

## A NEW TOTAL SYNTHESIS OF (±) STEGANONE<sup>1</sup>

Miljenko Merviĉ, Yehoshua Ben-David and Eugene Ghera\*

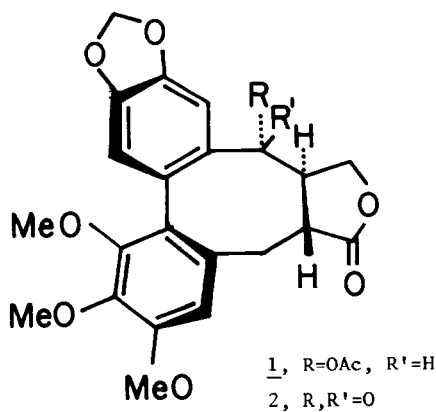
Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

**Abstract:** A new total synthesis of (±) steganone was completed by a route involving the cyclization of a 2,2'-bis(bromoacyl)biaryl derivative.

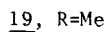
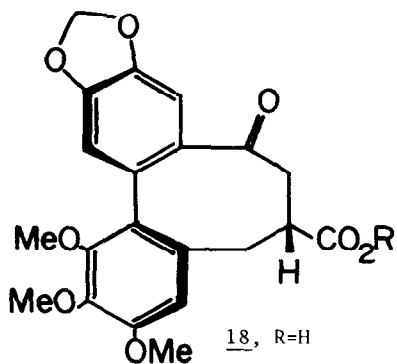
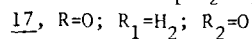
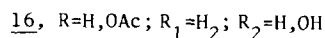
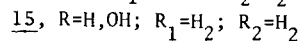
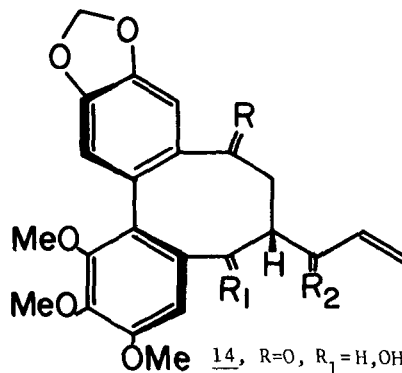
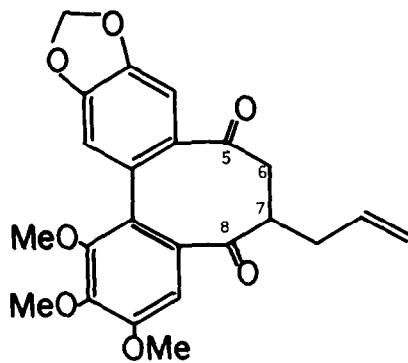
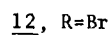
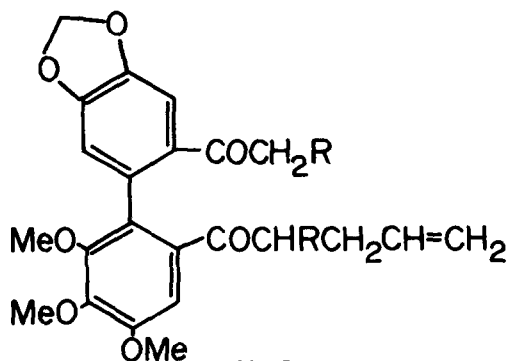
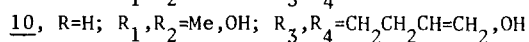
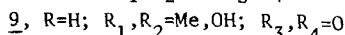
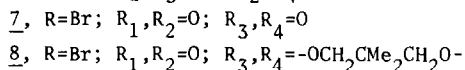
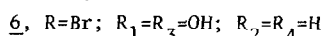
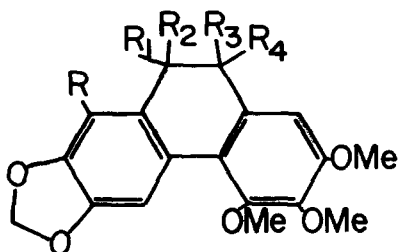
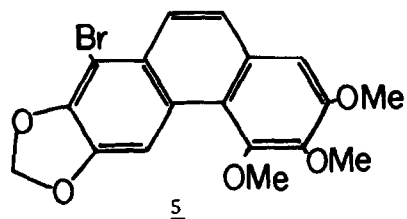
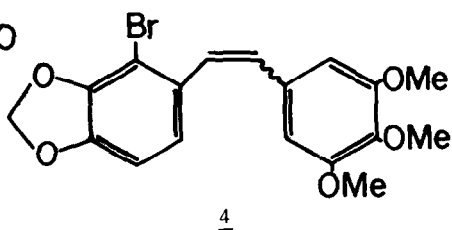
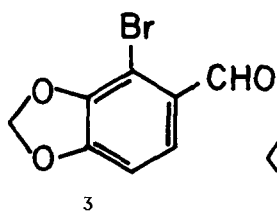
Steganacin (1) is a lignan lactone possessing antileukemic activity<sup>2</sup> and the interest in this substance and in the corresponding ketone, steganone (2), has been evidenced by the fact that several syntheses of these compounds were reported during the recent years.<sup>3</sup>

As part of our program of synthesis of biologically active lignans of the schizandrin family,<sup>4</sup> we describe now a new synthetic route leading to (±) steganone in which the 2,2'-bis(bromoacyl)-1,1'-biaryl derivative (12) was prepared and utilized for the elaboration of the bisbenzocyclooctadiene skeletal structure.

The required biaryl was synthesized by a sequence starting from the hitherto unreported 2-bromopiperonal<sup>5</sup> (3), mp 132°C, which was prepared by bromination with phenyltrimethylammonium perbromide<sup>6</sup> of the C-2 lithiated piperonal cyclohexylimine<sup>7</sup> (THF, -78°C) and subsequent hydrolysis of the imine group by passing the crude product through a silica column (76%). The Wittig reaction of 3 with 3,4,5-trimethoxybenzylphosphonium bromide (DMF, MeOLi, 90°C),<sup>8</sup> gave the stilbenes 4 (96%) which on photocyclization (I<sub>2</sub>, THF-cyclohexane)<sup>8</sup> afforded the phenanthrene 5, mp 195-196°C (91%). Hydroxylation (excess OsO<sub>4</sub> in pyridine, 240 h, room temperature), gave a mixture of diol 6 and quinone 7. After additional oxidation of the separated diol 6 (SO<sub>3</sub>-pyridine<sup>8</sup>), the yield of quinone 7, mp 265-267°C, was 86%. Selective ketalization of the ketone group remote from the bromosubstituted ring<sup>9</sup> (2,2-dimethyl-1,3-propanediol, p-TsOH, C<sub>6</sub>H<sub>6</sub>, 12 h reflux), gave the ketal ketone 8, mp 210°C (95%). The addition of methyl lithium to



the latter under controlled conditions (-100°C, 30 min, THF) resulted concomitantly in reductive debromination of the aromatic ring, affording, after acidification (10% HCl, MeOH),



the keto alcohol 9, mp 123-124°C (85% from 8). The Grignard reagent prepared from 4-bromo-1-butene (C<sub>6</sub>H<sub>6</sub>, 25°C) converted 9 into a single diol 10, mp 141-142°C (92%), which was cleaved (lead tetraacetate, benzene-pyridine 1:1, 1 h, 25°C) to the biaryl diketone 11, mp 101-103°C, obtained in 91% yield (or 51% overall yield starting from 2-bromopiperonal), IR (CHCl<sub>3</sub>) 1680 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.26 (s, 1H), 6.92 (s, 1H), 6.54 (s, 1H), 6.06 (s, 2H), 5.50-5.61 (m, 1H), 4.79-4.95 (brd, 2H), 3.90 (s, 6H), 3.54 (s, 3H), 2.17-2.47 (m, 4H), 2.30 (s, 3H). Selective α-monobromination of the two acyl groups in 11 was effected via the corresponding bis-silyl enol ether (butyllithium, -78°C, Me<sub>3</sub>SiCl in THF-HMPA 10:1), which was treated with N-bromosuccinimide<sup>10,11</sup> (THF, 0°C) to give the dibromides 12 (79%) as a mixture of diastereomers, due to restricted biaryl rotation. The cyclization of 12, induced by zinc-silver couple<sup>12</sup> in dimethylsulfoxide<sup>13</sup> was stereoselective with regard to the side chain and gave a mixture of two diketones 13 (57%)<sup>14</sup> isomeric by biaryl rotation and interconvertible in solution, at 25°C; IR (CHCl<sub>3</sub>) 1670 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.27 (s, 1H), 6.58 (s, 1H), 6.47 (s, 1H) and 7.05 (s, 1H), 6.66 (s, 1H), 6.57 (s, 1H), aromatic protons of each isomer, respectively. The reduction of the latter with LiAlH(t-BuO)<sub>3</sub> at -10°C (200 mol%, THF, 2 h) was remarkably selective, affecting mainly the C-8 ketone group and affording a single keto alcohol (14), mp 209°C (61%),<sup>15</sup> out of eight possible regio- and stereoisomers; IR (KBr) 1665 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, aromatic protons) δ 7.73 (s, 1H), 6.91 (s, 1H), 6.68 (s, 1H). The 5,8-diol (21%), obtained as byproduct, was recycled by oxidation to 13 (Jones reagent). Mesylation of 14 (MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 2h) and treatment of the crude mesylate with lithium triethylborohydride (THF, 16 h, 25°C; H<sub>2</sub>O<sub>2</sub>-NaOH, 1 h) afforded a single alcohol (15), mp 141-142°C (66% from 14), <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.18 (s, 1H), 6.65 (s, 1H), 6.56 (s, 1H). Acetylation<sup>16</sup> followed by allylic oxidation in the side chain<sup>17</sup> (t-BuO<sub>2</sub>H, ScO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 25°C, 30 h) gave the stereoisomeric hydroxyacetates 16 (67% from 15) and recovered unreacted acetate (17%). Deacetylation (LiAlH<sub>4</sub>, THF) and oxidation of the diols with pyridinium dichromate<sup>18</sup> (CH<sub>2</sub>Cl<sub>2</sub>, 7 h, 25°C) produced the diketone 17, mp 136°C (71% from 16); IR (CHCl<sub>3</sub>) 1655, 1615 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ 7.68 (s, 1H), 6.66 (s, 1H), 6.54 (dd, J=10,18 Hz, 1H), 6.34 (dd, J=1,18 Hz, 1H), 6.30 (s, 1H), 6.07 (spd, 2H), 5.87 (dd, J=10,1 Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.57 (s, 3H), 3.29-2.52 (m, 5H). Cleavage of the side chain (OsO<sub>4</sub>, NaIO<sub>4</sub>, dioxane-H<sub>2</sub>O, 25°C, 3 h) afforded a single keto acid 18 (89%), characterized as the keto ester 19 (CH<sub>2</sub>N<sub>2</sub>), mp 133-134°C, which was identical with the keto ester<sup>19</sup> having the biaryl configuration of steganone. The structure of 19 was also confirmed by thermal equilibration which gave a mixture of the two keto esters, isomeric by rotation about the biaryl bond.<sup>3c,19</sup> The keto acid 18 was converted directly to steganone, mp 228-230°C,<sup>19</sup> by hydroxymethylation-oxidation as described previously.<sup>3c</sup>

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References and Notes

1. Dedicated to Professor Ralph A. Raphael on the occasion of his 60th birthday.
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13. To a stirred mixture of 12 (1 mmol), NaHCO<sub>3</sub> (4 mmol), NaI (2 mmol) and Zn-Ag couple<sup>12</sup> (60 mmol) was added under anhydrous conditions 100 ml of dimethyl sulfoxide (oil bath, 100°C, 30 min).
14. Diketone 12 obtained as byproduct in the cyclization reaction (16%) was separated after the next step from 14, being unaffected under the given reduction conditions.
15. This selectivity is rationalized by the conformational properties of the eight-membered ring, which will be treated elsewhere. The assigned structure has been determined by <sup>1</sup>H NMR decoupling experiments and the shown stereochemical relationship between biaryl ske ing and side chain has been confirmed in subsequent steps.
16. The oxidation yields were lower in the presence of a free C-5 hydroxyl.
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19. We are indebted to Prof. R.A. Raphael and Dr. J.P. Robin for comparison samples.

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