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SYNTHESES OF 4(R)-SILYLOXY-6(S)-IODOMETHYL-TETRAHYDROPYRAN-2-ONE AND ITS ENANTIOMER, BUILDING BLOCKS FOR HMG-COA REDUCTASE INHIBITORS

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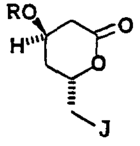
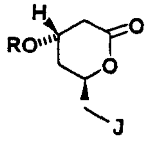
Abstract: Optically pure 4(R),6(S)-iodolactone 1 was obtained from α-D-(+)-glucose in 17 steps with 17% overall yield. Its enantiomer 4(S),6(R)-iodolactone 1' was obtained from acetonedicarboxylic acid in 9 steps in 37% overall yield and with 70% ee. Key steps in the synthesis of 1' are enzyme (PLE)-catalyzed saponification of prochiral di-n-propyl-3-hydroxyglutarate 7 and iodolactonization of 11.

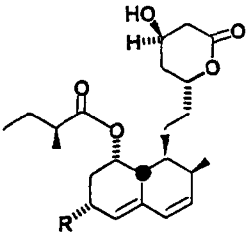


1



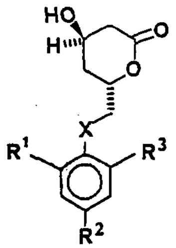
1'

R= (tert.-Bu)SiPh$_2$



2

a: R = H
b: R = CH_3



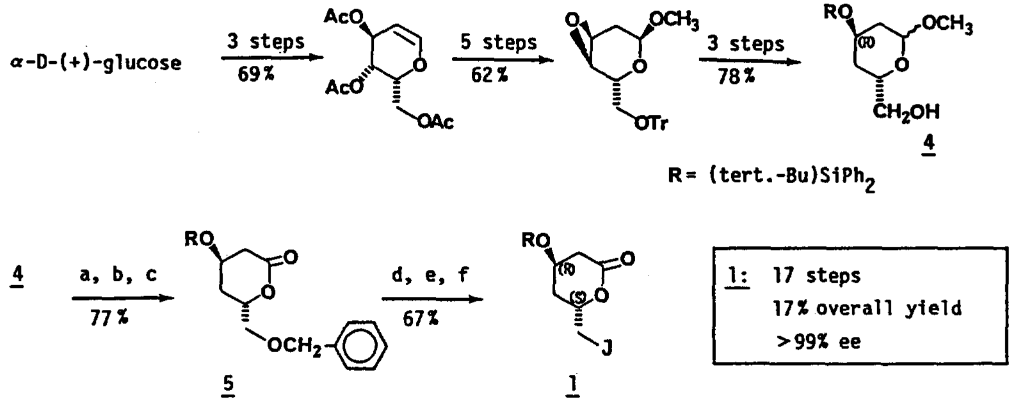
3

a: X = O
b: X = S

The enantiomeric iodolactones 1 and 1' are of interest as building blocks for structurally simplified analogs of compactin 2a [1] or mevinolin 2b [2], potent inhibitors of HMG-CoA reductase, the rate limiting enzyme in cholesterol biosynthesis. [3] We have shown that biological activity is largely retained, when the hexahydronaphthaline moiety of 2a (containing five chiral centres) is replaced by suitably substituted achiral aromatic rings and the connection with the lactone moiety is chemically modified by the presence of an oxygen- (→3a) [4] or a sulfur atom (→3b) [5] in the two atom bridge. In this paper, we describe independent syntheses of optically active 1 and its enantiomer 1'.

In a "chiral pool" approach, 1 was synthesized with >99% ee in 17 steps from α-D-(+)-glucose in 17% overall yield (scheme 1). Starting material [9] 4 was obtained as described in lit. [6-9] on a multikilogram scale. Hydroxyl protection of 4, hydrolysis of the lactol ether and subsequent oxidation of the lactol [10] gave 5. Reductive debenzylation, subsequent tosylation and Finkelstein iodination gave 1 [11].

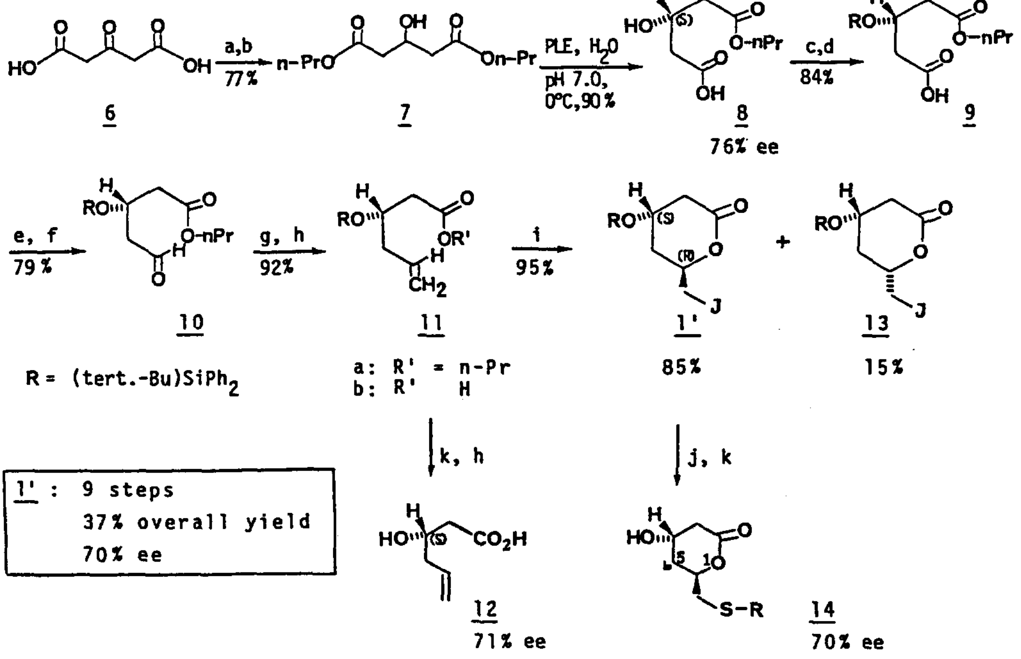
scheme 1



1: 17 steps
17% overall yield
>99% ee

a: 1) n-BuLi, HMPT, -70°C, 2) BzBr, -70°C ⟶ 25°C, 95% . b: AcOH, H_2O, THF, 75°C, 86% .
c: CrO_3, pyridine, CH_2Cl_2, 10°C, 94% . d: Pd/C, H_2, 92% . e: TosCl, pyridine, CH_2Cl_2,0°C,80%.
f: NaI, acetone, reflux, 91% .

scheme 2



1' : 9 steps
37% overall yield
70% ee

a: n-Pr-OH, HCl gas, 0°C, 85% . b: Raney-Ni, NEt_3 (1 vol %), n-PrOH, H_2 , 25°C, 91%.
c: R-Cl (2.4 equiv.), imidazol (3.6 equiv.), CH_2Cl_2, 0°C. d: Na_2CO_3, H_2O, 25°C, 84%.
e: BH_3·THF (1.3 equiv.), -20°C→0°C, 6 h. f: PCC (2 equiv.), kieselguhr,CH_2Cl_2, 25°C,
79% . g: CH_3PPh_3Br, toluene, $KN(SiMe_3)_2$, -15°C→0°C, 93% . h: 1) NaOH, EtOH, H_2O, 25°C;
2) AcOH, 99% . i: I_2 (5 equiv.), Et_2O, $NaHCO_3$ (3 equiv.), 0°C, 95% . j: ArylSH (2 equiv.),
dry CH_3CO_2K (2 equiv.), DMSO, 25°C, 2 h, 97% . k: $(n\text{-}Bu)_4NF$ (3 equiv.), AcOH (1.5 equiv.),
THF, 0°C, 16 h, 80%.

Recent literature [12,13] would discourage an introduction of chirality by an enzyme catalyzed hydrolysis of a prochiral 3-hydroxyglutaric diester. [14] We obtained the halfester 8 [10,15] in 90% isolated yield with 76% ee [16] when the di-n-propylester 7 was saponified under pig liver esterase (PLE)-catalysis at 0°C [17] (scheme 2). Silyl-protection of 8 gave 9 [10] after hydrolysis of the silylester. The acid 9 was reduced to the aldehyde 10 [10] in two steps via the corresponding alcohol. Attempts to perform a Rosenmund reduction [18] of the acid chloride of 9 gave 10 in only 20-30% yield. Wittig methylenation of 10 proceeded with 93% yield to give 11a [10], when the ylid from triphenylmethylphosphonium bromide (1.1 equiv.) and bis(trimethylsilyl) potassium amide (1.15 equiv.) was formed in toluene (0°C, 3 h), 10 (1.0 equiv.) added at -15°C and the mixture allowed to warm to 0°C (2 h). An aliquote of 11a was deprotected and saponified. The resulting free ß-hydroxyacid 12 [10] had 71% ee [16], demonstrating that the transformation of 8 into 11a is accompanied by only a negligible loss of optical purity. [19] Iodolactonization of 11b gave in 95% yield a mixture of 1' [20] (85%), and 13 [10] (15%, ^{1}H-nmr) as a colorless semisolid. 13 can be removed by recrystallization [21] or chromatography [22]. Attempts to check the ee of 1' by ^{1}H-nmr/optishift were unsuccessful. Therefore chromatographically purified 1' was coupled with p-chlorothiophenol to give 14 [23] (R : p-Cl-C_6H_4). 14 had 70 ± 5% ee (^{1}H-nmr/optishift) [24], in excellent agreement with the optical purity of 12 and 8. One recrystallization [25] of 14 increased its optical purity to >95% ee as shown by ^{1}H-nmr/optishift [24] and specific rotation [26].
Since it is known that lithiumborohydride selectively reduces esters in the presence of carboxylic acids it can be anticipated, that not only 1' but also 1 with the same ee can be obtained from 9 in analogy to scheme 2. [27,28]

This paper is dedicated to Professor E.J. Corey on the occasion of his 60th birthday.

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10 All compounds described gave correct ^{1}H-nmr and ms spectra.
11 Mp. 78-79°C [from (i-Pr)$_2$O/n-hexane, <25°C], $[\alpha]_D^{24}$= -0.89° (c= 1.08, acetone). ^{1}H-nmr ($CDCl_3$): δ = 1.08 (s,9H), 1.52-1.66 (m,1H), 2.00-2.12 (m,1H), 2.43 (dd,1H), 2.61 (dt,1H), 3.38 (AB of ABX,2H), 4.32 (qui,1H), 4.74 (m,1H), 7.37- 7.51 (m,6H), 7.60-7.68 (m,4H). MS (70eV,50°C): m/z= 494 (M^+,0.5%), 437 (M-tert.-Bu), 395, 269, 225 (100%), 199, 183.