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AN ASYMMETRIC SYNTHESIS OF CIS-4-t-BUTYLDIMETHYLSILOXY-2-CYCLOPENTEN-1-OL AND CIS-4-TETRAHYDROPYRANYLOXY-2-CYCLOPENTEN-1-OL, VERSATILE CHIRAL SYNTHETIC INTERMEDIATE FOR PROSTANOIDS

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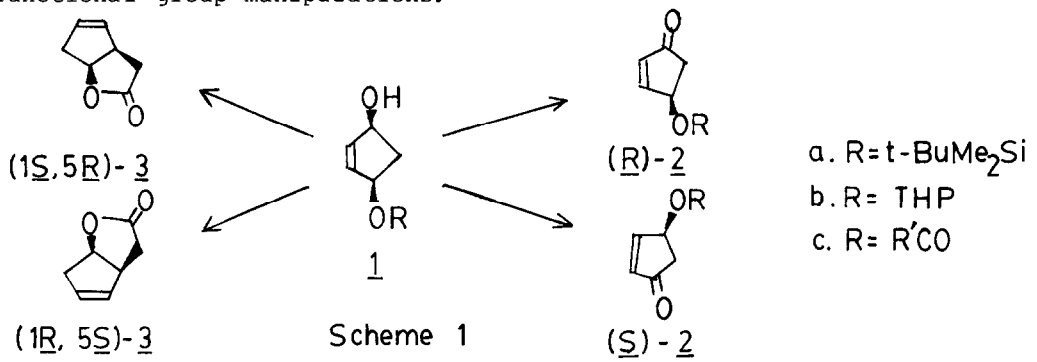
Abstract: cis-4-t-Butyldimethylsiloxy-2-cyclopenten-1-ol and cis-4-tetrahydropyranyloxy-2-cyclopenten-1-ol were obtained with high enantiomeric excesses (ee) by the reaction of cis-3,4-epoxycyclopentan-1-ol derivatives with chiral lithium amide. An application to the syntheses of both (S)- and (R)-4-hydroxy-2-cyclopentenone was demonstrated.

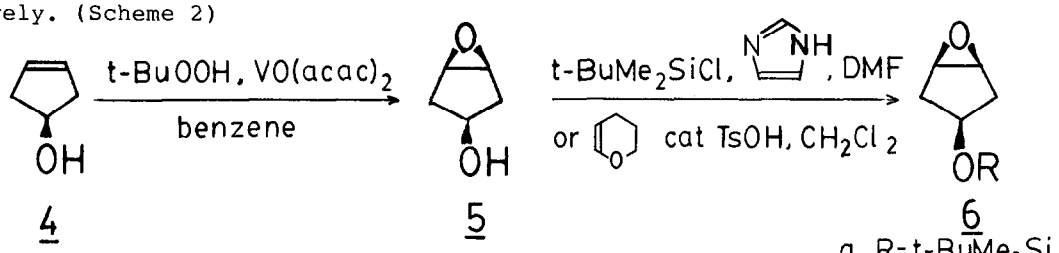
Chiral cis-4-t-butyldimethylsiloxy-2-cyclopenten-1-ol (1a) (R= t-BuMe_2Si) and cis-4-tetrahydropyranyloxy-2-cyclopenten-1-ol (1b) (R=THP) are attractive synthetic intermediates because they can be easily converted to both enantiomers of 4-hydroxy-2-cyclopentenone derivative (2) and cis-2-oxabicyclo[3.3.0]oct-6-en-3-one (3),[1a,c,e] versatile synthetic blocks for the enantioselective synthesis of prostaglandines and various cyclopentanoid natural products.[2] In several reports, enantioselective enzymatic hydrolysis of cis-1,4-diacyloxy-2-cyclopentene[1a,b,c,d] or enantioselective acylation of cis-2-cyclopenten-1,4-diol[1e,f] was used for the synthesis of chiral cis-4-acyloxy-2-cyclopenten-1-ol (1c) (R=R'CO). 1b was derived from 1c by functional group manipulations.[1b,c,e]



Scheme 1

Here we wish to report the direct asymmetric synthesis of 1a and 1b from 3-cyclopenten-1-ol (4)[3] by applying the asymmetric reaction developed by us.[4]

Initially, 4 was converted stereoselectively to cis-3,4-epoxycyclopentanol (5)[5] by the hydroxy-directed epoxidation with $VO(acac)_2$ and t-butyl hydroperoxide in benzene.[6] Then, cis-4-t-butyldimethylsiloxy-1,2-epoxycyclopentane (6a)[7] and cis-4-tetrahydropyranyloxy-1,2-epoxycyclopentane (6b)[7] were obtained by treating 5 with t-butyldimethylsilyl chloride in DMF[8] or dihydropyrane in CH_2Cl_2 in the presence of catalytic amount of p-toluenesulfonic acid[9] in 65 % or 49 % yield from 4, respectively. (Scheme 2)



4 5 6

a. R=t-BuMe$_2$Si
b. R=THP

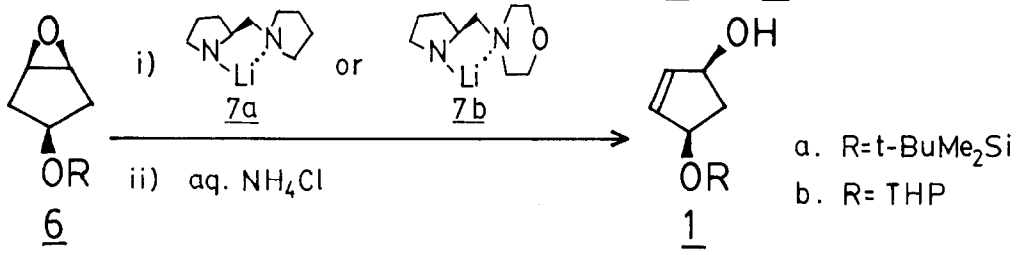
Scheme 2

Then, an asymmetric transformation of 6a to 1a was examined in various kinds of solvent with lithium (S)-2-(pyrrolidinomethyl)pyrrolidide (7a) or lithium (S)-2-(morpholinomethyl)pyrrolidide (7b). The best result was obtained in case that the reaction was carried out in benzene using 7a to yield (1S,4R)-1a[7] in 92 % with 90 % ee. 1b was also obtained with high ee. The results are summarized in Table.

A typical experimental procedure is as follows; to a benzene solution (3 ml) of (S)-2-(pyrrolidinomethyl)pyrrolidine (132 mg, 0.86 mmol) was added a hexane solution (0.5 ml) of butyllithium (0.77 mmol) under a nitrogen atmosphere at 4 °C. After 0.5 h at that temperature, 6a (102 mg, 0.48 mmol) in benzene (2 ml) was added at 4 °C and stirring was continued for 3 h. Then, aq. NH_4Cl and ether were added, and the organic layer was washed with water and brine. After drying (anhydrous Na_2SO_4) and evaporation of the solvent *in vacuo*, the oily substance was purified by silica-gel column-chromatography (hexane:ether=1:1) to give 1a (94 mg, 92 %), $[\alpha]_D^{22}$ +21.5 ° (c 0.94, $CHCl_3$).

Further, the syntheses of both (R)- and (S)-4-hydroxy-2-cyclopentenone (8) were achieved by simple functional group manipulations using (1S,4R)-1a. Oxidation of (1S,4R)-1a with pyridinium chlorochromate (PCC)[10] led to (R)-2a (86 %, $[\alpha]_D^{25}$ +58.1 ° (c 1.13, CH_3OH); lit. $[\alpha]_D^{20}$ +32 ° (c 0.051, CH_3OH) for 56 % ee of (R)-2a,[11a] $[\alpha]_D$ +62.2 [11b]), which was deprotected with AcOH-THF-H_2O (3:1:1)[8] to yield (R)-8 (83 %, $[\alpha]_D^{25}$ +81.3 ° (c 1.55, $CHCl_3$),

Table. Asymmetric Synthesis of 1a and 1b.

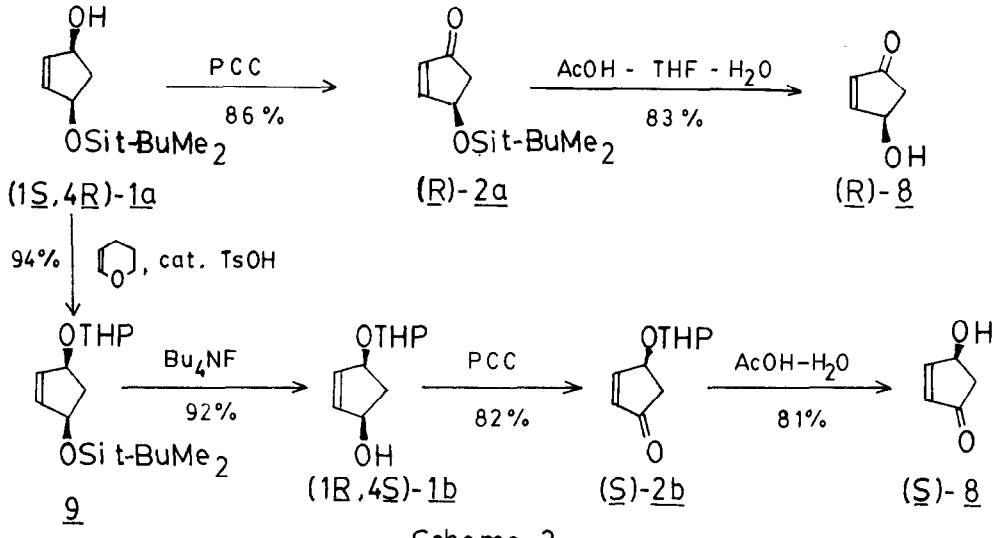


epoxide	lithium amide	solvent	yield/ %[a]	$[\alpha]_D$ (c, $CHCl_3$)	ee/ %[b]
6a	7a	THF	76	$[\alpha]_D^{20}$ +16.5 ° (1.17)	66
		ether	83	$[\alpha]_D^{22}$ +16 9 ° (0.88)	70
		benzene	92	$[\alpha]_D^{22}$ +21.5 ° (0.94)	90 (86)[c]
		toluene	84	$[\alpha]_D^{22}$ +20.0 ° (0.89)	84
		hexane	91	$[\alpha]_D^{22}$ +21.0 ° (0.82)	88
	7b	THF	65	$[\alpha]_D^{22}$ +5.7 ° (0.69)	26
		benzene	78	$[\alpha]_D^{16}$ +19.7 ° (0.68)	89
6b	7a	THF	89	$[\alpha]_D^{19}$ +23.2 ° (0.82)	62[d]
		benzene	77	$[\alpha]_D^{18}$ +27.3 ° (0.77)	89[d]

a) Isolated yield.
b) Determined by conversion to (4R,1S)-4-hydroxy-2-cyclopentenyl benzoate.[1e]
c) Determined by conversion to (S)- and (R)-4-acetoxy-2-cyclopentenone followed by ^1H NMR analysis in the presence of $Eu(hfbc)_3$.[12]
d) Optical rotation value of 1b has been reported ($[\alpha]_D^{20}$ -20.3 ° (c 1.3, $CHCl_3$),[1e] $[\alpha]_D^{20}$ +21.5 ° (c 3.12, $CHCl_3$) for 86 % ee of (1S,4R)-1b[1c]), but it would not be possible to calculate the ee based on these value because there is another chiral center in the tetrahydropyrane ring in 1b.

$[\alpha]_D^{26}$ +83.5 ° (c 2.00, CH_3OH); lit. $[\alpha]_D^{20}$ -94.1 ° (c 3.4, $CHCl_3$) for (S)-8,[1e] $[\alpha]_D^{24}$ +83.1 ° (c 1.70, CH_3OH) for 94 % ee of (R)-8[12]). (S)-8 ($[\alpha]_D^{24}$ -79.3 ° (c 1.5, $CHCl_3$), $[\alpha]_D^{28}$ -85.1 ° (c 1.34, CH_3OH)) was obtained as follows; i) conversion of (1S,4R)-1a into (1R,4S)-1-t-butyldimethylsiloxy-4-tetrahydropyranyloxy-2-cyclopentenol (9)[7] (dihydropyrane, cat. p-toluenesulfonic acid, CH_2Cl_2;[9] 94 %, $[\alpha]_D^{24}$ +2.04 ° (c 1.08, $CHCl_3$)), ii) removal of t-butyldimethylsilyl group (Bu_4NF, THF)[8] leading to (1R,4S)-1b (92 %, $[\alpha]_D^{27}$ -22.3 ° (c 1.25, $CHCl_3$); lit. $[\alpha]_D^{20}$ -20.3 ° (c 1.3, $CHCl_3$),[1e] $[\alpha]_D^{20}$ +21.5 ° (c 3.12, $CHCl_3$) for 86 % ee of (1S,4R)-1b[1c]); iii) oxidation (PCC) of (1R,4S)-1b to (S)-2b (82 %, $[\alpha]_D^{29}$ -54.9 ° (c 0.97, $CHCl_3$); lit.[1e] $[\alpha]_D^{20}$ -70.5 ° (c 1.3, $CHCl_3$)); iv) followed by deprotection (AcOH-H_2O, (7:3); 81 %).[1e] (Scheme 3)

Both (R)- and (S)-8 were derived to (R)- and (S)-4-acetoxy-2-cyclo-



Scheme 3

pentenone, and the ee of those were 86 % by ^{1}H NMR spectra taken with $Eu(hfbc)_3$.[12]

It should be noted that the chiral cyclopentenol derivative 1, a useful synthetic intermediate for the enantioselective synthesis of various cyclopentanoid natural products, was easily obtained with high ee by the reaction of achiral epoxide with chiral lithium amide.

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