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FIRST PRACTICAL ASYMMETRIC SYNTHESIS OF R-(-)-and S-(+)- MEVALONOLACTONES FROM A SINGLE ACHIRAL PRECURSOR

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Abstract: A new asymmetric synthesis of R-(-)- and S-(+)- mevalonolactones is described. Starting from a single achiral precursor, the synthesis proceeds by a nine-steps sequence, via Sharpless epoxidation of an appropriate allylic alcohol.

Mevalonolactone 1 is the well known biogenetic precursor of terpenoids and steroids[1] and, as demonstrated by incorporation methods, only the (R)-isomer 1a is transformed into mevalonate pyrophosphate[2].

Therefore, the need of optically pure (R)- and (S)- mevalonolactone (the natural and unnatural isomer, 1a and 1b respectively), has been increasing to establish the exact contribution of both enantiomers to some important biosynthetic steps (see also the recent reports[3] on the inhibition of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase by gastric administration of R,S mevalonolactone).

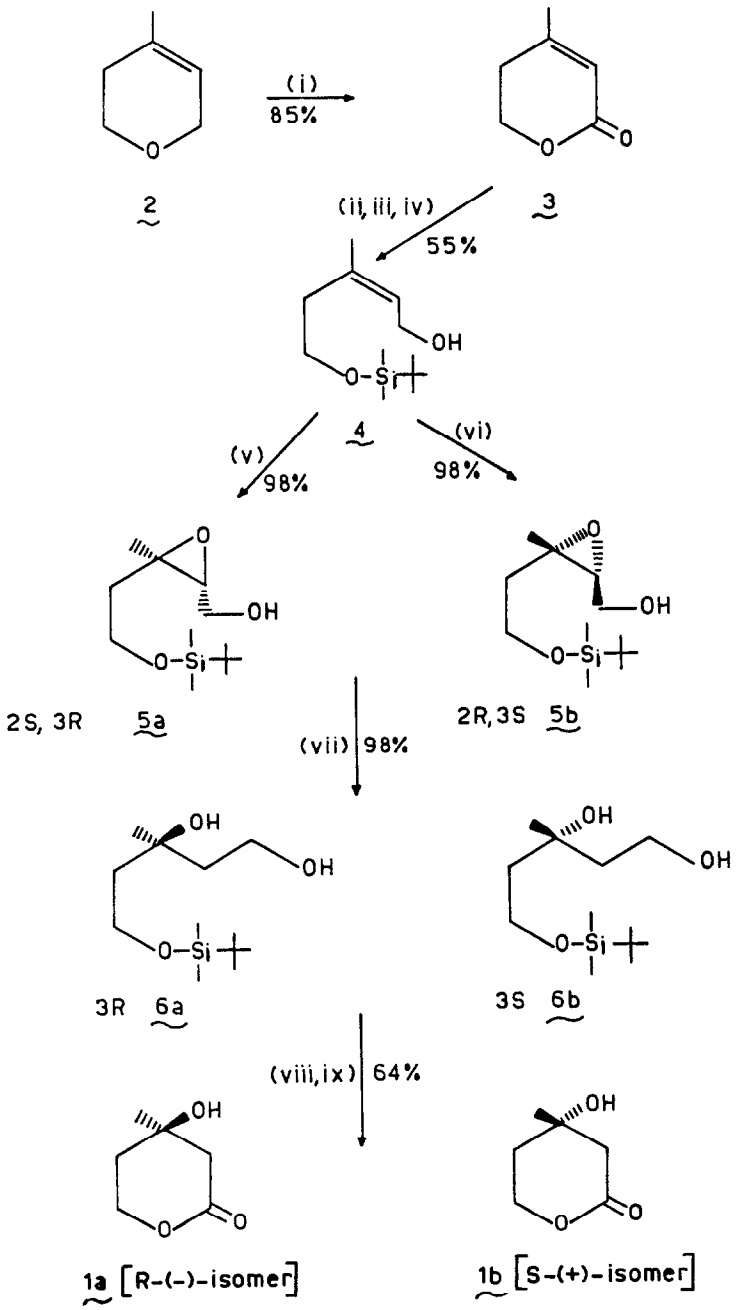
Apart from the resolution methods[4], enzymatic syntheses[5] and transformations from chiral precursors (linalool[6a,6b] and quinic acid[6c]) seemed up to now to be the best sources for the preparation of 1a and 1b.

Recently, two asymmetric syntheses of 1a appeared. However, one[7] proceeds only with 17% enantiomeric excess, using as chiral reagent a p-tolyl sulfoxide obtained by an enzymatic process; the other one[8a], although affording a product with an excellent optical purity (87% e.e.), gave an overall chemical yield of only 2.6%, using as chiral reagent an oxathiane derived in 29% yield from natural (+)-pulegone[8b].

We now describe a synthesis (Scheme 1) which was planned to should give a new practical route for the preparation of both (-)R- and (+)S-enantiomers of mevalonolactone.

We choose as our single achiral precursor the anhydromevalonolactone 3[9] which is now easily available from commercial 4-methyl-5,6-dihydropyran 2 by a procedure developed by us[10]. Lactone 3 was transformed into the appropriate allylic alcohol 4 by a three step, already described procedure[11] with 55% overall yield. The Sharpless epoxidation procedure (8 hr, -30 °C)[12] with either

SCHEME I



Reagents: (i)PCC, CH_2Cl_2, 70 °C, 8 h. (ii)KOH 12N, reflux, 15min; CH_3I,DMF r.t., 24h.(iii)TBMS-Cl, DMAP,NEt_3, CH_2Cl_2.(iv)DIBAH, toluene 0 °C, 1h. (v)$Ti(OiPr)_4$,(+)L-tartrate diethyl, TBHP, CH_2Cl_2, -30 °C, 12h.(vi)$Ti(OiPr)_4$, (-)D-tartrate diethyl, TBHP, CH_2Cl_2, -30 °C, 12h. (vii)$LiBH_4$, THF anh. reflux 2h., MeOH, CO_2.(viii)$RuCl_3$ aqu., $NaIO_4$, CCl_4, CH_3CN, H_2O, r.t., 1h. (ix)pTsOH, CH_2Cl_2.

(+)-or (-)-diethyltartrate as the chiral reagent gave as unique products the expected enantiomeric epoxy alcohols 5a and 5b[13] in high yields and with excellent e.e.[14].

The best conditions for the subsequent reduction of the oxirane ring were $LiBH_4$ in anhydrous THF (2 hr/reflux, under N_2) with careful destruction of excess $LiBH_4$ (MeOH, H_2O), neutralization of the aqueous solution (CO_2) and repeated extraction of the product with AcOEt. In this way, 6a and 6b[16] were obtained in excellent yield (98%) from 5a and 5b respectively.

Finally alcohols 6a and 6b were oxidized ($RuCl_3$, CCl_4, CH_3CN, H_2O, $NaIO_4$)[17] to the corresponding hydroxyacids[18] and the crude products were deprotected and lactonized with careful exposure (CH_2Cl_2 solution) to a catalytic amount of pTsOH. Pure mevalonolactone 1a (natural isomer) and 1b (unnatural isomer) (64% overall yield from 6a and 6b) were obtained by silica gel chromatography[19] and in respect of their IR, NMR, MS spectra were found to be indistinguishable from an authentic sample of racemic 1 (Fluka).

The optical purity of 1a and 1b was examined with both $[\alpha]_D$ measurements[20], and with ^{1}H-NMR spectral measurements using chiral shifts reagents[21].

In particular the last method, based on a recent ^{1}H-NMR experiment[6b], gave an excellent value of e.e. for both enantiomers (1a, e.e. 89%; 1b, e.e. 88%). As a result of the good chemical yield (28.7%) for the nine-steps synthesis, we believe this new route can be considered a good source for the obtaining of almost pure (R)-and (S)-mevalonolactones. Further experiments are in progress for the utilization of the chiral epoxy alcohols 5a and 5b as starting material for the asymmetric synthesis of other natural products.

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9) 3 has been already used as precursor for several syntheses of natural products (sex pheromones as grandisol and lineatin; partial fragments of verrucarin A and J); see for full references the following ref. 10.

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13) 5a : oil $[\alpha]_{302}^{20}$ = -22°(C = 1.8%, $CHCl_3$); H.R. m/s, M^+ = 231.143 (calcd. 231.1416).
5b : oil $[\alpha]_{302}^{20}$ = +24°(C = 1%, $CHCl_3$); H.R. m/s, M^+ = 231.142 (calcd. 231.1416).
5a and 5b: 80 MHz ^{1}H-NMR ($CDCl_3$): δ 0.11 (s, 6H, $(CH_3)_2$-Si); 0.92 (s, 9H, $(CH_3)_3$-C); 1.36 (s, 3H, H_3C-C(3)); 1.6-2.0 (m, 2H, H_2C-C(4)); 3.00 (dd, J=1.5 Hz, J=5.6 Hz, 1H, CH-C(2)); 3.08 (t, J=5.1 Hz, 1H, OH), 3.37-4.03 (cm, 4H, H_2-C-C(1) and H_2C-C(5)).

14) The consideration about the good enantiomeric yields in the obtaining of 5a and 5b is, of course, referred to the final obtaining of 1a and 1b whose e.e. was measured as later described.

15) In this reduction step, the use of labelled hydride (e.i. $LiBD_4$) allows to incorporate labelled atom at C_3 position, which can be utilized for biochemical experiment (see ref. 4).

16) 6a and 6b: 80 MHz ^{1}H-NMR ($CDCl_3$): δ 0.10 (s, 6H, $(CH_3)_2$-Si); 0.91 (s, 9H, $(CH_3)_3$-C); 1.29 (s, 3H, CH_3-C(3)); 1.5-2.1 (cm, 4H, CH_2-C(2) and CH_2-C(4)); 3.6-4.1 (cm, 4H, CH_2-C(1) and CH_2-C(5)); 3.75 (bs, 1H, OH), 4.25 (bs, 1H, OH).

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18) A short exposure (15 min) of the alcohol seemed to be sufficient to undergo to a complete oxidation of the primary hydroxyl group. A longer reaction time caused losses in the yield of the process.

19) The reaction was hardly followed by TLC (silica gel, benzene-acetate 1:1 as eluent, Rf 0.3) because of the difficulty to discern the lactone ($KMnO_4$ spraying with slight heating). After 15 min the CH_2Cl_2 solution was concentrated and poured on a silica gel column, eluting with CH_2Cl_2-MeOH 8:2 and recognizing the product by TLC as above descrived.

20) 1a : $[\alpha]_D^{20}$ = -20.9 (C = 1%, EtOH), lit. = -23.0 [6a], e.e. 90%;
1b : $[\alpha]_D^{20}$ = +19.7 (C = 0.7%, EtOH), lit. = +22.8 [6a], e.e. 86.4%.

21) The enantiomeric excesses were determined by ^{1}H-NMR experiments on a Bruker WP 80 SY (80 MHz), using Eu $(hfc)_3$ as shift reagent, in a 0.3 molar ratio with (R) and (S) mevalonolactones.

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