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HIGHLY STEREOSELECTIVE ASYMMETRIC SYNTHESIS OF (R)-(-)-MEVALOLACTONE

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Summary. An asymmetric synthesis of (R)-(-)-mevalolactone in over 87% enantiomeric purity is described.

Mevalonic acid (or the δ-lactone in equilibrium with it) is the biogenetic precursor of terpenes and steroids.[1] The biosynthetic path of its incorporation in these molecules has been elucidated elegantly by Cornforth and coworkers;[2] only the R-isomer is active in the first biosynthetic step, viz. conversion to mevalonate pyrophosphate.

Mevalonic acid has been synthesized and resolved shortly after the discovery of its biogenetic role by Folkers.[3] However, only one asymmetric synthesis other than a purely enzymatic one[4] has been described,[5] and it proceeds with only 17% enantiomeric excess (e.e.). Optically active mevalolactone has also been synthesized from chiral precursors: linalool[6a] and quinic acid.[6b]

We describe here an asymmetric synthesis of mevalolactone in over 87% e.e. using a chiral 1,3-oxathiane auxiliary reagent similar to those previously described.[7,8] The reagent used in the present work, 1, derived from (+)-pulegone, has been described elsewhere.[9] Our synthesis is summarized in Scheme 1.

Treatment of oxathiane 1 with butyllithium at -78° in THF followed by addition of acetaldehyde gave a mixture of diastereomeric alcohols (2) in quantitative yield. Oxidation of 2 by the method of Swern[10] yielded the corresponding ketone 3 (83%). Since the synthesis is based on optically pure pulegone[9] and the reagent 1 is further purified by crystallization, it may be assumed that 3 is enantiomerically pure; its diastereomeric purity (exclusively equatorial acetyl[7,11]) is indicated by its C-13 spectrum which displays a single set of 13 signals. Compound 3 had mp. 45.0-45.5°C, $[\alpha]_D^{25}$ + 91.7° and analyzed correctly for C,H and S.

To a solution of 9.30g (38 mmol) of 3 in 500 ml dry THF was added 4.09g (43 mmol) of anhydrous $MgCl_2$.[12] After refluxing 5 min. the solution became almost clear. It was cooled to -78°C and 91.2 mmol of vinylmagnesium bromide (0.865M soln. in THF) was added over 70 min, followed by stirring at -78°C for 1.5 hr. Saturated aqueous NH_4Cl was then added, THF was evaporated at reduced pressure and the residue was partitioned between water (added) and methylene chloride. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure to give 10.63 g of viscous oil. Proton NMR spectroscopy suggested that the product was a 95:5 mixture of the diastereomers of 4 obtained in essentially quantitative combined yield. The oil was dissolved in n-pentane (10 ml) and the solution placed in a freezer (-20°C). The product

(9.06g, 90%) crystallized and was collected, mp. 47.5-50.5°C, diastereomer excess (d.e.) 96.6%. One further recrystallization from EtOH/n-pentane raised the mp. to 50.7-51.5°C d.e. 99.6%, analysis, proton and C-13 NMR and IR spectra compatible with 4.[13]

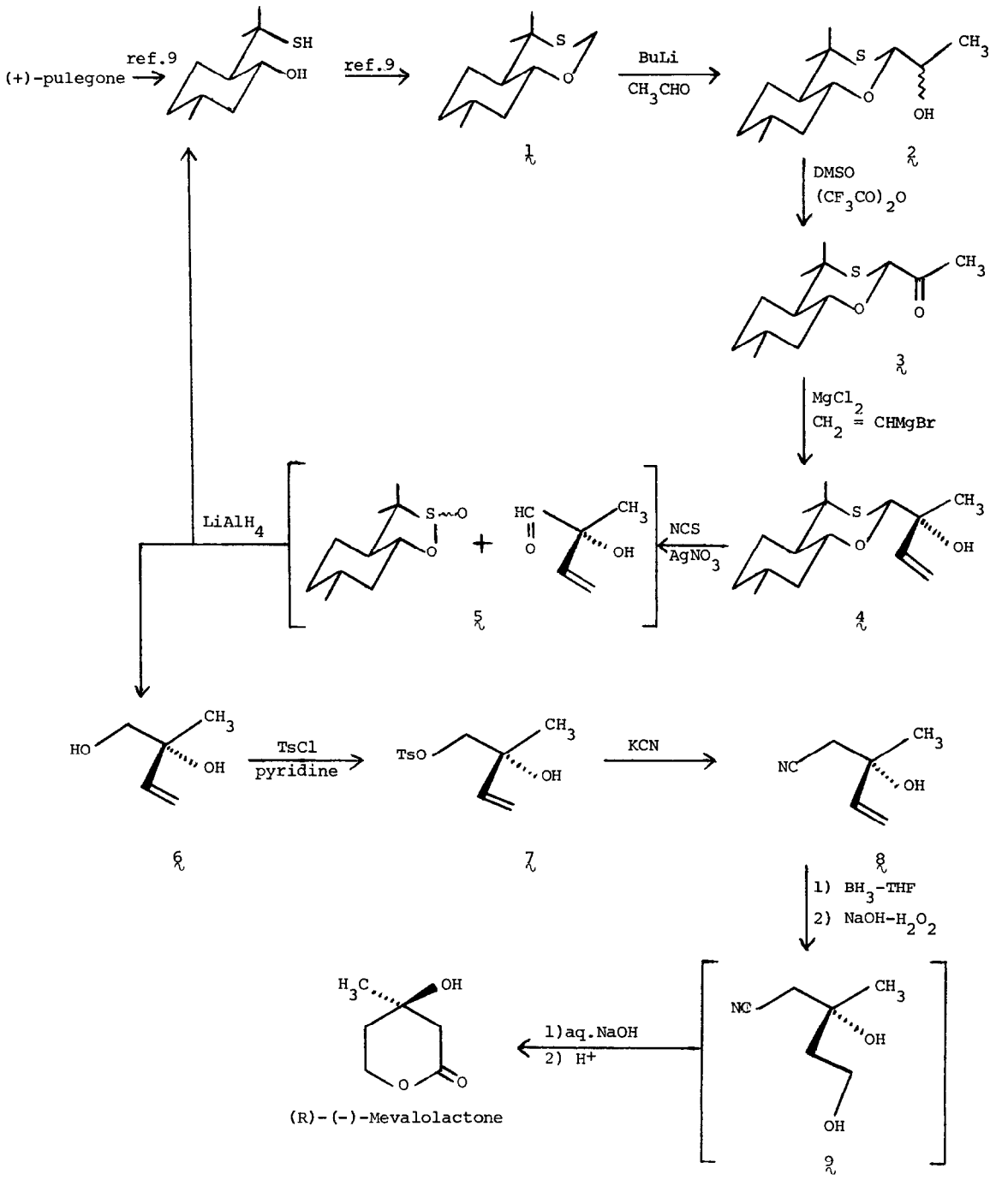
To a mixture of 9.35g (70 mmol) N-chlorosuccinimide, 12.69g (76 mmol) silver nitrate and 17.14g (160 mmol) 2,6-lutidine in 280 ml 80% acetonitrile, a solution of 5.38g (20 mmol) of 4, 96.6% d.e., in 80 ml acetonitrile was added over 5 min with water bath cooling.[14] The water bath was removed and the mixture stirred for 45 min. It was cooled again, 30 ml of saturated aqueous Na_2SO_3 was added, the precipitate was filtered and washed with methylene chloride and ether. The combined filtrate was dried over Na_2SO_4, filtered, and concentrated at reduced pressure (below 35°C). The residue was taken up in a small amount of absolute ether and added slowly (over 8 hr) to a suspension of 16g of $LiAlH_4$ in 200 ml ether and 350 ml THF. The reaction mixture was stirred overnight and then carefully treated with saturated aqueous sodium sulfate. The resulting precipitate was filtered and washed with methylene chloride. The combined solvents were dried over Na_2SO_4 and K_2CO_3, decanted and concentrated; the residue (6) was purified by column chromatography (silica gel, 10:1 ether, hexane as eluent). Concentration and distillation (Kugelrohr, bath temp. 120°C) at 17 mm yielded 0.352g (17%) of 6, $[\alpha]_{25}^{D}$ + 6.47° (CH_2Cl_2, = c = 5.6), IR and proton NMR spectrum were compatible with structure 6.

In one run where 4 of 84% d.e. was used, the e.e. of the product was determined, by the use of Eu(hfc)$_3$, to be 84%, indicating absence of racemization in the hydrolysis step.

A solution of 0.352g (3.45 mmol) of 6 in 2 ml pyridine was added, at 0°C, to 0.822g (4.31 mmol) p-toluenesulfonyl chloride in 3 ml pyridine. The mixture was kept in a refrigerator overnight, then poured into ice water and extracted with ether. The extract was washed with 3N HCl followed by water, dried over Na_2SO_4, decanted, concentrated (ambient temperature) and the crude product (7) used for the next step.

The above tosylate (7) was dissolved in 3.1 ml ethanol and 2.5 ml water. KCN (0.647g, 10.35 mmol) was added at 0°C and the homogenous solution was stirred overnight at room temperature. The organic solvent was then removed at reduced pressure, water was added to the residue and the mixture was extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, decanted, concentrated and the residue (8) purified by Kugelrohr distillation at 1 mm (bath temp. 107-120°C). Yield 0.229g (60%), ^1H NMR spectrum identical with that reported in the literature for the racemate.[15]

(R)-(-)-Mevalolactone (10). To a solution of 8 (0.222g, 2 mmol) in 5 ml THF, 4 mmol of BH_3.THF (1M in THF) was added over 14 min. at 0°C and the mixture was stirred for 2 hr. Water (0.5 ml) was added cautiously and stirring continued for 40 min. Aqueous NaOH (3N, 3 ml) and 0.35 ml 30% aqueous H_2O_2 were added successively with stirring, followed by warming at 40°C for 1 hr. THF was distilled at reduced pressure (20 mm, 40°C) and the resulting solution of crude 9 was hydrolyzed as described in the literature.[16] After addition of aqueous NaOH (3N, 0.5 ml) the reaction mixture was heated for 20 hr. (bath temp. ca. 100°C), then cooled with ice and acidified to pH 3 with 4N H_2SO_4. The solution was extracted with 10 75-ml portions of chloroform and the extract dried over Na_2SO_4, decanted and concentrated at reduced pressure. The residue was purified by silica gel TLC (20x20 cm, using benzene - ethyl acetate 1:1 R_f ca. 0.3-0.5, area occupied by lactone discerned by opaque appearance under UV). The occupied area was scraped off and eluted with chloroform which was removed under reduced pressure. Yield of 10: 0.077g (30%),


(+)-pulegone
ref.9
ref.9
BuLi
CH_3CHO
DMSO
$(CF_3CO)_2O$
$MgCl_2$
$CH_2 = CHMgBr$
$LiAlH_4$
NCS
$AgNO_3$
TsCl
pyridine
KCN
1) BH_3-THF
2) $NaOH-H_2O_2$
1)aq.NaOH
2) H^+
(R)-(-)-Mevalolactone

Scheme 1

$[\alpha]_D^{25}$ -20.0°C (c = 0.4, EtOH), lit.[6a] -23.0. The ^{1}H NMR and IR spectral characteristics were identical with those of an authentic sample of the racemate purchased from US Biological Corporation.

The material was converted to the benzhydrylamide as described,[17] mp. 99-101°C (lit.[6] 98-99°C). Determination of e.e. by means of Eu(hfc)$_3$ (^{1}H NMR, Bruker-250 MHz instrument, 2000 scans) showed a single enantiomer (benzyhydrylic proton, clearly doubled in the racemate). Addition of ca. 10% of the racemate and repitition of the Eu(hfc) experiment clearly showed the presence of the second enantiomer; e.e. is thus estimated as exceeding 90%, the rotation (corresponding to 87% e.e.) presumably being lowered by a slight chemical impurity.

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