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Optically active cyclopropanols from the enzymatic resolution of dimethyl α-alkylsuccinates. Synthesis of chiral 2-vinylcyclobutanones and cyclohexenones.

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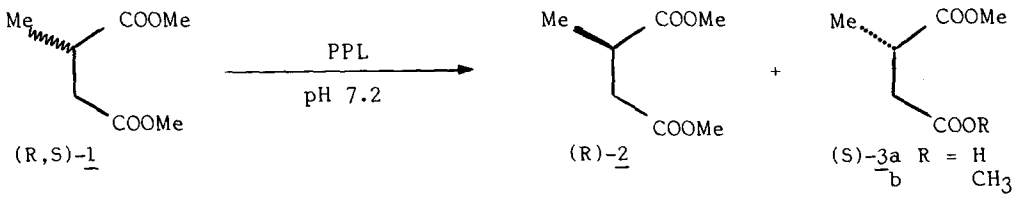
Abstract. (+)-(R) [or (-)-(S)] dimethyl α-methylsuccinates, obtained by the enantioselective hydrolysis of the racemic diester by porcine pancreatic lipase, undergo acyloin cyclization followed by stereoselective ring contraction to provide 1-alkenylcyclopropanols with high enantiomeric excesses.

The cyclopropane ring not only constitutes an attractive synthon involved in many useful chemical transformations [1] but is also present in a large number of natural products [2]. Recent approaches to optically active cyclopropanes involve separation of diastereoisomers [3], enantioselective enzymatic hydrolysis[4], stereospecific cyclopropanation of chiral precursors [5], stereocontrolled cyclization of chiral esters [6], ring contraction of a cyclobutanol prepared from natural (+) α-pinene[7], addition of the α-carbanion of (R_S)-(+)sulfinylcyclopropane [8].

We have previously shown that 1-hydroxycyclopropanecarboxaldehyde derivatives provide convenient keystones for the construction of four-, five- and eight-membered ring moieties leading to jasmonoïd and spirovetivane derivatives, to dicranenone A, methylenomycin B and precapnelladiene[9]. We report herein the first synthesis of optically active cyclopropanols from racemic dimethyl α-methyl succinates.



(R,S)-1 (R)-2 (S)-3a R = H
b CH_3

(+)-(R) Dimethyl 2-methylsuccinate 2 is now readily available on a preparative scale and with high optical purity (> 95% ee) from the enantioselective hydrolysis of the racemic ester 1 by porcine pancreatic lipase (PPL) ; its enantiomer (-)-(S)-3b (>96% ee) was obtained after esterification of the half ester (-)-(S)-3a [10]. Acyloin cyclization of (+)-(R)-2 by sodium in the presence of $ClSiMe_3$ [11] provided the (+)-(R)-3-methyl-1,2-disiloxycyclobutene 4 ($[\alpha]_D^{20}$ = +21°, c 2.78, CCl_4) ; while acyloin cyclization of (-)-(S)-3b led to the enantiomer (-)-(S)-4 ($[\alpha]_D^{20}$ = -22°, c 2.82, CCl_4) in 78% yield. Bromination of (+)-(R)-4 at -20°C in CCl_4 gave the labile (R)-(+)-3-methyl-1,2-cyclobutanedione 5[12]; on the other hand, successive additions of bromine at -50°C in pentane and of a 2M NaOH aqueous solution at 0°C [14] led, after acidification (2M HCl), essentially to the (-)-(1S,2R) 1-hydroxy-2-methylcyclopropanecarboxylic acid 6a and after esterification (MeOH, $SOCl_2$, reflux) to the (-)-(1S,2R) methyl ester 6b, in 98% yield.

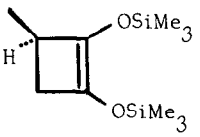
From chemical and spectroscopic data, it has been claimed that the ring contraction of 4 gave the hydroxyacid 6a with exo-configuration of the carboxy group, exclusively [14]. However gas chromatography, mass spectroscopy and n.m.r. examination of the product of the reaction (R)-4 ⟶ (1S,2R)-6b evidenced the formation of ~5% of the diastereoisomer (1R,2R)-7 (diastereoselectivity 95:5). Recrystallization of the acid (1S,2R)-6a [15] allowed, after esterification, the obtention of the stereochemically pure ester (-)-(1S,2R)-6b [16]. Moreover the optical purity of this hydroxyester, easily determined by comparison of its n.m.r spectra (250 MHz) recorded in the presence of chiral $Eu(hfc)_3$ with those of racemic 6b (prepared from racemic succinate 1, following the same procedure), was superior to 94% (> 97%, from recrystallized acid (1S,2R)-6a). In the same way, ring contraction of the disiloxycyclobutene (-)-(S)-4 provided the (+)-(1R,2S) hydroxy acid 8a and after esterification the (+)-(1R,2S) hydroxy ester 8b, with 95% ee [17].

It is worthy of note that the chirality of the stereocenter was not affected during the sodium induced acyloin cyclization of the enolizable α-methyl succinates (R)-2 and (S)-3b involving the intermediacy of radical-anions [11] as well as during the base-induced ring contraction of the bromination products of the (R)- and (S)-3-methyl-1,2-disiloxycyclobutenes 4, i.e., the (R)- and (S)-3-methyl-1,2-cyclobutanediones 5.

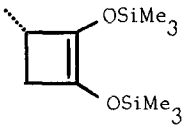
Such a comparable chiral stability has been recently reported for the reductive transformation of methyl (S)-β-bromoisobutyrate leading, via its sodium homoenolate, to a 1:1 diastereomeric mixture of 1-methoxy-2-methyl-1-trimethylsiloxycyclopropanes, which, upon bromination (0°C), were transformed back to the starting bromide without loss of optical purity [18].

It must be underlined that PPL-induced hydrolysis of the racemic hydroxyester 6b, following the reported procedure [10], provided (1S,2R)-6b with 6.5% e.e., only.

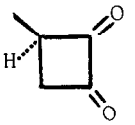
Silylation ($ClSitBuMe_2$, DMF, imidazole, 35°C) of the hydroxyester (-)-(1S,2R)-6b, then reduction (DIBAH, toluene, -70°C) followed by oxidation (DMSO-$(COCl)_2$), led to the chiral (-)-(1S,2R) cyclopropanecarboxaldehyde 9 [19] (94% overall yield). Wittig reaction ($(MeO)_2P(O)CH_2CO_2Me$, THF, n-BuLi, 20°C) gave the ethyl E- α,β-unsaturated carboxylate 10 (96% yield). Upon treatment with methanol and $ClSiMe_3$ (catalytic) at 40°C for 24 hr the vinylcyclopropane (1S,2R)-10 underwent quantitative $C_3 \longrightarrow C_4$ ring enlargement into a 70/30 regiomeric mixture of 3-methyl- 12 and 4-methyl-2(carbomethoxymethyl)cyclobutanones 13, as evidenced by n.m.r. double irradiation [20]. On the other hand, reduction (DIBAH, toluene, -78°C) of the chiral ester 10 gave the allylic alcohol (-)-(1S,2R)-11 which, upon treatment with BF_3, Et_2O (catalytic, $CHCl_3$) underwent regioselective $C_3 \longrightarrow C_4$ ring enlargement into the (+)-(2R,3R)-3-methyl-2-vinylcyclobutanone 14 exclusively, as evidenced from chromatographic and spectroscopic data [21]. Reduction ($LiAlH_4$, ether, reflux, 30 mn) gave a 63:37 mixture of isomeric cyclobutanols (+)-(2S,3R) 15 which, upon treatment with KH (1 equiv.) in THF at reflux for 1 hr underwent total $C_4 \longrightarrow C_6$ ring enlargement [22] into the 5-methyl cyclohex-3-en-1-ols 16 [23]. Oxidation with Jones reagent and treatment of the resulting non-conjugated enone with basic activity 3 alumina (5% ether in pentane) yielded the (+)-(S)-5-methyl cyclohex-2-en-1-one 17 ($[\alpha]_D$ = +81°, c 1.04, $CHCl_3$), with 91% optical purity [24], after the overall transformation from racemic succinate 1. Synthetic applications of these highly stereoselective ring rearrangements are currently under investigation.



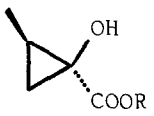
(+)-(R)-4



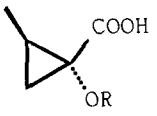
(-)-(S)-4



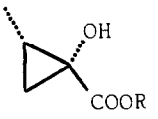
(R)-5



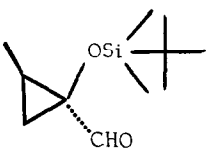
(-)-(1S,2R)-6 a R = H
b CH3



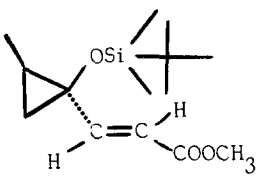
(1R,2R)-7



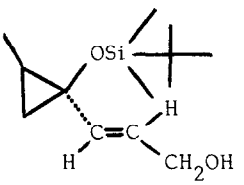
(+)-(1R,2S)-8 a R = H
b CH3



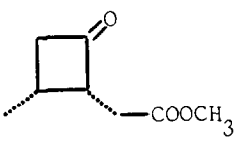
(-)-(1S,2R)-9



(-)-(1S,2R)-10



(-)-(1S,2R)-11



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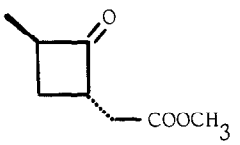
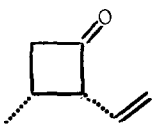
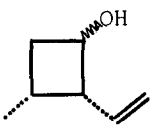


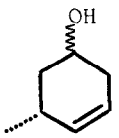
13



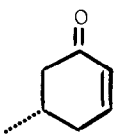
(+)-(2R,3R)-14



(+)-(2R,3R)-15



16



(+)-(S)-17

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12. IR (CCl_4) (cm^{-1}) : 1775 and 1800 (γ C=O) ; NMR ^1H (CCl_4,δppm) 1.25 (d, J = 6.7 Hz, 3H); 2.30 - 3.35 (m, 3H) ; ^{13}C ($CDCl_3$,δppm) 214.4, 208.2, 50.6, 49.2, 15.5 ; MS (e/m) M^+ 98 (3.5%). Contrary to the parent 1,2-cyclobutanedione (m.p. 65°C) 13 (R)-5 is an unstable liquid which was not isolated.

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15. M.p. 75°C (ether-hexane), lit. (14) m.p. of the racemic 6a 64-65°C (xylene); $[\alpha]_D$ = -57°, c 1.51, $CHCl_3$.

16. B.p. 74°C/15 mm., lit., (14) 87°C/20 mm ; $[\alpha]_D$ = -41°, c 2.95, CCl_4.

17. In the presence of chiral $Eu(hfc)_3$ (40% w/w) the methyl ester signal of (±) 6b was decoupled into two equal singlets ; while (1S,2R)-6b showed mainly a methyl ester singlet (ratios 97:3 from crude 6a and 98.5:1.5 from recrystallized 6a), and (1R,2S)-8b mainly the other singlet (ratio 2.5:97.5).

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19. $[\alpha]_D$ = -45°, c 2.37, $CHCl_3$. When prepared from unrecrystallized 6a, n.m.r. spectra evidenced two diastereomeric aldehydic protons (ratio 96:4) at δ 9.0 and 9.4 ppm, respectively.

20. Upon complexation with chiral $Eu(hfc)_3$, the methyl ester signals of 14 and 15 were decoupled showing, by comparison with the racemic compounds, high enantiomeric purities.

21. $[\alpha]_D$= +68°, c 0.99, $CHCl_3$; IR ($CDCl_3$) (cm^{-1}) 1780 (γ C=O), 1640 (γ C=C) ; NMRδ($CDCl_3$ (250 MHz) (ppm) 1.15 (d, J = 4 Hz, 3H), 2,50 (dq, ^2J = 17.15 Hz, ^3Jtrans = 4.22 Hz, ^4Jcis = 2.2 Hz, 1H) ; 2.72 (m, 1H), 3.25 (qd, ^2J = 17.15 Hz, ^3Jcis = 9.15 Hz, ^4Jtrans = 2.8 Hz, 1H) ; 3.98 (m, 1H); 5.25 (m, 2H) ; 5.72 (m, 1H). MS (e/m) : 110 (M^+, 1.6), 82 (7), 42 (10), 68 (M- C_2H_2O, 100).

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23. Two stereoisomers as evidenced from n.m.r. spectra.

24. By comparison with the optical rotation ($[\alpha]_D$ = -90°) of (-)-(R)-17 prepared from (+) pulegone: N.L. Allinger and C.K. Riew, J. Org. Chem., 1975, 40, 1316 ; W. Oppolzer and M. Petrzilka, Helv. Chim. Acta, 1978, 61, 2756 ; D. Liotta, G. Lima and M. Saindane, J. Org. chem., 1982, 47, 1258.

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