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SYNTHESIS OF THE ENANTIOMERS OF 3-HYDROXY-1,7-DIOXASPIRO[5.5]UNDECANE, A MINOR COMPONENT OF THE OLIVE FLY PHEROMONE

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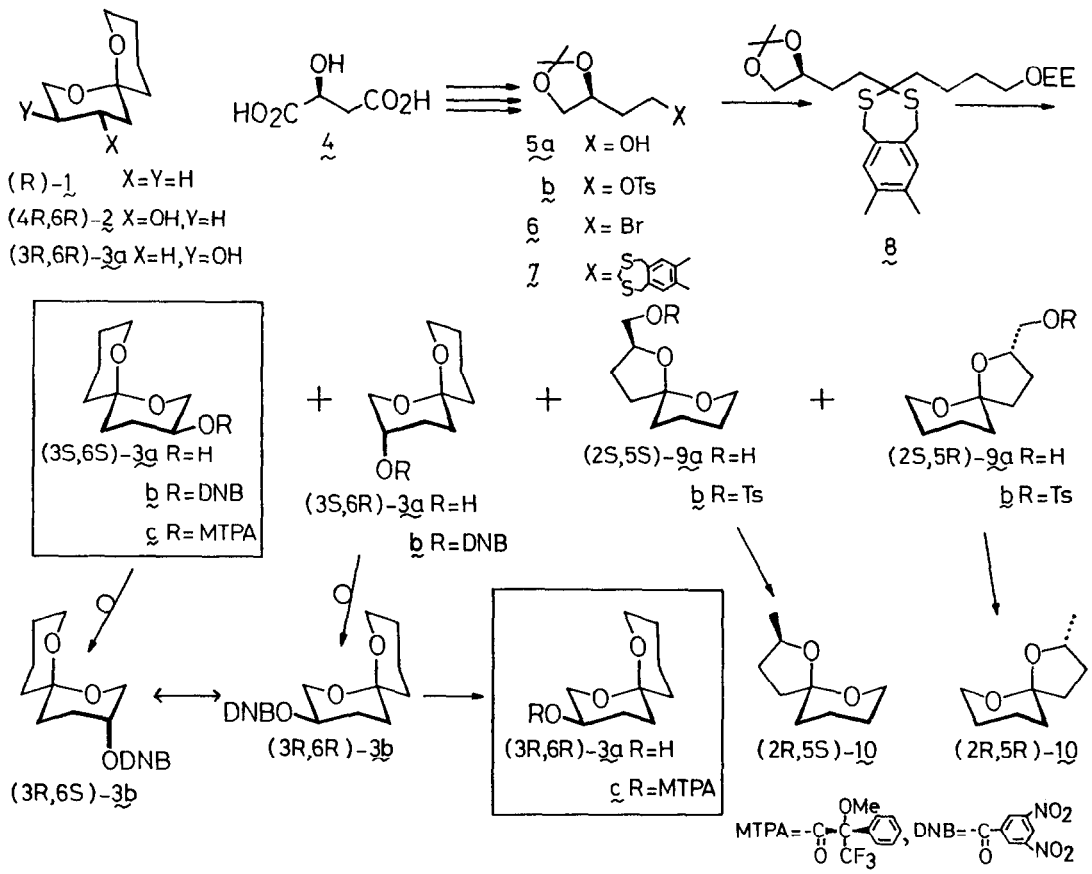
Summary: (3R,6R)-(-)-3-Hydroxy-1,7-dioxaspiro[5.5]undecane 3a and its antipode were synthesized from (S)-malic acid.

We recently reported the synthesis of the enantiomers of 1,7-dioxaspiro[5.5]undecane 1 and 4-hydroxy-1,7-dioxaspiro[5.5]undecane 2,[1] the former being the major and the latter being the minor components of the pheromone of the olive fly, Dacus oleae.[2,3] Herein we report the first synthesis of both the enantiomers of 3-hydroxy-1,7-dioxaspiro[5.5]undecane 3a, the other minor component of that pheromone.[3] Racemic 3a was previously synthesized by Baker et al.[3]

(S)-Malic acid 4 furnished pure 5a, $[\alpha]_D^{21}$-2.4°(c=3.91,MeOH), by the known method.[4] This was converted to a bromide 6, $[\alpha]_D^{21}$-27.2°(c=1.25,$CHCl_3$), via 5b in the conventional manner. Alkylation of 7,8-dimethyl-1,5-dihydro-2,4-benzodithiepin[5] with 6(n-BuLi/THF)gave 7(88%),mp 108.5∿109°,$[\alpha]_D^{23}$+1.6°(c=2.76,$CHCl_3$) Further alkylation of 7 with $I(CH_2)_4OEE$(n-BuLi/THF) gave 8(83%). Treatment of 8 with $CuCl_2 \cdot 2H_2O$ and CuO in Me_2CO-H_2O(99:1) under reflux[6] yielded a complex mixture of products. Fortunately separation of the mixture into four pure isomers was possible by chromatography (Merck Lobar column, Grösse B;$CHCl_3$-MeOH= 30:1). The isomers were eluted in the following order:(2S,5R)-9a(9%),$[\alpha]_D^{22}$-80.8°(c=1.63,ether);(2S,5S)-9a(15%),$[\alpha]_D^{22}$+91.3°(c=1.67,ether);(3S,6R)-3a(18%), $[\alpha]_D^{21.5}$-129°(c=0.93,ether)[7]; and (3S,6S)-3a(33%),mp 98.5∿99.0°,$[\alpha]_D^{22.5}$+115°(c= 0.92,ether).[8] The structures of these isomers were assigned on the basis of the NMR spectral comparison with the published NMR data of 3a by Baker[3] and of 9a by Ireland.[9] Especially our data from lanthanide shifts experiments on (3S, 6S)- and (3S,6R)-3a were in complete accord with Baker's data.[3] The two isomers of 9a were converted to the corresponding tosylates 9b, whose reduction with LAH gave (2R,5S)- and (2R,5R)-10. Their IR,^{1}H-NMR,^{13}C-NMR, and MS data were in agreement with those reported by Francke et al.[10,11]

The next task was the conversion of (3S,6R)-3a to (3R,6R)-3a. For that purpose,(3S,6R)-3a was treated with 3,5-dinitrobenzoic acid, Ph_3P and EtO_2CN= NCO_2Et in THF to effect the Mitsunobu inversion[12] yielding (3R,6R)-3b(78%),mp 155∿156°,$[\alpha]_D^{22}$-69.9°(c=1.60,$CHCl_3$).[13] This was hydrolyzed with aq KOH/THF-MeOH to give (3R,6R)-3a,mp 98.5∿99°,$[\alpha]_D^{22}$-112°(c=0.92,ether). Its IR,^{1}H-NMR and ^{13}C-NMR data were identical with those of (3S,6S)-3a. Finally transformation of (3S,6S)-3a to (3R,6R)-3a was also realized as follows. The Mitsunobu inversion of (3S,6S)-3a gave (3R,6S)-3b(87%),mp 173∿173.5°,$[\alpha]_D^{21.5}$+71.7°(c=1.10, $CHCl_3$).[13] This in CH_2Cl_2 was treated with $Zn(OTf)_2$ to effect equilibration and



the resulting mixture was separated by prep TLC to give (3R,6S)-3b (70%) and (3R,6R)-3b (29%), the latter of which afforded (3R,6R)-3a after hydrolysis.[14,15]

REFERENCES AND FOOTNOTES

1) K.Mori,T.Uematsu,H.Watanabe,K.Yanagi,M.Minobe,Tetrahedron Lett.25,3875 (1984). 2) R.Baker,R.Herbert,P.E.Howse,O.T.Jones,W.Francke,W.Reith,J.C.S.Chem. Commun.52(1980). 3) R.Baker,R.H.Herbert,A.H.Parton,Ibid.601(1982). 4) A.I. Meyers, J.P.Lawson,Tetrahedron Lett.23,4883 (1982). 5) K.Mori,H.Hashimoto,Y. Takenaka,T.Takigawa,Synthesis 720(1975). 6) K.Narasaka,T.Sakashita,T.Mukaiyama,Bull.Chem.Soc.Jpn.45,3724(1972). 7) Spectral data of (3S,6R)-3a:^{1}H-NMR [100MHz,Eu(fod)$_3$,C_6D_6] δ1.1∿1.9(4H,m), 2.0∿2.5(3H,m),2.5∿3.1(2H,m),3.30(1H,dt, J=6,12Hz),3.80(1H,dm,J=11Hz),3.96(1H,dt,J=3,11Hz),4.48(1H,dd,J=2,12Hz),5.20 (1H,dm,J=12 Hz),5.73(1H,m,br);^{13}C-NMR(25MHz,C_6D_6) δ18.91,25.61,25.71,30.24, 35.58,60.70,64.50,64.89,95.18. 8) Spectral data of (3S,6S)-3a:^{1}H-NMR[100MHz, Eu(fod)$_3$,C_6D_6] δ1.1∿2.7(8H,m),2.98(1H,m),3.50(1H,ddt,J=4,10,12Hz),3.8∿4.2(2H, m),4.9∿5.4(2H,m),5.66(1H,m,br);^{13}C-NMR(25MHz,C_6D_6) δ19.15,25.56,28.61,35.04, 35.29,60.38,64.99,66.35,94.38. 9) R.E.Ireland,P.Häblich,Chem.Ber.114,1418 (1981). 10) W.Francke,W.Reith,V.Sinnwell,Chem.Ber. 113,2686(1980). 11) W. Francke,G.Hindorf,W.Reith,Angew.Chem.Int.Ed.17,862(1978);Idem.Naturwiss.66, 619(1979). 12) O. Mitsunobu,Synthesis 1 (1981). 13) (3S,6S)-3b,mp 154∿155° $[\alpha]_D^{22}$+69.5°(c=0.80,$CHCl_3$), was also prepared from (3S,6S)-3a by treatment with 3,5-dinitrobenzoic acid, DCC and DMAP in CH_2Cl_2. (3S,6R)-3b, mp 173∿173.5°, $[\alpha]_D^{22}$-68.8°(c=0.63,$CHCl_3$),was prepared from (3S,6R)-3a. 14) A remarkable feature of this equilibration was the fact that the (3R,6S)-3b with an axial substituent was the predominant isomer. Even in a different solvent (CCl_4, C_6H_6,ether,MeOH) or with TsOH as the catalyst, (3R,6S)-3b was predominant. At present we have no explanation for this phenomenon. 15) Both (3R,6R)- and (3S,6S)-3a were of 100% e.e. as checked by the HPLC analyses of (3R,6R)- and (3S,6S)-3c.

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