

enzymatic operation was 57%. The pure *trans*-acetate (**t-3**) thus obtained afforded pure *trans*-diol (**t-2**) in quantitative yield on methanolysis in the presence of potassium carbonate at room temperature.

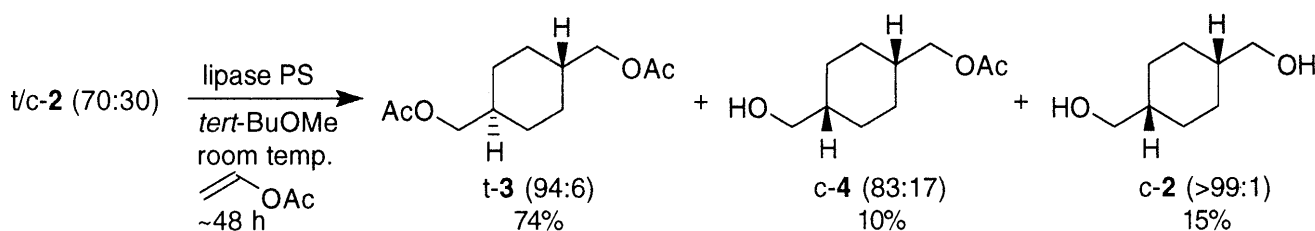


Chart 2

We next examined the lipase-mediated hydrolysis of the diacetate mixture (*t/c*-3) in aqueous condition. It is well recognized that when the same lipase is used, both the transesterification and the hydrolysis occur at the same chiral center.⁷⁾ The same is true for the diastereomeric mixture (*t/c*-3) (*trans/cis*=70:30), which afforded the pure *trans*-diol (**t-2**) in 66% yield accompanied by 31% yield of the *cis*-enriched monoacetate (**c-4**) (*trans/cis*=16:84) in the presence of lipase PS in a phosphate buffer solution,⁸⁾ though the process took 7 days. Thus, it was concluded that hydrolytic conditions were more appropriate for the separation of pure *trans*-diol (**t-2**).

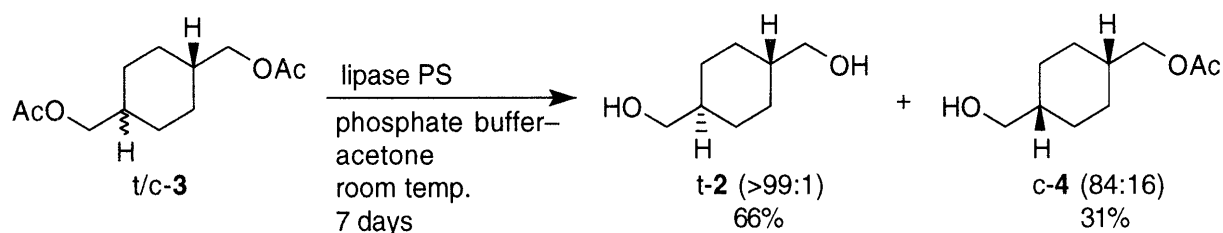


Chart 3

The pure *cis*-diol (**c-2**) as well as the mixture diol (*t/c*-2) recovered from the mixture acetates (*t/c*-3) and (*t/c*-4) could be equilibrated to the *trans*-enriched mixture (*t/c*≈4:1), which may be recycled. Thus, the pure *cis*-diol (**c-2**) was fused at 180 °C with sodium hydroxide (0.1 eq) for 15 min⁴⁾ to furnish a mixture consisting of 82 parts of the *trans*-2 and 18 parts of the *cis*-2 in 92% yield after direct distillation (~165 °C/5 Torr) from a reaction flask.

Having obtained pure *trans*-1,4-cyclohexanedimethanol (**t-2**), we converted it to tranexamic acid (**1**). To minimize ditosylation, the *trans*-diol (**t-2**) was treated with 0.7 eq of *p*-toluenesulfonyl chloride to afford the monotosylate (**5**) in 47% yield (84% based on the consumed **2**) with recovery of 44% of the unchanged **2**, which was recycled. Treatment of the tosylate (**5**) with sodium azide gave the azide (**6**), in 93% yield, which on Jones oxidation afforded the carboxylic acid (**7**) in 87% yield. Finally, the azide

(7) was hydrogenated on 10% palladium-on-charcoal in 1% hydrochloric acid to give pure tranexamic acid (1) as hydrochloride¹⁾ in 70% yield after purification by recrystallization.

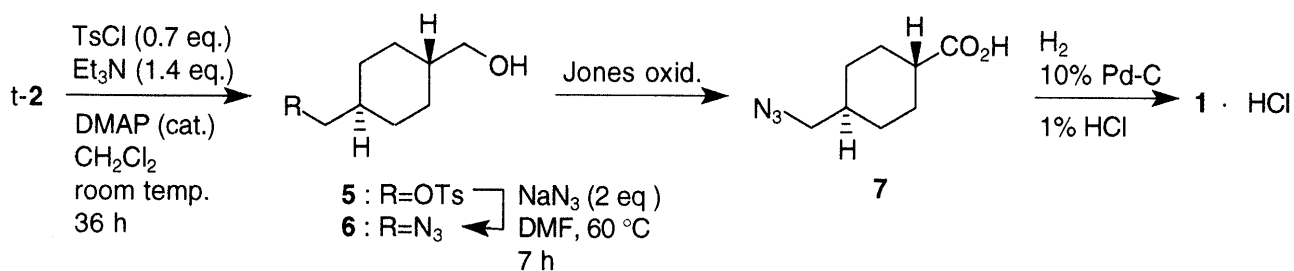


Chart 4

In conclusion, the present investigation has established a route to diastereomerically pure tranexamic acid (1) starting from a diastereomeric mixture of *trans*- and *cis*-1,4-cyclohexanedimethanol (t/c-2) formally without loss of the *cis*-component, employing a lipase-mediated separation and a base-induced equilibration.

REFERENCES AND NOTES

- 1) a) M. Shimizu, T. Naito, A. Okano, T. Aoyagi, *Chem. Pharm. Bull.*, **13**, 1012 (1965); b) T. Naito, A. Okano, S. Kadoya, T. Miki, M. Inaoka, R. Moroi, M. Shimizu, *ibid.*, **16**, 357, 728 (1968).
- 2) M. Levine, R. Sedlecky, *J. Org. Chem.*, **24**, 115 (1959).
- 3) A description of a lipase-mediated separation of a 1,4-cyclohexanedimethanol mixture (t/c-2) by acylation in an organic solvent appeared while the present investigation was going on. However, neither lipase PS nor hydrolytic conditions were employed. See S. Geresh, E. Elbaz, R. Glaser, *Tetrahedron*, **49**, 4939 (1993).
- 4) Y. Tatsuno, S. Yoneda, N. Okamoto, Y. Ishii, K. Kato, Japan Kokai, 2-131442 (1990).
- 5) Cf. A. M. Klibanov, *Acc. Chem. Res.*, **23**, 114 (1990).
- 6) The reaction was carried out in *tert*-butyl methyl ether (10 ml/mmol of t/c-2) in the presence of lipase-PS-on-Celite (10 mg/mmol of t/c-2) at room temperature and separated by silica gel column chromatography. The *trans/cis* ratio was determined by ¹H NMR analysis (300 MHz) of the diacetate (3): t-3 exhibits AcOCH₂- at δ 3.46, while the c-3 exhibits them at δ 3.55.
- 7) For examples, K. Laumen, D. Breitgoff, M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, **1988**, 1459; S. Takano, T. Yamane, M. Takahashi, K. Ogasawara, *Tetrahedron: Asymmetry*, **3**, 837 (1992); S. Takano, O. Yamada, H. Iida, K. Ogasawara, *Synthesis*, **1994**, 592.
- 8) The reaction was carried out in a mixture of 0.2 M phosphate buffer and acetone (9:1) (10 ml/mmol of 3) in the presence of lipase PS-on-Celite (10 mg/mmol of 3) and separated by silica gel column chromatography.

(Received December 26, 1994; accepted February 1, 1995)