(*R*)-2-Alkoxycarbonyl-1-formyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolines from D-(−)-Tartaric Acid: Synthesis of (*S*)-Homolaudanosine and (*S*)-2,3,9,10,11-Pentamethoxyhomoprotoberberine

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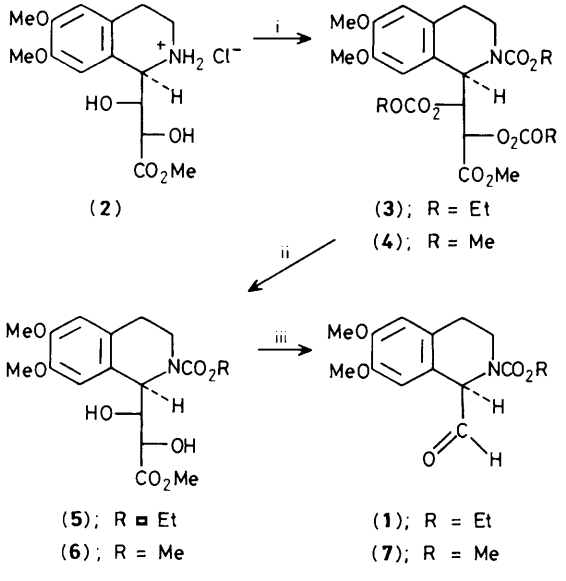
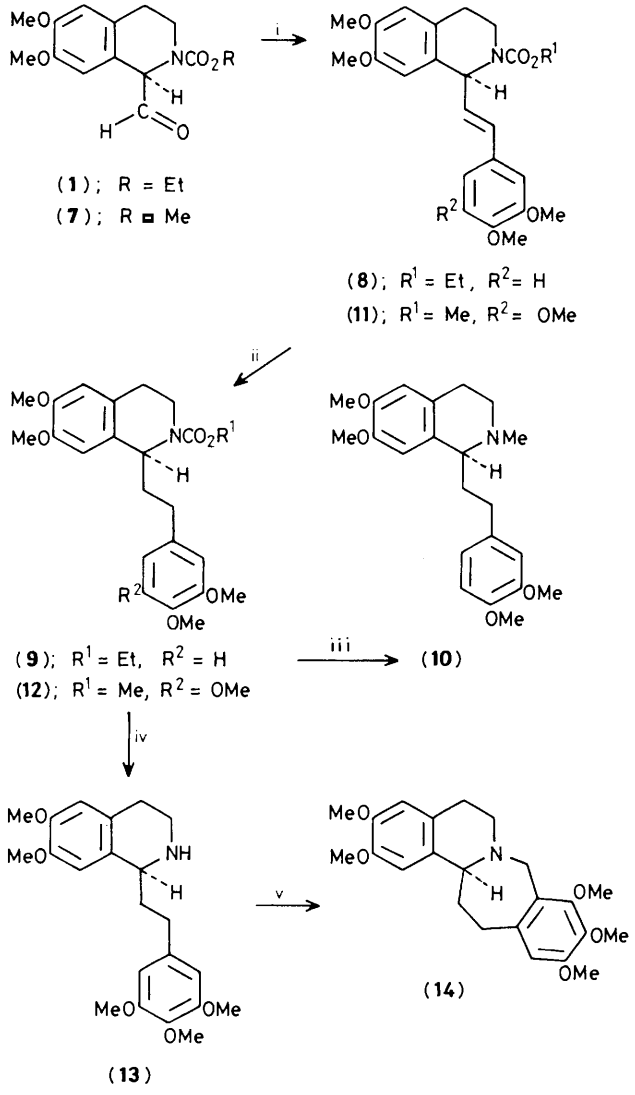
The title aldehydes were prepared from D-(−)-tartaric acid and their utility in the asymmetric synthesis of phenylethylisoquinolines demonstrated by the preparation of (*S*)-homolaudanosine and (*S*)-2,3,9,10,11-pentamethoxyhomoprotoberberine.

In recent publications,[1—3] we have demonstrated that (*R*)- and (*S*)-2-ethoxycarbonyl-1-formyl-1,2,3,4-tetrahydro-6,7-dimethoxyquinolines, (*R*)-(**1**) and (*S*)-(**1**), are useful intermediates in asymmetric synthesis of isoquinoline alkaloids of high enantiomeric purity. We report here a new and more direct route to the (*R*)-2-alkoxycarbonyl aldehydes beginning from D-(−)-tartaric acid. The method is considerably better than those already described beginning either from (*R*)-glyceraldehyde[1,2] or from (*R*)- or (*S*)-calycotomine.[3] (The corresponding enantiomeric aldehydes would be equally accessible from the enantiomeric tartaric acid.) We also demonstrate the utility of the aldehydes in the synthesis of phenylethylisoquinolines by the preparation of (*S*)-homolaudanosine[4,5] and (*S*)-2,3,9,10,11-pentamethoxyhomoprotoberberine[6] using a Wittig reaction in a key step in both syntheses.

Scheme 1 outlines the improved procedure for the preparation of (*R*)-(**1**) and its lower homologue, (*R*)-(**7**). Compound (**2**) was prepared by the method employed by Dörnyei and Szántay[7] for the preparation of its enantiomer. Treatment of (**2**) with an excess of ethyl or methyl chloroformate afforded compounds (**3**) and (**4**), respectively. The ester groups were



Scheme 1. *Reagents and conditions:* i, $ClCO_2R$, pyridine, 5—10 °C, 1 h {(**3**), m.p. 159—161 °C, $[\alpha]_D^{25}$ + 112.8° (*c* 1.66 in $CHCl_3$), 86%; (**4**), m.p. 178—180 °C, $[\alpha]_D^{25}$ + 114.8° (*c* 1.97 in $CHCl_3$), 86%}; ii, NaOMe, MeOH, 25 °C, 4 h {(**5**), oil, $[\alpha]_D^{25}$ + 29.3° (*c* 1.21 in $CHCl_3$), 80%; (**6**), oil, $[\alpha]_D^{25}$ + 27.3° (*c* 1.63 in $CHCl_3$), 70%}; iii, $NaIO_4$ in H_2O added to (**5**) or (**6**) in MeOH, 5 °C, 1 h {(**1**), oil, $[\alpha]_D^{25}$ −10° ($CHCl_3$), 95%; (**7**), oil, 90%, aldehyde (**7**) racemizes too readily at 25 °C to make an accurate measurement of its specific rotation}.



Scheme 2. *Reagents and conditions:* i, (**1**) → (**8**), ylide derived from 3,4-dimethoxybenzyltriphenylphosphonium chloride, THF, −60 °C, 2 h, then 10 h at 0 °C {(**8**), oil, $[\alpha]_D^{25}$ + 135.5° (*c* 0.90 in $CHCl_3$), 69%}; (**7**) → (**11**), ylide derived from 3,4,5-trimethoxybenzyltriphenylphosphonium chloride, conditions as for (**1**) → (**8**) {(**11**), oil, $[\alpha]_D^{25}$ + 129.4° (*c* 0.94 in $CHCl_3$), 66%}; ii, EtOH, Adams' catalyst, H_2 (1 atm) {(**9**), oil, $[\alpha]_D^{25}$ + 64.9° (*c* 1.68 in $CHCl_3$), 97%; (**12**), oil, $[\alpha]_D^{25}$ + 66.2° (*c* 1.12 in $CHCl_3$), 98%}; iii, (**9**) → (**10**), $LiAlH_4$, THF, reflux, 1.5 h {(**10**), oil, $[\alpha]_D^{25}$ + 8.61° (*c* 0.85 in EtOH), lit.[4] $[\alpha]_D^{25}$ + 11.0° (*c* 0.21 in EtOH); 70%}; iv, (**12**) → (**13**), MeLi, THF, 25 °C, 1 h {(**13**), oil, $[\alpha]_D^{25}$ −12.3° (*c* 1.71 in $CHCl_3$), 53%}; v, (**13**) hydrobromide, CH_2O, H_2O, 3 h, 100 °C, glass, 58% {(**14**) hydrochloride, glass, $[\alpha]_D^{25}$ −97.8° (*c* 1.07 in MeOH), lit.[6] $[\alpha]_D^{25}$ −112.5° (MeOH)}.

selectively removed from (**3**) and (**4**) by methanolysis yielding the carbamates (**5**) and (**6**). Aldehydes (**1**) and (**7**) were then obtained by periodate cleavage of the glycol function present in (**5**) and (**6**). Both aldehydes are prone to racemization, particularly (**7**), and should be used immediately after isolation.

Reaction of (**1**) (Scheme 2) with the ylide, derived from 3,4-dimethoxybenzyltriphenylphosphonium chloride by treatment of a suspension of the salt in tetrahydrofuran (THF) with n-butyl-lithium first at −78 °C and then at −20 °C (each for 0.5 h), afforded the *trans*-alkene (**8**) ($J_{7',8'}$ 16 Hz) which was catalytically reduced to carbamate (**9**). The conversion of (**9**) into (+)-homolaudanosine (**10**) was effected by reduction with lithium aluminium hydride. The alkaloid was isolated as an oil in an overall chemical yield from (*R*)-(**1**) of 47% and in 78% enantiomeric excess (e.e.).

In the route to homoprotoberberine (**14**) carbamate (**12**) was prepared using an analogous sequence of reactions to that employed for the preparation of (**9**). Thus, aldehyde (**7**) was treated with the ylide derived from 3,4,5-trimethoxybenzylphosphonium chloride affording the alkene (**11**) ($J_{7',8'}$ 15 Hz) and the latter was hydrogenated to carbamate (**12**). The removal of the carbamate group was difficult; it proved to be exceedingly stable to alkaline hydrolysis, and, although it was effectively removed by treatment of (**12**) with trimethylsilyl chloride and NaI in acetonitrile, the reaction was accompanied by extensive racemization. However, treatment of (**12**) with an excess of methyl-lithium provided the amine (**13**) in 53% yield with no loss of optical purity. The homoprotoberberine (**14**) was obtained when the hydrobromide of (**13**) was treated in aqueous solution with formaldehyde. Compound (**14**) was isolated as a hydrobromide in 20% chemical yield based on (**7**) and in 87% e.e. It was converted into the hydrochloride for measurement of optical activity for comparison with the published value.[6]

All of the compounds were homogeneous in thin-layer chromatography in several solvent systems and the mass spectra (electron impact and chemical ionisation) and ^{1}H n.m.r. spectra were compatible with the assigned structures.

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References

1 Z. Czanrocki, D. B. MacLean, and W. A. Szarek, *J. Chem. Soc., Chem. Commun.*, 1985, 1318.
2 Z. Czarnocki, D. B. MacLean, and W. A. Szarek, *Can. J. Chem.*, 1986, **64**, 2205.
3 Z. Czarnocki, D. B. MacLean, and W. A. Szarek, *Bull. Soc. Chim. Belg.*, 1986, **95**, 749.
4 A. J. Aladesanmi, C. J. Kelley, and J. D. Leary, *J. Nat. Prod.*, 1983, **46**, 127.
5 A. I. Meyers, M. Boes, and D. A. Dickman, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 458.
6 A. Brossi and S. Teitel, *Helv. Chim. Acta*, 1969, **52**, 1228.
7 G. Dörnyei and Cs. Szántay, *Acta Chim. Acad. Sci. Hung.*, 1976, **89**, 161.