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

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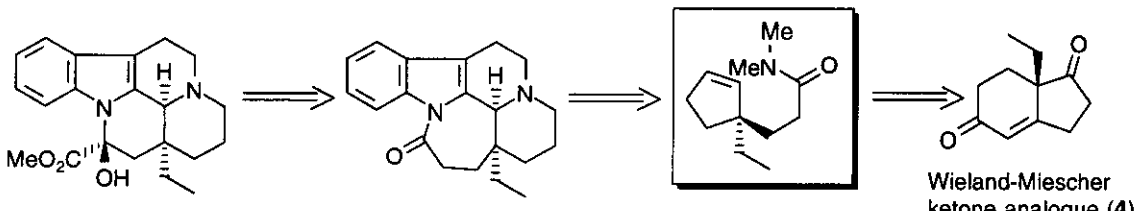
Abstract —— A key intermediate for the synthesis of (+)-vincamine, the major alkaloid of *Vinca minor* and an important cerebral vasodilatory agent, has been synthesized in an enantioconvergent way from either (*R*)- or (*S*)-enantiomer of 2-carbethoxy-2-cyclopenten-1-ol obtained by lipase-mediated resolution.

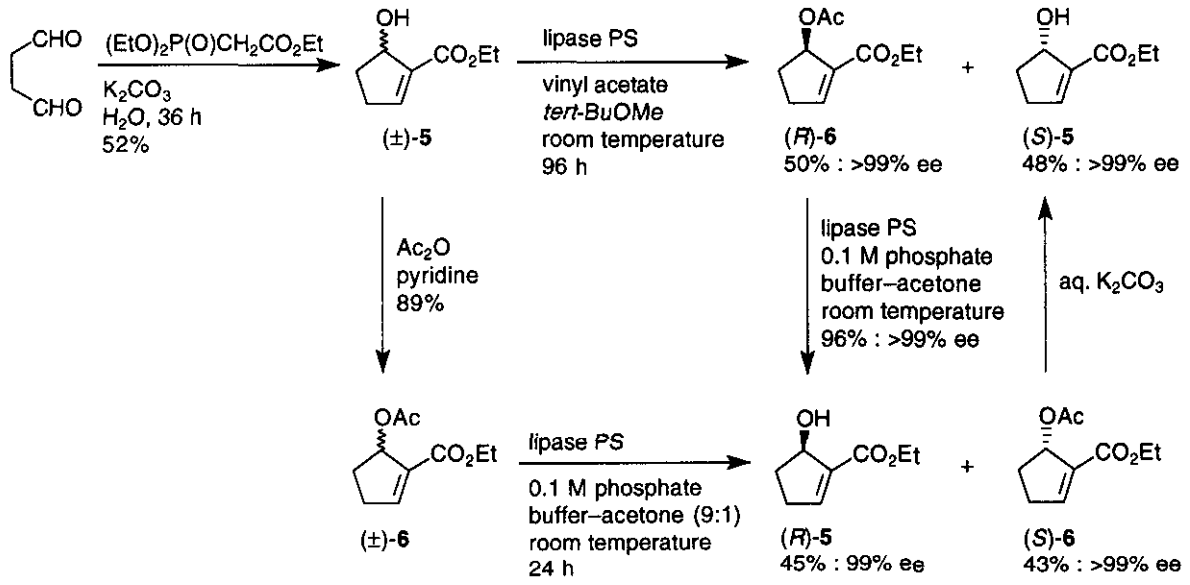
Ten years ago[1] we disclosed an enantiocontrolled entry to (+)-homoeburnamonine (**2**), an immediate synthetic intermediate of (+)-vincamine[2] (**1**), the major alkaloid of *Vinca minor* and an important cerebral vasodilatory agent, starting from the optically active Wieland-Miescher ketone analogue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



Scheme 1

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

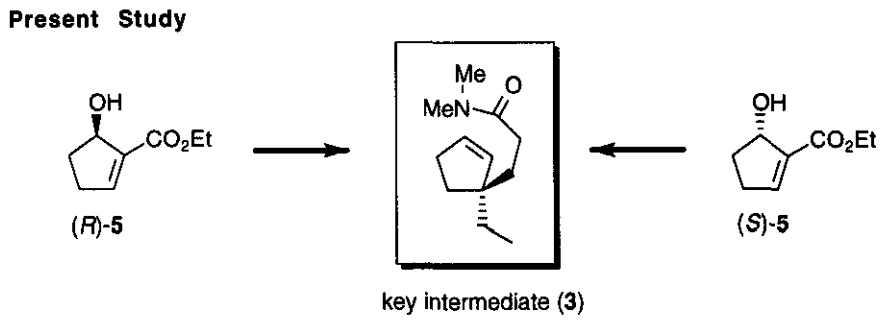
† Dedicated to the memory of Professor Yoshio Ban.



Scheme 2

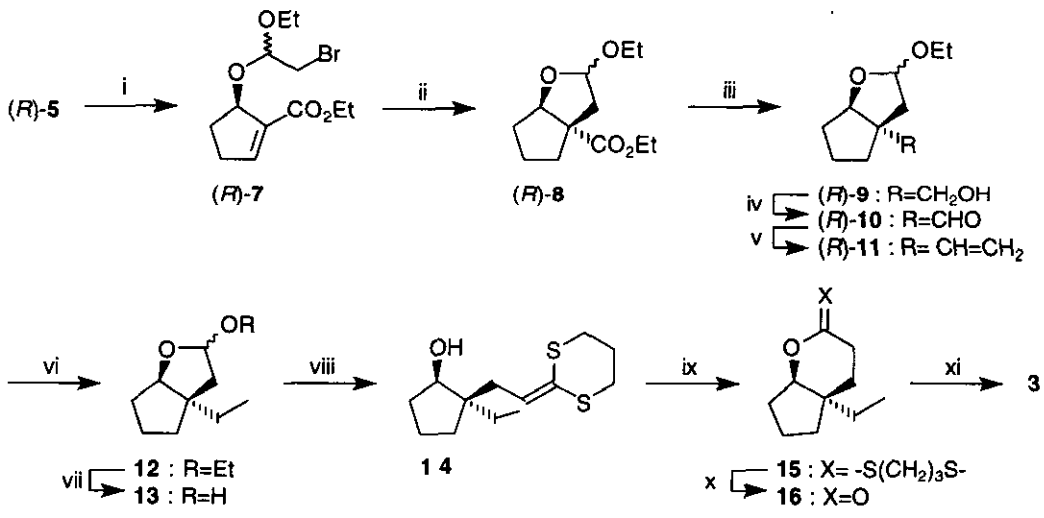
phosphonate ester in water, using lipase in both organic and aqueous media to afford the optically pure cyclopentenol (**5**) in both enantiomeric forms in satisfactory yields (**Scheme 2**).

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**).



Scheme 3

Thus, we first treated the (*R*)-alcohol (*R*)-**5** with an excess ethyl vinyl ether in the presence of *N*-bromosuccinimide (NBS)[5] 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[6] 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[7] [(*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,[8] and acid-treatment, the acetal (**12**) furnished the lactone dithioacetal (**15**), $[\alpha]_D^{30}$ +134.0° (*c* 0.79, $CHCl_3$), in 63% overall yield *via* the lactol (**13**) and the ketene dithioacetal (**14**). Exposure of **15** to methyl iodide in aqueous acetonitrile[9] allowed facile hydrolytic removal of the thioketal group to give the δ-lactone (**16**), $[\alpha]_D^{30}$ +45.1° (*c* 0.72, $CHCl_3$), without difficulty. Finally, **16** was refluxed with hexamethylphosphoric triamide (HMPA) to give the key cyclopentene (**3**), $[\alpha]_D^{29}$ –36.6° (*c* 0.44, $CHCl_3$) [lit.,[1] $[\alpha]_D^{25}$ –8.0° (*c* 1.04, $CHCl_3$)], by concurrent amide formation and elimination.[1,10]



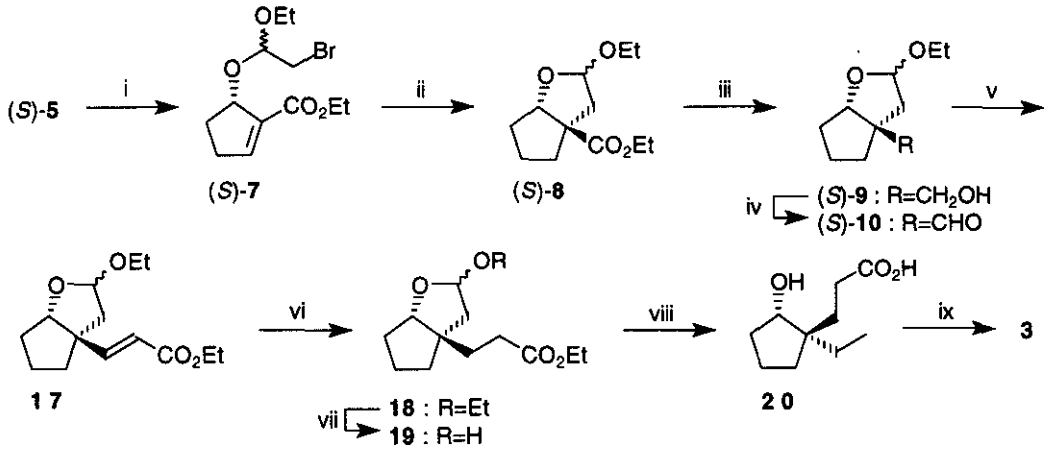
Scheme 4

Reagents and conditions: i) NBS (3 equiv.), ethyl vinyl ether (10 equiv.), no solvent, 0 °C ~ room temperature, 73.0%. ii) *n*-Bu_3SnH (1.5 equiv.), AIBN (0.1 equiv.), benzene, 80 °C, 94.7%. iii) $LiAlH_4$, THF, 0 °C, 99.7%. iv) Swern oxidation, 89.1%. v) Ph_3PMeBr, *n*-BuLi, THF, 0 °C, 83.6%. vi) H_2, PtO_2 (cat.), AcOEt, room temperature, 94.7%. vii) PPTS (cat.), aq. MeCN, 70 °C, 81.5%. viii) $TMSCH(SCH_2)_2CH_2$, *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 α,β-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° (*c* 1.01, $CHCl_3$), through concurrent dehydration and amide formation.[11] 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_3SnH (1.5 equiv.), AIBN (0.1 equiv.), benzene, 80 °C, 92.3%. iii) $LiAlH_4$, THF, 0 °C, 98.9%. iv) Swern oxidation, 75.8%. v) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C, 97.5%. vi) H_2, PtO_2 (cat.), AcOEt, room temperature, 99.2%. vii) PPTS, aq. MeCN, reflux, 74.2% (88% conversion). viii) KOH (7 equiv.), $NH_2NH_2{\cdot}H_2O$ (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.

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12. Spectral data of the representative compounds: **3**: Ir (neat) ν_{max}: 1649 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ: 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** (α-OEt): Ir (neat) ν_{max}: 3452 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ: 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** (β-OEt): Ir (neat) ν_{max}: 3444 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ: 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**: ^1H Nmr (300 MHz, $CDCl_3$) δ: 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) ν_{max}: 1745 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ: 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).

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