Tetrahedron: Asymmetry Vol. 3, No. 9, pp. 1165-1187, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

Baker's Yeast-Induced Asymmetric Reduction of the Keto Group Activated by the Cyclopropane Unit.

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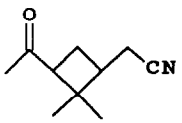
(*Received* 8 *June* 1992)

Abstract: Certain cis-3-substituted 2,2-dimethyl-1-(2-oxopropyl)-cyclopropanes are effectively reduced by baker's yeast to give predominantly (*S*)-isomers of the corresponding 2-hydroxypropyl derivatives. Reduction of the 2-oxopropyl group proceeds more rapidly (ca. 3.5 times) and with higher stereoselectivity [(*S*):(*R*) = 98:2] when the group is attached to the (*S*)-carbon of the cyclopropane unit than of the keto group attached to the (*R*)-carbon [(*S*):(*R*) = (88):(12)]. Yeast reduction of the keto derivatives is effectively carried out when substituents at C-3 are as follows: CH_2COOCH_3, $-CH_2COCH_3$, -CN, $-CH_2CN$, $-CH_2CH_2OH$, and the relative rates of reduction are 36:36:15:13:7. No reduction occurs when substituents at C-3 are propyl, 2-methyl-2-hydroxypropyl or 2-methyl-1,3-dioxolan-2-yl methyl groups.

Introduction

Enzymes and enzyme systems have recently become an effective tool of organic synthesis. Stereoselective transformations induced by enzymes afford various optically active organic products[1]. Synthesis using baker's yeast is the most popular procedure feasible at any organic chemistry laboratory[2]. Out of many yeast-induced reactions the most essential one seems to be the carbonyl group reduction[3], especially in such compounds as β-ketoesters, α-hydroxyketones, β-diketones, aromatic and α,β-unsaturated ketones and other ketones bearing a functional group in the α- or β-positions of the carbonyl group. Also, reductions of ω-ketoacids by yeast to the respective ω-hydoxy acids were reported[4]. Some ω-ketoacids and related compounds (ω-ketoesters, ω-ketoaldehydes and ω-ketonitriles) form a group of the so-called *seco*-terpenoids produced by cleavage of carbon cycles at the carbon-carbon double bond in natural terpene compounds. The *seco*-derivatives are important intermediates for the synthesis of different useful compounds from natural terpenoids. We have investigated the synthetic utility of terpene ω-ketonitriles (**1-4**)[5], in particular, stereoselective modification of the keto group. Out of the ketonitriles of varied structure, only one compound was reduced by yeast: ketonitrile (**4**) containing the cyclopropane fragment in the β-position of the carbonyl group. Since no data were available on carbonyl group "activation" by the cyclopropane

fragment[6], we have made up our mind to investigate this in detail using as an example the readily available *seco*-derivatives of the natural compound (+)-3-carene.



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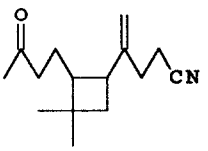

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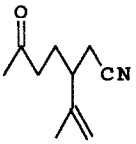

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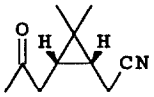


(4)

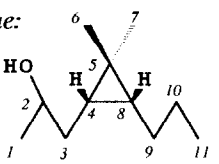
Results and Discussion

We have synthesized some 3-substituted 2,2-dimethyl-1-(2-oxopropyl)-cyclopropanes (**4-8, 19, 22-28**) and studied their reductions by baker's yeast (Scheme 1). All the keto derivatives examined were prepared starting from the known *seco*-derivatives (**4**)[5] and (**5**)[7] according to schemes 2 and 3. Compounds (**4-8**) were reduced, though at varying rates (Fig. 1), to the hydroxy derivatives (**9-13**). Only the expected (*S*)-isomer was formed, the content of (*R*)-isomers being in each case below 2%, except for the case of diketone (**6**) (see below). The isomer ratio of yeast reduction products was determined by comparing n.m.r. spectra of the products obtained with those of authentic epimer mixtures resulting from the reduction of the starting ketones with sodium borohydride. The ^{1}H n.m.r. spectra (200 MHz) of these epimers vary little, therefore the mixtures were analyzed using ^{13}C spectroscopy. The ^{13}C n.m.r. data for yeast reduction products and the corresponding epimer alcohols are given in Table 1. Since differences in ^{13}C chemical shifts for $CDCl_3$ solutions of (**9-13**) of different concentration (at least within 0.2 to 2.0 mmol/ml) are comparable to those in epimer pairs, we used solutions of the same concentration.

Table 1.

^{13}C n.m.r. data for yeast reduction products and their epimers (δC, ppm, for $CDCl_3$ solutions).

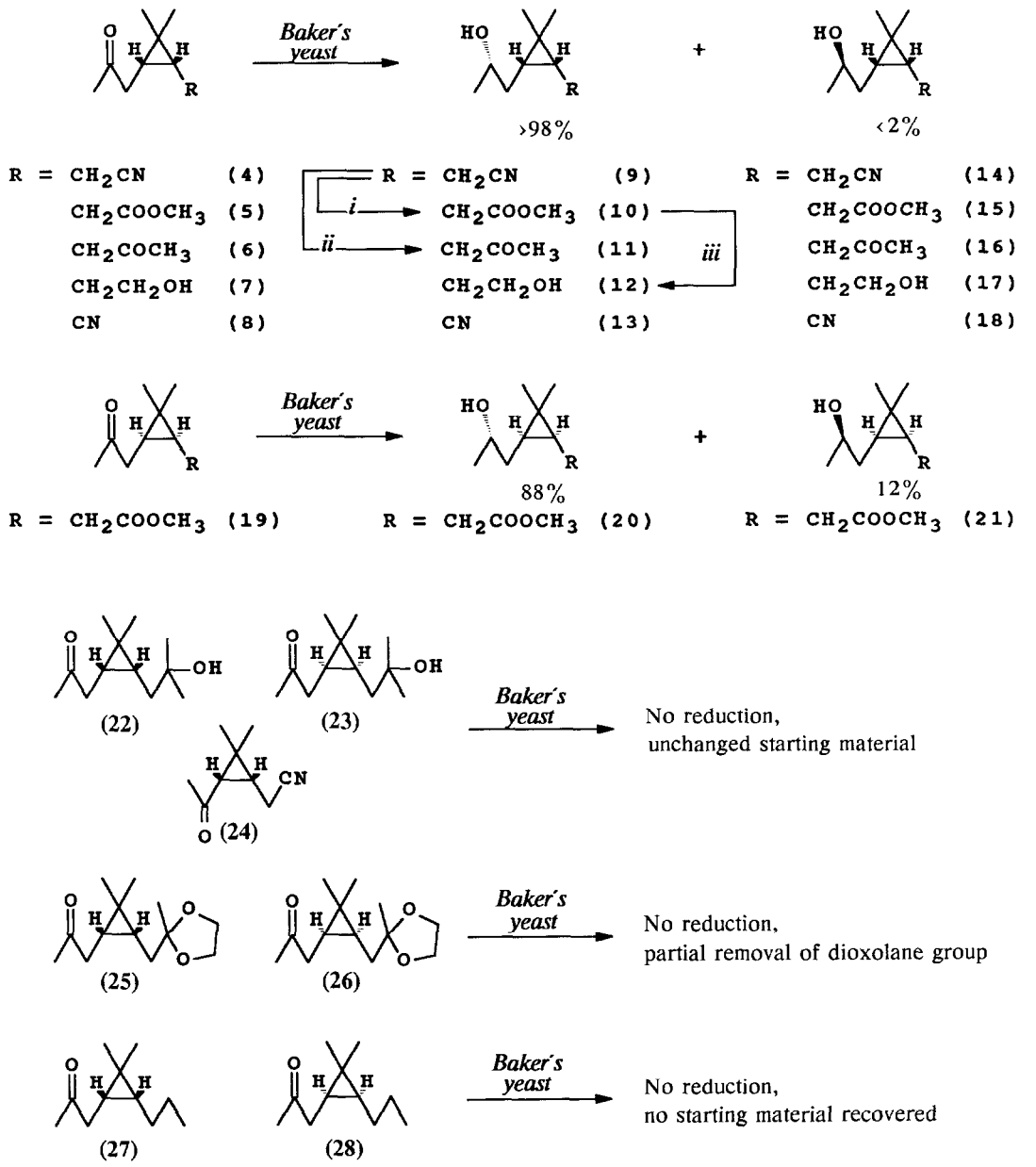
numbering scheme:



carbon number	(9)[a]	(14)[a]	(10)[b]	(15)[b]	(11)[c]	(16)[c]	(12)[d]	(17)[d]	(13)[c]	(18)[c]
1	22.54	22.77	22.60	22.84	22.73	22.95	22.79	23.36	23.37	23.02
2	67.03	67.49	67.52	68.13	67.61	68.24	67.97	68.91	66.77	67.14
3	32.72	32.94	33.42	33.60	33.64	33.79	33.55	33.63	34.82	34.89
4	22.27	22.84	22.21	22.94	22.22	22.99	22.79	23.50	27.28	27.00
5	17.15	16.94	16.67	16.35	16.67	16.24	16.46	15.89	23.60	23.13
6	27.95	27.87	28.42	28.42	28.50	28.53	28.95	28.95	26.46	26.59
7	14.16	14.16	14.78	14.78	15.05	15.05	15.12	15.12	16.51	16.51
8	21.32	21.40	21.48	21.60	20.97	21.03	22.27	23.26	14.31	14.74
9	13.04	12.95	29.56	29.56	39.28	39.21	27.73	27.37	119.25	119.36
10	119.57	119.47	173.99	174.18	208.86	209.19	63.06	63.06		
11					29.36	29.48				

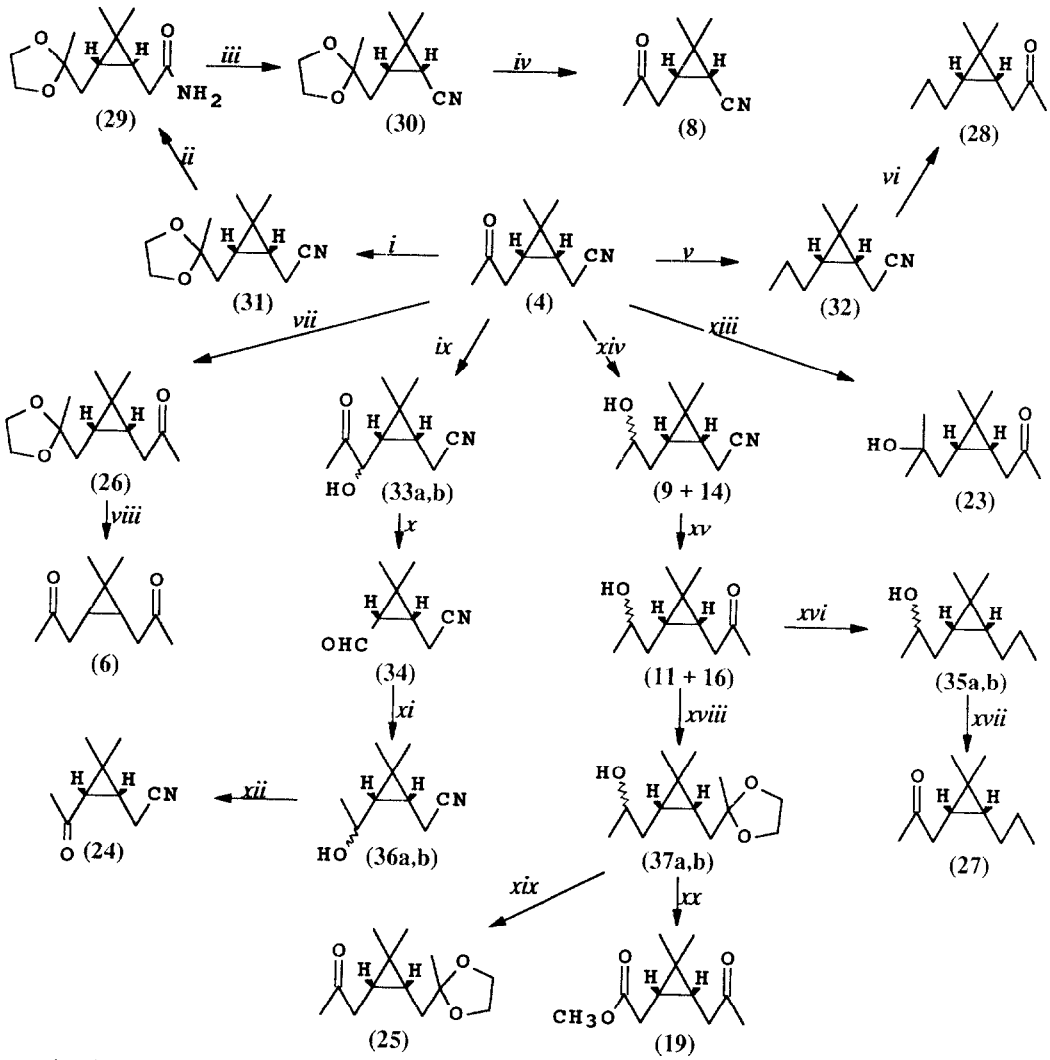
[a]*c* = 1.37 M; [b]*c* = 0.79 M, δ(OCH_3) 51.28; [c]*c* = 0.55 M; [d]*c* = 0.41 M; [e]*c* = 0.29 M.

Scheme 1



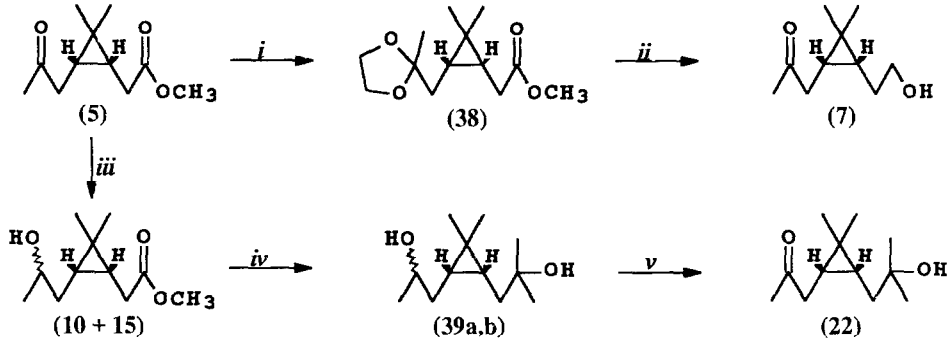
Reagents: i) KOH, $HOCH_2CH_2OH$-H_2O (1:1), reflux, 20min; CH_2N_2, Et_2O, 71%.
ii) CH_3MgI, C_6H_6, reflux, 4h, 77%. *iii)* $LiAlH_4$, THF, reflux, 3h, 77%.

Scheme 2



Reagents: *i)* $HOCH_2CH_2OH$, *p*TsOH, C_6H_6, reflux, 6h, 92%. *ii)* H_2O_2, NaOH, H_2O/CH_3OH, (2:1), 20-25°C, 1h, 63%. *iii)* KOBr + H_2O/CH_2Cl_2 + $PhCH_2NEt_3Cl$, 20-25°C 15min, reflux 1.5h, 95%. *iv)* 1N aq. HCl, CH_3OH, reflux, 30min, 99%. *v)* Zn/Hg, conc. aq. HCl, EtOH, reflux, 4h, 48%. *vi)* CH_3MgI, C_6H_6, reflux, 3h, 68%. *vii)* CH_3MgI, C_6H_6, reflux, 1h, 96%. *viii)* 1N aq. HCl, CH_3OH, 50°C, 1h, 45%. *ix)* KOH, Br_2, CH_3OH, 0°C, 85%. *x)* KIO_4, CH_3COCH_3, reflux, 5h, 82%. *xi)* CH_3MgI, Et_2O, 25°C, 1h, 98%. *xii)* CrO_3, CH_3COCH_3, 25°C, 1h, 60%. *xiii)* CH_3MgI, C_6H_6, reflux, 5h, 67%. *xiv)* $NaBH_4$, CH_3OH, -20°C, 83%. *xv)* CH_3MgI, C_6H_6, reflux, 1h, 91%. *xvi)* *p*TsNHNH$_2$, EtOH, reflux, 30min, quantitative; $LiAlH_4$, THF, reflux, 48h, 42%. *xvii)* CrO_3, CH_3COCH_3, 25°C, 1h, 88%. *xviii)* *p*TsOH, $HOCH_2CH_2OH$, C_6H_6, reflux, 6h, 48%. *xix)* CrO_3, DMFA, conc. H_2SO_4, 25°C, overnight, 77%. *xx)* NaOH, Br_2, dioxane, 80°C, 40min; 1N aq. HCl; CH_2N_2, Et_2O, 12%.

Scheme 3



Reagents: i) $HOCH_2CH_2OH$, Py·HCl, C_6H_6, reflux, 4h, 88%. *ii)* $LiAlH_4$, THF, reflux, 1.5h, 71%. *iii)* $NaBH_4$, CH_3OH, -20°C, 91%. *iv)* CH_3MgI, C_6H_6, reflux, 5h, 60%. *v)* CrO_3, CH_3COCH_3, 25°C, 1h, 50%.

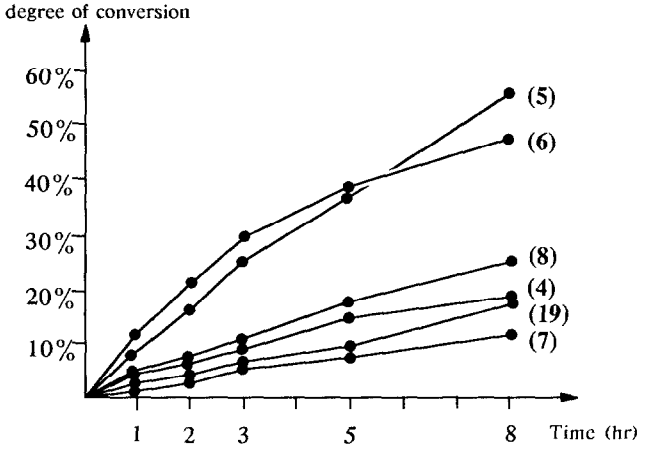
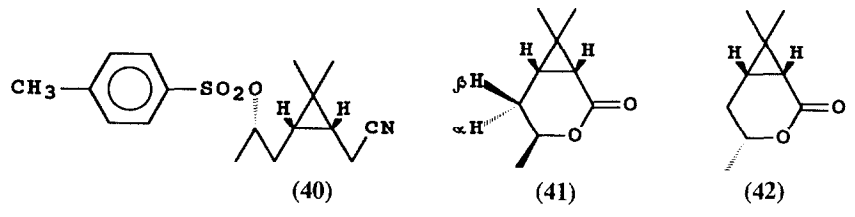


Figure 1. Relative rates of yeast reduction of ketones (**4-8, 19**). The bioreduction of the ketones was done as described in the **Experimental.**

The stereochemistry of reduction products was determined as follows. Hydroxynitrile (**9**) was treated with p-toluenesulfonyl chloride to form a crystalline derivative (**40**) which was subjected to X-ray structure analysis. As seen from Figure 2, the carbinol carbon in tosylate (**40**) has an (*S*)-configuration. Consequently, hydroxynitrile (**9**) also has (*S*)-configuration. Configuration of reduction products (**10-12**) was established by chemical correlation with hydroxynitrile (**9**). Thus, an alkaline hydrolysis of nitrile (**9**) with subsequent esterification with diazomethane gave the hydroxyester identical to compound (**10**), the product of yeast reduction of ketoester (**5**). Reduction of hydroxyester (**10**) with lithium aluminium hydride in THF solution gave diol (**12**). The Grignard

reaction of hydroxynitrile (9) with methylmagnesium iodide afforded hydroxyketone (11). Configuration of hydroxynitrile (13) was established as follows. As a result of alkaline hydrolysis and subsequent lactonization of the hydroxyacid, hydroxynitrile (13) led to δ-lactone (41) where the carbinol atom configuration is found by determining methyl group orientation at the carbinol atom in a six-membered cycle. There are two isomeric lactones (41) and (42). We have carried out molecular mechanics calculations[8] for lactone molecules (41) and (42) using the MMX program. For lactone (41), two stable six-membered half-chair conformations were found to be possible: (41a) and (41b), the (41a) conformation with an axial methyl group being 3.64 kcal/mol more stable (Fig. 3). For the lactone epimer (42), however, there is only one stable conformation (42a). In the attempted calculations of the conformation of (42b), the energy minimization procedure again led to isomer (42a). After that we have calculated the spin-spin coupling constant values ^3J(HH) according to a previously reported procedure[9] using the refined geometry of conformation isomers (41a,b) and (42a). The results are summarized in Table 2. Comparison of the calculated and experimental parameters unambiguously shows that the lactone formed from hydroxynitrile (13) has an (*S*)-configuration of the carbinol carbon. Thus, similarly to other yeast reduction products (9-12), hydroxynitrile (13) also has an (*S*)-configuration of the novel asymmetric carbon atom.



(40) (41) (42)

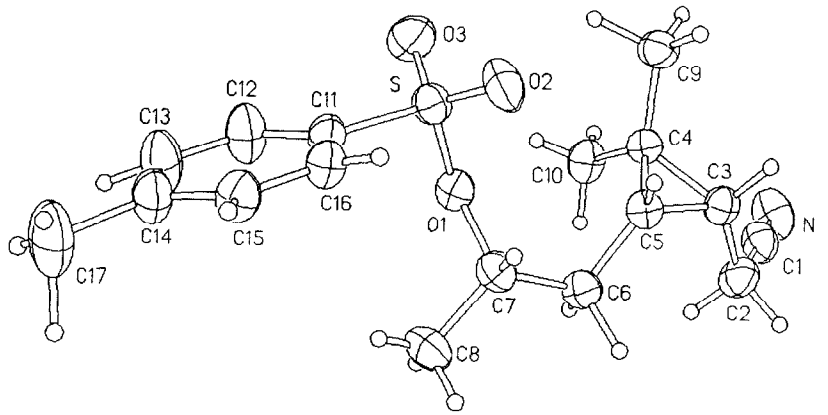
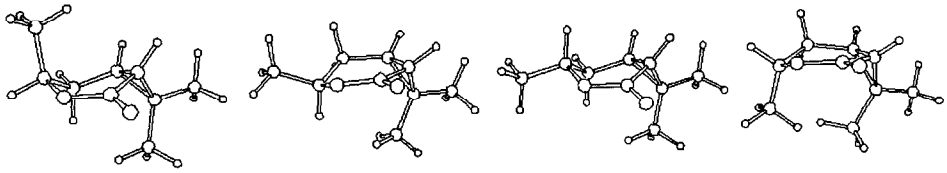


Figure 2. Molecular structure of (*1R,3S*)-2,2-dimethyl-3-[(*2S*)-2-(*p*-toluenesulfonyloxy)-propyl]cyclopropaneacetonitrile (**40**), 30% probability ellipsoids.



(41a) (41b) (42a) (42b)

Table 2. Calculated and experimental ^1H n.m.r. data for lactones (**41**) and (**42**).

	(41a)	(41b)	(42a)	(42b)	(41)	(42)
steric energy (*kcal/mol*)[a]	24.11	27.75	23.95	unstable		
population, % (25°C)	99.8	0.2	100	0		
			$^3J(H^i\text{-}H^j)$, Hz			
			calculated[b]		experimental	
$J(H^2\text{-}H^{3\alpha})$	4.9	5.8	10.8		5.6	11.8
$J(H^2\text{-}H^{3\beta})$	2.8	10.1	3.2		2.6	3.1
$J(H^4\text{-}H^{3\alpha})$	4.5	1.7	4.5		5.0	5.0
$J(H^4\text{-}H^{3\beta})$	9.1	4.3	9.1		9.0	9.9

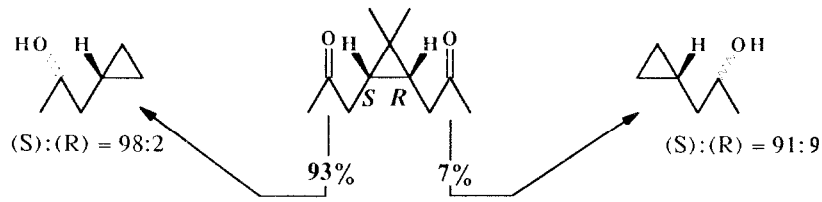
[a] according to the molecular mechanics calculations (MMX program);

[b] based on specified geometry as described earlier[9].

The keto derivative (**19**) being an enantiomer of ketone (**5**) is also reduced by yeast to alcohols, with the (*S*)-isomer being predominant. The main product of reduction of ketones (**19**) is compound (**20**) whose ^{13}C n.m.r. spectrum coincides with that of compounds (**15**). In this case, however, the diastereoselectivity is appreciably lower, the product ratio being: (**20**):(**21**) = 88:12. Moreover, for compound (**19**) the reduction is ca. 3.5 times as slow as for enantiomer (**5**), as seen from Figure 1.

As mentioned above, the content of (*R*)-isomers (**9**, **11-13**) in the reductions of keto derivatives (**4,5,7,8**) is as low as 2%, except for the products of diketone (**6**) reduction. The reduction of diketone (**6**) by yeast leads to a hydroxyketone whose ^{13}C n.m.r. spectrum shows two signal sets of two diastereomers with intensity ratio 92:8; the main component corresponds to hydroxyketone (**11**) formed in the Grignard reaction of hydroxynitrile (**9**) with methylmagnesium iodide. Hydroxyketone (**11**) produced from hydroxynitrile (**9**) has $[\alpha]$ + 23.7 , while the authentic 1:1.1 mixture of epimers (**11** + **16**) prepared according to Scheme 2 has $[\alpha]$ + 13.9 . Thus, the specific rotation of epimer (**16**) should equal approximately $[\alpha]$ + 5.0 . Compound (**3**) is an achiral diketone where both keto groups may be reduced. The first keto group attached to (*S*)-carbon of the cyclopropane unit leads to epimers (**11**) and (**16**), whereas the second keto group attached to (*R*)-carbon of the cyclopropane unit should lead to epimers (-)-(**11**) and (-)-(**16**). Yeast reduction of diketone (**6**) gave

hydroxyketone ([∝] + 21.5) with the ratio [(**11**) + (-)-(**11**)] : [(**16**) + (-)-(**16**)] = 92:8 found from the ^{13}C n.m.r. spectrum. One may expect the same selectivity (*S*):(*R*) = 98:2 of the reduction of the keto group attached to (*S*)-carbon of cyclopropane of diketone (**6**) as that found for compounds (**4,5,7,8**). If so, it will be easy to calculate the stereoselectivity (*S*):(*R*) = 91:9 of the reduction of another keto group (attached to (*R*)-carbon of the cyclopropane unit) of (**6**):



This is in good agreement with the results of yeast reduction of the enantiomeric pair (**5**) and (**19**).

We have also tried yeast reduction for 7 more keto-derivatives of related structure (**22-28**) (Scheme 1) but no appreciable reductions followed, as shown by GLC using authentic samples of the corresponding hydroxy derivatives. Compounds (**22-24**) were isolated unchanged. In incubation with yeast of dioxolane derivatives (**25**) and (**26**), the dioxolane protection was partially removed, giving rise to impurity of diketone (**6**) and its reduction products. Enantiomeric ketones (**27**) and (**28**) seemed to be bound irreversibly with yeast cells or utilized by yeast giving much more polar undetermined compounds instead of expected alcohols (**35a,b**).

Differences in the behaviour of some synthesized ketones in their reduction by yeast may be associated with peculiarities in the structure of these derivatives. Thus, compound (**24**) is a derivative of cyclopropyl methyl ketone, as opposed to all other compounds synthesized which are derivatives of cyclopropylmethyl methyl ketone. The ketone (**24**) is certainly sterically more hindered than the rest compounds, and some sterically hindered ketones are known to be unreactive with yeast[6,10]. Moreover, in contrast to the readily reduced compounds (**4-8**), the derivatives (**22, 23, 25, 26**) have at C-2 atom of the cyclopropane unit a bulky substituent, the 2-hydroxy-2-methylpropyl group [compounds (**22**), (**23**)] or 2-methyl-1,3-dioxolan-2-ylmethyl group [compounds (**25**), (**26**)]. Just the presence of such bulky substituents in a molecule may be the reason of the fact that these compounds are not appreciably reduced by yeast. Though it should be noted for the sake of justice that the effective size of substituent at C-2 of the cyclopropane unit in the series of cyclopropane derivatives studied is not the only factor affecting the rate of yeast reduction. Thus, the effective size of substituent at C-2 in compounds (**4**) and (**8**) is smaller than in compounds (**5**) and (**6**), but the latter two compounds are reduced markedly more readily.

The hydrolyzing activity of baker's yeast is well known, and the reaction of ester hydrolysis is the usual synthetic method[6,11]. But we did not find the products of ester group hydrolysis for compounds (**5**) and (**19**). As a rule, ethers are not hydrolysed by yeast, and the acetal and ketal protections are widely used in yeast reduction[12]. At the same time, removal of acetal protection by yeast was described[13], so a partially removal of the ethylene ketal protection in the process of incubation of compounds (**25**) and (**26**) with yeast is not too surprising.

As for simple ketones (**27**) and (**28**) having the keto group as the only functional group in the molecule, they behave in a different way as compared to all the rest compounds which we studied: in 1h after the substrate emulsion had been added to yeast suspension, neither the starting material nor the reduction products could be detected in any appreciable amount using standard isolation technique (extraction of supernatant with diethyl ether at room temperature). Having employed a more vigorous isolation procedure (refluxing of the reaction mixture with ether without preliminary centrifugation), we isolated in poor yield a mixture of unidentified compounds much more polar than the expected reduction product.

Despite the fact that the derivatives of type (**37a,b**), (**36a,b**), (**35a,b**) and (**39a,b**) were not obtained as diastereomerically pure products of yeast reduction of the corresponding ketones, at least three epimer pairs, (**37a,b**), (**35a,b**) and (**39a,b**) could be unambiguously assigned the (*R*)- and (*S*)-isomer signals in n.m.r spectra. As seen from Table 1, there are quite definite differences in resonance positions of carbons **C**-1, **C**-2, **C**-3, **C**-4 and **C**-5 for the (*R*)- and (*S*)-isomers, which allow one possible to make assignments in the spectra of mixtures of compounds (**37a,b**), (**35a,b**) and (**39a,b**) (see **Experimental**).

Experimental

General experimental procedures - All the solvents used were reagent quality. Petroleum ether refers to that fraction which boils in the range 40-70°C and was redistilled prior to use. Diethyl ether was freshly distilled. Removal of all solvents was carried out under reduced pressure and all commercial reagents were used without additional purification. Analytical TLC plates were **Silufol** (Czecho-Slovakia). Analytical GLC was performed on a **Chrom-5** instrument (Czecho-Slovakia) equipped with a quartz capillary column (20mx0.2mm, 0.5μm cross-linked SE-30). Preparative column chromatography was performed on SiO_2 ("KSK", Russia, 100-200mesh, air dried and activated at 140°C for 5h) using mixtures of Et_2O and petroleum ether as eluents. ^1H and ^{13}C n.m.r. spectra were obtained as $CDCl_3$ solutions (unless otherwise stated) using a **Bruker AC-200** instrument (^1H-200.13MHz, ^{13}C-50.32MHz) with a solvent signal as internal standard: δ_H 7.24 ppm and δ_C 76.90 ppm (numbering scheme is given in Table 1). ^1H n.m.r. spectra of lactones (**41**) and (**42**) were obtained using a **Bruker AM-400** instrument (400.13MHz). I.r. spectra were obtained as CCl_4 solutions (unless otherwise stated) using a **Specord M-80** infrared spectrophotometer. A **Polamat A** polarimeter was used to measure optical rotation at 580 nm. Melting points were obtained using a **Kofler** melting point apparatus and are uncorrected. Microanalyses were obtained using a **Hewlett Packard 185** analyser and a **Carlo Erba 1106** analyser. Mass spectra were obtained on a **Finnigan MAT 8200** instrument using the Electron Impact Ionisation technique (140°C, 70eV).

Reduction of cyclopropane derivatives by baker's yeast.

General kinetic measurement procedure - Industrial yeast (10g of wet-packed frozen yeast GOST 171-81 by the Novosibirsk Yeast Plant, Novosibirsk, Russia) was suspended at room temperature in a solution of glucose (20g) in distilled water (100ml). The substrate (10mmol) was emulsified in a

solution of emulsifier (0.05g of $C_nH_{2n+1}C_6H_4O(C_2H_4O)_mH$, n = 10÷12, m = 6÷7) in the mixture of ethanol (1ml) and water (9ml). The yeast suspension and the substrate emulsion were placed into the bench-scale mechanically-agitated batch fermenter which was maintained at 37.0°C. After a certain period of time, a portion (1ml) of the reaction mixture was extracted with Et_2O (5ml), the ethereal solution was dried ($MgSO_4$) and concentrated at reduced pressure to an oily product which was then analysed by GLC. The conversion degree of the starting ketone (see Fig. 1) was determined as a ratio of the square of reduction product peak to the total square of peaks of the starting ketone and reduction product.

General preparative procedure - Yeast (100g) was suspended in a solution of glucose (100g) in water (500ml), and this suspension was kept at room temperature for 1h. An emulsion of substrate (2.0g) in a solution of the emulsifier (0.2g) and ethanol (1ml) in water (9ml) was added to the suspension of yeast and mixed by shaking manually several times. After 1 day, the gas production stopped, so more glucose (50g) was added and incubation was continued for a day. After 1 day, a new portion of glucose (50g) was added and incubation was continued for a day. The reaction mixture was centrifugated at 2000x*g* for 30min., and the supernatant was saturated with **NaCl** and extracted with Et_2O (3x100ml). The combined ethereal solutions were washed with brine (50ml), dried ($MgSO_4$) and concentrated to give the crude product which was chromatographed on a silica gel column to afford the unreacted ketone and corresponding hydroxy derivative:

starting material		reduction product		
ketone	*g*	crude product, *g*	ketone, *g*	resultant alcohol, *g*
(4)	1.00	1.30	0.55	0.30
(5)	1.00	1.22	0.07	0.66
(6)	1.00	1.31	0.22	0.52
(7)	0.50	0.56	0.35	0.083
(8)	1.00	1.10	0.49	0.42
(19)	0.20	0.23	0.13	0.052

Reduction of compounds **(1,2,3,22,23,24)** failed and the starting ketones were isolated in 80-90% yield.

Incubation of compounds **(25,26)** with yeast gave no reduction of the starting ketones which were isolated in 70-80% yield. The crude product was shown to contain a number of impurities, diketone **(6)** and its reduction products **(11,16)** being predominant (GLC, TLC).

Incubation of compounds **(27,28)** resulted in disappearance of the starting ketones and the crude products (5-15% yield) contained a number of polar compounds together with traces of the starting materials (GLC, TLC).

(1R,3S)-2,2-Dimethyl-3-[(2S)-2-hydroxypropyl]cyclopropaneacetonitrile **(9)**: $[\alpha]^{22}$ + 7.9 (*c* 5.31 in $CHCl_3$); δ_H 0.65 (1H, *m*, H-4), 0.79 (1H, *m*, H-8), 0.88 (3H, *s*, H-7), 0.99 (3H, *s*, H-6), 1.10

(3H, *d*, J 6.2Hz, H-1), 1.31 (2H, *m*, H-3), 2.17 (2H, *d*, J 8.5Hz, H-9), 3.74 (1H, *tq*, J 6.2 and 6.2Hz, H-2); *m/z* 167 (M^+). ^1H and ^{13}C n.m.r. spectroscopy of the product indicated impurity of <2% of the epimer (**16**).

(1R,3S)-2,2-Dimethyl-3-[(2S)-2-(p-toluenesulfonyloxy)propyl]cyclopropaneacetonitrile (**40**). Hydroxynitrile (**9**) [250mg, 1.5mmol, prepared by yeast reduction of ketonitrile (**4**)] was treated with **TsCl** in benzene in the presence of Et_3N followed by chromatography of the crude product affording the *title compound* (415mg, 86%), m.p. 58-59°C (petroleum ether-**EtOAc**); $[\alpha]^{28}$ -19.0 (*c* 2.84 in $CHCl_3$); (Found: C 63.7; H 7.3; N 4.4; S 9.8. $C_{17}H_{23}NO_3S$ requires C 63.5; H 7.2; N 4.4; S 10.0%); $\nu_{max.}$ (in KBr) 2235 (**CN**), 1365 and 1180 (**S=O**) cm^{-1}; n.m.r data (numbering scheme is as given in Table 1): δ_H 0.57 (1H, *ddd*, J 8.8, 6.9, 6.9Hz, H-4), 0.75 (1H, *ddd*, J 8.8, 7.7, 7.7Hz, H-8), 0.88 (3H, *s*, H-7), 1.00 (3H, *s*, H-6), 1.21 (3H, *d*, J 6.2Hz, H-1), 1.52 (2H, *m*, H-3), 2.15 (2H, *m*, H-9), 2.41 (3H, *s*, CH_2Ar), 4.60 (1H, *tq*, J 6.2 and 6.2Hz, H-2), 7.31 (2H, *d*, J 8.1Hz, H-Ar), 7.76 (2H, *d*, J 8.1Hz, H-Ar); δ_C 13.15 t (C-9), 14.24 q (C-7), 17.68 s (C-5), 20.28 q (C-1), 21.39 q (CH_3-Ar), 21.50 d (C-8), 21.90 d (C-4), 27.93 q (C-6), 30.97 t (C-3), 79.56 d (C-2), 119.24 s (C-10), 127.56 d, 129.63 d, 134.26 s and 144.47 s (C-Ar).

Crystal data for (**40**): $C_{17}H_{23}NO_3S$, M = 321.43, orthorhombic, space group $P2_12_12_1$, a = 7.420(1), b = 8.462(2), c = 27.868(6) Å. Crystal dimensions 0.28x0.39x0.47 mm^3, V = 1749.8(4) $Å^3$, Z = 4, D_c = 1.22 g/cm^3, μ = 1.7 mm^{-1}, F(000) = 688, Syntex-P2 diffractometer with graphite-monochromated **Cu** K_α radiation, λ = 1.54178 Å. Of 1539 measured intensities (Θ-2Θ scan, 2Θ < 120°), 1429 were considered observed (F > 4σ). After absorption correction, the structure was solved using SHELX86, refinement was carried out using SHELX76 by full-matrix least-squares procedures (all non-H atoms anisotropic, H atoms isotropic). The final R and R_w values are 0.0400 and 0.0450, S = 0.95, $w^{-1} = \sigma^2 + 0.0035\ F^2$. Refinement of the enantiomeric structure afforded R = 0.0487, R_w = 0.0575, S = 1.27, so the absolute configuration of sulfonate (**40**) corresponds to that shown in Figure 2. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited in the Cambridge Crystallographic Data Centre.

Methyl (1R,3S)-2,2-Dimethyl-3-[(2S)-2-hydroxypropyl]cyclopropaneacetate (**10**): $[\alpha]^{22}$ +5.0 (*c* 4.02 in $CHCl_3$), δ_H 0.57 (1H, *ddd*, J 8.8, 6.9, 6.9Hz, H-4), 0.80 (1H, *ddd*, J 8.8, 7.2, 7.2Hz, H-8), 0.83 (3H, *s*, H-7), 0.99 (3H, *s*, H-6), 1.11 (3H, *d*, J 6.2Hz, H-1), 1.31 (2H, *m*, H-3), 2.16 (2H, *m*, H-9), 3.59 (3H, *s*, CH_3OOC-), 3.74 (1H, *tq*, J 6.2 and 6.2Hz, H-2); *m/z* 200 (M^+). ^1H and ^{13}C n.m.r. spectroscopy of the product indicated impurity of <2% of the epimer (**15**).

A solution of hydroxynitrile (**9**) [20mg, 0.12mmol, prepared by yeast reduction of ketonitrile (**4**)] and **KOH** (50 mg, 0.89mmol) in a mixture of water (0.5ml) and ethylene glycol (2.0ml) was refluxed for 20 min, diluted with water (10ml) and washed with Et_2O (5ml). The aqueous phase was acidified with 1N **HCl** (1ml) and extracted with Et_2O (5ml). The ethereal extract was dried ($MgSO_4$), treated with an excess of ethereal solution of CH_2N_2, and evaporated to give an oily product (30mg). Column chromatography of the crude product afforded the *title compound* (17mg,

71%): $[\alpha]^{25}$ + 4.0° (*c* 3.01 in **$CHCl_3$**). ^1H and ^{13}C n.m.r. spectra of the product were identical with those of the product obtained by yeast reduction of ketoester (**5**).

Methyl (1S,3R)-2,2-Dimethyl-3-[(2S)-2-hydroxypropyl]cyclopropaneacetate (**20**): $[\alpha]^{22}$ + 10.9 (*c* 5.34 in **$CHCl_3$**). ^1H and ^{13}C n.m.r. spectroscopy of the product indicated impurity of 12% of the epimer (**21**).

(1R,3S)-2,2-Dimethyl-3-[(2S)-2-hydroxypropyl]-1-(2-oxopropyl)cyclopropane (**11**): $[\alpha]^{22}$ + 21.5 (*c* 5.12 in **$CHCl_3$**); δ_H 0.59 (1H, *ddd*, J 8.8, 6.9, 6.9Hz, H-4), 0.78 (1H, *ddd*, J 8.8, 7.0, 7.0Hz, H-8), 0.82 (3H, *s*, H-7), 1.00 (3H, *s*, H-6), 1.11 (3H, *d*, J 6.2Hz, H-1), 1.29 (2H, *m*, H-3), 2.08 (3H, *s*, H-11), 2.27 (2H, *d*, J 7.0Hz, H-9), 3.72 (1H, *tq*, J 6.2 and 6.2Hz, H-2); *m/z* 184 (M^+). ^1H and ^{13}C n.m.r. spectroscopy of the product indicated impurity of 8% of the epimer (**16**).

Grignard reaction of hydroxynitrile (**9**) [100mg, 0.60mmol, prepared by yeast reduction of ketonitrile (**4**)] with **MeMgI** (**C_6H_6**, reflux, 4h) afforded the *title compound* (85mg, 77%, after chromatography of the crude product): $[\alpha]^{19}$ + 23.7° (*c* 5.73 in **$CHCl_3$**).

(1R,3S)-2,2-Dimethyl-3-[(2S)-2-hydroxypropyl]-1-(2-hydroxyethyl)cyclopropane (**12**): $[\alpha]^{23}$ + 6.8 (*c* 6.01 in **$CHCl_3$**); δ_H 0.48 (2H, *m*, H-4,8), 0.87 (3H, *s*, H-7), 1.00 (3H, *s*, H-6), 1.16 (3H, *d*, J 6.0Hz, H-1), 1.38 (2H, *m*, H-3), 1.46 (2H, *q*, J 6.8Hz, H-9), 2.65 (1H, *br s*,OH), 3.60 (2H, *t*, J 6.8Hz, H-10), 3.82 (1H, *tq*, J 6.0 and 6.0Hz, H-2); *m/z* 172 (M^+). ^1H and ^{13}C n.m.r. spectroscopy of the product indicated impurity of <2% of the epimer (**17**).

Reduction of hydroxyester (**10**) (100mg, 0.50mmol) with an excess of **$LiAlH_4$** (THF, reflux, 3h) afforded the *title compound* (66mg, 77%, after chromatography of the crude product): $[\alpha]^{19}$ + 7.2 (*c* 3.90 in **$CHCl_3$**).

(1R,3S)-2,2-Dimethyl-3-[(2S)-2-hydroxypropyl]cyclopropanecarbonitrile (**13**): $[\alpha]^{23}$ + 12.5 (*c* 9.29 in **$CHCl_3$**); δ_H 1.09 (3H, *s*, H-7), 1.14 (3H, *s*, H-6), 1.15-1.30 (2H, *m*, H-4,8), 1.18 (3H, *d*, J 6.2Hz, H-1), 1.45 (1H, *m*, H-3a), 1.65 (1H, *m*, H-3b), 2.2 (1H, *br s*,OH), 3.86 (1H, *m*, H-2); *m/z* 153 (M^+). ^1H and ^{13}C n.m.r. spectroscopy of the product indicated impurity of <2% of the epimer (**18**).

(1R,4S,6S)-4,7,7-Trimethyl-3-oxabicyclo[4.1.0]heptan-2-one (**41**) and *(1R,4R,6S)-4,7,7-trimethyl-3-oxabicyclo[4.1.0]heptan-2-one* (**42**). Hydrogen peroxide (30%, 1ml) was added dropwise to a boiling solution of a mixture of hydroxynitriles (**13** + **18**) (74mg, 0.48mmol) and **KOH** (85g, 1.5mmol) in a mixture of **EtOH** (2ml) and water (1ml). The reaction mixture was refluxed for 10h. Ethanol was evaporated and the resultant mixture was diluted with **H_2O** (2ml) and washed with **Et_2O** (2ml). The aqueous phase was acidified with 1N aq.**HCl** (pH 1) and extracted with **Et_2O** (2x2ml). The combined ethereal extracts were dried (**$MgSO_4$**) and evaporated to leave a yellowish oil which was then dissolved in benzene (2ml). *p*-**TsOH** (1mg) was added and the reaction mixture was heated at

reflux in a Dean-Stark water separator (30min). Evaporation of solvent followed by chromatography of the crude product afforded the mixture of lactones (**41**) and (**42**) (1:1.4, according to ^{1}H n.m.r. spectrum) (31mg, 42%), $[\alpha]^{23}$ + 64.6 (*c* 5.36 in $CHCl_3$); $\nu_{max.}$ 1738 (C=O); ^{1}H n.m.r. data [400 MHz, in C_6D_6, o(C_6D_5H) 7.25 ppm], for (**41**): δ_H 0.75 (1H, *ddd*, J 9.0, 8.0, 4.9Hz, H-4), 0.86 (3H, *s*, H-7), 0.98 (3H, *s*, H-6), 1.09 (3H, *dd*, J 6.6, 0.5Hz, H-1), 1.19 (1H, *ddd*, J 15.0, 9.0, 2.6Hz, H-3), 1.35 (1H, *d*, J 8.0Hz, H-8), 1.50 (1H, *dddq*, J 15.0, 5.6, 4.9, 0.5Hz, H-3), 4.10 (1H, *qdd*, J 6.6, 5.6, 2.6Hz, H-2); for (**42**): δ_H 0.88 (1H, *ddd*, J 9.8, 8.0, 5.0Hz, H-4), 0.88 (3H, *s*, H-7), 0.98 (3H, *s*, H-6), 1.00 (3H, *d*, J 6.2Hz, H-1), 1.05 (1H, *ddd*, J 15.0, 11.8, 5.0Hz, H-3), 1.27 (1H, *d*, J 8.0Hz, H-8), 1.38 (1H, *ddd*, J 15.0, 9.8, 3.1Hz, H-3), 3.82 (1H, *qdd*, J 6.2, 11.8, 3.1Hz, H-2); ^{13}C n.m.r. data, for (**41**): δ_C 16.10 *q* (C-7), 21.37 *q* (C-1), 22.02 *d* (C-4), 23.83 *t* (C-3), 24.52 *d* (C-8), 25.72 *s* (C-5), 27.56 *q* (C-6), 75.68 *d* (C-2), 171.20 *s* (C-9); for (**42**): δ_C 16.08 *q* (C-7), 20.22 *q* (C-1), 23.50 *d* and 24.30 *d* (C-4,8), 24.94 *s* (C-5), 26.44 *t* (C-3), 27.18 *q* (C-6), 77.24 *d* (C-2), 171.18 *s* (C-9).

(1R,4S,6S)-4,7,7-Trimethyl-3-oxabicyclo[4.1.0]heptan-2-one (**41**). Hydrolysis and lactonization of hydroxynitrile (**13**) (65mg, 0.44mmol) afforded the *title compound* (22mg, 32%) as a colorless oil, $[\alpha]^{18}$ + 88.2 (*c* 1.30 in $CHCl_3$); *m/z* 154 (M^+).

Preparation of the starting materials for bioreduction.

3-Acetyl-2,2-dimethylcyclobutaneacetonitrile (**1**), *3-(3-cyano-1-methylenepropyl)-1,1-dimethyl-2-(3-oxobutyl)cylobutane* (**2**), *3-(1-methyl-1-ethenyl)-6-oxoheptanenitrile* (**3**) and *(1R,3S)-2,2-dimethyl-3-(2-oxopropyl)cyclopropaneacetonitrile* (**4**) with $[\alpha]^{23}$ -12.7 (*c* 3.77 in $CHCl_3$) were prepared as described earlier[5]. *Methyl (1R,3S)-2,2-dimethyl-3-(2-oxopropyl)cyclopropaneacetate* (**5**) with $[\alpha]^{23}$ - 20.3 (*c* 5.51 in $CHCl_3$) was synthesized according to the work[7].

(1R,3S)-2,2-Dimethyl-3-(2-hydroxy-2-methylpropyl)-1-(2-oxopropyl)cyclopropane (**23**). To a stirred solution of MeMgI (30mmol) in a mixture of Et_2O (10ml) and benzene (40ml), a solution of ketonitrile (**4**) (1.65g, 10mmol) in benzene (10ml) was added dropwise. The mixture was stirred under reflux for 5h. Water (5ml) and 1N aq.HCl (45ml) were added dropwise. The organic phase was washed with 0.5N aq.Na_2CO_3 (10ml), brine (10ml), dried ($MgSO_4$) and evaporated to leave a yellowish oil (1.81g). The crude product was chromatographed to give the *title compound* (1.32g, 67%): $[\alpha]^{22}$ + 17.8 (*c* 5.13 in $CHCl_3$) {lit.[14] $[\alpha]_D^{30}$ + 41 (*c* 1.92%, $CHCl_3$)}; $\nu_{max.}$ (1% in $CHCl_3$) 3600 (O-H), 1710 (C=O) cm^{-1}; δ_H 0.62 (1H, *ddd*, J 9.0, 6.5, 6.5Hz, H-4), 0.77 (1H, *m*, H-8), 0.79 (3H, *s*, H-7), 1.01 (3H, *s*, H-6), 1.14 (6H, *s*, H-11,12), 1.28 (2H, *m*, H-3), 2.0 (1H, br s, OH), 2.07 (3H, s, H-1), 2.24 (2H, *d*, J 6.5 Hz, H-9); δ_C 15.15 *q* (C-7), 16.52 *s* (C-5), 20.90 *s* and 21.58 *s* (C-4,8), 28.50 *q* (C-6), 28.56 *q* (C-11), 29.44 *q* (C-1), 29.53 *q* (C-12), 37.94 *t* (C-9), 39.38 *t* (C-3), 70.51 *s* (C-10), 209.03 *s* (C-2); *m/z* 198 (M^+).

(1S,3R)-2,2-Dimethyl-3-(2-hydroxy-2-methylpropyl)-1-[(2RS)-2-hydroxypropyl]cyclopropane (**39a,b**). Reaction of hydroxyester (**10** + **15**) (2.00g, 10mmol) with **MeMgI** (30mmol) was carried out as described above for the preparation of hydroxyketone (**23**). Chromatography of the crude product (1.60g) afforded a mixture (*ca.* 1.1:1, according to ^{1}H n.m.r. spectrum) of epimeric diols (**39a**) and (**39b**) (1.20g, 60%): $[\alpha]^{21}$ -2.2 (*c* 2.72 in **CHCl$_3$**); (Found: **C** 72.4; **H** 12.0. **$C_{12}H_{24}O_2$** requires **C** 72.0; **H** 12.1%); $\nu_{max.}$ 3615 (**O-H**) cm^{-1}; *m/z* 200 (M^+); n.m.r. data for (**39a**) [(*S*)-isomer]: δ_H 0.5 (**2H**, *m*, **H-4,8**), 0.85 (**3H**, *s*, **H-7**), 1.01 (**3H**, *s*, **H-6**), 1.15 (**3H**, *d*, J 6.0Hz, **H-1**), 1.18 (**6H**, *s*, **H-11,12**), 1.3 (**4H**, *m*, **H-3,9**), 2.15 (**2H**, *br s*, **OH**), 3.63 (**H**, *dq*, J 6.0, 6.0Hz, **H-2**); δ_C 15.48 *q* (**C-7**), 16.59 *s* (**C-5**), 21.77 *d* (**C-8**), 22.14 *d* (**C-4**), 22.81 *q* (**C-1**), 28.73 *q* (**C-11**), 28.91 *q* (**C-6**), 29.67 *q* (**C-12**), 33.90 *t* (**C-3**), 38.09 *t* (**C-9**), 67.91 *d* (**C-2**), 70.86 *s* (**C-10**); for (**39b**) [(*R*)-isomer]: δ_H 0.5 (**2H**, *m*, **H-4,8**), 0.82 (**3H**, *s*, **H-7**), 1.02 (**3H**, *s*, **H-6**), 1.16 (**3H**, *d*, J 6.0Hz, **H-1**), 1.18 (**6H**, *s*, **H-11,12**), 1.3 (**4H**, *m*, **H-3,9**), 2.15 (**2H**, *br s*, **OH**), 3.61 (**H**, *dq*, J 6.0, 6.0Hz, **H-2**); δ_C 15.40 *q* (**C-7**), 16.07 *s* (**C-5**), 21.71 *d* (**C-8**), 23.31 *d* (**C-4**), 23.41 *q* (**C-1**), 28.54 *q* (**C-11**), 28.91 *q* (**C-6**), 30.20 *q* (**C-12**), 33.90 *t* (**C-3**), 37.84 *t* (**C-9**), 68.77 *d* (**C-2**), 70.86 *s* (**C-10**).

(1S,3R)-2,2-Dimethyl-3-(2-hydroxy-2-methylpropyl)-1-(2-oxopropyl)cyclopropane (**22**). To a stirred solution of a mixture of diols (**39a,b**) (0.65g, 3.2mmol) in acetone (20ml), powdered **CrO_3** (0.35g, 3.5mmol) was added portionwise, and stirring was continued at room temperature for 1h. The reaction mixture was diluted with petroleum ether (20ml) and the resultant mixture was percolated through a silica gel column (10x0.5cm). The eluate was evaporated to leave a yellow oil (0.47g). The crude product was chromatographed to give the *title compound* (0.32g, 50%): $[\alpha]^{21}$ -17.1° (*c* 6.67 in **CHCl$_3$**). I.r., ^{1}H and ^{13}C n.m.r. spectra of the product were identical with those of the enantiomer (**23**).

(1R,3S)-2,2-Dimethyl-3-propylcyclopropaneacetonitrile (**32**). To a stirred mixture of ketonitrile (**4**) (1.65g, 10mmol), **EtOH** (30ml) and amalgamated zinc dust (20g), conc. aq. **HCl** (20ml) was added, and stirring was continued for 1h. The reaction mixture was kept under reflux for 4h. The reaction mixture was extracted with petroleum ether (2x50ml), the combined extracts were dried (**$MgSO_4$**) and concentrated to leave a colourless oil (1.20g). The crude product was chromatographed to give the *title compound* (0.72g, 48%): $[\alpha]^{22}$ + 2.6 (*c* 8.70 in **CHCl$_3$**); (Found: **C** 79.3, **H** 11.3, **N** 9.6. **$C_{10}H_{17}N$** requires **C** 79.4; **H** 11.3, **N** 9.3%); $\nu_{max.}$ 2243 (**CN**) cm^{-1}; n.m.r. data: δ_H 0.55 (**1H**, *ddd*, J 8.9, 6.9, 6.9Hz, **H-4**), 0.77 (**1H**, *m*, **H-8**), 0.86 (**3H**, *t*, J 7.0Hz, **H-1**), 0.91 (**3H**, *s*, **H-7**), 1.01 (**3H**, *s*, **H-6**), 1.1-1.4 (**4H**, *m*, **H-2,3**), 2.19 (**2H**, *d*, J 7.3Hz, **H-9**); δ_C 12.95 *t* (**C-9**), 13.63 *q* (**C-1**), 14.01 *q* (**C-7**), 17.27 *s* (**C-5**), 21.63 *d* (**C-8**), 22.68 *t* (**C-2**), 25.70 *t* (**C-3**), 26.00 *d* (**C-4**), 28.22 *q* (**C-6**), 119.66 *s* (**C-10**); *m/z* 151 (M^+).

(1R,3S)-2,2-Dimethyl-1-(2-oxopropyl)-3-propylcyclopropane (**28**). Reaction of nitrile (**32**) (1.20g, 7.9mmol) with **MeMgI** (9mmol) in benzene (50ml) (3h at reflux) followed by chromatography of

crude product (1.10g) afforded the *title compound* (0.90g, 68%): $[\alpha]^{20}$ + 11.9 (*c* 3.28 in **$CHCl_3$**); (Found: **C** 78.8, **H** 11.8. **$C_{11}H_{20}O$** requires **C** 78.5; **H** 12.0%); $\nu_{max.}$ 1720 (**C=O**) cm^{-1}; δ_H 0.45 (**1H**, *ddd*, J 9.0, 7.0, 7.0Hz, H-4), 0.75 (**1H**, *ddd*, J 8.9, 7.0, 7.0Hz, **H-8**), 0.84 (**3H**, *s*, H-7), 0.85 (**3H**, *t*, J 7.0Hz, H-1), 1.02 (**3H**, *s*, **H-6**), 1.2 and 1.3 (**2H** *m* and **2H** *m*, H-2,3), 2.28 (**2H**, *d*, J 7.0Hz, **H-9**); δ_C 13.87 *q* (**C-1**), 14.80 *q* (**C-7**), 16.81 *s* (**C-5**), 21.29 *d* (**C-8**), 22.91 *t* (**C-2**), 26.00 *d* (**C-4**), 26.49 *t* (**C-3**), 28.81 *q* (**C-6**), 29.34 *q* (**C-11**), 39.36 *t* (**C-9**), 209.21 *s* (**C-10**); *m/z* 168 (M^+).

(1R,3S)-2,2-Dimethyl-3-(2-methyl-1,3-dioxolan-2-ylmethyl)cyclopropaneacetonitrile (**31**). A mixture of ketonitrile (**4**) (50g, 0.303mol), ethylene glycol (28.2g, 0.454mol), benzene (150ml) and *p*-**TsOH** (0.5g, 2.6mmol) was heated at reflux in a Dean-Stark water separator (**6h**). The organic layer was separated, washed with 0.5N aq.**Na_2CO_3** (30ml) and brine (30ml), dried (**Na_2SO_4**) and evaporated, affording the crude dioxolane (**31**) (58g, 92%) as a brown oil. A portion of this material was chromatographed to give a pure sample of the *title compound* for characterization, $[\alpha]^{19}$ + 32.5° (*c* 10.7 in **$CHCl_3$**); (Found: C 68.8, H 9.1, N 6.7. **$C_{12}H_{19}NO$** requires C 68.9; H 9.2; **N** 6.7%); $\nu_{max.}$ 2250 (**CN**) cm^{-1}; δ_H 0.6-0.8 (2H, *m*, **H-4,8**), 0.94 (**3H**, *s*, **H-7**), 1.05 (**3H**, *s*, **H-6**), 1.28 (**3H**, *s*, H-1), 1.57 and 1.51 (AB-part of ABX system, J_{AB} 13.5Hz, J_{AX} 5.5Hz, J_{BX} 4.8Hz, H-3), 2.29 and 2.11 (AB-part of ABX system, J_{AB} 17.9Hz, J_{AX} 6.8Hz, J_{BX} 7.9Hz, **H-9**), 3.9 (4H, *m*, -**OCH_2CH_2O**-); δ_C 13.41 *t* (**C-9**), 14.34 *q* (**C-7**), 17.17 *s* (**C-5**), 21.48 *d* and 21.65 *d* (**C-4,8**), 23.88 *q* (**C-1**), 28.12 *q* (**C-6**), 33.42 *t* (**C-3**), 64.58 *t* and 64.62 *t* (-**OCH_2CH_2O**-), 109.45 *s* (**C-2**), 119.66 *s* (**C-10**); *m/z* 194 (M^+-CH_3).

(1R,3S)-2,2-Dimethyl-3-(2-methyl-1,3-dioxolan-2-ylmethyl)cyclopropaneacetamide (**29**). A solution of **NaOH** (13.3g, 0.333mol) in water (133ml) was added to a solution of the crude dioxolane (**29**) (58g, 0.277mol) in methanol (260ml). The addition of 30% **H_2O_2** (133ml) was begun dropwise with vigorous stirring at 25°C. After the temperature has started to rise, the mixture was cooled to 20°C; and the addition of **H_2O_2** was continued at 20-25°C. The mixture was then stirred for 1h at 20°C, saturated with **NaCl**, and extracted with ether (300, 2x150ml). The combined ethereal extracts were washed with brine (50ml), dried (**Na_2SO_4**), and evaporated affording the crude amide (**29**) (40g, 63%) as a viscous yellow oil. A portion of the crude product was chromatographed to give a pure sample of the *title compound* for characterization, $[\alpha]^{18}$ -4.5 (*c* 5.18 in **$CHCl_3$**); (Found: C 63.5, H 9.3, N 6.2. **$C_{12}H_{21}NO_3$** requires C 63.4; H 9.3; N 6.2%); $\nu_{max.}$ 3530, 3490, 3415, and 3350 (N-H), 1680 (C=O), 1585 (N-H) cm^{-1}; δ_H 0.75 (2H, *m*, **H-4,8**), 0.87 (3H, *s*, **H-7**), 1.05 (3H, *s*, **H-6**), 1.29 (3H, *s*, **H-1**), 1.55 (2H, *m*, H-3), 2.12 (2H, *d*, J 6.7Hz, **H-9**), 3.90 (4H, *m*, -**OCH_2CH_2O**-), 6.0 (2H, *br.s*, -**NH**); δ_C 14.97 *q* (**C-7**), 16.78 *s* (**C-5**), 21.54 *d* and 22.20 *d* (**C-4,8**), 23.82 *q* (**C-1**), 28.54 *q* (**C-6**), 31.73 *t* (**C-9**), 33.69 *t* (**C-3**), 64.53 *t* (-**OCH_2CH_2O**-), 109.94 *s* (**C-2**), 175.72 *s* (**C-10**); *m/z* 227 (M^+).

(1R,3S)-2,2-Dimethyl-3-(2-methyl-1,3-dioxolan-2-ylmethyl)cyclopropanecarbonitrile (**30**). To a stirred solution of **KOH** (104g, 0.698mol) in water (250ml), Br_2 (112g, 0.698mol) was added dropwise at 15°C. Benzyltriethylammonium chloride (1.5g, 6.6mmol) was added. A solution of the crude amide (27) (39g, 0.172mol) in CH_2Cl_2 (124ml) was then added dropwise at 20-25°C and stirring was continued at the same temperature for 15min, and then under reflux for 1.5h. The organic phase was separated, the water phase was extracted with ether (2x100ml). The combined organic solutions were washed with brine (30ml), dried (Na_2SO_4), and evaporated, affording the crude product (32g, 95%) as a brown liquid. A portion of the crude product was chromatographed to give a pure sample of the *title compound* for characterization, $[\alpha]^{19}$ -22.4 (*c* 1.61 in $CHCl_3$); (Found: C 67.6, H 8.8, N 7.1. $C_{11}H_{17}NO_2$ requires C 67.7, H 8.8; N 7.2%); $\nu_{max.}$ 2241 (CN) cm^{-1}; δ_H 1.14 (3H, *s*, H-7), 1.20 (3H, *s*, H-6), 1.3 (2H, *m*, H-4,8), 1.37 (3H, *s*, H-1), 1.81 (2H, *d*, J 6.0Hz, H-3), 3.95 (4H, *m*, $-OCH_2CH_2O-$); δ_C (CCl_4-$CDCl_3$ 2:1 v/v): 14.73 *q* (C-7), 16.72 *d* (C-8), 23.11 *s* (C-5), 23.82 *q* (C-1), 26.23 *q* (C-6), 26.66 *d* (C-4), 35.15 *t* (C-3), 64.53 *t* ($-OCH_2CH_2O-$), 109.16 *s* (C-2), 118.83 *s* (C-9); *m/z* 180 ($M^+ - CH_3$).

(1R,3S)-2,2-Dimethyl-3-(2-oxopropyl)cyclopropanecarbonitrile (**8**). A mixture of the crude dioxolane (**30**) (39g, 0.20mol), methanol (200ml) and 1N aq.HCl (50ml) was refluxed for 30min. The solvent was evaporated, and brine (100ml) was added. The mixture was extracted with ether (3x100ml), the combined ethereal extracts were dried (Na_2SO_4) and evaporated, affording the crude nitrile (**8**) (30g, 99%). A portion of this material was further purified by chromatography to give a pure sample of the *title compound* for bioreduction and characterization, $[\alpha]^{19}$ -39.1 (*c* 5.27 in $CHCl_3$); (Found: C 71.6, H 8.7, N 9.2. $C_9H_{13}NO$ requires C 71.5; H 8.7; N 9.3%); $\nu_{max.}$ 2240 (CN), 1720 (C=O) cm^{-1}; δ_H 1.12 (3H, *s*, H-7), 1.14 (3H, *s*, H-6), 1.36 (2H, *m*, H-4,8), 2.16 (3H, *s*, H-1), 2.63 (2H, *m*, H-3); δ_C 14.38 *d* (C-8), 16.43 *q* (C-7), 23.17 *s* (C-5), 24.73 *d* (C-4), 26.25 *q* (C-6), 29.81 *q* (C-1), 39.88 *t* (C-3), 118.79 *s* (C-9), 205.76 *s* (C-2); *m/z* 151 (M^+).

(1R,3S)-2,2-Dimethyl-3-(2-methyl-1,3-dioxolan-2-ylmethyl)-1-(2-oxopropyl)cyclopropane (**26**). A solution of the crude dioxolane (29) (6.0g, 29mmol) and MeMgI (42mmol) in benzene (60ml) was refluxed for 1h. Water (1ml) was added dropwise with vigorous stirring. The aqueous saturated $(NH_4)_2SO_4$ (50ml) was added, and the organic layer was separated. The aqueous phase was extracted with ether (2x50ml). The combined organic extracts were washed with 0.5N Na_2CO_3 (30ml) and brine (30ml), dried (Na_2SO_4), and evaporated, affording the crude ketone (28) (6.3g, 96%) as a yellow oil. A portion of the crude product was chromatographed to give a pure sample of the *title compound* for bioreduction and characterization, m.p. 41-43°C (EtOAc), $[\alpha]^{22}$ + 29.7 (*c* 3.70 in $CHCl_3$); (Found: C 69.6; H 9.6. $C_{13}H_{22}O_3$ requires C 69.0; H 9.8%); $\nu_{max.}$ 1720 (C=O) cm^{-1}; δ_H (CCl_4-$CDCl_3$ 2:1 v/v): 0.47 and 0.58 (1H *m* and 1H *m*, H-4,8), 0.62 (3H, *s*, H-7), 0.84 (3H, *s*, H-6), 1.00 (3H, *s*, H-11), 1.25 and 1.20 (AB-part of ABX system, J_{AB} 14.0Hz, $J_{AX} = J_{BX}$ 6.0Hz, H-9), 1.85 (3H, *s*, H-1), 2.10 and 1.95 (AB-part of ABX system, J_{AB} 18.0Hz, J_{AX} 6.5Hz,

J_{BX} 7.0Hz, H-3), 3.61 (4H, *m*, -OCH_2CH_2O-); δ_C (in CCl_4-$CDCl_3$ 2:1 v/v): 14.87 *q* (C-7), 16.16 *s* (C-5), 20.45 *d* and 21.11 *d* (C-4,8), 23.68 *q* (C-11), 28.37 *q* (C-6), 28.84 *q* (C-1), 33.68 *t* (C-9), 38.87 *t* (C-3), 64.02 *t* and 64.07 *t* (-OCH_2CH_2O-), 109.32 *s* (C-10), 205.75 *s* (C-2); *m/z* 226 (M^+).

2,2-Dimethyl-1,3-bis(2-oxopropyl)cyclopropane (**6**). A mixture of the crude dioxolane (**26**) (5.0g, 22mmol), methanol (50ml) and 1N aq.HCl (25ml) was stirred at 50°C for 1h. Brine (150ml) was added, and the mixture was extracted with ether (3x50ml). The combined ethereal extracts were washed with brine (20ml), dried (Na_2SO_4), and evaporated, affording the crude product (3.8g) which was purified by chromatography to give the *title compound* (1.8g, 45%); $\nu_{max.}$ 1720 (C=O) cm^{-1}; δ_C [in CCl_4 - cyclohexane-d_{12} 10:1 v/v, $\delta(CCl_4)$ 97.00ppm]: 15.87 *q* (C-7), 17.76 *s* (C-5), 22.15 *d* (C-4,8), 29.44 *q* (C-6), 29.79 *q* (C-1,11), 39.95 *t* (C-3,9), 206.21 *s* (C-2,10). The ^1H n.m.r. spectrum of the product was identical with that published earlier[15].

(1R,3S)-2,2-Dimethyl-3-[(2RS)-2-hydroxypropyl]-1-(2-oxopropyl)cyclopropane (**11 + 16**). To a stirred solution of MeMgI (0.173mol) in benzene (50ml), a solution of hydroxyitrile (**9 + 14**) (7.44g, 0.045mol) in benzene (20ml) was added dropwise. The mixture was stirred under reflux for 1h. Water (50ml) and 10N aq.HCl (20ml) were added dropwise. The organic phase was separated, the aqueous phase was extracted with ether (3x60ml). The combined organic extracts were washed with 5% aq.KOH (20ml), brine (20ml), dried (Na_2SO_4) and evaporated to leave the crude mixture of epimeric hydroxyketones (**11 + 16**) (7.5g, 91%) as a yellowish viscous oil. A portion of the crude product was chromatographed to give a pure sample of the *title compound*, (*ca.* 1:1.1, according to ^1H n.m.r. spectrum), $[\alpha]^{22}$ +16.7 (*c* 2.75 in $CHCl_3$); (Found: C 71.5; H 10.7. $C_{11}H_{20}O_2$ requires C 71.7; H 10.9%); $\nu_{max.}$ 3636 (O-H), 1722 (C=O) cm^{-1}; δ_H for (**16**): 0.54 (1H, *m*, H-4), 0.77 (3H, *m*, H-8), 0.81 (3H, *s*, H-7), 0.99 (3H, *s*, H-6), 1.10 (3H, *d*, J 6.2Hz, H-1), 1.27 (2H, *m*, H-3), 2.08 (3H, *s*, H-11), 2.29 (2H, *m*, H-9), 3.72 (1H, *tq*, J 6.2 and 6.2Hz, H-2); *m/z* 184 (M^+).

(1S,3R)-2,2-Dimethyl-3-(2-methyl-1,3-dioxolan-2-ylmethyl)-1-[(2RS)-2-hydroxypropyl]cyclopropane (**37a,b**). A mixture of the crude hydroxyketones (**11 + 16**) (7.5g, 41mmol), ethylene glycol (5g, 81mmol), benzene (120ml) and *p*-TsOH (0.5g, 2.6mmol) was heated at reflux in a Dean-Stark water separator (6h). The organic layer was separated, washed with 0.5N aq.Na_2CO_3 (20ml) and brine (20ml), dried (Na_2SO_4) and evaporated affording the crude product (7.5g) as a yellow viscous oil, which was then purified by chromatography to give a mixture of epimeric dioxolanes [(**37a**):(**37b**) = 1:1.3, according to ^1H n.m.r. spectrum) (4.5g, 48%), $[\alpha]^{18}$ -3.5 (*c* 7.96 in $CHCl_3$); (Found: C 68.3, H 10.6. $C_{13}H_{24}O_3$ requires C 68.4; H 10.6%); $\nu_{max.}$ 3625 (O-H) cm^{-1}; n.m.r data for (**37a**) [(*S*)-isomer]: δ_H 0.49 (1H, *m*, H-4), 0.59 (1H, *m*, H-8), 0.81 (3H, *s*, H-7), 0.98 (3H, *s*, H-6), 1.11 (3H, *d*, J 6.0Hz, H-1), 1.29 (3H, *s*, H-11), 1.3 (2H, *m*, H-3), 1.5 (2H, *m*, H-9), 3.8 (1H, *m*, H-2), 3.88 (4H, *s*, -OCH_2CH_2O-); δ_C 15.35 *q* (C-7), 16.58 *s* (C-5), 21.58 *d* (C-8), 21.99

d (C-4), 22.78 *q* (C-1), 23.63 *q* (C-11), 28.81 *q* (C-6), 33.88 *t* and 33.95 *t* (C-3 and C-9), 64.43 *t* (-OCH_2CH_2O-), 67.81 *d* (C-2), 110.28 *s* (C-10); for (37b) [(*R*)-isomer]: δ_H 0.49 (1H, *m*, H-4), 0.59 (1H, *m*, H-8), 0.84 (3H, *s*, H-7), 0.99 (3H, *s*, H-6), 1.13 (3H, *d*, J 6.0Hz, H-1), 1.29 (3H, *s*, H-11), 1.3 (2H, *m*, H-3), 1.5 (2H, *m*, H-9), 3.8 (1H, *m*, H-2), 3.88 (4H, *s*, -OCH_2CH_2O-); δ_C 15.28 *q* (C-7), 16.02 *s* (C-5), 21.39 *d* (C-8), 23.06 *d* (C-4), 23.27 *q* (C-1), 23.75 *q* (C-11), 28.81 *q* (C-6), 33.82 *t* and 33.95 *t* (C-3 and C-9), 64.43 *t* (-OCH_2CH_2O-), 68.59 *d* (C-2), 110.28 *s* (C-10); *m/z* 228 (M^+).

(1S,3R)-2,2-Dimethyl-3-(2-methyl-1,3-dioxolan-2-ylmethyl)-1-(2-oxopropyl)cyclopropane (**25**). To a stirred solution of the crude dioxolane (**37**) (1.57g, 6.9mmol) in DMFA (30ml), powdered CrO_3 (3.0g, 30mmol) was added portionwise at 0°C followed by addition of concentrated H_2SO_4 (0.03g). The reaction mixture was stirred at room temperature for 2h and allowed to stay overnight. The reaction mixture was diluted with water (250ml) and extracted with benzene (100, 2x50, 30ml). The combined organic extracts were washed with a solution of Na_2SO_3 (0.5g) in 1N aq.HCl (50ml), 0.5N aq.Na_2CO_3 (30ml), brine (30ml), dried (Na_2SO_4) and evaporated affording the crude product (1.51g) as a dark oil, which was then purified by chromatography to give the *title compound* (1.20g, 77%), m.p. 43-44°C (EtOAc); $[\alpha]^{18}$ -21.8 (*c* 5.05 in $CHCl_3$). I.r., ^1H and ^{13}C n.m.r. spectra of the product were identical with those of the enantiomer (**26**).

Methyl (1S,3R)-2,2-Dimethyl-3-(2-oxopropyl)cyclopropaneacetate (**19**). A solution of the crude alcohol (**37**) (2.0g, 8.8mmol) in dioxane (5ml) was added dropwise to a stirred solution of NaOBr (5.4g NaOH + 8.1g Br_2) in water (27ml). The reaction mixture was stirred at 80°C for 40min. The neutral products were extracted with diethyl ether (5x20ml). The combined ethereal solutions were evaporated, the residue was dissolved in dioxane (5ml) and this solution was oxidized with a new portion of NaOBr (5.4g NaOH + 8.1g Br_2 + 27ml H_2O). The reaction mixture was washed with diethyl ether (3x20ml). The combined aqueous solutions were treated with Na_2SO_3 (1g), acidified (pH 1) with 1N aq.HCl, saturated with NaCl, and extracted with diethyl ether (3x50ml). The combined organic extracts were washed with brine (30ml), dried (Na_2SO_4) and evaporated affording a viscous oil which was treated with an ethereal solution of CH_2N_2 (2%, 30ml). The resultant ethereal solution was washed with 1N aq.HCl (10ml), 0.5N aq.Na_2CO_3 (20ml), brine (10ml), dried (Na_2SO_4) and evaporated, affording the crude product (0.60g) which was further purified by chromatography to give the *title compound* (0.21g, 12%), $[\alpha]^{22}$ -19.5 (*c* 3.10 in $CHCl_3$). I.r., ^1H and ^{13}C n.m.r. spectra of the product were identical with those of the enantiomer (**5**).

(1R,3S)-2,2-Dimethyl-3-[(2RS)-2-hydroxypropyl]-1-propylcyclopropane (**35a,b**). A mixture of hydroxyketones (**11** + **16**) (1.84g, 10.0mmol) was added to a solution of *p*-toluenesulfonylhydrazide[16] (1.90g, 10.2mmol) in 95% EtOH (50ml), and the mixture was refluxed for 30min. The solvent was evaporated, and the residue was dried in vacuum. $LiAlH_4$ (1.15g, 30mmol) was added portionwise to a solution of the resultant hydrazone in THF (100ml). The reaction mixture was refluxed for 48h.

Methanol (10ml) was added dropwise followed by the addition of 5N aq.**HCl** (50ml). The reaction mixture was extracted (2x100ml) with the 1:1 mixture of petroleum ether and diethyl ether. The combined ethereal extracts were washed with 1N aq.**NaOH** (20ml), brine (50ml), dried (**$MgSO_4$**) and evaporated to leave a yellow oil (1.52g). The crude product was chromatographed to give the *title compound* (0.71g, 42%) [**(35a)**:**(35b)** *ca.* 1.2:1, according to ^1H n.m.r. spectrum), $[\alpha]^{20}$ + 7.4 (*c* 6.08 in **$CHCl_3$**); (Found: C 77.4, H 12.8. **$C_{11}H_{22}O$** requires C 77.6; H 13.0%); $\nu_{max.}$ 3630 (O-H) cm^{-1}; *m/z* 170 (M^+); n.m.r. data for **(35a)** [(*S*)-isomer]: δ_H 0.42 (2H, *m*, H-4,8), 0.83 (3H, *t*, J 7.1Hz, H-11), 0.87 (3H, *s*, H-7), 1.00 (3H, *s*, H-6), 1.15 (3H, *d*, J 6.2Hz, H-1), 1.25-1.45 (6H, *m*, H-3,9,10), 3.78 (1H, *qt*, J 6.2 and 6.2Hz, H-2); δ_C 13.96 *q* (C-11), 15.08 *q* (C-7), 16.71 *s* (C-5), 22.79 *d* (C-4), 22.95 *q* (C-1), 23.12 *t* (C-10), 26.18 *d* (C-8), 26.63 *t* (C-9), 29.18 *q* (C-6), 34.00 *t* (C-3), 68.46 *d* (C-2); n.m.r. data for **(35b)** [(*R*)-isomer]: δ_H 0.42 (2H, *m*, H-4,8), 0.83 (3H, *t*, J 7.1Hz, H-11), 0.83 (3H, *s*, H-7), 1.00 (3H, *s*, H-6), 1.17 (3H, *d*, J 6.2Hz, H-1), 1.25-1.45 (6H, *m*, H-3,9,10), 3.78 (1H, *qt*, J 6.2 and 6.2Hz, H-2); δ_C 13.96 *q* (C-11), 15.02 *q* (C-7), 16.57 *s* (C-5), 22.94 *d* (C-4), 22.98 *q* (C-1), 23.09 *t* (C-10), 26.22 *d* (C-8), 26.73 *t* (C-9), 29.24 *q* (C-6), 34.04 *t* (C-3), 68.79 *d* (C-2).

(1S,3R)-2,2-Dimethyl-3-propyl-1-(2-oxopropyl)cyclopropane (**27**). Oxidation of the mixture (**35a,b**) (0.35g, 2.1mmol) with **CrO_3** (0.25g, 2.5mmol) in acetone (15ml) [as described above for the preparation of the mixture of diols (**39a,b**)] afforded the crude product (0.33g) which was chromatographed to give the *title compound* (0.31g, 88%), $[\alpha]^{22}$ -12.3 (*c* 5.68 in **$CHCl_3$**). I.r., ^1H and ^{13}C n.m.r. spectra of the product were identical with those of the enantiomer (**28**).

Methyl (1R,3S)-2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-ylmethyl)cyclopropaneacetate (**38**). A solution of (**5**) (3.00g, 15.1mmol) and ethylene glycol (1.88g, 30.3mmol) in benzene (50ml) was treated with **Py·HCl** (0.5g, 4.3mmol) and the solution heated at reflux in a Dean-Stark water separator (4h). The reaction mixture was diluted with diethyl ether (100ml) and washed with water (30ml), 0.5N aq.**Na_2CO_3** (30ml), brine (30ml), dried (**$MgSO_4$**) and evaporated to give the crude dioxolane (**38**) (3.2g, 88%). A portion of the crude product was chromatographed to give a pure sample of the *title compound*, $[\alpha]^{19}$ + 15.8 (*c* 10.9 in **$CHCl_3$**); (Found: C 64.3, H 9.1. **$C_{13}H_{22}O_4$** requires C 64.4; H 9.2%); $\nu_{max.}$ 1730 (**C=O**) cm^{-1}; δ_H 0.67 (1H, *ddd*, J 9.2, 6.7, 6.7Hz, H-4), 0.84 (1H, *ddd*, J 9.2, 7.5, 7.0Hz, H-8), 0.85 (3H, *s*, H-7), 1.02 (3H, *s*, H-6), 1.26 (3H, *s*, H-1), 1.50 (2H, *d*, J 6.7Hz, H-3), 2.22 and 2.14 (AB-part of ABX system, J_{AB} 16.4Hz, J_{AX} 7.0Hz, J_{BX} 7.5Hz, H-9), 3.61 (3H, *s*, **CH_3O**-), 3.87 (4H, *s*, -**OCH_2CH_2O**-); δ_C 14.93 *q* (C-7), 16.79 *s* (C-5), 21.32 *d* and 21.58 *d* (C-4,8), 23.72 *q* (C-1), 28.50 *q* (C-6), 29.90 *t* (C-9), 33.83 *t* (C-3), 51.31 *q* (**CH_3O**), 64.53 *t* (-**OCH_2CH_2O**-), 109.96 *s* (C-2), 173.89 *s* (C-10); *m/z* 242 (M^+).

(1R,3S)-2,2-Dimethyl-3-(2-oxopropyl)-1-(2-hydroxyethyl)cyclopropane (**7**). The crude dioxolane (**38**) (2.0g, 8.3mmol) was added to a suspension of **$LiAlH_4$** (0.5g, 13mmol) in THF (50ml) and the reaction mixture was refluxed for 1.5h. Ethanol (10ml) was added dropwise followed by addition of

10N aq.HCl (10 ml) and the reaction mixture was stirred at room temperature for 30min. Water (150ml) was added and the product extracted (Et_2O, 100, 2x50, 30ml). The combined organic extracts were washed with brine (40ml), dried ($MgSO_4$) and evaporated affording the crude product (1.5g) which was chromatographed to give the *title compound* (1.0g, 71%), $[\alpha]^{17}$ -14.0 (*c* 3.72 in $CHCl_3$); (Found: C 70.5, H 10.7. $C_{10}H_{18}O_2$ requires C 70.6; H 10.7%); $\nu_{max.}$ 3623, 3615 (O-H), 1710 (C=O) cm^{-1}; δ_H 0.55 (1H, *m*, H-8), 0.82 (1H, *m*, H-4), 0.84 (3H, *s*, H-7), 1.01 (3H, *s*, H-6), 1.4 (2H, *m*, H-9), 1.8 (1H, *br s*, OH), 2.10 (3H, *s*, H-1), 2.30 (2H, *m*, H-3), 3.56 (2H, *t*, J 6.5Hz, H-10); δ_C 14.87 *q* (C-7), 16.41 *s* (C-5), 21.06 *d* (C-4), 22.71 *d* (C-8), 27.59 *t* (C-9), 28.58 *q* (C-6), 29.45 *q* (C-1), 39.17 *t* (C-3), 62.72 *t* (C-10), 209.34 *s* (C-2); *m/z* 170 (M^+)

(1R,3R)-2,2-Dimethyl-3-[(1RS)-1-hydroxy-2-oxopropyl]cyclopropaneacetonitrile (33a,b) Ketonitrile (4) (30.0g, 182mmol) was added at 0°C to a stirred solution of KOH (50.9g, 908mmol) in MeOH (150ml). Br_2 (58.0g, 363mmol) was then added dropwise at vigorous stirring at the same temperature. The reaction mixture was filtered, and the filtrate was evaporated to leave an oily residue which was treated with $CHCl_3$ (150ml). The organic extract was washed with brine (40ml), dried (Na_2SO_4) and evaporated to give the crude hydroxyketone (33a,b) (28.1g, 85%) as a brown oil. A portion of the crude material was chromatographed, affording a pure sample for characterization [mixture of (33a) and (33b) *ca.* 1.7:1, according to ^1H n.m.r. spectrum), $[\alpha]^{19}$ + 2.3 (*c* 1.77 in $CHCl_3$); (Found: C 66.4, H 8.2, N 7.5. $C_{10}H_{15}NO_2$ requires C 66.3; H 8.3; N 7.7%); $\nu_{max.}$ (*c* 1% in $CHCl_3$) 3490 (O-H), 2255 (CN), 1715 (C=O) cm^{-1}; n.m.r. data, for (33a): δ_H 0.72 (1H, *dd*, J 11.0 and 9.0Hz, H-4), 1.1 (1H, *m*, H-8), 1.11 (3H, *s*, H-7), 1.26 (3H, *s*, H-6), 2.16 (3H, *s*, H-1), 2.25 (1H, *dd*, J 17.5 and 9.5Hz, H-9a), 2.70 (1H, *dd*, J 17.5 and 5.5Hz, H-9b), 3.6 (1H, *br s*, OH), 3.73 (1H, *d*, J 11.0Hz, H-3); δ_C 13.94 *t* (C-9), 15.50 *q* (C-7), 19.95 *s* (C-5), 22.71 *d* (C-8), 24.59 *q* (C-1), 27.75 *q* (C-6), 30.01 *d* (C-4), 73.93 *d* (C-3), 119.27 *s* (C-10), 208.08 *s* (C-2); for (33b): δ_H 0.78 (1H, *dd*, J 9.5 and 9.0Hz, H-4), 1.1 (1H, *m*, H-8), 1.10 (3H, *s*, H-7), 1.13 (3H, *s*, H-6), 2.23 (3H, *s*, H-1), 2.59 and 2.46 (AB-part of ABX system, J_{AB} 17.5Hz, J_{AX} 6.8Hz, J_{BX} 8.5IIz, H-9), 3.6 (1H, *br s*, OH); δ_C 13.94 *t* (C-9), 14.53 *q* (C-7), 18.91 *s* (C-5), 23.17 *d* (C-8), 25.12 *q* (C-1), 28.14 *q* (C-6), 29.25 *d* (C-6), 74.24 *d* (C-3), 119.20 *s* (C-10), 208.93 *s* (C-2); *m/z* 163 ($M^+ - H_2O$).

(1R,3S)-2,2-Dimethyl-3-formylcyclopropaneacetonitrile (34). A mixture of the crude nitrile (33) (28.0g, 155mmol), KIO_4 (36.9g, 160mmol) and acetone (70ml) was refluxed for 5h. The mixture was filtered and the filtrate was evaporated to leave an oily residue which was treated with diethyl ether (150ml). The ethereal solution was washed with brine (40ml), dried (Na_2SO_4) and evaporated to give the crude aldehyde (34) (17.5g, 82%) as a brown liquid. Chromatography of a portion of the crude product gave a sample for characterization, $[\alpha]^{19}$ + 136 (*c* 17.7 in $CHCl_3$); (Found: C 70.1, H 8.0, N 10.3. $C_8H_{11}NO$ requires C 70.0; H 8.1; N 10.2%); $\nu_{max.}$ 2738, 1708 (HC=O), 2260 (CN) cm^{-1}; n.m.r. data: δ_H 1.23 (3H, *s*, H-7), 1.27 (3H, *s*, H-6), 1.67 (1H, *q*, J 7.7Hz, H-8), 1.98

(1H, *dd*, J 7.7 and 2.6Hz, H-4), 2.85 and 2.77 (AB-part of ABX system, J_{AB} 17.5Hz, $J_{AX} = J_{BX}$ 7.7Hz, H-9), 9.89 (1H, *d*, J 2.6 Hz, H-3); δ_C 12.31 *t* (C-9), 13.30 *q* (C-7), 28.12 *q* (C-6), 30.62 *s* (C-5), 31.93 *d* (C-8), 36.00 *d* (C-4), 118.71 *s* (C-10), 199.94 *d* (C-3); *m/z* 137 (M^+).

(1R,3S)-2,2-Dimethyl-3-[(1RS)-1-hydroxyethyl]cyclopropaneacetonitrile (**36a,b**). A solution of the crude aldehyde (**34**) (3.0g, 22mmol) in Et_2O (15ml) was added dropwise with vigorous stirring to a solution of **MeMgI** (22mmol) in Et_2O (50ml), stirring was continued (25°C, 1h) and 1N aq.HCl (30ml) was added. The organic layer was separated and the aqueous phase was extracted with Et_2O (3x50ml). The combined organic extracts were washed with 0.5N aq.Na_2CO_3 (30ml), brine (30ml), dried (Na_2SO_4) and evaporated to leave the crude hydroxynitrile (**36a,b**) (3.3g, 98%) as a dark brown oil. A portion of the crude product was chromatographed to give a pure sample for characterization, (Found: C 70.5, H 9.8, N 9.1. $C_9H_{15}NO$ requires C 70.6; H 9.9; N 9.1%); $\nu_{max.}$ 3621 (O-H), 2259 (CN) cm^{-1}. The product was further chromatographed to give pure isomers (**36a**) and (**36b**). (**36a**) - $[\alpha]^{19}$ + 8.2 (*c* 2.43 in $CHCl_3$); n.m.r. data (CCl_4-$CDCl_3$ 2:1 v/v): δ_H 0.70 (1H, *dd*, J 9.5 and 9.0Hz, H-4), 0.89 (1H, *ddd*, J 9.0, 8.0 and 7.5Hz, H-8), 1.09 (3H, *s*, H-7), 1.15 (3H, *s*, H-6), 1.23 (3H, *d*, J 6.0Hz, H-2), 1.80 (1H, *br s*, OH), 2.27 and 2.24 (AB-part of ABX system, J_{AB} 17.0Hz, J_{AX} 7.7Hz, J_{BX} 7.6Hz, H-9), 3.45 (1H, *dq*, J 9.5 and 6.0Hz, H-3); δ_C 13.38 *t* (C-9), 14.49 *q* (C-7), 18.34 *s* (C-5), 22.54 *d* (C-8), 24.40 *q* (C-2), 28.50 *q* (C-6), 34.23 *d* (C-4), 65.03 *d* (C-3), 118.44 *s* (C-10). (**36b**) - $[\alpha]^{19}$ + 53.9° (*c* 2.04 in $CHCl_3$); n.m.r. data (CCl_4-$CDCl_3$ 2:1 v/v): δ_H 0.68 (1H, *dd*, J 10.0 and 9.0Hz, H-4), 0.93 (1H, *ddd*, J 9.0, 8.0 and 7.0Hz, H-8), 1.00 (3H, *s*, H-7), 1.06 (3H, *s*, H-6), 1.16 (3H, *d*, J 6.2Hz, H-2), 2.23 (1H, *br s*, OH), 2.25 (1H, *dd*, J 17.5 and 8.0Hz, H-9a), 2.53 (1H, *dd*, J 17.5 and 7.0Hz, H-9b), 3.40 (1H, *dq*, J 10.0 and 6.2Hz, H-3); δ_C 13.38 *t* (C-9), 14.63 *q* (C-7), 18.62 *s* (C-5), 22.80 *d* (C-8), 24.28 *q* (C-2), 28.61 *q* (C-6), 34.22 *d* (C-40, 64.66 *d* (C-3), 119.34 *s* (C-10); *m/z* 153 (M^+).

(1R,3S)-2,2-Dimethyl-3-acetylcyclopropaneacetonitrile (**24**). Oxidation of the mixture (**36a,b**) (3.3g, 22mmol) with CrO_3 (3.0g, 30mmol) in acetone (30ml) [as described above for the preparation of the mixture of diols (**39a,b**)] afforded the crude product (2.2g) which was chromatographed to give the *title compound* (2.0g, 60%), $[\alpha]^{18}$ + 112 (*c* 6.88 in $CHCl_3$); (Found: C 71.5, H 8.6, N 9.3. $C_9H_{13}NO$ requires C 71.5; H 8.7; N 9.3%); $\nu_{max.}$ 2242 (CN), 1685 (C=O) cm^{-1}; δ_H 1.12 (3H, *s*, H-7), 1.19 (3H, *s*, H-6), 1.52 (1H, *q*, J 8.0Hz, H-8), 1.89 (1H, *d*, J 8.0Hz, H-4), 2.23 (3H, *s*, H-2), 2.82 and 2.74 (AB-part of ABX system, J_{AB} 17.5Hz, $J_{AX} = J_{BX}$ 8.0Hz, H-9); δ_C 11.74 *t* (C-9), 12.86 *q* (C-7), 28.35 *q* (C-7), 28.52 *s* (C-5), 30.66 *d* (C-8), 33.36 *q* (C-2), 34.84 *d* (C-4), 119.20 *s* (C-10), 206.28 *s* (C-3); *m/z* 151 (M^+).

Preparation of diastereomeric mixtures of hydroxy derivatives.

(1R,3S)-2,2-Dimethyl-3-[(2RS)-2-hydroxypropyl]cyclopropaneacetonitrile (**9 + 14**). An externally cooled and stirred solution of ketonitrile (**4**) (8.3g, 50mmol) in methanol (50ml) was treated portionwise

with $NaBH_4$ (1.9g, 50mmol) while the reaction temperature was kept at -20°C. The reaction mixture was allowed to heat to room temperature, diluted with water (200ml) and extracted with Et_2O (3x100ml). The combined ethereal solutions were washed with brine (50ml), dried ($MgSO_4$) and evaporated to leave a yellowish oil (7.7g). The crude product was distilled under reduced pressure to give a mixture (*ca.* 1:1.1, according to ^1H n.m.r. spectrum) of epimeric hydroxynitriles (**9**) and (**14**) (6.9g, 83%): b.p. 121-122°C (2mm Hg); $[\alpha]^{21}$ +9.6 (*c* 4.80 in $CHCl_3$); (Found: C 71.4; H 10.3; N 8.2. $C_{10}H_{17}NO$ requires C 71.8; H 10.3; N 8.4%); $\nu_{max.}$ 3627 (O-H), 2235 (CN) cm^{-1}. δ_H for (**14**): 0.62 (1H, *m*, H-4), 0.79 (1H, *m*, H-8), 0.88 (3H, *s*, H-7), 0.99 (3H, *s*, H-6), 1.09 (3H, *d*, J 6.2Hz, H-1), 1.31 (2H, *m*, H-3), 2.19 and 2.11 (AB-part of ABX system, J_{AB} 17.4Hz, J_{AX} 7.2Hz, J_{BX} 7.8Hz, H-9), 3.71 (1H, *tq*, J 6.2 and 6.2Hz, H-2).

Reductions of the keto derivatives (**5**), (**7**), (**8**) and (**19**) were carried out by the same method with subsequent purification of crude products by column chromatography.

Methyl (1R,3S)-2,2-Dimethyl-3-[(2RS)-2-hydroxypropyl]cyclopropaneacetate (**10** + **15**) (mixture *ca.* 1:1.1, according to ^1H n.m.r. spectrum), b.p. 102-103°C (2mm Hg); $[\alpha]^{21}$ -4.7 (*c* 7.61 in $CHCl_3$); (Found: C 65.7; H 10.0. $C_{11}H_{20}O_3$ requires C 66.0; H 10.1%); $\nu_{max.}$ 3628 (O-H), 1740 (C=O) cm^{-1}; δ_H for (**15**): 0.53 (1H, *ddd*, J 8.9, 6.5, 6.5Hz, H-4), 0.81 (1H, *ddd*, J 8.9, 8.0, 6.5, H-8), 0.82 (3H, *s*, H-7), 0.99 (3H, *s*, H-6), 1.11 (3H, *d*, J 6.2Hz, H-1), 1.31 (2H, *m*, H-3), 2.20 and 2.12 (AB-part of ABX system, J_{AB} 16.8Hz, J_{AX} 6.5Hz, J_{BX} 8.0Hz, H-9), 3.59 (3H, *s*, CH_3OOC-), 3.74 (1H, *tq*, J 6.2 and 6.2Hz, H-2).

(1R,3S)-2,2-Dimethyl-3-[(2RS)-2-hydroxypropyl]-1-(2-hydroxyethyl)cyclopropane (**12** + **17**) (mixture *ca.* 1:1.2, according to ^1H n.m.r. spectrum), $[\alpha]^{22}$ +2.5 (*c* 9.46 in $CHCl_3$); (Found: C 69.6, H 11.8. $C_{10}H_{20}O_2$ requires C 69.7; H 11.7%); $\nu_{max.}$ 3618 (O-H) cm^{-1}; δ_H for (**17**): 0.45-0.50 (2H, *m*, H-4,8), 0.85 (3H, *s*, H-7), 0.99 (3H, *s*, H-6), 1.15 (3H, *d*, J 6.2Hz, H-1), 1.36 (2H, *m*, H-3), 1.47 (2H, *m*, H-9), 2.6 (1H, *br s*, OH), 3.62 (2H, *m*, H-10), 3.84 (1H, *tq*, J 6.2 and 6.2Hz, H-2).

(1R,3S)-2,2-Dimethyl-3-[(2RS)-2-hydroxypropyl]cyclopropanecarbonitrile (**13** + **18**) (mixture *ca.* 1:1.2, according to ^1H n.m.r. spectrum), $[\alpha]^{23}$ -12.1 (*c* 5.79 in $CHCl_3$); (Found: C 70.5, H 9.6, N 8.8. $C_9H_{15}NO$ requires C 70.6; H 9.9; N 9.1%); $\nu_{max.}$ 3614 (O-H), 2228 (CN) cm^{-1}; δ_H for (**18**): 1.11 (3H, *s*, H-7), 1.14 (3H, *s*, H-6), 1.15-1.30 (2H, *m*, H-4,8), 1.18 (3H, *d*, J 6.0Hz, H-1), 1.60 (2H, *t*, J 6.0Hz, H-3), 2.1 (1H, *br s*, OH), 3.86 (1H, *tq*, J 6.0, 6.0Hz, H-2).

Methyl (1S,3R)-2,2-Dimethyl-3-[(2RS)-2-hydroxypropyl]cyclopropaneacetate (**20** + **21**) (mixture *ca.* 1.1:1, according to ^1H n.m.r. spectrum), $[\alpha]^{21}$ +2.6 (*c* 8.02 in $CHCl_3$); I.r., ^1H and ^{13}C n.m.r. spectra of the product were identical with those of the mixture (**10** + **15**).

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