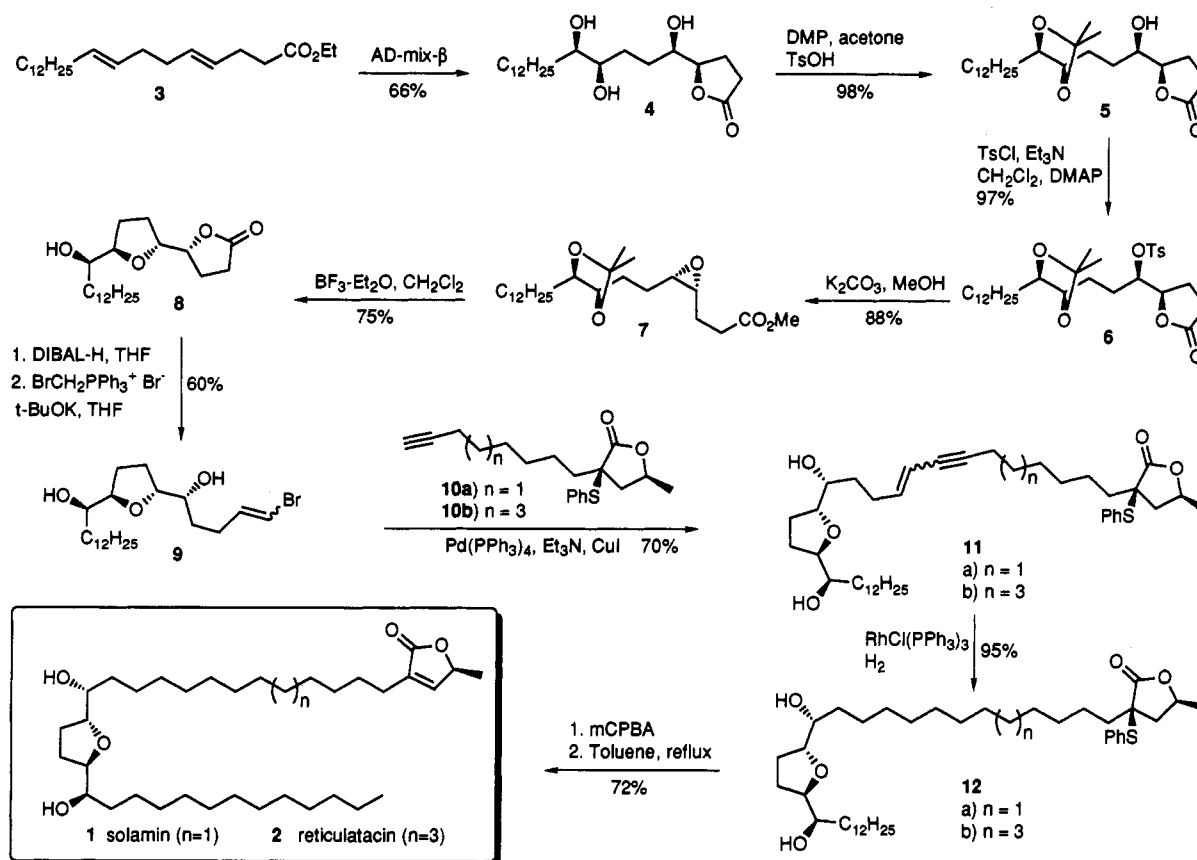
(12) Satisfactory analytical and spectroscopic data were obtained for all compounds reported in the paper.

(13) Compound **6**: HRMS calcd for C<sub>31</sub>H<sub>55</sub>O<sub>7</sub>SCs (M + Cs<sup>+</sup>) 699.2332, found 699.2311.

(14) Compound **7**: oil, [α]<sub>D</sub> +18.96° (c = 2.83, CHCl<sub>3</sub>). Anal. Calcd for C<sub>25</sub>H<sub>46</sub>O<sub>5</sub>: C, 70.38; H, 10.87. Found: C, 70.31; H, 10.87. <sup>1</sup>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<sub>3</sub>·Et<sub>2</sub>O. Compound **8**: mp 95–96 °C, [α]<sub>D</sub> –7.36° (c = 1.44, CHCl<sub>3</sub>). Anal. Calcd for C<sub>21</sub>H<sub>38</sub>O<sub>4</sub>: C, 71.14; H, 10.80. Found: C, 70.98; H, 10.83. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 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).

## Scheme I



9.<sup>16</sup> Completion of the carbon skeletons to give enynes **11a** and **11b** was achieved through a Pd(0)-catalyzed cross-coupling reaction ( $\text{Pd}(\text{PPh}_3)_4$ , CuI,  $\text{Et}_3\text{N}$  in THF, 50 °C, 2 h) of **9** with either **10a** or **10b**, both having the appropriate *S* configuration at the position  $\alpha$  to the lactone carbonyl.<sup>17</sup> 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**.<sup>18</sup> Finally, oxidation of the sulfide to sulfoxide with *m*-chloroperbenzoic acid in  $\text{CH}_2\text{Cl}_2$  (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,  $[\alpha]_D = +22.0^\circ$  ( $c = 0.2$ , MeOH); lit.<sup>6</sup> mp 64–68 °C,  $[\alpha]_D = +21.2^\circ$  ( $c = 0.16$ , MeOH)) and **2** (mp 80–81 °C,  $[\alpha]_D = +25.6^\circ$  ( $c = 0.5$ ,  $\text{CHCl}_3$ ); lit.<sup>7</sup> mp 80–80.5 °C,  $[\alpha]_D = +26^\circ$  ( $c = 0.5$ ,  $\text{CHCl}_3$ )) were found by <sup>1</sup>H

(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  $\text{NH}_4\text{Cl}$ . Compound **9**: oil; HRMS calcd for  $\text{C}_{22}\text{H}_{41}\text{O}_3\text{BrCs}$  ( $\text{M} + \text{Cs}^+$ ) 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.<sup>3</sup>) 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  $\text{C}_{41}\text{H}_{70}\text{O}_3\text{SCs}$  ( $\text{M} + \text{Cs}^+$ ), 807.3977, found 807.3977. <sup>1</sup>H NMR ( $\text{CDCl}_3$ ): 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  $\text{C}_{43}\text{H}_{74}\text{O}_3\text{SCs}$  ( $\text{M} + \text{Cs}^+$ ), 835.4311, found 835.4309. <sup>1</sup>H NMR ( $\text{CDCl}_3$ ): 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).

NMR, <sup>13</sup>C NMR, IR, and MS to be identical to the naturally occurring compounds.<sup>6,7</sup>

Using the sulforhodamine B assay,<sup>19</sup> the cytotoxicities of **1** and **2** were evaluated against a broad spectrum of tumor cell lines as well as normal cells for comparison.<sup>20</sup> On the average, solamin, **1**, exhibited  $\text{IC}_{50}$  values at micromolar concentrations, in agreement with the previously reported cytotoxicities for the natural solamin using epidermoid carcinoma (KB) cell line.<sup>6</sup> 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.<sup>7</sup>

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.<sup>2</sup> 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.

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

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