

DETERMINATION OF THE ABSOLUTE STRUCTURES OF CIS-TRIKENTRIN A  
 AND TRANS-TRIKENTRIN A BY SYNTHESIS OF THEIR ENANTIOMERS

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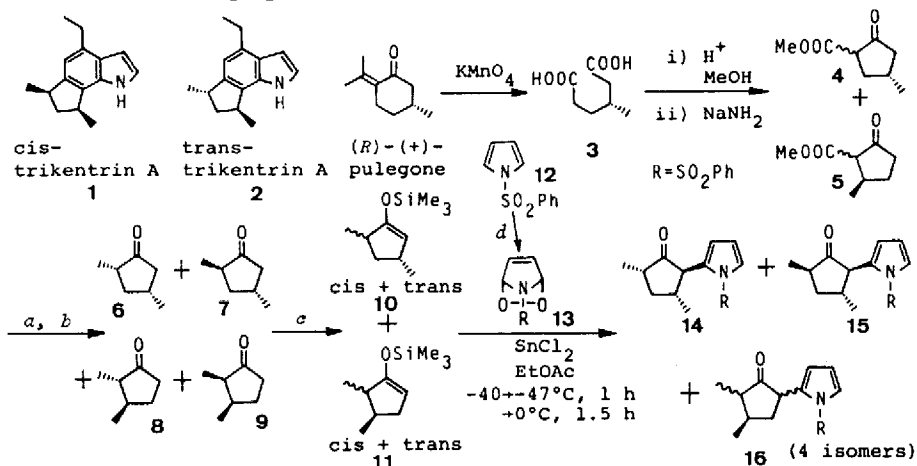
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Abstract : (-)-cis-Trikentrin A (20) and (-)-trans-trikentrin A (21) were synthesized from (R)-3-methyladipic acid by way of pyrrole derivatives 14, 15, and 17, establishing the absolute structure of the natural cis- and trans-trikentrins A to be 1 and 2.

Indole derivatives, cis-trikentrin A (1) and trans-trikentrin A (2) are constituents of an extract of the marine sponge *Trikentron flabelliforme*. These uniquely substituted indoles exhibit growth inhibitory activity against the gram positive bacteria.<sup>1,2</sup> Here we report the first synthesis of optically active trikentrins 20 and 21, utilizing our previous findings about a novel preparative method of polyalkylindole derivatives.<sup>3</sup> This study clarified that the absolute structures of cis-trikentrin A and trans-trikentrin A are expressed as 1 and 2.

Purified (R)-3-methyladipic acid (3), mp 85-86°C (Et<sub>2</sub>O-hexane), [ $\alpha$ ]<sub>D</sub><sup>23.5</sup> +10.8° (c 10.0, CHCl<sub>3</sub>), obtained from commercial (R)-(+)-pulegone, was converted to a mixture of methyl methylcyclopentanonecarboxylates 4 and 5, according to the literature<sup>4</sup> (Chart 1). This was further transformed into an inseparable mixture of dimethylcyclopentanones 6, 5a, 7, 5a, 8, 5b and 9<sup>5b</sup> in the ratio<sup>5c</sup> of 2:1:1.3:0.1 in 71% yield. These ketone compounds were then trimethylsilylated to give a mixture of 10 and 11 in 90% yield,<sup>6</sup> which were condensed with 1-benzenesulfonylpyrrole (12) by the reaction using its endoperoxide 13.<sup>7</sup> Silica gel chromatography [hexane-CH<sub>2</sub>Cl<sub>2</sub> (3:2)] afforded two groups of mixtures, 14+15<sup>8</sup> (4:1) and 16

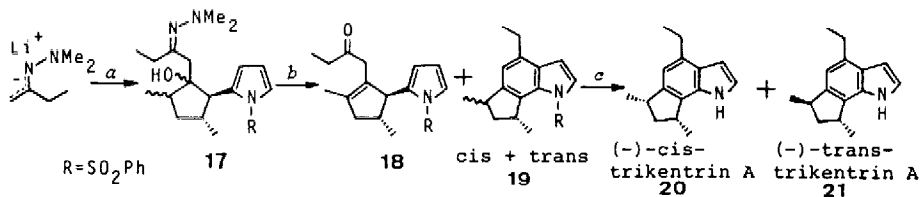


a: NaOMe, MeOH, -18°C, 1 h and then MeI, -18-20°C, 14.5 h. b: 47% HBr-H<sub>2</sub>O, 120°C, 6 h. c: LDA, THF, Me<sub>3</sub>SiCl, ca. -80°C, 15 min. d: hν (halogen lamp), O<sub>2</sub>, methylene blue, CH<sub>2</sub>Cl<sub>2</sub>, -63--40°C, 5 h.

Chart 1

in 37% and 19% yields, respectively, calculated from 12.

With the requisite chiral 3,5-dimethyl-2-pyrrolylcyclopentanones in hand, we next elaborated the elongation of a four-carbon side chain having a functional group suitable for the subsequent indole formation (Chart 2). 2-Butanone *N,N*-dimethylhydrazone was our choice and its lithium salt<sup>9</sup> was treated with a mixture of 14 and 15 in toluene-diethyl ether (1:1) to afford 17 in 61% yield, accompanied by the recovered 14+15 (32.5%) with the altered ratio (*ca.* 11:1) of *cis* and *trans* isomers.<sup>10</sup> Product 17 was directly submitted to indole cyclization by heating in 2-propanol containing sulfuric acid.<sup>3c</sup> An inseparable mixture of the indole derivatives 19<sup>8</sup> (*cis* : *trans* = *ca.* 4:3) was obtained in 73% yield with the formation of a by-product 18<sup>8</sup> in 12% yield. Alkaline hydrolysis of 19 gave (-)-*cis*-trikentrin A<sup>8</sup> (20), [ $\alpha$ ]<sub>D</sub><sup>24</sup> -68.6° (*c* 1.03, CHCl<sub>3</sub>) and (-)-*trans*-trikentrin A<sup>8</sup> (21), [ $\alpha$ ]<sub>D</sub><sup>24</sup> -26.8° (*c* 0.68, CHCl<sub>3</sub>) in 52% and 37% yields respectively. The identity of 20 and 21 with the natural compounds 1, [ $\alpha$ ]<sub>D</sub><sup>24</sup> +48° (*c* 2.47, CHCl<sub>3</sub>) and 2, [ $\alpha$ ]<sub>D</sub><sup>24</sup> +23.3° (*c* 1.0, CHCl<sub>3</sub>), was confirmed by comparing their <sup>1</sup>H and <sup>13</sup>C NMR spectra, except the sign of the optical rotation. This implies the establishment of the absolute structures of 1 and 2. Analogous facile synthesis of the marine indoles of the trikentrin B series is now in progress.<sup>11</sup>



*a*: 14+15, PhMe-Et<sub>2</sub>O (1:1), -75--65°C, 1 h. *b*: 6.5% H<sub>2</sub>SO<sub>4</sub> in 2-propanol, reflux, 14 h. *c*: 20% KOH in DME-MeOH-H<sub>2</sub>O (1:1:1), 85-90°C, 6.5 h.

Chart 2

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