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THE SYNTHESIS OF (*R*)-1-(2-OXOCYCLOPENTYLIDEN)-2-ALKANOLS AND THE (*S*)-FORMS, AND THEIR BIO-ANTIMUTAGENIC ACTIVITY AGAINST UV-INDUCED *Escherichia coli* WP2 B/r *Trp*⁻

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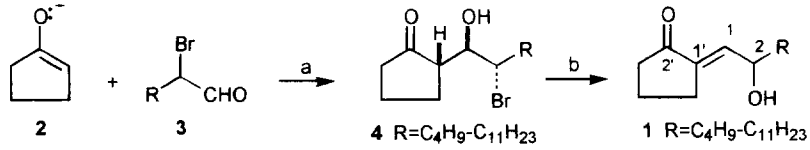
Abstracts: (*R*)-1-(2-oxocyclopentyliden)-2-alkanols (**1r-a** and **1r-b**) and the (*S*)-forms, **1s-a** and **1s-b**, were enantiomerically synthesized from (*R*)-2-[(*R*)-*O*-MEMmandelyloxy]alkanals (**6r-a** and **6r-b**) and the (*S*)-alkanals, **6s-a** and **6s-b**. The (*R*)-isomers (**1r-a** and **1r-b**) showed bio-antimutagenic acitivity against UV-induced *Escherichia coli* WP2 B/r *Trp*⁻.

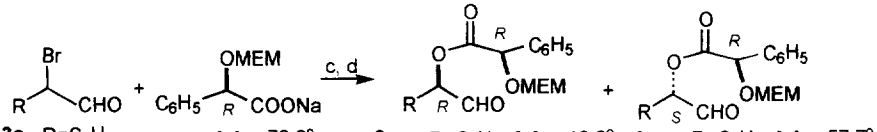
The activity which suppresses the mutation frequency of the DNA-harmed cells such as UV-induced *Escherichia coli* WP2 B/r *Trp*⁻ was emphasized by T. Kada *et al* as the bio-antimutagenicity[1,2], and the γ-oxygenated α,β-unsaturated carbonyls were known as the exceptionally active bio-antimutagen[3,4,5], while they also showed the mutagenic, cytotoxic and bactericidal activity like (*S*)-(+)-4-hydroxynonanal[6]. The relationships between bio- antimutagenic activity and the absolute configuration of the oxygenated γ-carbon has not been reported. We have synthesized racemic 1-(2-oxocyclopentyliden)-2-alkanols **1**; by aldol reaction of cyclopentanone enolate (**2**) with 2-bromoalkanals **3**, and successive treatment of the aldol products **4** with sodium acetate[5]. Since the octanol-derivative **1a** showed the bio-antimutagenic activity [AD_{50} (the half inhibition-dose of mutation frequency of UV-induced *E. coli* WP2 B/r *Trp*⁻]=79 μg/ml)[5], and the decanol-derivative **1b**, considerable activity (AD_{50}=6.7 μg/ml)[5], we planned to synthesize the optically active **1a** and **1b**. In this paper, we describe the enantiomeric synthesis of (*R*)-1-(2-oxocyclopentyliden)-2-octanol (**1r-a**) and the decanol-derivative **1r-b** and their (*S*)-forms, **1s-a** and **1s-b**, and their bio-antimutagenic activity against UV-induced *E. coli* WP2 B/r *Trp*⁻.

2-Bromooctanal **3a** (1 equimol) was reacted with the preheated suspension (55°C for 1.5 hr in DMF+HMPA=3:2) of sodium (*R*)-*O*-MEMmandelate (**5**, 1.1 equimol) at 55°C for 1 hr in N_2 atmosphere to give the mixture of the diastereoisomers of (*R*)-2-[(*R*)-*O*-MEMmandelyloxy]octanal (**6r-a**) and the (*S*)-form **6s-a** in



2 **3** **4** R=C_4H_9-$C_{11}H_{23}$ **1** R=C_4H_9-$C_{11}H_{23}$

a, -78°C for 30 min in THF. b, AcONa in DMF+HMPA(3:2) at 60°C for 6 hr.



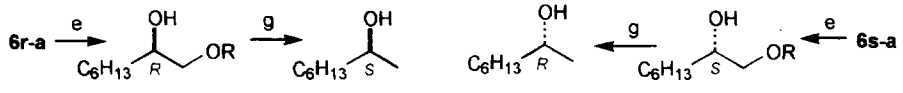
3a R=C_6H_{13}
3b R=C_8H_{17}

5 $[\alpha]_D$=-72.8° (c=0.9, H_2O)

6r-a R=C_6H_{13} $[\alpha]_D$=-19.8° (c=1.0, EtOH)
6r-b R=C_8H_{17} $[\alpha]_D$=-15.3° (c=0.60, EtOH)

6s-a R=C_6H_{13} $[\alpha]_D$=-57.7° (c=0.59, EtOH)
6s-b R=C_8H_{17} $[\alpha]_D$=-61.7° (c=0.60, EtOH)

c, Addition of **3** to the suspension of the sodium salt (**5**) preheated at 55°C for 1.5 hr. in DMF+ HMPA (3:2), and stirring for 1 hr. d, Silica gel flash column (Hexane+EtOAc=3:1, and 2:1)



7r R=H $[\alpha]_D$=+13.1° (c=0.74, EtOH)
9r R=Ts

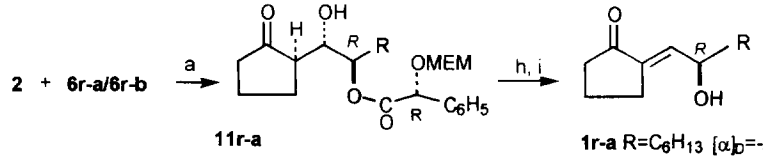
10s $[\alpha]_D$=+10.3° (c=0.23, EtOH) 98% ee

10r $[\alpha]_D$=-10.6° (c=0.31,EtOH) 97% ee

7s R=H $[\alpha]_D$=-13.5°
9s R=Ts

e, $LiAlH_4$/THF. f, TsCl/pyridine. g, $LiAlH_4$/THF

(*S*)-2-octanol $[\alpha]_D$=+10.5° (c=0.20, EtOH); (*R*)-2-octanol $[\alpha]_D$=-10.9° (c=0.40, EtOH)

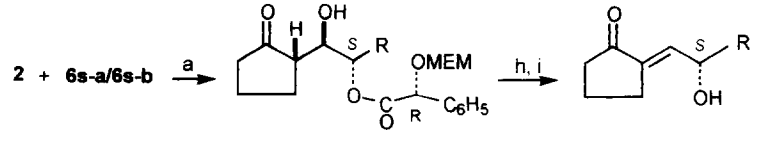


11r-a

11r-b R=C_8H_{17}

1r-a R=C_6H_{13} $[\alpha]_D$=-20.5° (c=0.51, EtOH), 90% ee

1r-b R=C_8H_{17} $[\alpha]_D$=-19.3° (c=0.88, EtOH), 89% ee by NMR anal.



11s-a R=C_6H_{13}

11s-b R=C_8H_{17}

1s-a R=C_6H_{13} $[\alpha]_D$=+20.6° (c=0.49, EtOH), 89% ee

1s-b R=C_8H_{17} $[\alpha]_D$=+20.7° (c=1.76, EtOH), 94% ee by NMR anal.

h, AcONa at 70°C for 24 hr in DMF+HMPA(3:2). i, TLC separation (hexane:EtOAc=3:1, 4 developments)

99% yield, which was separated into optically active **6r-a** (35% yield) and **6s-a** (47% yield) using a flash column (silica gel, hexane:EtOAc=3:1 and then 2:1)[7,8]. Their optical purity was determined as follows. The aldehyde **6r-a** was transformed into (*R*)-octane-1,2-diol (**7r**, quantitative yield) by $LiAlH_4$ reduction in addition with (*R*)-2-*O*-MEM-2-phenylethane-1,2-diol (**8**), successively to (*R*)-1-tosylate **9r**, 56% yield) by tosylation and finally to (*S*)-2-octanol (**10s**, 93% yield, 98% ee, Scheme) by $LiAlH_4$ reduction. The (*S*)-aldehyde **6s-a** was similarly transformed to (*S*)-octane-1,2-diol (**7s**, quantitative yield), to (*S*)-1-tosylate **9s** (56% yield), and finally to (*R*)-2-octanol (**10r**, 95% yield, 97%ee, Scheme). The configuration at C_2 of each aldehyde, **6r-a** and **6s-a**, could also be determined. (*R*)-2-[(*R*)-*O*-MEM-mandelyloxy]decanal (**6r-b**, 32% yield) and the (*S*)-form (**6s-b**, 34% yield) were prepared by similar substitution reaction[9].

(*R*)-2-[(*R*)-*O*-MEMmandelyloxy]octanal (**6r-a**) and the (S)-form **6s-a** were, respectively, reacted with cyclopentanone enolate (**2**, prepared from cyclopentanone and LDA at -78°C for 30 min in THF) at -78°C for 30 min in THF to give each aldol product [8,10](**11r-a**, 93% yield by NMR analysis, and **11s-a**, 93% yield by NMR analysis). Each aldol product, **11r-a** and **11s-a**, was treated with AcONa in the mixed solvent of DMF and HMPA (3:2) at 65-70°C for 24 hr in N_2 atmospher, and successively purified with silica gel TLC (hexane:EtOAc=3:1, 4 developments), to afford (*R*)-1-(2-oxocyclopentyliden)-2-octanol (**1r-a**, $[\alpha]_D$=-20.5° (c=0.51, EtOH)) in 53% yield, and the (*S*)-octanol-derivative **1s-a** ($[\alpha]_D$=+20.6° (c=0.49, EtOH)) in 53% yield[11]. By the similar aldol reaction of **6r-b** and **6s-b** with cyclopentanone (93% and 94% yield by NMR analysis), and the successive elimination reaction and purification described above, **1r-b** (44% yield, $[\alpha]_D$= -19.3° (c=0.88, EtOH)) and the **1s-b** (51% yield, $[\alpha]_D$=+20.7° (c=1.76, EtOH)) were synthesized. Optically active enones, **1r** and **1s**, were identified with the racemic authentic samples[5] on the NMR spectra[12]. The optical purity of each enone, **1r** and **1s**, was determined on the NMR spectra of their MTPA-esters[13], and found to be **1r-a**, 90% ee; **1s-a**, 89% ee; **1r-b**, 89% ee and **1s-b**, 94% ee[14].

1r-a and **1r-b** showed the bio-antimutagenic activity against UV-induced *E. coli* WP2 B/r *Trp*⁻ (AD_{50}=50 μg/ml and 4.5 μg/ml, respectively), and did not show the microbicidal activity in the dose of 120 μg/ml, while both (*S*)-forms, **1s-a** and **1s-b**, showed neither bio-antimutagenic nor microbicidal activity in the dose of 150 μg/ml.

References and Notes

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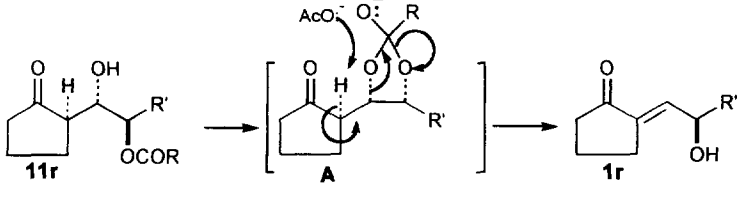
7. The reaction with use of excess amounts (1.5 equimols) of the sodium salt (**5**) (at 55°C for 16 hr) and with unsolubilization of the salt without preheating of the suspension caused the α-rearrangement reaction to yield 1-[(R)-*O*-MEMmandelyloxy]-2-octanone (**12**) in addition with **6s-a**.
8. Principal NMR signals for identification of the products. $^{1}H[^{13}C]\delta$ ppm: **6r-a**, 3.37 (3H, s, OMe [58.96]), 5.00 (1H, dd, J=8.4 & 4.9 Hz, 2 [78.90]), 5.34 (1H, s, mandelyl [76.70], 9.31 (1H, bs, 1 [197.89], [170.59, COO]. **6s-a**, 3.50 (3H, s, OMe [58.99]), 4.99 (1H, dd, 8.8 & 4.4 Hz, 2 [78.73]), 5.36 (1H, s, mandelyl, [76.77]), 9.52 (1H, bs, 1 [198.00]), [170.59, COO]. **6r-b**, 3.37 (3H, s, OMe [58.97]), 5.00 (1H, dd, 9.5 & 4.8 Hz, 2 [78.90]), 5.33 (1H, s, mandelyl, [76.73]), 9.31 (1H, d, J=0.6 Hz, 1 [197.89]), [170.59]. **6s-b**, 3.37 (3H, s, OMe [58.98]), 4.99 (1H, dd, J=9.0 & 4.5 Hz, 2[78.75]), 5.36 (1H, s, mandelyl, [76.58]), 9.52 (1H, bd, J=0.6 Hz, 1 [197.97]), [170.54, COO]. **11r-a**, 3.61 (1H, dd, $J_{1\text{-}1'}$=8.2 Hz, $J_{1\text{-}2}$=3.9 Hz, 1 [72.85]), 4.91 (1H, dt, $J_{1\text{-}2}$=3.6, $J_{2\text{-}3}$=9.8 & 2.6 Hz, 2 [76.49]), 5.24 (1H, s, mandelyl [76.90]), [170.52, COO], [222.60, CO]. **11s-a**, 3.87 (1H, dd, $J_{1\text{-}1'}$=8.3, $J_{1\text{-}2}$=2.8 Hz, 1 [73.09]), 4.81 (1H, dt, $J_{1\text{-}2}$=2.8, $J_{2\text{-}3}$=108 & 3.2 Hz, 2 [76.33]), 5.26 (1H, s, mandelyl [76.68]), [170.81, COO], [222.86, CO]. **11r-b**, 3.61 (1H, dd, $J_{1\text{-}1'}$=8.1, $J_{1\text{-}2}$=3.6 Hz, 1 [72.86]), 4.91 (1H, $J_{1\text{-}2}$=3.6, $J_{2\text{-}3}$=9.8 &2.6 Hz, 2 [76.51]), 5.24 (1H, s, mandelyl [76.91]), [170.53, COO], [222.62, CO]. **11s-b**, 3.87 (1H, dd, $J_{1\text{-}1'}$=8.3, $J_{1\text{-}2}$=3.0 Hz, 1 [73.10]), 4.81 (1H, dt, $J_{1\text{-}2}$=3.0, $J_{2\text{-}3}$=10.1 & 2.7 Hz, 2 [76.35]), 5.26 (1H, s, mandelyl [76.67]), [170.81, COO], [222.87, CO].
9. The optically active 2-hydroxyalkanals have been prepared from (S)-aminoacids: M. Larcheveque and Y. Petit, bull. Soc. Chim. Fr., **1989**, 130-139. H. Hagiwara, K. Kimura, and H. Uda, J. Chem. Soc., **1992**, 693-700.
10. The configuration of the aldol products, **11r** and **11s**, was determined to be 1,1'-threo; 1,2- erythro on the basis of the comparison of the coupling constants of the aldol products (**4**, R=C_6H_{13}) obtained from the aldol reaction of cyclopentanone with 2-bromooctanal[5]. By silica gel TLC purification, these products partially isomerized to the 1,1'-erythro; 1,2-erythro isomers in similarity to **4**[5].
11. The enones **1r** was supposed to be formed by the elimination of the mandelyloxy moiety via the cyclic intermediate like **A** as shown below, since the attack of the C_1-hydroxyl group to the C_2 ester-carbonyl was suggested to be more favorable than to C_2 to form the epoxide with (1*S*,2*S*)-configuration.



12. All new compounds showed reasonable precise MS spectra.
13. J. A. Dale and H. S. Mosher, *J. Am, Chem. Soc.*, **95**, 512-519 (1973).
14. On the 500Mhz-NMR spectrum of each MTPA-ester of **1r** and **1s**, the C_1-proton signals of each optical isomer appeared in 0.08-0.1 ppm-separation, while the C_2-proton signals of each isomer were overlapped.

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