

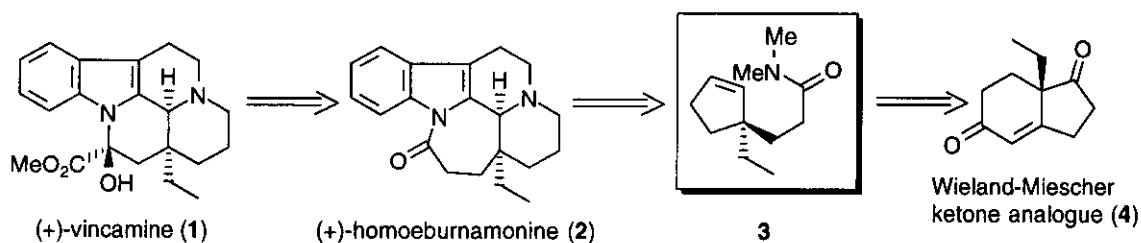
# AN ENANTIOCONVERGENT CONSTRUCTION OF THE KEY INTERMEDIATE OF (+)-VINCAMINE†

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**Abstract** — A key intermediate for the synthesis of (+)-vincamine, the major alkaloid of *Vinca minor* and an important cerebral vasodilatory agent, has been synthesized in an enantioconvergent way from either (*R*)- or (*S*)-enantiomer of 2-carbethoxy-2-cyclopenten-1-ol obtained by lipase-mediated resolution.

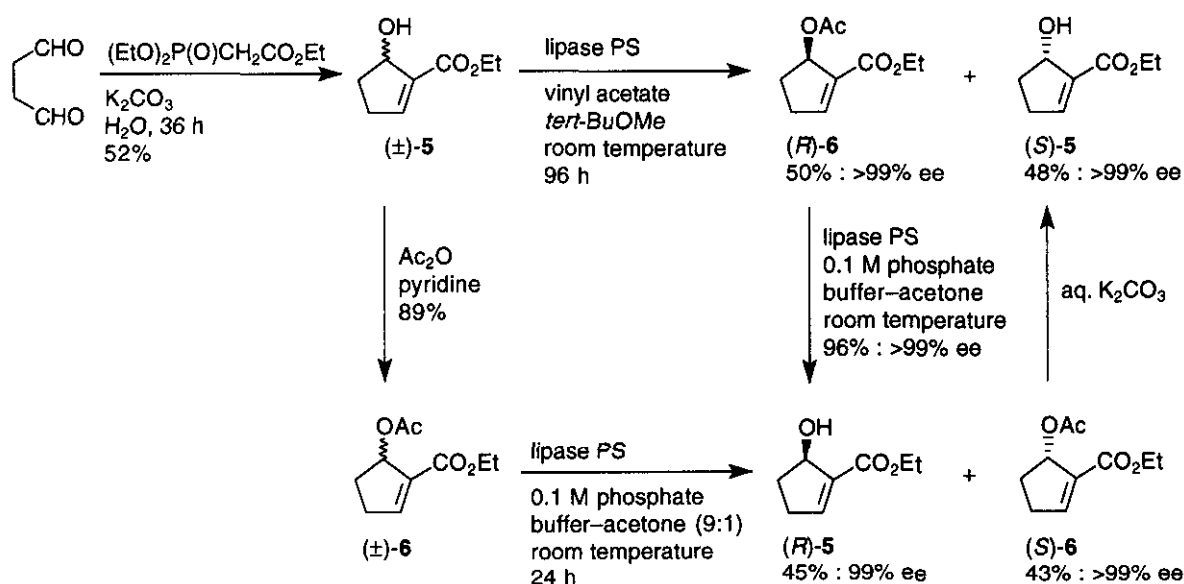
Ten years ago<sup>1</sup> we disclosed an enantiocontrolled entry to (+)-homoeburnamonine (**2**), an immediate synthetic intermediate of (+)-vincamine<sup>2</sup> (**1**), the major alkaloid of *Vinca minor* and an important cerebral vasodilatory agent, starting from the optically active Wieland-Miescher ketone analogue (**4**) via the key cyclopentene compound (**3**) (Scheme 1).



Scheme 1

Meanwhile, we developed<sup>3</sup> an efficient enantiocomplementary kinetic resolution of racemic 2-carbethoxy-2-cyclopenten-1-ol [(±)-**5**], readily accessible by tandem aldol-Wittig reaction<sup>4</sup> between butanedial and the

† Dedicated to the memory of Professor Yoshio Ban.

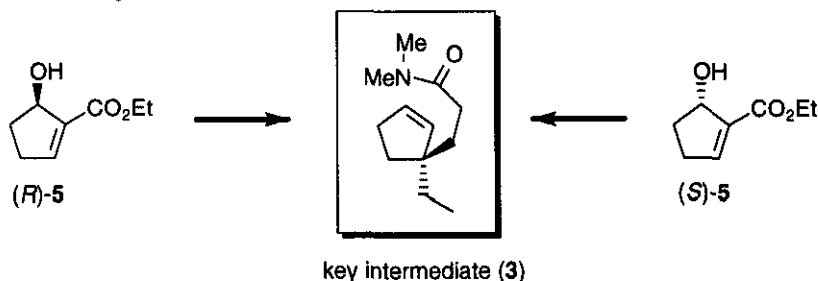


Scheme 2

phosphonate ester in water, using lipase in both organic and aqueous media to afford the optically pure cyclopentenol (**5**) in both enantiomeric forms in satisfactory yields (Scheme 2).

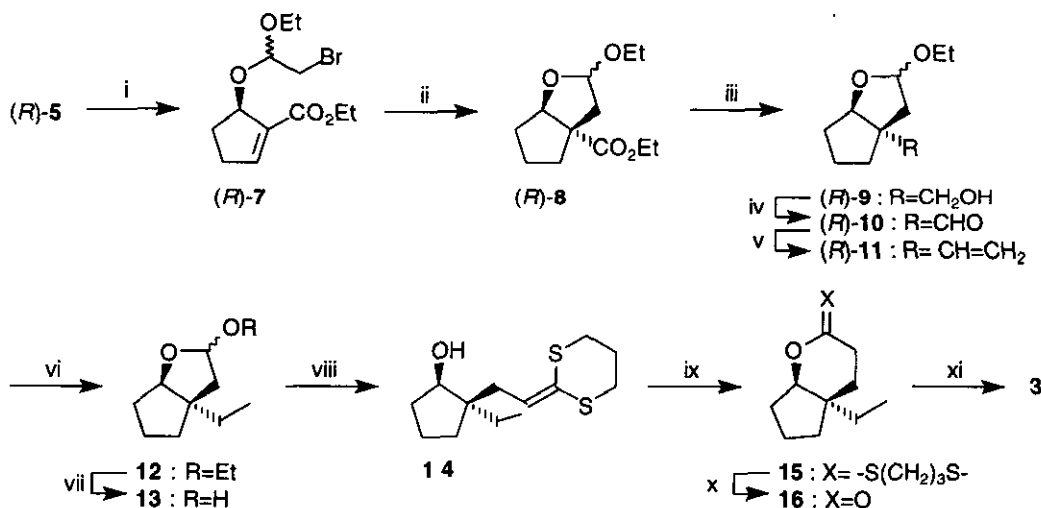
In order to interrelate these two findings, we explored an alternative enantiocontrolled route to the key cyclopentene compound (**3**) using either *R*- or *S*-enantiomer of the optically pure cyclopentenols (*R*)- and (*S*)-**5** thus obtained. We present herewith our successful enantioconvergent transformation of both enantiomeric cyclopentenols, (*R*)- and (*S*)-**5**, into the same key cyclopentene (**3**) employing a radical cyclization as a key step (Scheme 3).

#### Present Study



Scheme 3

Thus, we first treated the (*R*)-alcohol (*R*)-5 with an excess ethyl vinyl ether in the presence of *N*-bromosuccinimide (NBS)<sup>5</sup> to give the bromoacetal [(*R*)-7] in a good yield as a mixture of the epimers at the acetal carbon. Treatment of the mixture with 1.5 equiv. of tri-*n*-butylstannane in the presence of a catalytic amount of azo-bis-isobutyronitrile (AIBN) in benzene<sup>6</sup> at reflux temperature afforded the cyclic acetal [(*R*)-8] as a mixture of epimers at the acetal carbon. The mixture was reduced with lithium aluminum hydride to give the primary alcohol<sup>7</sup> [(*R*)-9] which on the Swern oxidation gave the aldehyde [(*R*)-10] in an excellent overall yield. One carbon unit was added to (*R*)-10 by the Wittig reaction to give the olefin [(*R*)-11] which was then hydrogenated to afford the acetal (12) bearing a quaternary ethyl group. On sequential acid-hydrolysis, condensation with 2-lithio-2-trimethylsilyldithiane,<sup>8</sup> and acid-treatment, the acetal (12) furnished the lactone dithioacetal (15), [ $\alpha$ ]<sub>D</sub><sup>30</sup> +134.0° (*c* 0.79, CHCl<sub>3</sub>), in 63% overall yield *via* the lactol (13) and the ketene dithioacetal (14). Exposure of 15 to methyl iodide in aqueous acetonitrile<sup>9</sup> allowed facile hydrolytic removal of the thioketal group to give the  $\delta$ -lactone (16), [ $\alpha$ ]<sub>D</sub><sup>30</sup> +45.1° (*c* 0.72, CHCl<sub>3</sub>), without difficulty. Finally, 16 was refluxed with hexamethylphosphoric triamide (HMPA) to give the key cyclopentene (3), [ $\alpha$ ]<sub>D</sub><sup>29</sup> -36.6° (*c* 0.44, CHCl<sub>3</sub>) [lit.,<sup>1</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> -8.0° (*c* 1.04, CHCl<sub>3</sub>)], by concurrent amide formation and elimination.<sup>1,10</sup>



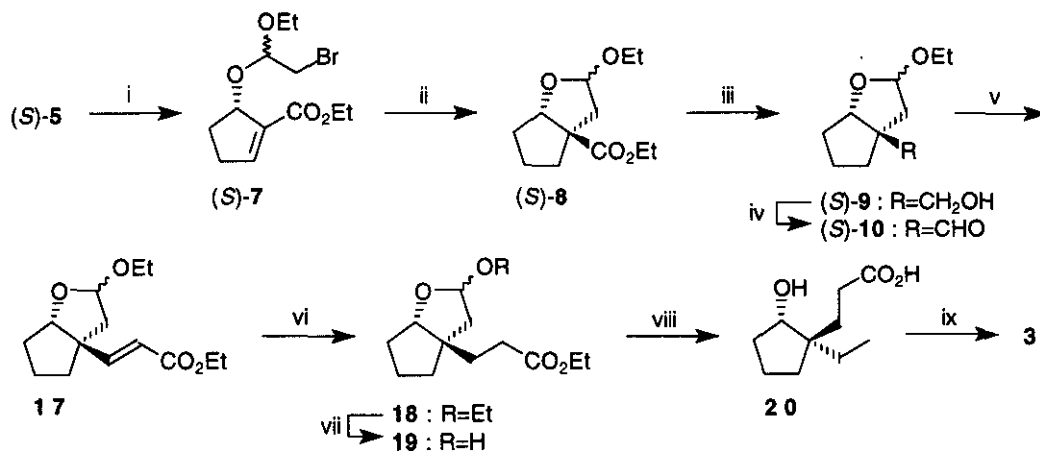
#### Scheme 4

**Reagents and conditions:** i) NBS (3 equiv.), ethyl vinyl ether (10 equiv.), no solvent, 0 °C ~ room temperature, 73.0%. ii) *n*-Bu<sub>3</sub>SnH (1.5 equiv.), AIBN (0.1 equiv.), benzene, 80 °C, 94.7%. iii) LiAlH<sub>4</sub>, THF, 0 °C, 99.7%. iv) Swern oxidation, 89.1%. v) Ph<sub>3</sub>PMeBr, *n*-BuLi, THF, 0 °C, 83.6%. vi) H<sub>2</sub>, PtO<sub>2</sub> (cat.), AcOEt, room temperature, 94.7%. vii) PPTS (cat.), aq. MeCN, 70 °C, 81.5%. viii) TMSCH(SCH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>, *n*-BuLi, THF, -20 °C ~ room temperature. ix) 1% HCl-dioxane, room temperature, 76.8% (2 steps). x) MeI, aq. MeCN, 60 °C, 91.1%. xi) HMPA, reflux, 73.3%.

Overall yield of **3** from (*R*)-alcohol [(*R*)-**5**] was 20% in 11 steps (Scheme 4).

Having succeeded in transformation of the (*R*)-cyclopentenol [(*R*)-**5**] into the key cyclopentene (**3**), we next examined the transformation of the enantiomeric (*S*)-alcohol [(*S*)-**5**] into the same cyclopentene (**3**). Thus, (*S*)-**5** was first transformed into the (*S*)-aldehyde [(*S*)-**10**] in 55% overall yield in four steps by employing the same procedure as for the (*R*)-enantiomer [(*R*)-**10**].

The aldehyde [(*S*)-**10**] thus obtained was elongated by the Horner-Emmons reaction to give the  $\alpha,\beta$ -unsaturated ester (**17**) excellently as a mixture of epimers at the acetal carbon. On sequential hydrogenation, acid-catalyzed hydrolysis of the acetal bond, and the Wolff-Kishner reduction, **17** yielded the hydroxy acid (**20**) bearing a quaternary ethyl group *via* **18** and **19**. Finally, the hydroxy acid (**20**) was refluxed with HMPA to afford the key cyclopentene (**3**),  $[\alpha]_D^{30} -36.8^\circ$  (*c* 1.01,  $\text{CHCl}_3$ ), through concurrent dehydration and amide formation.<sup>11</sup> Overall yield of **3** from (*S*)-alcohol [(*S*)-**5**] was 31% in 9 steps (Scheme 5).



#### Scheme 5

**Reagents and conditions:** i) NBS (3 equiv.), ethyl vinyl ether (10 equiv.), no solvent, 0 °C ~ room temperature, 79.2%. ii) *n*-Bu<sub>3</sub>SnH (1.5 equiv.), AIBN (0.1 equiv.), benzene, 80 °C, 92.3%. iii) LiAlH<sub>4</sub>, THF, 0 °C, 98.9%. iv) Swern oxidation, 75.8%. v) (EtO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Et, NaH, THF, 0 °C, 97.5%. vi) H<sub>2</sub>, PtO<sub>2</sub> (cat.), AcOEt, room temperature, 99.2%. vii) PPTS, aq. MeCN, reflux, 74.2% (88% conversion). viii) KOH (7 equiv.), NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O (9 equiv.), 160 °C. ix) HMPA, reflux, 66.9% (2 steps).

In conclusion, we have developed an alternative procedure for the construction of the key synthetic intermediate (**3**) of a medicinally important indole alkaloid (+)-vincamine (**1**) using either (*R*)- or (*S*)-enantiomer of 2-carbethoxy-2-cyclopenten-1-ol (**5**) in an enantioconvergent way.

#### ACKNOWLEDGEMENTS

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12. Spectral data of the representative compounds: **3**: Ir (neat)  $\nu_{\max}$ : 1649  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.69 (dt,  $J=5.9, 2.2$  Hz, 1H), 5.42 (dt,  $J=5.9, 2.2$  Hz, 1H), 2.99 (s, 3H), 2.93 (s, 3H), 2.40-2.18 (m, 4H), 1.86-1.54 (m, 4H), 1.46-1.36 (m, 2H), 0.83 (t,  $J=7.3$  Hz, 3H). **R-9** ( $\alpha$ -OEt): Ir (neat)  $\nu_{\max}$ : 3452  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.12 (d,  $J=4.8$  Hz, 1H), 4.38 (d,  $J=5.1$  Hz, 1H), 3.82-3.63 (m, 3H), 3.52-3.37 (m, 2H), 2.16 (d,  $J=13.6$  Hz, 1H), 1.93-1.80 (m, 2H), 1.70-1.49 (m, 5H), 1.20 (t,  $J=7.1$  Hz, 3H). **R-9** ( $\beta$ -OEt): Ir (neat)  $\nu_{\max}$ : 3444  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.09 (dd,  $J=5.7, 2.0$  Hz, 1H), 4.34-4.26 (m, 1H), 3.76 (dq,  $J=9.5, 7.1$  Hz, 1H), 3.60-3.46 (m, 2H), 3.42 (dq,  $J=9.5, 7.1$  Hz, 1H), 2.22 (dd,  $J=13.4, 5.7$  Hz, 1H), 2.12-1.94 (m, 1H), 1.92-1.47 (m, 7H), 1.20 (t,  $J=7.1$  Hz, 3H). **15**:  $^1\text{H}$  Nmr (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.89 (d,  $J=5.1$  Hz, 1H), 3.51-3.37 (m, 1H), 3.03-2.89 (m, 1H), 2.70-2.53 (m, 2H), 2.18-2.06 (m, 1H), 2.03-1.67 (m, 8H), 1.67-1.48 (m, 2H), 1.39-1.28 (m, 1H), 1.21 (br q,  $J=7.4$  Hz, 2H), 0.84 (t,  $J=7.5$  Hz, 3H). **16**: Ir (neat)  $\nu_{\max}$ : 1745  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.33 (dd,  $J=5.7, 2.8$  Hz, 1H), 2.51-2.31 (m, 2H), 2.08-1.26 (m, 10H), 0.91 (t,  $J=7.3$  Hz, 3H).