Enantioselective Synthesis of Useful Chiral Precursors, Unsymmetrical Propane-1,3-diol Derivatives, from Malonic Acid

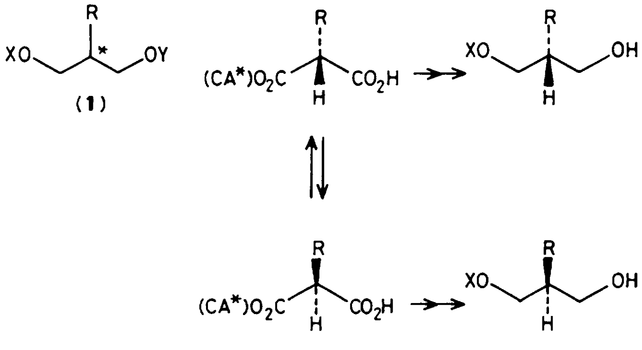
Masataka Ihara,[a] Masanobu Takahashi,[a] Nobuaki Taniguchi,[a] Keiichiro Fukumoto,[a]* and Tetsuji Kametani[b]

[a] *Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan*
[b] *Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan*

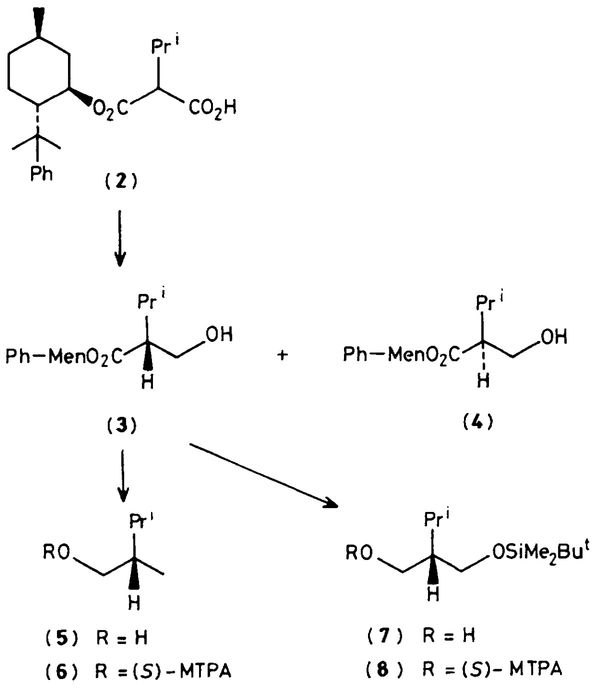
Syntheses of chiral synthons *via* monosubstituted malonic chiral half esters were studied and chiral 3-silyloxypropanols were enantioselectively synthesised.

Optically active unsymmetrical propane-1,3-diol derivatives (**1**) should be useful chiral synthons, but methods have not so far been reported for their chemical synthesis.[1] We envisaged that if equilibrium existed between the two epimers of monoalkylmalonic half esters, a versatile and selective synthesis of valuable chiral building blocks should be available (Scheme 1). Studies using menthyl and phenylmenthyl half esters led us to the following successful results.

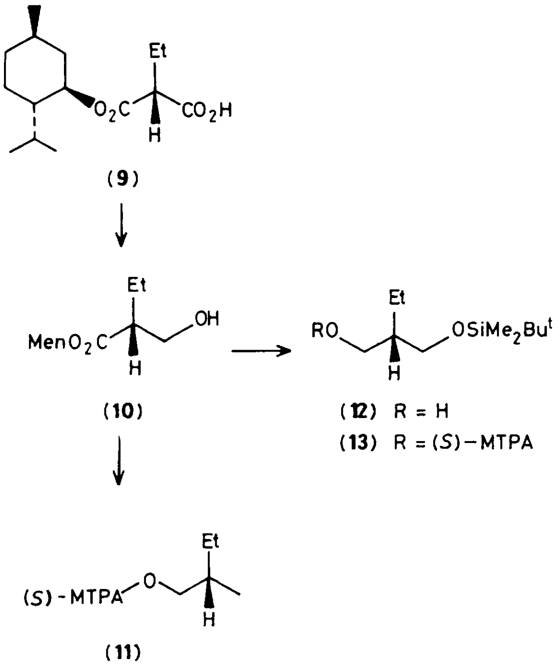
Condensation of isopropylmalonic acid with (−)-phenylmenthol[2] (1 equiv.) using dicyclohexylcarbodiimide (DCC) in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP)[3] gave in 66% yield a mixture of two epimeric half esters (**2**) in a *ca.* 2 : 1 ratio, which was converted, in 83% yield, into a mixture of the two alcohols (**3**) and (**4**) in the ratio of 83.9 : 16.1, *via* reduction of the corresponding 1-succinimido ester with $NaBH_4$ (Scheme 2).[4] We considered that the thermodynamic equilibration occurred at the stage of the succinimido ester formation. The two isomers were easily separated by standard silica gel column chromatography. The major product (**3**) was transformed, in 74% overall yield, into the primary alcohol (**5**) in three steps: (i) chlorination with PPh_3 and CCl_4, (ii) dechlorination with Bu^n_3SnH and AIBN, and (iii) reduction with Bu^i_2AlH. The corresponding (*S*)-MTPA [MTPA = methoxy(trifluoromethyl)phenylacetyl] ester (**6**), prepared by treatment with (*S*)-MTPAOH,[5] DCC, and DMAP, showed the CH_2O protons as a pair of double doublets at δ 4.07 and 4.30 (*J* 10.5, 7.0; *J* 10.5, 6.0 Hz) in the ^1H n.m.r. spectrum, indicating the (*S*,*S*) configuration.[6] Protection of the hydroxy group of (**3**) as the t-butyldimethylsilyl derivative (98% yield) followed by reduction with Bu^i_2AlH (93% yield) afforded the alcohol (**7**), $[\alpha]_D^{28}$ −8.51° (*c* 2.5, $CHCl_3$), whose optical purity



Scheme 1. (CA*) = chiral alcohol derivative.



Scheme 2. PhMen = phenylmenthyl.



Scheme 3. Men = menthyl.

was verified as its MTPA ester (**8**) [>99% enantiomeric excess (e.e.)].

The 500 MHz ^1H n.m.r. ($CDCl_3$) and 25 MHz ^{13}C n.m.r. ($CDCl_3$) spectra of the oily half ester prepared from ethylmalonic acid and (−)-menthol as above indicated the ratio of the two epimers as 11:9. When the product was set aside for several days at room temperature, the oily compound became crystalline, m.p. 71—73 °C, $[\alpha]_D^{25}$ −56.4° (*c* 1.64, $CHCl_3$). Surprisingly, the 500 MHz ^1H n.m.r. and ^{25} MHz ^{13}C n.m.r.[†] spectra showed that the crystalline compound, obtained in 82% yield from ethylmalonic acid, was nearly a single stereoisomer (>99% diastereoisomeric excess). This indicates that crystallisation-induced asymmetric transformation (second-order asymmetric transformation) had occurred.

The crystalline menthol derivative (**9**) was converted into the alcohol (**10**) in 71% yield in two steps: (i) chlorination with $(COCl)_2$ and (ii) reduction with $Bu^n_4NBH_4$[7] at −78 °C, without any significant epimerisation (Scheme 3). H.p.l.c. analysis showed that the alcohol (**10**) was >98% pure. The (*S*)-MTPA ester (**11**), derived from (**10**) as above, showed the CH_2O protons as a pair of doublets in the ^1H n.m.r. spectrum, indicating the (*S*,*S*)-absolute configuration.[6] The ^1H n.m.r. spectrum of (**11**) was identical with that of an authentic sample prepared from (*S*)-(−)-2-methylbutan-1-ol and (*S*)-MTPA.

The optical purity (>99% e.e.) of the propane-1,3-diol derivative (**12**), $[\alpha]_D^{26}$ −11.41° (*c* 1.42, $CHCl_3$), synthesised from (**10**) in 81% overall yield as above, was determined from the ^1H n.m.r. spectrum of its (*S*)-MTPA ester (**13**).

Examples of second-order asymmetric transformations are few[8] and, as far as we know, the phenomenon had not been utilised for the synthesis of chiral synthons. The present method should be applicable to syntheses of a variety of chiral building blocks since numerous monoalkylmalonic acids can be prepared easily. The chiral auxiliaries are recyclable and an efficient auxiliary is being sought.

We thank Prof. S. Yamaguchi, College of General Education, Tohoku University, for discussions on the n.m.r. spectra of MTPA esters.

Received, 3rd November 1986; Com. 1568

[†] The crystalline compound (**9**) showed 15 ^{13}C n.m.r. signals: $\delta_C(CDCl_3)$ 175.45(C=O), 168.96(C=O), 75.83(CH), 53.46(CH), 46.88(CH), 40.55(CH_2), 34.16(CH_2), 31.36(CH), 26.00(CH), 23.22(CH_2), 22.32(CH_2), 21.98(CH_3), 20.71(CH_3), 16.01(CH_3), and 11.74(CH_3), while one secondary carbon (δ 40.71 and 40.55) and one tertiary carbon (δ 26.11 and 26.00) were observed as separated signals in the spectrum of the oily material.

References

1. B. Bosnich, 'Asymmetric Catalysis,' Martinus Nijhoff, Dordrecht, 1986.
2. E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.*, 1975, **97**, 6908.
3. B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522.
4. J. Nikawa and T. Shiba, *Tetrahedron Lett.*, 1979, 981.
5. J. A. Dale, D. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
6. F. Yasuhara, S. Yamaguchi, R. Kasai, and O. Tanaka, *Tetrahedron Lett.*, 1986, **27**, 4033.
7. D. J. Raber and W. C. Guida, *J. Org. Chem.*, 1976, **41**, 690.
8. J. Jacques, A. Collet, and S. H. Wilen, 'Enantiomers, Racemates, and Resolutions,' Wiley, New York, 1981, and references cited therein.