Enantiospecific synthesis of (+)- and (−)-trachelanthic acids *via* asymmetric dihydroxylation and their conversion to the pyrrolizidine alkaloids indicine and intermedine

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Asymmetric dihydroxylation of (*E*)-ethyl 2-isopropylbut-2-enoate with AD-mix-α and AD-mix-β, followed by saponification, gives (−)- and (+)-trachelanthic acids, respectively, which are each coupled *via* their acetonides with (+)-retronecine to yield the pyrrolizidine alkaloids indicine and intermedine.

Indicine **1**[1] and its stereoisomer intermedine **2**[2,3] are widely distributed pyrrolizidine alkaloids that are related structurally by coupling of the necine base (+)-retronecine **3** with enantiomeric necic acids (trachelanthic acids).[4] The *N*-oxide of **1** (INO), also a natural product,[1] showed early promise as an antitumour agent in clinical trials,[5–7] but unpredictable hepatic toxicity in treated patients interrupted those studies.[8]

The necic acid constituents of **1**, (2*R*, 3*S*)-2,3-dihydroxy-2-isopropylbutanoic acid [(−)-trachelanthic acid, **4**], and **2** [(+)-**4**] have been obtained by resolution of racemic trachelanthic acid,[9] and (−)-**4** can be prepared by an indirect route[10] or one that requires separation by HPLC of diastereoisomeric derivatives.[11,12] No enantiodivergent pathway to (+)- and (−)-trachelanthic acids from a common intermediate has been devised, and no enantiospecific synthesis of intermedine **2**, the parent alkaloid of (+)-**4**, has been reported. Here we describe a solution that fills this void and opens a practical route to both indicine **1** and intermedine **2** from (+)-**3** and ethyl acetoacetate.

Sharpless asymmetric dihydroxylation (AD) has been shown to provide an efficient means for introducing a vicinal diol functionality into a prochiral alkene with high enantiomeric excess.[13] In forecasting the outcome of AD methodology as applied to (*E*)-ethyl 2-isopropylbut-2-enoate **5**, the original Sharpless mnemonic[14] is ambiguous when alkene substituents are treated from the viewpoint of steric size alone. Thus, the steric barricade which occupies the northwest quadrant of the catalytic binding pocket and which would oppose the isopropyl substituent of **5** when the latter is resident in the orientation shown is in conflict with the steric demand of the eastern boundary. The latter clearly specifies that the alkenic hydrogen rather than the methyl substituent of **5** should occupy the southeast quadrant where a larger steric barrier exists. However, the revised Sharpless mnemonic that posits a region in the southwest quadrant attractive to flat unsaturated groups (Fig. 1)[15] would stipulate that the ester group of **5** should occupy this domain. This feature of the AD binding mechanism reinforces the steric constraints imposed by open and sterically congested northeast and southeast quadrants, respectively.

Assuming the alignment of **5** is as shown in Fig. 1, the prediction can be made that AD-mix-α containing the $(DHQ)_2$-PHAL ligand should favour hydroxylation from the *si-si* face of the alkene to yield ethyl (2*R*, 3*S*)-trachelanthate. Conversely AD-mix-β [$(DHQD)_2$-PHAL] should lead to the enantiomeric (2*S*, 3*R*) dihydroxy ester. (*E*)-Ethyl 2-isopropylbut-2-enoate was therefore prepared in geometrically pure form in order to test the accuracy of this prediction.

The monoanion of ethyl acetoacetate was alkylated with isopropyl bromide, and the resulting keto ester **6** was reduced with zinc borohydride to give an 11:1 mixture of *syn* and *anti* β-hydroxy esters **7** and **8**, respectively (Scheme 1). The *syn* diastereoisomer **7** was treated with phosphorus oxychloride in pyridine and (*E*)-ethyl 2-isopropylbut-2-enoate **5** was obtained in good yield after chromatographic purification. The reaction of **5** with AD-mix-α in the presence of methanesulfonamide proceeded slowly but afforded dihydroxy ester (+)-**9** in high yield.† After conversion of **9** to the monobenzoate (−)-**10**, analysis by HPLC using a Chiralcel OD column showed that AD had taken place with 90% ee. In an analogous fashion, the reaction of **5** with AD-mix-β gave (−)-**9** which was shown *via* its benzoate (+)-**10** to be of 85% ee. Saponification of (+)- and (−)-**9** by conventional means proved troublesome due to retroaldol fission, but hydrolysis of these esters with barium hydroxide octahydrate was uneventful and furnished (−)- and (+)-trachelanthic acids, respectively. After crystallization, the properties of (+)- and (−)-**4** were in excellent agreement with those recorded on the enantiomeric acids previously obtained by resolution of the racemate.[2]

Before esterifying (+)-retronecine **3** with trachelanthic acid, it was necessary to protect the diol of the latter. This was conveniently accomplished as the acetonide **11** (Scheme 2). Coupling of (+)-**11**, prepared from (−)-**4**, with (+)-**3**, obtained by hydrolysis of the readily available alkaloid (−)-retrorsine, in the presence of dicyclohexylcarbodiimide, 4-(dimethylamino)-pyridine and camphorsulfonic acid occurred exclusively at the more sterically accessible primary (C-9) alcohol to give indicine

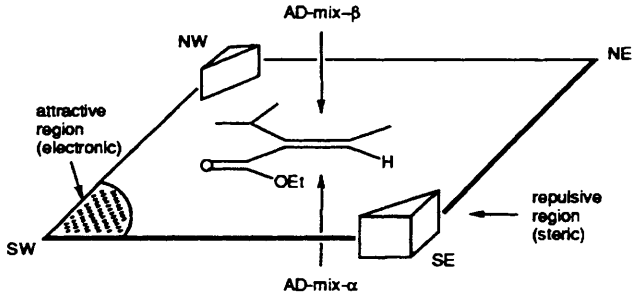

Fig. 1 Mnemonic (revised) for Sharpless asymmetric dihydroxylation of **5**

acetonide. The protecting group was removed by acidic hydrolysis to furnish (+)-indicine **1** with properties identical to those reported for the natural material. A parallel sequence departing from (−)-**11** prepared from (+)-trachelanthic acid, yielded (+)-intermedine **2** whose properties were also in accord with those recorded for the natural alkaloid. (+)-Indicine **1** was characterized as its stable aminoborane derivative **12**, a surrogate for indicine *N*-oxide (INO) that is presently undergoing evaluation as an anticancer agent.

In summary, Sharpless asymmetric dihydroxylation affords an exceptionally direct and efficient route to (−)- and (+)-trachelanthic acids **4**, and thus to their parent alkaloids indicine **1** and intermedine **2**. In principle this approach, which provides the first asymmetric synthesis of (+)-**2**, is potentially applicable to other stereoisomeric necic acids such as viridifloric acid. Furthermore, the high enantioselectivity observed in the AD reaction with **5** lends support to the modified version of the mnemonic that predicts facial selectivity in the dihydroxylation of prochiral alkenes.

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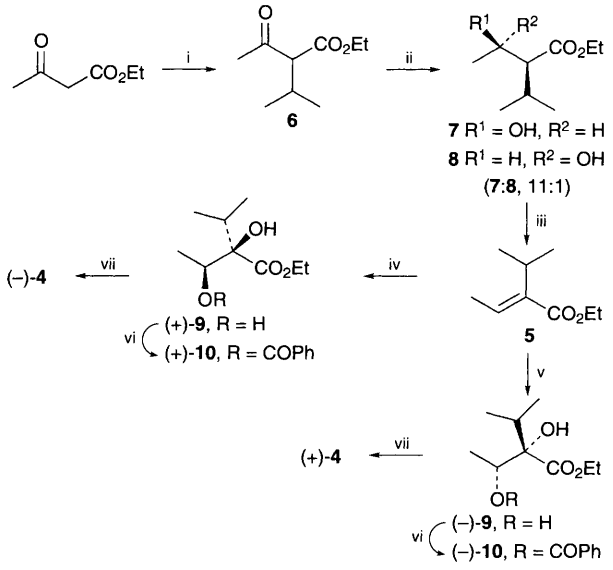
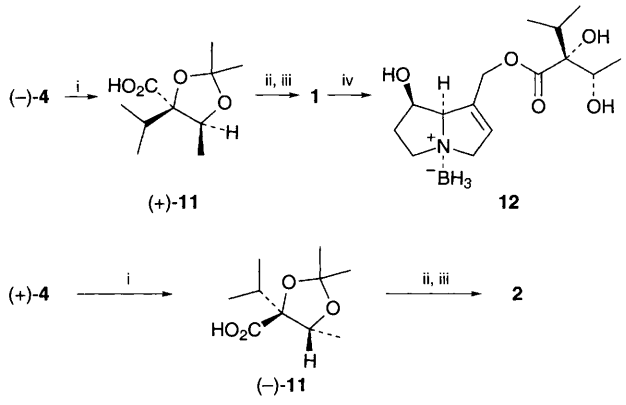


Scheme 1 *Reagents and conditions*: i, NaOEt, Pr^{i}Br, EtOH, heat, 18 h, 51%; ii, $Zn(BH_4)_2$, Et_2O, −50 °C, 6 h, 97%; iii, $POCl_3$, py, 25 °C for 12 h, then 100 °C for 1 h, 78%; iv, AD-mix-α, $MeSO_2NH_2$, Bu^{t}OH–H_2O (1 : 1), 0 °C, 42 h, 81%, 90% ee; v, AD-mix-β, $MeSO_2NH_2$, Bu^{t}OH–H_2O (1 : 1), 0 °C, 42 h, 83%, 85% ee; vi, PhCOCl, py, CH_2Cl_2, 25 °C, 18 h, 73%; vii, $Ba(OH)_2{\cdot}8H_2O$, H_2O, heat, 0.5 h, 96% from (+)- and (−)-**9**



Scheme 2 *Reagents and conditions*: i, $Me_2C(OMe)_2$, HCl (cat), 25 °C, 2 h [76% from (−)-**4**, 57% from (+)-**4**]; ii, DCC, DMAP, camphorsulfonic acid (cat), toluene, then (+)-**3**, 25 °C, 6 d; iii, 1 mol dm^{-3} HCl, 25 °C, 8 h [84% from (+)-**11**, 53% from (−)-**11**]; iv, 1 mol dm^{-3} BH_3·THF, 25 °C, 1 h, 89%

Footnote

† Preparation of (+)-**9**. A solution of AD-mix-α (1.3 g) in *tert*-butyl alcohol and water (9 ml, 1 : 1) was stirred at room temp. for 5 min. Methanesulfonamide (86 mg, 904 μmol) was added, and the solution was cooled to 0 °C. (*E*)-Ethyl 2-isopropylbut-2-enoate (150 mg, 904 μmol) was added, and the solution was stirred at 0 °C for 42 h. Sodium sulfite (1.37 g, 10.8 mol) was added in portions, and the solution was stirred for 30 min at room temp. Water (10 ml) was added, the solution was extracted with ethyl acetate (3 × 10 ml), and the combined organic extracts were washed with 2 mol dm^{-3} potassium hydroxide (2 × 7 ml), water (2 × 7 ml) and brine (7 ml). The solvent was removed by distillation, and the residue was chromatographed on silica using 40% ethyl acetate in hexane as eluent to give 104 mg (81%) of **9** as a clear oil: $[\alpha]_D^{23}$ +5.5 (*c* 2.13, $CHCl_3$).

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