Baker's Yeast Mediated Transformations in Organic Chemistry

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Received April 25, 1989 (Revised Manuscript Received July 2, 1990)

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I. Introduction and General Remarks

Microbial transformations, and yeast-mediated transformations in particular, have been widely used since the early days of mankind for the production of bread, dairy products, and alcoholic beverages. All of these early applications used mixed cultures of microorganisms, and all of these biotechnological operations have primarily been directed in the areas of agriculture and human nutrition. It was the merit of Pasteur in 1862[1] to lay a scientific foundation of one of these early applications, namely the oxidation of alcohol to acetic acid by using a pure culture of *Bacterium xylinum*.[2] Investigations of the oxidation of glucose to gluconic acid[3] by *Acetobacter aceti* and of sorbitol to sorbose by *Acetobacter sp.*[4] followed. The reducing action of fermenting yeast, *Saccharomyces cerevisiae*, was first observed by Dumas in 1874.[5] He reported that, on addition of finely powdered sulfur to a suspension of fresh yeast in a sugar solution, hydrogen sulfide was liberated. The reduction of furfural to furfuryl alcohol under the anaerobic conditions of fermentation by means of living yeast[6,7] was the first "phytochemical reduction"[8] of an organic molecule described in literature. Numerous further enzymatic or microbial biotransformations, bioconversions, biodegradations, and fermentations followed, and as Chaleff[9] pointed out, in the initial excess of enthusiasm[10] that invariably accompanies the birth of a new field,[11] biotransformations were hailed as a panacea that would ultimately displace traditional organic chemistry.[12,13] But the role is one of support rather than supplantation, of synergy rather than rivalry;[9] biotransformations should be employed when a given reaction step is not easily accomplished by "ordinary" chemical methods.[14]

Contrary to the very early applications, biotransformations are carried out today by pure cultures of microorganisms or plant cells or with purified enzymes, and they should always be considered as a way of performing selective modifications of defined pure compounds into defined final products.[15] The main differences between biotransformations and fermentations have clearly been listed by Yamada.[16]

The general goals of biotransformations may be considered to be as follows: resolution of racemates, selective conversion of functional groups among several groups of similar reactivities, introduction of a chiral center, and functionalization of a certain nonactivated carbon. Applications in the energy sector or with regard to applications in the areas of environmental pollution problems are of forthcoming interest.[17]

Several excellent reviews and monographs have been published on microbial/enzymic transformations. To

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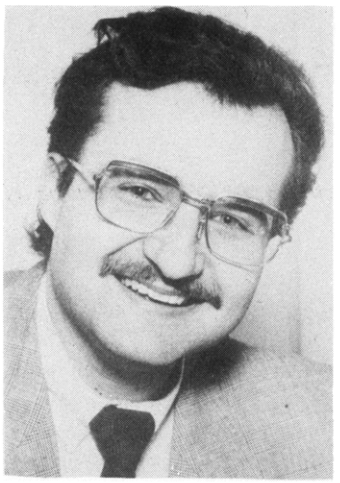


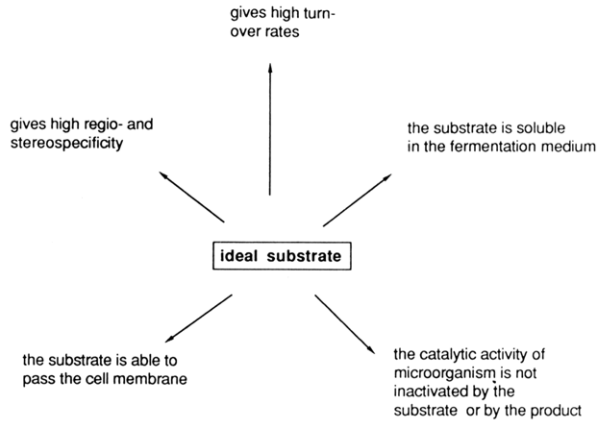
René Csuk was born in 1958 in Zürich (Switzerland). He received his M.Sc. from the Technical University in Graz (Austria) in 1981 and his Ph.D. (Prof. Dr. H. Weidmann) in 1984. He joined the University of Zürich (Prof. Dr. A. Vasella) for postdoctoral studies in 1986. His current interests include the stereocontrolled synthesis of natural products, bioorganic chemistry, and the invention of new reactions. Other active projects include the preparation and application of graphite-surface compounds.

Brigitte I. Glänzer was born in Bruck/Mur (Austria) and received her M.Sc. from the Technical University Graz. She carried out her doctoral work under the direction of Prof. Dr. H. Griengl on yeast and enzymic transformations, received her Ph.D in 1987, and joined the University of Zürich (Prof. Dr. A. Vasella) for postdoctoral studies in 1987. Her current research interests involve the synthesis of natural products and their fluorinated analogues and bioorganic transformations.

avoid excessive echoing of these reviews and of other literature in the field, background material will be limited to the minimum commensurate with both the diversity of the readership of this review and the chemical nature of the discussion to follow.

There are two different biotransformation systems, whole cells or isolated enzymes, and both display several advantages.[18] Availability of a certain microorganism is often a deciding factor for an organic chemist turning to the use of biotransformations in synthesis. For example, baker's yeast (BY), *Saccharomyces cerevisiae*, is a readily available microorganism (world output of BY, 600 000 tons/year[19]), but obtaining other microorganisms may require help from a microbiologist and access to fermentation facilities. A further disadvantage of the use of whole cells for laboratory-scale operations is that sterile growing of the cells sometimes is required and the workup is both time-consuming and messy due to separation of the product from the huge amounts of biomass; this process is very often complicated by side reactions that interfere or even dominate the desired transformation. Contrary, enzymes are more often specific for selected reactions and their use may require only small-sized equipment and simpler workup.[20] But enzymes are more expensive, and addition of enzyme cofactors or enzyme cofactor recycling might be necessary.[21,22] The ideal interactions between the substrate and the microorganism (Scheme 1) are scarcely found in praxi; some advice how to deal with basic problems often encountered in such biotransformations is provided in Scheme 2.[14,16,23,24]

SCHEME 1



There are some basic ways to perform a reaction with intact baker's yeast: One has to differentiate between using *previously* grown cells, e.g., active cells or spores,[25] biotransformations under *fermentative* conditions, or transformations with *immobilized* cells.

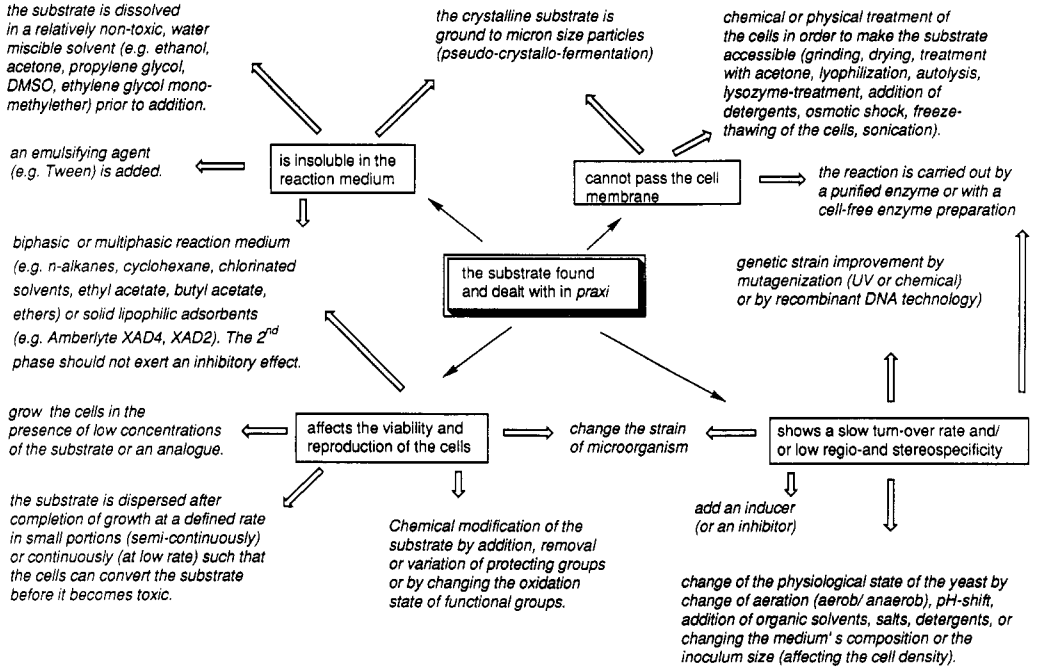
II. Reductions

A. General Remarks

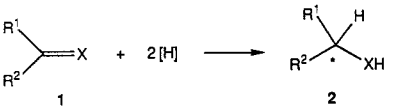
Unsaturated compounds **1** can be reduced by BY (Scheme 3). For **1** the enzyme has to distinguish between the *re* and the *si* face of the π-system to yield chiral **2**.[26]

The asymmetric reduction of carbonyl-containing compounds by BY constitutes one of the most widely applicable reactions. Originally described in 1898 for the reduction of furfural to furfuryl alcohol,[6,7] the widespread applications of this reaction are based on systematic investigations by MacLeod[27] and Hub.[28] Ketones with varying substituents (Me, Et, *n*-Pr, *n*-Bu, Bz) were reduced by BY, and the secondary alcohols obtained were mainly of *S* configuration. Only 3-hydroxyheptanol (from the reduction of 3-heptanone) was predominantly *R*-configured. Sterically hindered ketones (e.g., 4-octanone, *tert*-butyl methyl ketone, isobutyl isopropyl ketone, or *n*-amyl phenyl ketone) were not reduced at all. These results[27,28] suggested a

SCHEME 2



SCHEME 3



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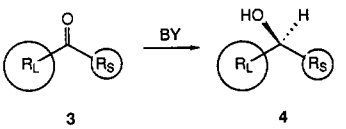
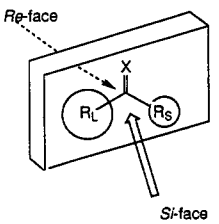




hydrogen transfer to the *re* face of the prochiral ketone **3**, with R_L representing a large substituent and R_S a small substituent adjacent to the carbonyl group (Scheme 4) to yield alcohol **4**.

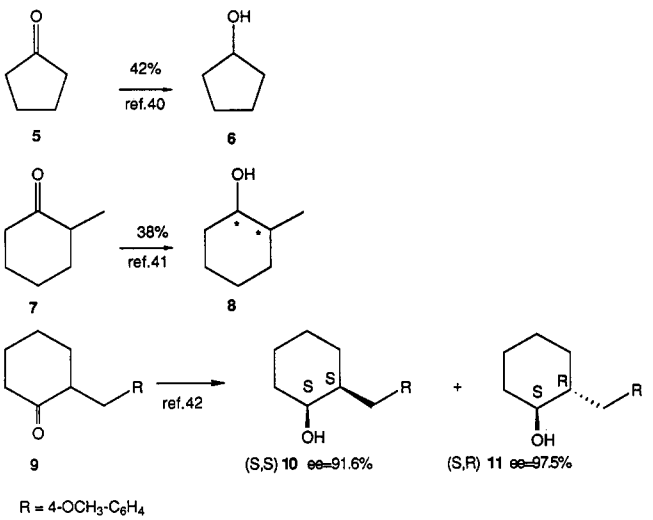
But, as Sih[29] pointed out, one should exercise considerable caution when Prelog's rule[30] is applied to intact cell systems.

B. Reduction of Monocarbonyl Compounds

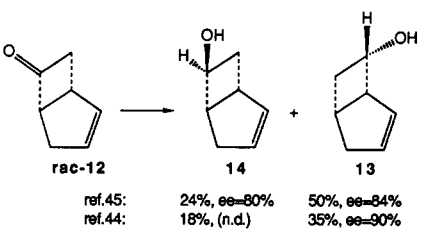
1. Reduction of Cycloalkanones

Only a few examples for the reduction of cycloalkanones[31] bearing no further functionalities (or obviously not participating remote functional groups) have been described so far;[32] however, there are numerous reports on the reduction of steroids,[33-38] but some of these reductions claimed for the action of BY are attributable to the action of bacteria having contaminated the yeast.[39] Cyclopentanone (**5**) (Scheme 5) was reduced into cyclopentanol (**6**),[40] and racemic 2-methylcyclohexanone (**7**) was found to yield dextrarotatory 2-methylcyclohexanol (**8**).[41] Similarly, **9** gave a 1:1 mixture of *cis*-(1*S*,2*S*)-2-(4-methoxybenzyl)-1-cyclohexanol (**10**) (91.6% ee) and of *trans*-**11** (97.5% ee).[42] Reduction of racemic *cis*-2,4-dimethyl-1-cyclohexanone provided all possible stereoisomers in 4% overall yield.[43]

SCHEME 5



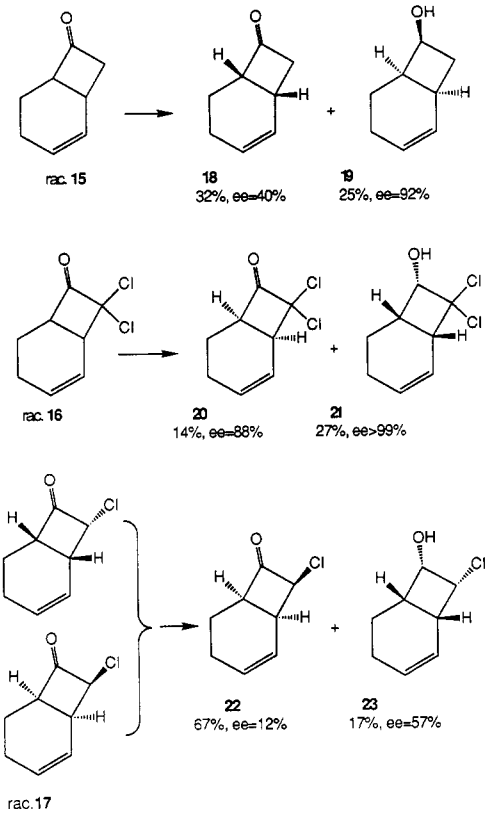
SCHEME 6



2. Reduction of Bi- and Polycyclic Cycloalkanones

The first reported reduction of a cyclobutanone is represented by the BY-mediated transformation of

SCHEME 7

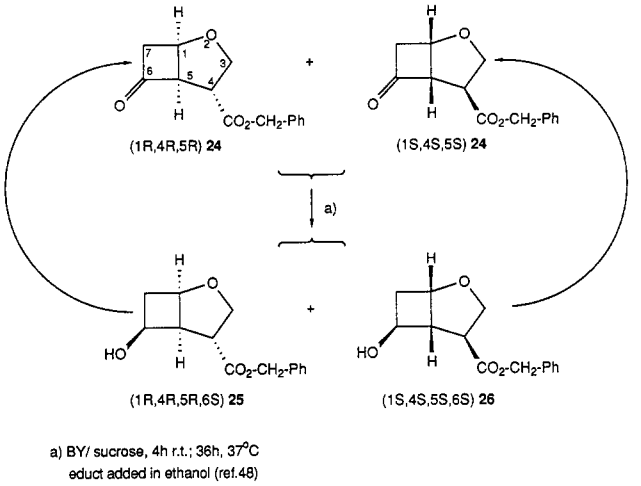


(±)-bicyclo[3.2.0]hept-2-en-6-one (**12**) (Scheme 6). **13** was obtained in about 90% optical purity; the optical purity of the byproduct **14** (obtained in ca. 18% yield) was not determined. It is of interest to note that additional riboflavin and commercial yeast nutrient were added to the reaction mixture.[44]

Since these bicycloheptenones represent important building blocks for the synthesis of prostaglandins PGE_2, $PGFA_{2\alpha}$, and PGA_2, the reduction of **12** was recently reinvestigated in more detail.[45] In order to improve the low substrate enantioselectivity achieved by using commercially available BY, other different yeast strains were screened and marked differences established (the ratio of **13** to **14** for different strains of *Saccharomyces cerevisiae* was found to be 1:1 to 7:1). In addition, the endo to exo ratio (**13** to **14**) changed on prolonged incubation (7:3 in 24 h to 3:2) but could kept constant (5:2), maintaining a glucose concentration of 350 g/L. The yeast reduction is inhibited by 50% at a concentration of 15 g/L of ketone **12**.[45] The best results for this reduction, however, were obtained with *Mortierella ramanniana* (Glaxo C2506), giving rise to an endo to exo ratio of >30:1; no increase in the conversion rate by increasing the oxygen-transfer rate but definitive requirement for oxygen were demonstrated.

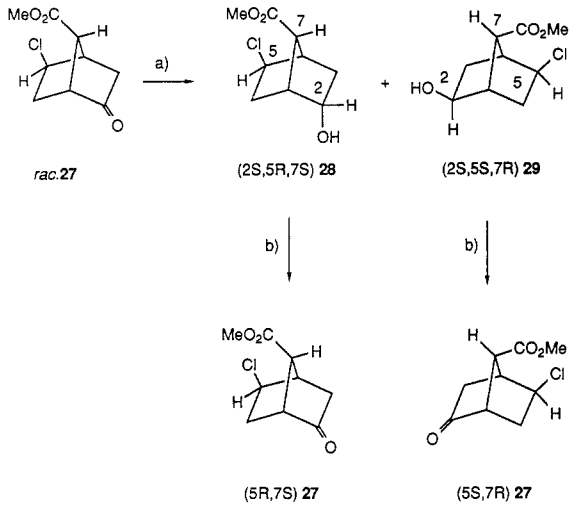
Reduction of the bicyclo[4.2.0]octenones **15**–**17** (Scheme 7) was found to be completely diastereoselective for reduction from the ketone's exo face in addition to being highly enantioselective. Thus, reduction of racemic **15** afforded 32% of **18** (40% ee) and 25% of **19**; **16** gave within 45 min 14% of **20** (88% ee) and 27% of **21** (ee >99%), whereas **17** yielded after 6 h 67% of **22** (12% ee) and 17% of **23** (57% ee).[46] An enzymic reduction of chlorinated bicyclo[3.2.0]hept-2-en-6-ones of similar substrate and product enantioselectivity has been reported.[47]

SCHEME 8



a) BY/ sucrose, 4h r.t.; 36h, 37°C
educt added in ethanol (ref.48)

SCHEME 9

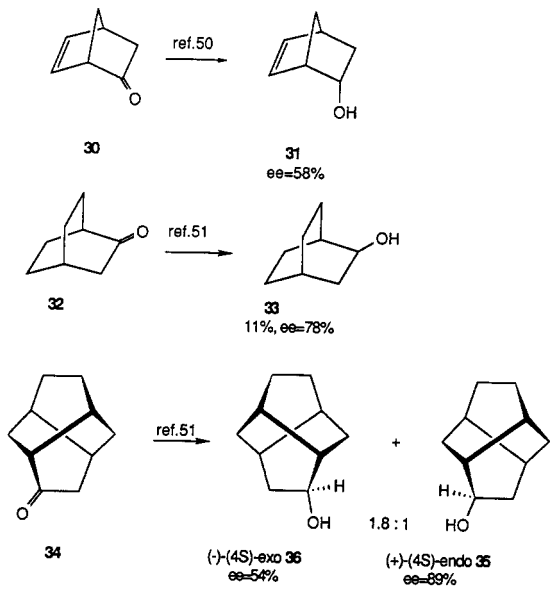


a) BY, 28°C, 2-3d, 90%; b) CrO_3/H_2SO_4/acetone
ref.49.

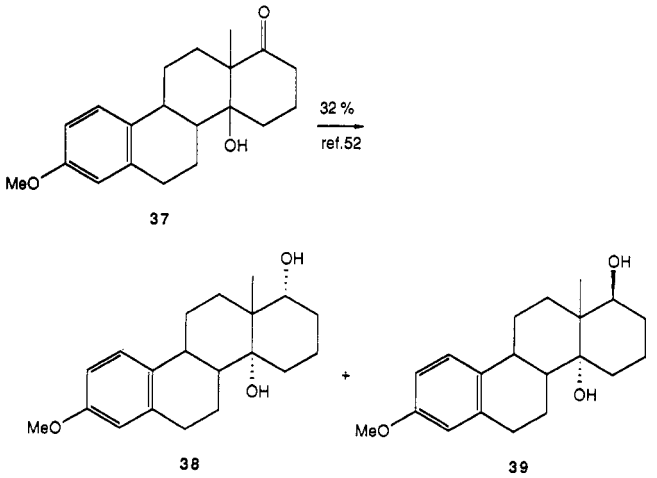
Similarly, reduction of racemic (1α,4α,5α)-4-(benzyloxycarbonyl)-2-oxabicyclo[3.2.0]heptan-6-one (**24**) (Scheme 8) by BY gave 59% of a separable mixture of the corresponding diastereomeric 6-hydroxybicycloheptanols **25** and **26** in 10% and 2% isolated yields, respectively. **25** and **26** afforded upon separate reoxidation with pyridinium chlorochromate the resolved enantiomers (1*R*,4*R*,5*R*)-**24** and (1*S*,4*S*,5*S*)-**24**. Interestingly, 2-(4-hydroxyphenyl)ethanol was obtained as a byproduct of this BY-mediated reduction.[48]

An analogous sequence of reduction and reoxidation for obtaining the pure enantiomers was used for preparation of enantiomerically pure methyl 5-chloro-2-oxobicyclo[2.2.1]heptane-7-carboxylates (**27**) from the corresponding racemate (Scheme 9). Racemic **27** afforded upon treatment with BY 90% of a mixture of methyl (2*S*,5*R*,7*S*)-5-chloro-2-hydroxybicyclo[2.2.1]-heptane-7-carboxylate (**28**) and methyl (2*S*,5*S*,7*R*)-5-chloro-2-hydroxybicyclo[2.2.1]heptane-7-carboxylate (**29**), which were each reoxidized by CrO_3/H_2SO_4/acetone to yield both enantiomers of **27**. A drawback of these reductions is the laborious workup, which could be improved by performing the reduction with *Candida utilis* and stopping the reduction at 52–53% conversion of racemic **27**.[49]

SCHEME 10



SCHEME 11



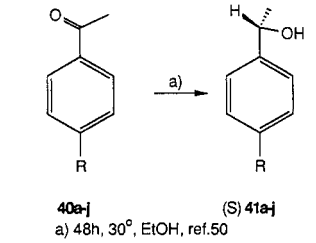
Anaerobic reduction of norbornenone (**30**) (Scheme 10) afforded only *endo*-norborneol (**31**) but with moderate enantioselectivity. As shown by differential scanning calorimetry, **31** crystallizes as a pseudoracemate and it is therefore not possible to improve the low ee (58%) by repeated recrystallization.[50] Bicyclo-[2.2.2]octan-2-one (**32**) afforded only 11% of **33** (78% ee). Racemic 4-twistanone (tricyclo[4.4.0.0^{3,8}]decan-4-one, **34**) gave a 1:1.8 mixture of endo and exo alcohols **35** and **36** of 89% and 54% ee, respectively.[51] Better yields and higher ee values were obtained with *Rhodotorula rubra*.[51]

Reduction of the racemic estradien derivative **37** (Scheme 11) with BY (*Saccharomyces cerevisiae* Heyen ex. Hansen) afforded in 32% yield the corresponding alcohols **38** and **39** in optically pure form whereas reduction of **37** using lithium aluminum hydride afforded the corresponding racemic materials. Better yields, however, were obtained by using *Rhizopus nigricans*.[52]

3. Reduction of Aliphatic Alkanones

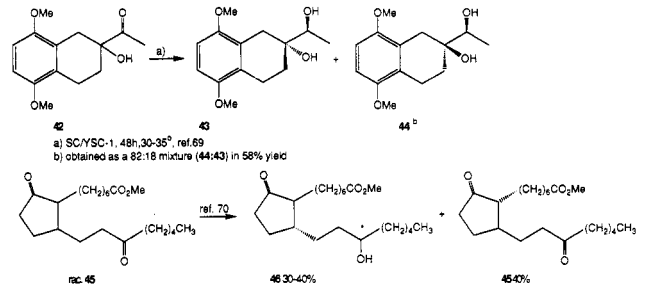
The reduction of aldehydes and ketones by means of fermenting BY is long known, and this subject as been covered in several reviews.[26,40,53-56] The stereochemical course of these reductions has been investigated by

SCHEME 12

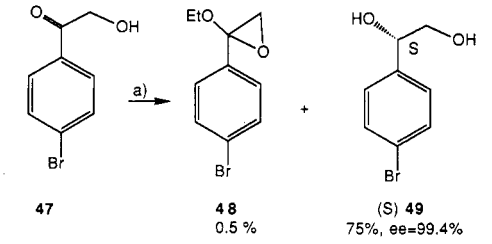


R	ref.
a OMe	28
b Me	50
c H	27,62-65,67,68
d F	50
e Cl	50
f Br	50
g I	65
h CO_2Me	50
i CN	50
j NO_2	50
Pentafluoro	66

SCHEME 13



SCHEME 14



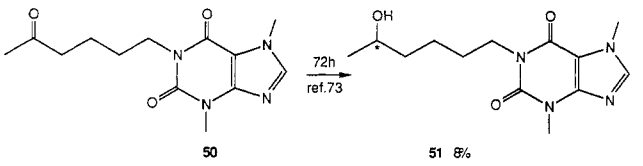
several deuteration studies.[57-59] Hence, the number of examples for these reductions of carbonyl groups with the carbonyl moiety being part of an acyclic chain will be limited. A variation of these reductions has been established by Simon et al.,[60,61] namely the electromicrobial reduction that brought about several advantages. This topic has been reviewed recently.[26]

Fermentative reduction of substituted acetophenones **40a-j** (Scheme 12) afforded (*S*)-1-arylethanols **41a-j** in low to moderate yields and ee values between 82% and 96%.[27,28,50,62-68] No influence on the steric course of the reduction was observed when the substituents were changed, but the velocity of the reaction was decreased by electron-donating substituents.[50,62]

The advantage of yeast-mediated reductions of ketones is their high *re* selectivity, often resulting in high optical yields of products. In addition, when the ketone carries a substituent capable of coordination through hydrogen bonding or lone-pair interaction, the products are predominantly of erythro configuration.

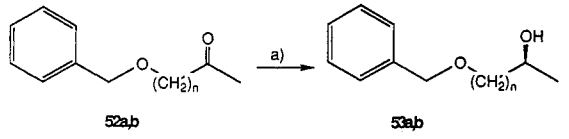
Thus, treatment of racemic **42** (Scheme 13) (cf. reduction of racemic **211**) with *Saccharomyces cerevisiae* (YSC-1/Sigma) gave 91% of the reduction products **43** and **44**,[69] which are synthetic intermediates for the synthesis of anthracyclinones. The racemic prostaglandin analogue **45** has been treated with resting cells of *Saccharomyces cerevisiae* (ATCC-4125), and 30–40% of alcohol **46** and 40% of starting material have been obtained.[70] It was not possible to assign unambiguously the stereochemistry at position C-15. The resolution of racemic estra-4,9-diene-3,17-dione by 48

SCHEME 15



50 51 8%

SCHEME 16



52a,b 53a,b

a n=1 76%, ee=90%

b n=2 52%, ee>95%

a) 30°, 6d, add. of educt in EtOH, ref. 74

SCHEME 17

54a-f 55a-f

	R	y[%]	ee[%]	conf.	ref.
a	n-C_5H_{11}	56	100	R	75
b	C_6H_5	45	100	R	76
c	CH_3	43.5	91	R	77-80
d	C_2H_5	37	100	R	78
e	$CH(CH_3)_2$	65	100	R	78
f	$(CH_3)_3C$	66	100	R	78

different microorganism has been investigated recently.[71]

Interestingly, the reduction of **47** (Scheme 14) gave crystalline **48**,[72a] which seems to be remarkably stable under these physiological conditions; however, (*R*)-**49**, as the main product, was obtained in 75% yield and 99.4% ee.[72a] Recently, the enantioselective reduction of 4-acetylpyridine by nonfermenting BY has been reported. Thus, (*S*)-1-(4-pyridyl)ethanol (79% yield) has been obtained with an ee of 96%.[72b] In addition, 1-(acyloxy)-3-azido-2-propanones (70–95% yield of (*S*)-1-(acyloxy)-3-azido-2-propanols, ee = 75 – >95%)[72c] and 3-(benzyloxy)-1-hydroxypropanone have been reduced (ee = 99% of (*S*)-3-(benzyloxy)-1,2-propanediol).[72d]

The biodegradation of pentoxifylline (**50**) (Scheme 15) (used in the treatment of cerebrovascular and peripheral vascular diseases) has been investigated. Thus, *Saccharomyces cerevisiae* NRRL Y2034 reduced **50** to give alcohol **51** with 8% conversion within 72 h. The highest conversion rates, however, have been obtained by using *Cryptococcus macerans*, *Curvularia falcata*, and *Rhodotorula mucilaginosa*.[73]

Synthesis of masked 1,2- or 1,*n*-diols has been investigated by several groups. Slow addition of educts **52a,b** (Scheme 16) (approximately 0.5 g of educt during 8–18 h) to a highly diluted yeast suspension (*Eridania* brand) gave access to the *S*-configured alcohols **53a,b** in 90% and 95% ee, respectively.[74]

More recent examples for the reduction of α-hydroxy ketones **54a–f** to yield the corresponding 1,2-diols **55a–f** are summarized in Scheme 17.[75–80]

Older examples for the bioreduction of aliphatic (hydroxy) carbonyl compounds have already been compiled in the literature.[40,54] In general, it was found[40] that larger amounts of yeast were required for the reduction of ketones than for the reduction of aldehydes.

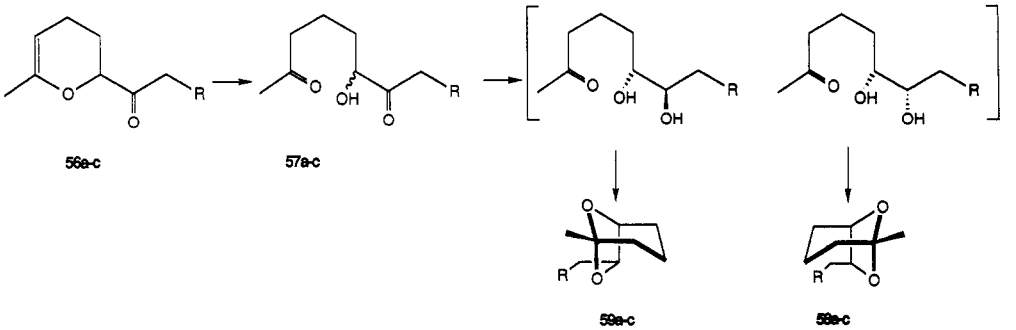
Recently, a kinetic resolution by BY has been used for the synthesis of *endo*-brevicomin.[81] Reduction of racemic **56a** (Scheme 18) with actively growing BY under anaerobic conditions afforded after initial formation of racemic **57a** 27% of **58a** (99% ee) and 2% of **59a** (98% ee). **56a** gave primarily endo product **58a** via syn-selective reduction, whereas in the reduction of **56b** the exo isomer **59b** predominated (18%). The observation of the opposite diastereoselectivity in the reduction of **56a** as compared to **56b** was attributed[81,82] to the loss of the precursor for the endo product by biodegradation. Finally, reduction of **56c** gave after 7 days only 9% of reduction products **59c** (3%) and **58c** (6%), but the ratio of **59c** to **58c** can be increased to 1:30 by using acyclic intermediate **57c** (yield 7.5%).[81]

The aggregation pheromone sulcatol ((*S*)-**60**) (Scheme 19) has been synthesized by reduction of 6-methylhept-5-en-2-one (**61**) in 80% yield and 94% ee.[83] This recent finding is in contrast to previous reports.[84] No reduction of the double bond was observed. Similarly, **62** was only reduced at the carbonyl moiety to give 34% of (*S*)-**63** in 99% ee. (*S*)-**63** has been used as a starting material in a Brefeldin A synthesis.[85]

4. Reduction of Sulfur-Containing Molecules

a. Thiocarbonyl Compounds. Thiols from the corresponding thioaldehydes are formed in an analogous manner as reported for the reduction of aldehydes. Thioacetaldehyde was very readily reduced to ethyl mercaptan,[86,87] thio-*n*-butyraldehyde as well as thio-

SCHEME 18

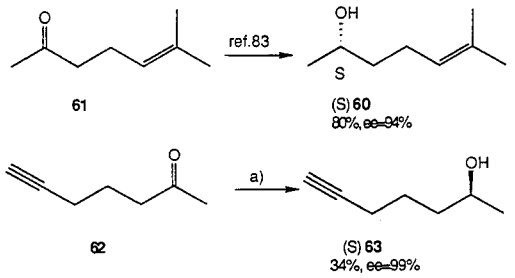


56a-c 57a-c 59a-c 58a-c

	R	y[%]	ee[%] 59	ee[%] 58	ratio 59/58
a	CH_3	29	0	99	1/16
b	H	32	98	99	2/1
c	C_2H_5	9	98	99	1/2

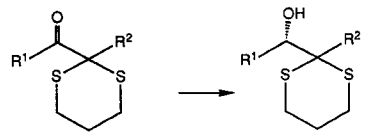
ref. 81,82

SCHEME 19



a) 8d, 34°, 60% conv., ref. 85

SCHEME 20



64a-r 65a-r

	R^1	R^2	t [d]	y [%]	ee [%]	ref.
a	CH_3	H	1	84	>96	91,96
b	C_2H_5	H	2	71	"	91,96
c	n-C_3H_7	H	4	92	"	91
d	n-C_4H_9	H	3	71	"	91
e	n-C_6H_{13}	H	8	38	"	96
f	CF_3	H	2h	96	67	96
g	CH_2OH	H	5	28	96	96
h	CH_2OAc	H	1	58	87	96
i	$CH_2OC_7H_7$	H	5	50	95	96
j	$CH_2O(4\text{-}OCH_3C_6H_4)$	H	6	27	98	96
k	CH_2OTHP[d]	H	3	37	96	96
l	$CH_2OCH_2OCH_3$	H	4	82	"	96
m	$CH_2OSi(CH_3)_2tC_4H_9$	H	7	<10	-	96
n	$(CH_2)_3OH$	H	10	74	96	91
o	CH_3	CH_3	2.5	50	"	91
p	CH_3	$CH_2CH{=}CH_2$	4	31	"	91
q	$(CH_2)_3CO_2CH_3$	H	hydrolysis of ester			92
	" c)	H	3	17	97	93
r	$(CH_2)_3CO_2{}^tBu$	H	3	65	99	92

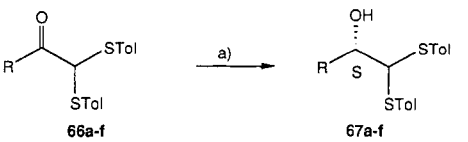
a) BY (Oriental); addn. of $MgSO_4$;glucose; ref.91
b) BY (Red star); without sugar; 70h; 25°; ref.92
c) SC 567; 1-7d; 28-58%; ee= 87-95%, ref.96
d) complete cleavage of THP-acetal

isobutyraldehyde gave the corresponding mercaptans;[88] diethyl thioether was reported to cleave to ethanethiol.[89]

b. 2-Thio-Substituted Ketones. The reduction of carbonyl groups with adjacent sulfur substituents by actively fermenting BY is critically dependent upon the substituents attached to the sulfur-containing group and to the carbonyl group. In cases where these substituent groups are bulky, very little reduction occurs. The relative ease of reduction decreases from β-keto sulfones to β-keto sulfoxides to β-keto sulfides.[90] Asymmetric reduction of α-keto thioacetals was achieved by fermenting BY to afford optically active α-hydroxy thioacetals, which are synthetic equivalents to chiral α-hydroxy aldehydes or ketones. Reduction of **64a–r** (Scheme 20) afforded **65a–r** with high ee and proceeded predominantly to the *S*-configured alcohols; only the allyl-substituted educt **64p** afforded the *R*-configured product **65p**.[91] The methyl ester **64q** was rapidly hydrolyzed with *Red-Star* BY, whereas the *tert*-butyl ester **64r** was stable and afforded **65r** in good yield.[92] **65q** (ee = 97%) could be obtained, although in low yield (17%), from SC567.[93]

Somewhat lower yields but still high enantiomeric excesses could be achieved upon reduction of 1,1-bis(*p*-tolylthio) ketones **66a–f** (Scheme 21) to the corresponding alcohols **67a–f**. The rate of reduction was shown to depend on the length of hydrocarbon and the type of substituent.[94,95] These results indicate that the use of the 1,3-dithione (as in **64**) instead of the bis(*p*-tolylthio)methane derivatives permits the synthesis of a broader range of α-alkoxycarbonyl compound equivalents.[96]

SCHEME 21

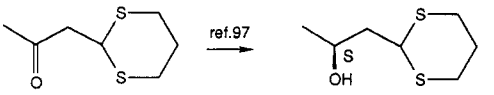


66a-f 67a-f

	R	t [d]	yield [%]	ee [%]
a	CH_3	3.5	50	>95
b	C_2H_5	7	<10	-
c	CF_3	3	25	>95
d	CH_2F	4	42	"
e	$CH_3OCH_2OCH_2$	6	50	"
f	CH_2Cl	7	<5	-

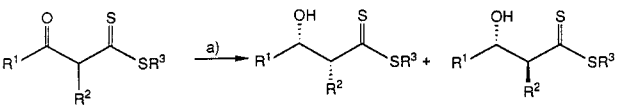
a) Educt in EtOH; 27-30°; ref.94-96

SCHEME 22



68 69

SCHEME 23



70a-d 71a-d 72c

	R^1	R^2	R^3	Product	y[%]	ee[%]
a	CH_3	H	CH_3	71a	50	>96
b	CH_3	H	C_2H_5	71b	30	"
c	CH_3	CH_3	CH_3	71:72=96:4	65	"
d	$-(CH_2)_4-$		CH_3	71d	27	"

a) Oriental yeast; glucose; 24h;

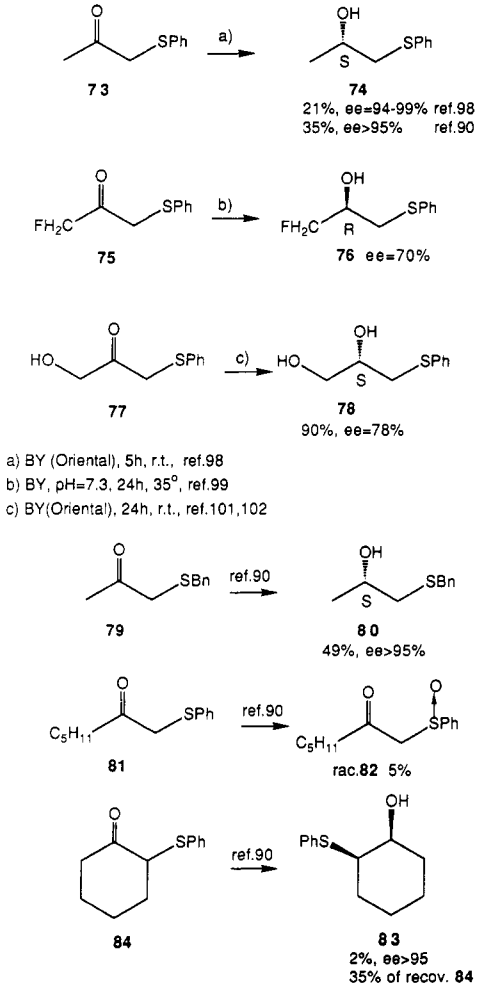
The β-keto thioacetal **68** (Scheme 22) was reduced in 99% ee to (*S*)-1-(1,3-dithian-2-yl)-2-hydroxypropane (**69**), a key intermediate for the synthesis of (*S,S*)-grahamimycin A1.[97]

Asymmetric reduction of the β-keto dithioester **70a–d** (Scheme 23) with BY produced mainly the corresponding optically pure (3*S*)-hydroxy thioester **71a–d**; **72c** was obtained as a low yield byproduct although with high ee (96%). The syn to anti ratio (**71c**:**72c**) is better than with the corresponding oxo isomers (cf. Scheme 81, compounds **357** and **358**), a fact that seems to be due to the enhanced enolization of the β-keto groups by the thiocarbonyl moiety. Thus, changing the oxygen atoms in an ester group of a β-keto ester to sulfur atoms can control the diastereoselectivity of the reduction quite efficiently.[100]

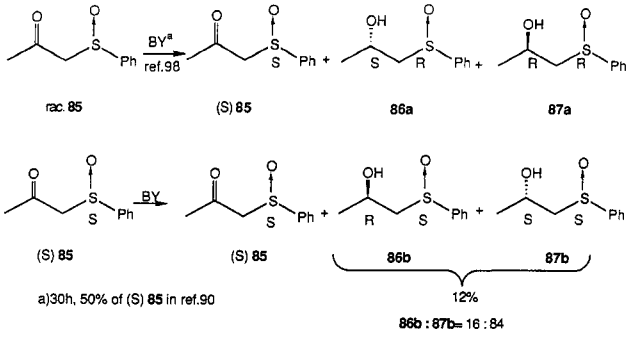
Many β-keto sulfides have been reduced by BY. Thus, (phenylthio)acetone (**73**) (Scheme 24) gave (*S*)-(+)-2-hydroxypropyl phenyl sulfide (**74**) with high ee but rather low yield;[90,98] the corresponding 1,1,1-trifluoropropyl phenyl sulfide was not reduced at all by BY[99] whereas the 1-fluoro-2-oxopropyl phenyl sulfide (**75**) gave under similar conditions (*R*)-**76** with 70% ee.[99]

Fair ee (78%) was achieved upon reduction of 1-hydroxy-3-(phenylthio)-2-propanone (**77**) to yield

SCHEME 24



SCHEME 25

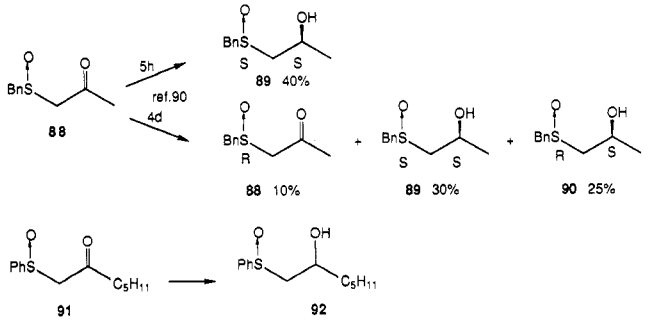


(*S*)-3-(phenylthio)-1,2-propanediol (**78**) (90%), which was successfully used for the synthesis of both enantiomers of the insect pheromone δ-*n*-hexadecanolide and for the synthesis of the deoxy sugars L-rhodinose and D-amicetose.[101,102]

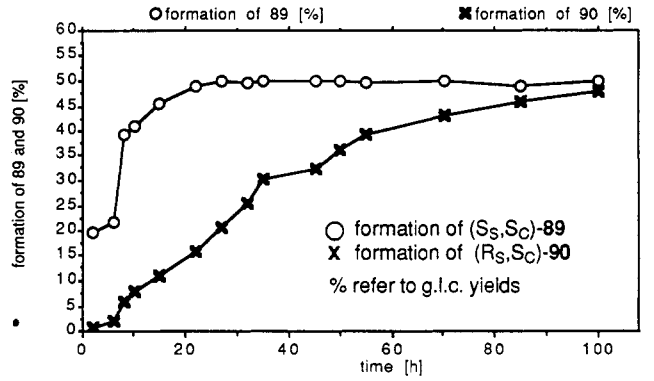
The structural analogue **79** gave 49% of *S*-configured **80** whereas **81** was not reduced but oxidized in about 5% yield to **82**.[90] A very low yield of only 2% of *cis*-**83** (and 38% recovery of starting material) was found for the cyclohexanone derivative **84**.[90] Generally, the reduction of these β-keto sulfides proceeded with relative difficulties and only at low concentrations of the substrate.[90]

Reduction of racemic 1-(phenylsulfinyl)acetone (**85**) (Scheme 25) resulted in formation of (*S*)-**85** and a mixture of diastereomeric **86a**/**87a**; the ratio of **85** to

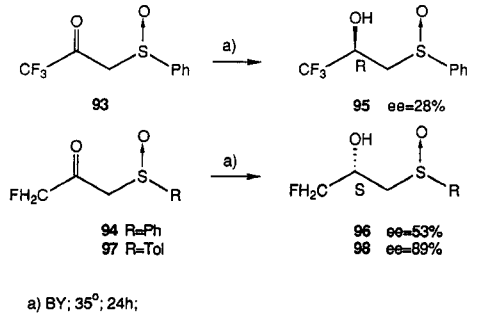
SCHEME 26



SCHEME 27



SCHEME 28

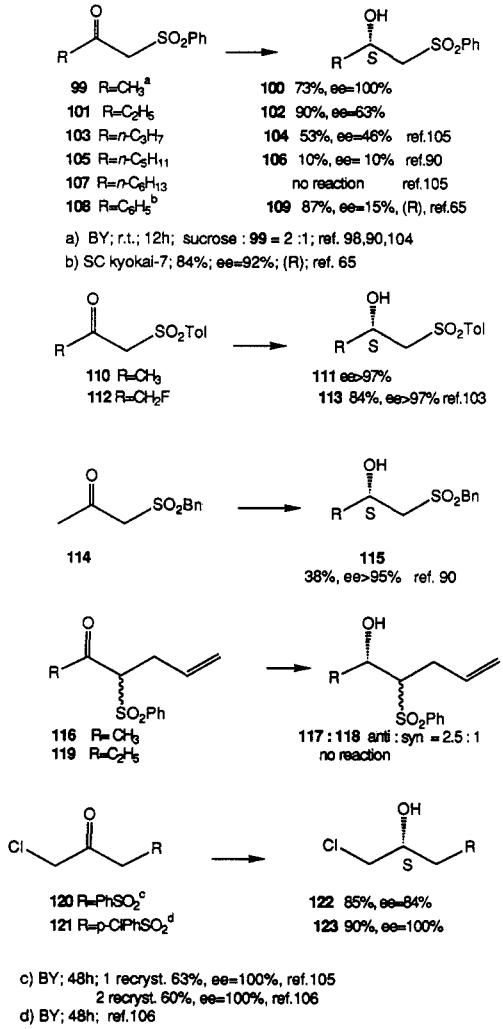


86a/**87a** (55:45 to 42:58) (**86a**/**87a** as a 79:21 to 89:11 mixture) depended on the supplied sucrose concentration. By means of recrystallization, optically pure (*S*)-**85** was obtained in 28% yield, whose further reduction with BY afforded an 84:16 mixture of **87b** and **86b**.[98] Reduction of a mixture of **73** and (*S*)-**85** showed that **73** is reduced much faster.[98] (*R*)-**85** is reduced in high chemical and more than 95% optical yield whereas (*S*)-**85** is reduced in both low chemical and optical yield (68%). The order of reducibility for these compounds was established to be (*R*)-**85** > **73** > (*S*)-**85**,[98] which is for unknown reasons contradictory to the general rule.[90]

Time dependency for the course of the reduction of **88** was encountered (Schemes 26 and 27). Thus, **88** gave after treatment with BY for 5 h 40% of (S_S,S_C)-**89**, whereas after 4 days 10% of (R_S)-**88**, 30% of (S_S,S_C)-**89**, and 25% of (R_S,S_C)-**90** were isolated.[90] Reduction of **91** proceeded again very slowly (2.5% within 12 h) to give a mixture of the corresponding hydroxy sulfoxides **92**, which could not be separated.[90]

Reduction of the fluorinated compounds **93** and **94** (Scheme 28) afforded an 87:13 mixture of diastereomers (R_C)-**95** and (S_C)-**96** with low ee values of 28% and 53%, respectively.[99] The stereochemistry on the sulfur atom

SCHEME 29



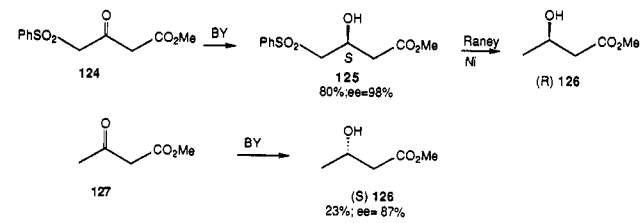
has not been assigned. The *p*-toluenesulfonyl analogue **97**, however, gave (*S*)-**98** of 89% ee.[103]

Several β-keto sulfones have been reduced by BY. Thus, (phenylsulfonyl)acetone (**99**) (Scheme 29) afforded (*S*)-2-hydroxypropyl phenyl sulfone (**100**) in 73%[98] or 98%[90] yield, and 97%[104] or 100%[98] ee. The rate of conversion was shown to depend on the ratio of educt to sucrose. Thus, the yield of 73% (ee = 100%) was obtained at a sucrose to **99** ratio of 2:1, whereas only 8% of **100** was obtained with sucrose:**99** = 1:2.[98] Interestingly, when the same experiment was performed without any sucrose, only 28% of product was obtained.[98]

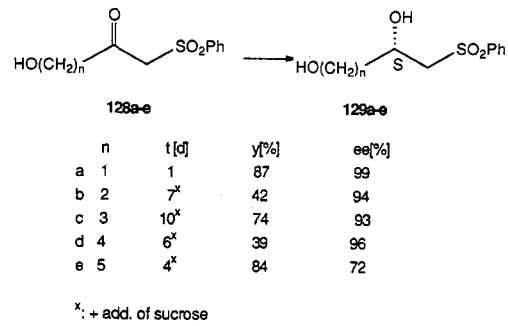
Decrease of the ee values resulted in an increase in the number of carbon atoms. Thus, **101** afforded (*S*)-**102** with 63% ee[104] and **103** gave (*S*)-**104** with 46% ee,[105] whereas reduction of **105** yielded only 10% of nearly racemic **106**.[90] No reduction by BY was observed for **107**.[105] **108** afforded upon reduction with BY (*R*)-**109** (87% yield and 15% ee).[65] Reduction with *Saccharomyces kyokai* 7, however, gave (*R*)-**109** with 84% yield and 92% ee.[65]

In addition to phenyl, tolyl-substituted compounds have been investigated. Similarly **110** (Scheme 29) was transformed into (*S*)-**111** (ee > 97%); the fluorine-containing educt **112** afforded (*S*)-**113** in 84% yield with an ee of >97%.[103] Finally, (benzylsulfonyl)acetone **114** gave 38% of **115** (ee > 95%).[90]

SCHEME 30



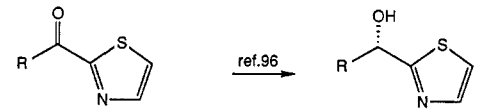
SCHEME 31



	n	t [d]	y[%]	ee[%]
a	1	1	87	99
b	2	7[x]	42	94
c	3	10[x]	74	93
d	4	6[x]	39	96
e	5	4[x]	84	72

[x]: + add. of sucrose

SCHEME 32



	R	t[d]	y[%]	ee[%]
a	CH_2OAc	1	29	88
b	CH_3	2	50	>95
c	nC_6H_{13}	3	28	28

116 gave diastereomers *anti*-**117** and *syn*-**118** in a ratio of 2.5:1, whereas the structural analogue **119** did not react at all.[104]

1-(Arylsulfonyl)-3-chloro-2-propanones **120** and **121** gave upon BY reduction 60% and 90% of enantiomerically pure (*S*)-**122** and (*S*)-**123**, respectively.[105,106]

BY reduction of **124** gave 80% of **125** (Scheme 30), which afforded on treatment with Raney nickel W4 (*R*)-**126**, whereas BY reduction of the β-keto ester **127** afforded the enantiomer (*S*)-**126** but the reduction of the sulfonyl ketone was more easily performed than the reduction of the β-keto ester.[65]

It was reported[108] that the introduction of a hydroxy group at the ω-position of a β-keto sulfone not only improved the enantioselectivity but also simplified conversion of the products into optically active lactones. Thus, β-keto sulfones **128a–e** (Scheme 31) gave the (*S*)-β,ω-dihydroxy sulfones **129a–e** with good to excellent ee.[108]

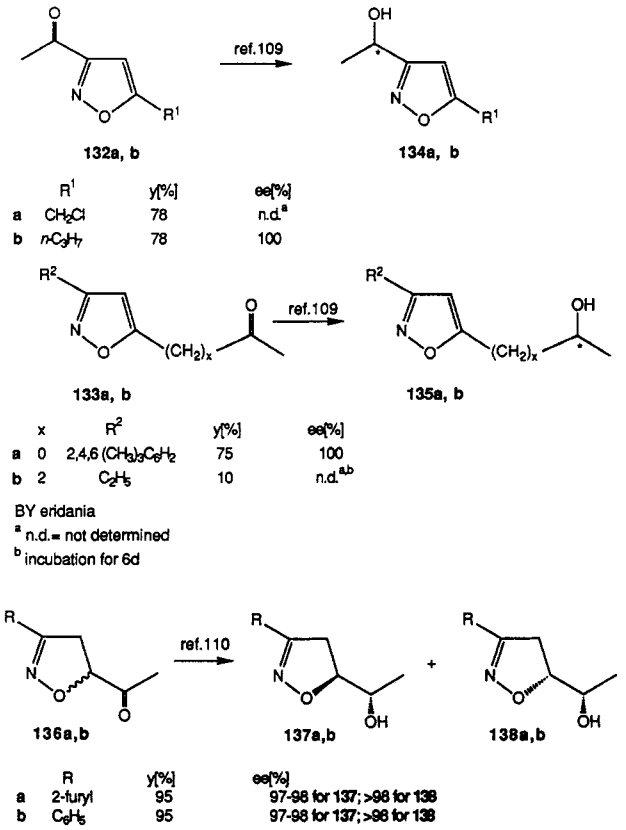
5. α-Heterocyclic Substituted Ketones

The reduction of 2-acylthiazoles **130a–c** (Scheme 32) gave poor yields of compounds **131a–c**. Only in the case of R = Me (**130b**) were yield and enantiospecificity satisfactory.[96]

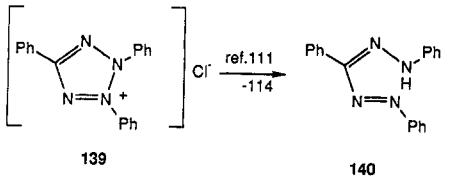
Better results, however, were obtained for the reduction of ketoisoxazoles **132a,b** and **133a,b** (Scheme 33) to carbinols **134a,b** and **135a,b**, respectively.[109]

Two examples have been provided for the reduction of 5-acetyl-2-isoxazolines[110] **136a,b**, which afforded at 35 °C (pH 3.3–8) **137a,b** (ee = 97–98%) and **138a,b** (ee > 98%). Alcohols **137** and **138** were formed at different rates, thus allowing partial kinetic resolution.[110] The

SCHEME 33



SCHEME 34

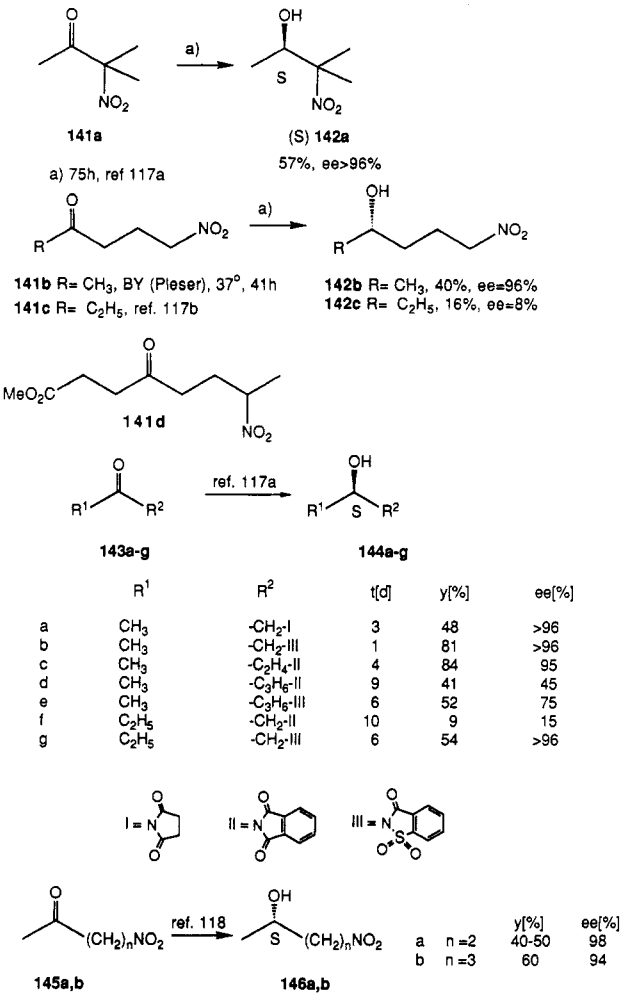


reduction of 2,3,5-triphenyltetrazolium chloride (**139**) (Scheme 34) to yield **140**[111-114] is noteworthy in this context.

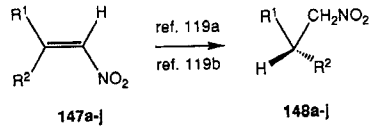
6. Nitrocarbonyl Compounds and Masked Amino Ketones

Although the reduction of aromatic nitro compounds is well documented,[40,115,116] no reduction of aliphatic nitro compounds seems to occur. Thus, the reduction of ketones containing additional nitro or imide moieties has been performed to give the corresponding secondary alcohols with excellent optical purities, but the nitro alcohols were relatively unstable under the conditions of the BY reduction because of decomposition by retro nitro aldol reactions.[117a] Despite these problems, 3-methyl-3-nitro-2-butanone (**141a**) (Scheme 35) gave 57% of the corresponding alcohol **142a** with an ee > 96%.[117a] **141b** afforded under aerobic conditions 40% of (*S*)-**142b**, **141c** gave **142c** albeit in low yield and with low ee, and **141d** gave nearly no reaction at all.[117b] Due to the instability of the nitro alcohols under the reaction conditions and the fact that some amino ketones are difficult to isolate due to Schiff base formation but also because of the high solubility of the corresponding amino alcohols in the aqueous phase, masked amino ketones **143a–g** have been investigated and the *S*-configured alcohols **144a–g** could be isolated.[117a]

SCHEME 35



SCHEME 36



	R¹	R²	y [%]	ee [%]
a	C_6H_5	H	26	n.d.
b	C_6H_5	CH_3	50	98
c	p-ClC_6H_4	CH_3	48	89
d	p-$Br-C_6H_4$	CH_3	57	94
e	p-$NO_2-C_6H_4$	CH_3	50	n.d.
f	C_6H_5	C_2H_5	64	97
g	C_6H_5	C_3H_7	23	89
h	C_6H_5	C_6H_{13}	--	--
i	C_6H_{13}	CH_3(E)	58	83
j	CH_3	C_6H_{13}(Z)	48	66

Similarly, **145a,b** gave the *S*-configured alcohols **146a,b** in about 40–60% yield, and good ee values of 98% and 94% could be achieved.[118]

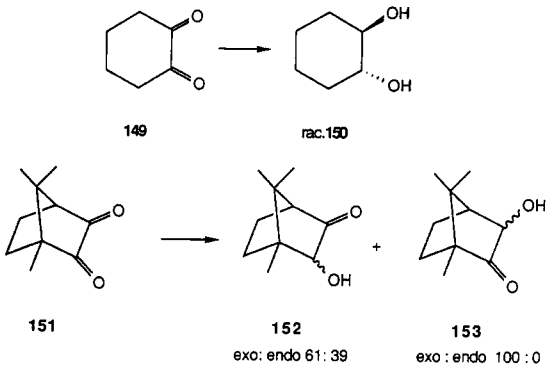
α,β-Unsaturated nitroalkenes **147a–j** (Scheme 36) were reduced with moderate to excellent ee to yield nitroalkanes **148a–j**.[119a,b]

C. Reduction of Dicarbonyl Compounds

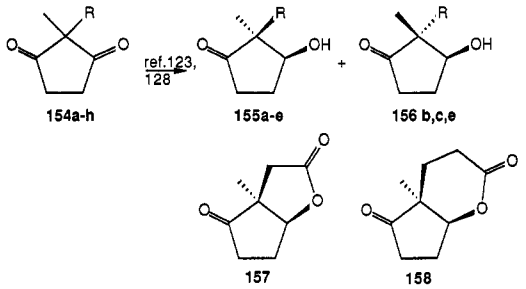
1. Cyclic Diketones

a. 1,2-Diketones. The reduction of cyclohexane-1,2-dione (**149**) (Scheme 37) gave racemic *trans*-cyclo-

SCHEME 37



SCHEME 38



Reduction of substituted cyclopentane-1,3-diones **154a-h**

educt	R	recovered educt [%]	yield [%] and product		diastereo-[a] selectivity	ref.
154a	$CH_2CH_2CH_3$	30	60	**155a**	100	123,124
154b	$CH_2CH{=}CH_2$	15	75	**155b/156b**	90:10	123[b]
154c	$CH_2C{\equiv}CH$	25	60	**155c/156c**	67:33	123,124
154d	$CH_2C(CH_3){=}CH_2$	10	75	**155d**	100	124
154e	$CH_2CH_2C{\equiv}N$	71	n.r.	**155e/156e**	96:4	128
154f	$CH_2CO_2CH_3$	80	9	**157**	100	128
154g	$CH_2CH_2CO_2CH_3$	25	52	**158**	100	128
154h	C_6H_5	n.r.	n.r.	**155h**	>98	125

[a] Assignments of previous works[123, 124] have been corrected; [b] additional references: 124, 126, 127.

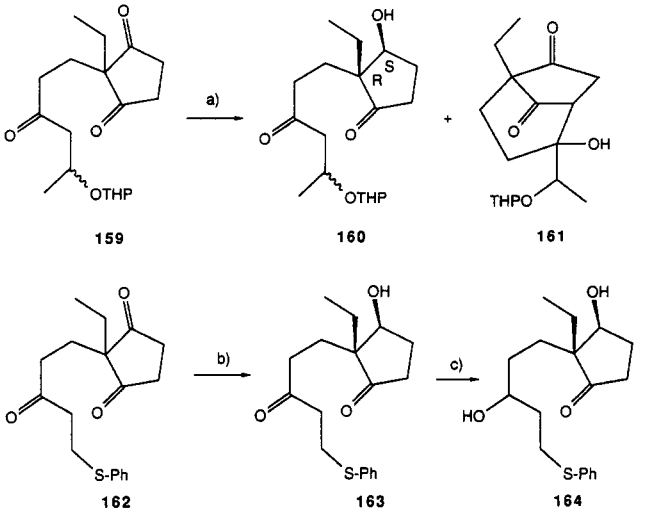
hexane-1,2-diol (**150**),[120] and under similar conditions camphorquinone (**151**) was transformed in 63% yield[40] into 3-hydroxycamphor (**152**) (exo:endo = 61:39) and *exo*-2-hydroxycamphor (**153**).

b. 1,3-Diketones. Similarly, asymmetric reductions of a series of 2,2-disubstituted 1,3-cycloalkanediones (Scheme 38) were investigated. First reports on these reductions were published in the mid-1960s[121a-122] followed by extensive recent studies by Brooks et al. These reductions can be regarded as an example of an enzyme-catalyzed distinction of a substrate containing two trigonal carbonyl centers with stereotopic faces and one prochiral tetrahedral carbon center where monoreduction generates two chiral centers. All of the products were obtained with ee > 98%.[123-128]

154f,g afforded lactones **157** and **158**, respectively. **155b** has been successfully used for the synthesis of the trichothecene mycotoxin anguidine[126,127,129] or for corriolin[123] and **155d** for the preparation of the diterpene zoapatanol.[124]

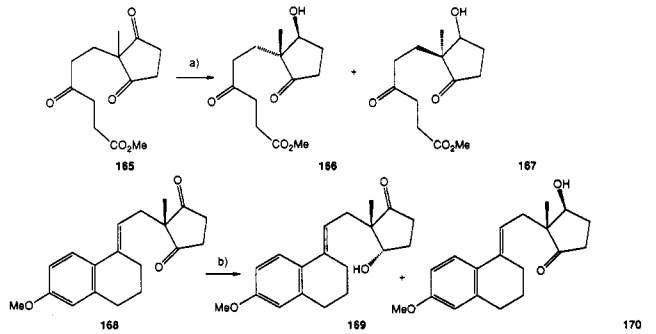
More complex 2,2-disubstituted 1,3-cyclopentanediones are potential precursors in the steroid field, and their reduction by BY has been investigated by several groups. **159** (Scheme 39) was cleanly reduced to **160** in 73%[130] or 78%[131] yield during 2[131] or 3[130] days. **161** was observed as a byproduct in about 4%[131] or 10%[130] yield. Similarly, **162** was reduced to (2*R*,3*S*)-**163**; **164** as a result of a second reduction was observed in approximately 13% yield. **164** was independently ob-

SCHEME 39



a) SC2346, 2-3d, 28-30°C, pH=6.7-7, educt in EtOH, ref. 130,131
b) SC2346, 25h, 30°C, pH=6.7-7, Tween80 added, educt in EtOH, ref. 132
13 % of **164** isolated, too.
c) SC2346, 47h, 30°C, pH 6.7-7, 5%, ref. 132

SCHEME 40



a) BY or *Schizosaccharomyces pombe* ATCC 2476, ref. 133,134

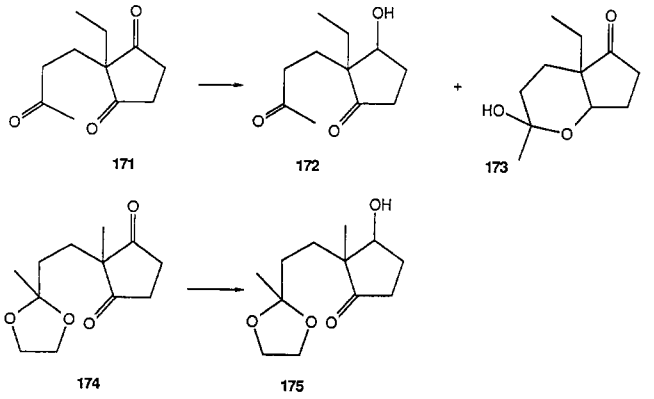
	y[%] of **169**	y[%] of 170	% direduction
b) Saccharomyces cerevisiae Y2246	30	20	20
Saccharomyces cerevisiae Y2250	60	15	10
Saccharomyces cerevisiae NCYC 1203	40	4	10

ref.121a

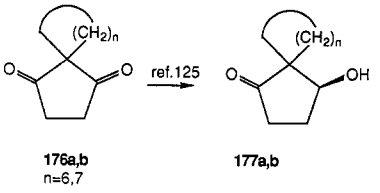
tained from **162** in 5% yield.[132] Reduction of **165** (Scheme 40) or BY (or *Schizosaccharomyces pombe* ATTC2476) resulted in the formation of **166** as the main product and **167** as the byproduct. Addition of activators[133] enhanced the rate and the extent of product formation and reduced the level of byproduct formation.[134]

As early as 1974 Lanzilotta[133] discovered activators for the reduction of cycloalkanediones. Allyl alcohol, acrylonitrile, methallyl alcohol, methacrylonitrile, acrylic aldehyde, α-methylacrylic aldehyde, and α,β-unsaturated ketones containing 3 to about 12 carbon atoms including cyclohex-1-en-3-one, methyl vinyl ketone, ethyl vinyl ketone, non-1-en-3-one, and dodec-1-en-3-one were shown to be activators. Typically, with *Saccharomyces cerevisiae* ATTC4097 or Y-147 NRRL, the reductions were performed for 24–120 h under aerobic conditions at 20–35 °C and pH 3.5–4.5; the activator to substrate ratio was about 1:1000 to 1:10 by weight.[133] A possible explanation for the effects of such activators could be that the activator compounds are suicide substrates for the oxidoreductases, affording undesired byproduct(s). Similarly, allylic alcohol was found to be a suicide substrate for the yeast alcohol de-

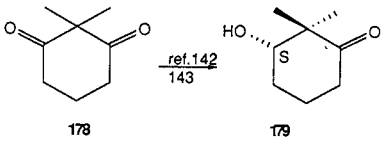
SCHEME 41



SCHEME 42



SCHEME 43



hydrogenase.[135] Unfortunately, application of these activator substances was up to now more or less only of theoretical interest but has only been scarcely used.[136]

Reduction of **168** with different fungi, bacteria, and yeasts[137] afforded changing amounts of **169** and **170**.[121a] The best result (85% yield) for **169** was obtained with *Bacillus thuringiensis* and for **170** with *Saccharomyces uvarum* (75% yield).[121a] A structural analogue has been reduced with acrylamide–*N*,*N*-methylenebisacrylamide immobilized *Saccharomyces cerevisiae*.[138]

Reduction of triketone **171** (Scheme 41) afforded, along with the reduction product of ketone **172**, cyclic hemiacetal **173**,[139] a problem that could be circumvented by using the acetal-protected compound **174** to yield **175**.[140,141]

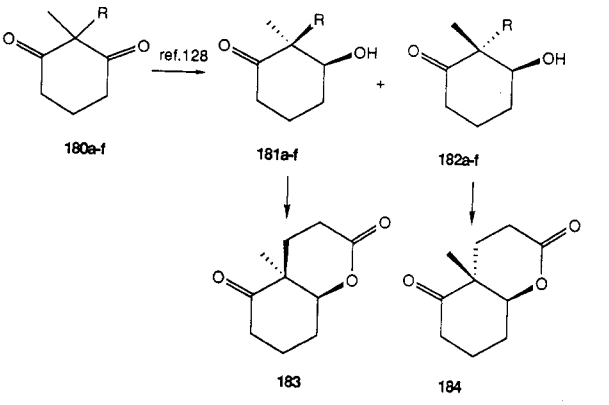
Spiro-fused diones **176a,b** (Scheme 42) were efficiently reduced to ketols **177a,b**.[125] The enantiomeric purity was >98% in each case, providing useful building blocks for both cyclopentanoid and cyclohexanoid natural products.

Cyclohexanoid 1,3-diketones **178** and **180a–f** (Schemes 43 and 44) have also been reduced (products **179** and **181–184**, respectively), with low diastereoselectivity as compared to the C_5 series (cf. Scheme 38).[128]

The simplest member of this class of compounds, 2,2-dimethylcyclohexane-1,3-dione (**178**) (Scheme 43), was reduced to (*S*)-**179** in 78% yield, and an excellent ee of 98.8% could be achieved upon addition of 0.2% Triton X to the fermentation broth with aeration.[142,143] Previous experiments with *Kloeckera magna* (ATTC 20109) gave **179** with comparatively lower yields and with lower ee. (The optical rotations reported for enantiomerically pure **179** are controversial.[143,144])

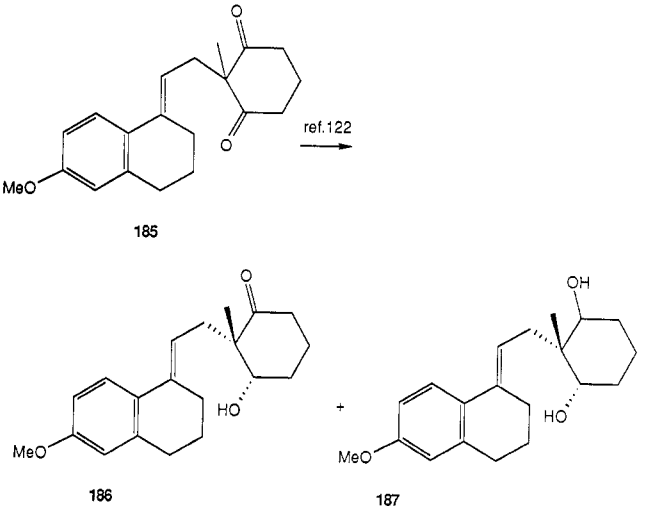
It is of interest to note that (*S*)-2,2-dimethyl-3-hydroxycyclohexane (**179**) is obtained in lower ee with

SCHEME 44



educt	R	recov. dione [%]	yield [%]	products
180a	$CH_2CH_2CH_3$	15	80	**181a:182a**=22:78
180b	$CH_2CH{=}CH_2$	15	80	**181b:182b**=45:55
180c	$CH_2C{\equiv}CH$	20	75	**181c:182c**=27:73
180d	$CH_2C(CH_3){=}CH_2$	20	49	**181d:182d**=40:60
180e	$CH_2CH_2C{\equiv}N$	30	49	**181e:182e**=30:70
180f	$CH_2CO_2CH_3$	60	49	**183:184** =35:65

SCHEME 45



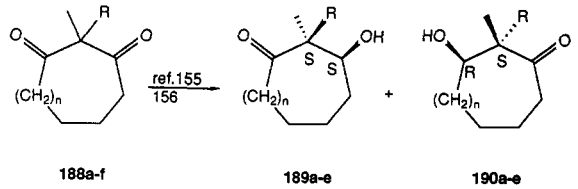
DMF/H_2O (1:38) as the solvent for this reaction.[145]

179 is a valuable intermediate and has been used both for the synthesis of (*S*)-2-hydroxy-β-ionon (isolated as a metabolite of β-ionone from the broth of *Aspergillus niger* and known to have an improving effect on tobacco flavor[146]) and for the synthesis of glycinoaclepin A (showing a significant hatch-stimulating activity for the soybean cyst nematode);[145] it has also been used for the synthesis of (–)-polygodial[147]—a hot-tasting sesquiterpene from *Polygonum hydropiper*,[148,149] which possesses antifeedant activity against African crop insects such as the army worm *Spodoptera exempla*.[150] Finally, **179** has been used for the synthesis[151] of the monoterpenoid karahana compounds of 6-oxabicyclo-[3.2.1]octane structure, being constituents of the Japanese hop, *Kumulus lupulus* s.[152–154] In addition, trimethyl-2-decalol was synthesized[142] in a straightforward manner.

Reduction of the steroid analogue **185** (Scheme 45) resulted in formation of **186** and **187** as products of direduction.[122]

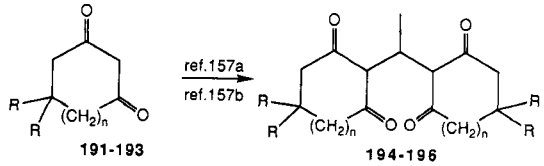
Reductions of cyclic 1,3-diketones being part of a medium-sized ring (Scheme 46) are not as effectively

SCHEME 46



educt	n	R	yield [%]	products [rel. %]	recovered educt [%]
188a	1	$-CH_2CH_2CH_3$	10	**189a:190a**= 2:98	75
188b	1	$-CH_2CH=CH_2$	20	**189b:190b**=100: 0	60
188c	1	$-CH_2C\equiv CH$	60	**189c:190c**= 71:29	30
188d	1	$-CH_2C(CH_3)=CH_2$	40	**189d:190d**= 55:45	50
188e	2	$-CH_2CH=CH_2$	5	**189e:190e**= 82:18	75
188f	3	$-CH_2CH=CH_2$	0	---	80

SCHEME 47



191 R=H, n=0
192 R=H, n=1
193 R=CH_3, n=1

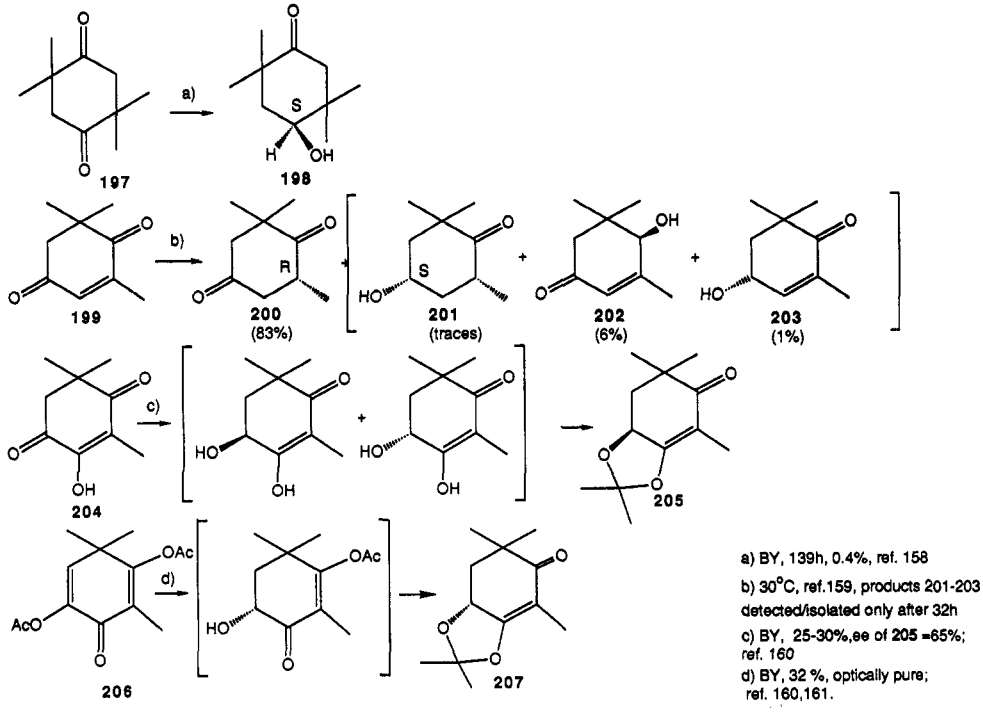
achieved as in the case of the five- or six-membered rings and resulted in high recovery rates. Of interest is the opposite diastereoselectivity in the yeast reduction of the propyl dione **188a** versus the allyl dione **188b** and the lack of stereoselectivity for the methyl allyl dione **188d**. The diastereoselectivity of the BY reduction parallels that of the $NaBH_4$ reduction of these compounds.[155,156]

In contrast to these results, cyclohexane-1,3-dione (**191**), cyclopentane-1,3-dione (**192**), and 5,5-dimethylcyclohexane-1,3-dione (**193**) (Scheme 47) gave dimers **194–196**, respectively, resulting from a dimerization of the 1,3-dione with acetaldehyde produced by fermenting yeast.[157a,b]

c. 1,4-Diketones. The reduction of cyclic diketones has not been limited to the 2,2-disubstituted 1,3-diones but has also found extension and applications for cyclic 1,4-diones (Scheme 48). 2,2,5,5-Tetramethyl-1,4-cyclohexanedione (**197**) was relatively inefficiently (0.4%) reduced. The desired reaction product, 4-hydroxy-2,2,5,5-tetramethylcyclohexan-1-one (**198**), however, was efficiently obtained by employing *Curvularia lunata* NRLL2380 (75 h, 98.2% yield, ee > 98%).[158]

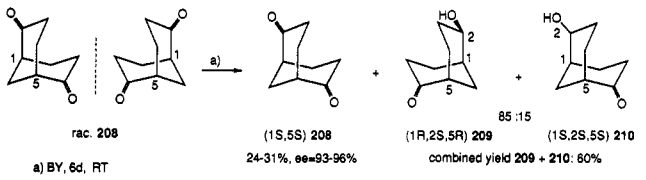
Of more success was the reduction of oxoisophorone (3,5,5-trimethyl-2-cyclohexene-1,4-dione, **199**), a precursor for the straightforward synthesis of cryptoxanthin and zeaxanthin. This reduction afforded in principal four reduction products although formed at different rate. In general, the reduction of the C–C double bond is very quickly achieved, and a maximum of the main reaction product **200** is reached within the first 32 h (83%). Then, **201** is formed from **200**. **202** and **203** are formed very slowly and in minor concentrations of 6% and 1%, respectively. The rate of formation of **200** is strongly dependent on the concentration of **199**, and best results (with respect to the desired **200**) were obtained with a concentration of 5–6 g/L of **199**. Between 7 and 12 g/L of **199** the fermentation process slowed, and finally, at a value of 12 g/L, inactivation of the cells was found. Interestingly, the yeast cells were inactivated by increasing concentrations of **201–203**, but not by **200**, which precipitated from the fermentation broth. Under optimum conditions the BY cells could be recycled up to six times.[159] Reduction of the 4-hydroxyisophorone analogue **204** followed by acetonization gave 25–30% of **205** with an ee of 65%. The low-tolerated substrate concentration (1 g/L up to 3 g/L if semicontinuous substrate feeding was applied) is a drawback of this method.[160] Use of **206** afforded upon ester hydrolysis and enantioselective double-bond

SCHEME 48

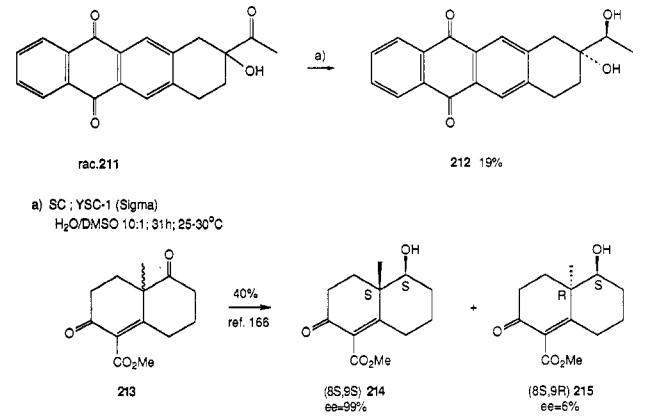


a) BY, 139h, 0.4%, ref. 158
b) 30°C, ref.159, products 201-203 detected/isolated only after 32h
c) BY, 25-30%,ee of **205** =65%; ref. 160
d) BY, 32 %, optically pure; ref. 160,161.

SCHEME 49



SCHEME 50



hydrogenation of the less hindered enol ester group followed by hydrolysis and acetonization enantiomerically pure **207** in 32% yield.[160,161]

Racemic bicyclo[3.3.1]nonane-2,6-dione (**208**) (Scheme 49), an intermediate for the synthesis of optically active adamantane compounds, was reduced by BY, and the (1*S*,5*S*)-**208** dione could be recovered in 24% yield (93% ee) on small preparative scale whereas in a larger scale preparation an ee of 66% was achieved (after 2 days), which increased to 83% after a total reaction time of 6 days (31% yield). (1*R*,2*S*,5*R*)-**209** (60%) and (1*S*,2*S*,5*S*)-**210** in an 85:15 ratio and 5% of diol were isolated. (1*S*,5*S*)-**208** of 60% ee (isolated after 18-h reaction time) was subjected to a second BY transformation (24 h) to yield (1*S*,5*S*)-**208** of 96% ee.[162]

No reduction of the cyclic diketone was achieved with compound **211** (Scheme 50); reduction only occurred at the side chain to afford **212** in 19% yield. The asymmetric center involved did not provide any effect on the stereoselectivity of the microbial reduction.[69]

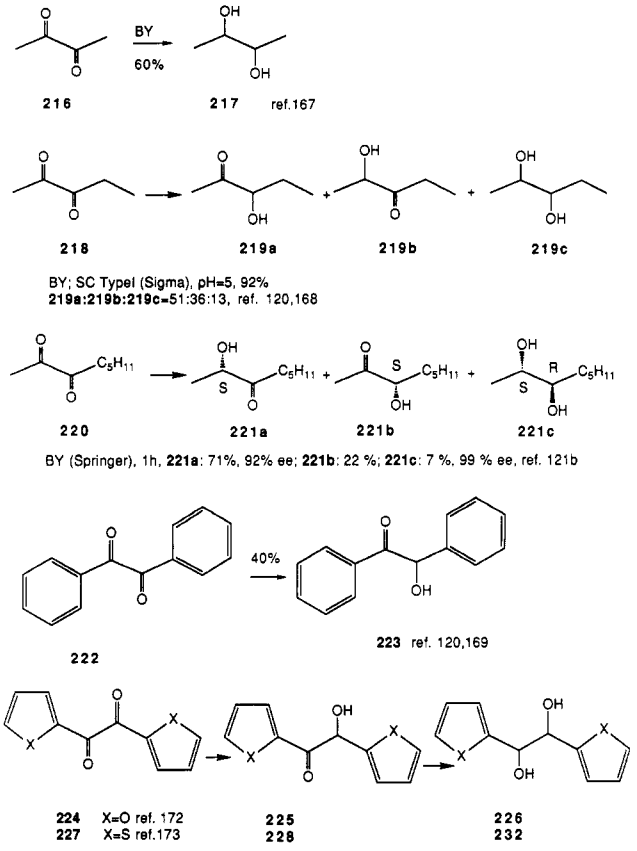
Very early attempts at reduction of quinones were successful although low yields were obtained. Anthrodiquinone yielded quinizarin,[163,164] phenanthraquinone,[164] thymoquinone,[163] α-naphthoquinone,[163] and *p*-xyloquinone[165] gave the corresponding hydroquinones, and tetrabromo-*o*-quinone[163] and anthraquinone[163] proved to be resistant to attack.

Microbial reduction of the racemic diketone **213** afforded 40% of an inseparable mixture of (8*S*,9*S*)-**214** and (8*S*,9*R*)-**215** in a ratio of 77:23.[166]

2. Acyclic Diketones

a. 1,2-Diketones. The reduction of acyclic 1,2-diketones by BY is a long-known reaction. Thus, butane-2,3-dione (**216**) (Scheme 51) gave 2,3-butanediol (**217**) in about 60% yield.[167] 2,3-Pentanedione (**218**) and 2,3-octanedione (**220**) gave mixtures of racemic mono- and direduction products **219a–c**[54,120,168] and **221a–c**[121b] in high yields. Similar results were obtained for 2,3-hexanedione,[120] and pentane-2,3,4-trione gave only 2.4% of pentane-2,3,4-triol.[54] Methylglyoxal was reduced

SCHEME 51



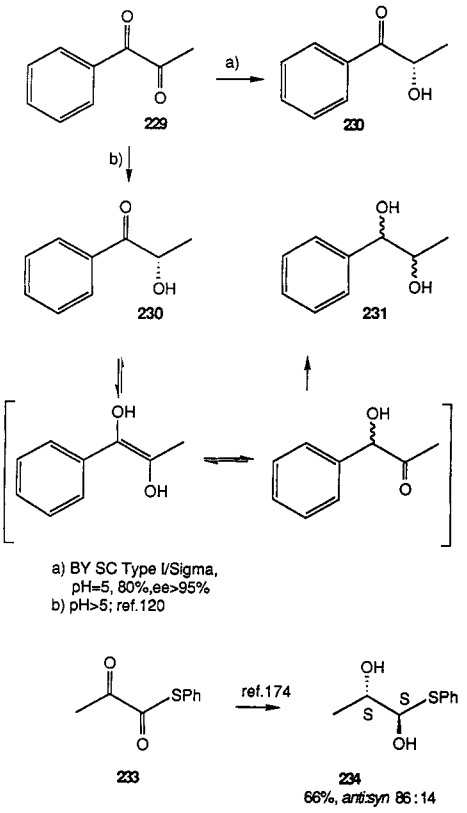
predominantly to D-1,2-propanediol in about 65% yield.[54]

The BY reduction of benzil (**222**) stopped at the monoreduction stage with benzoin (**223**),[120,169] whereas (*S*,*S*)-(94% ee)[170] or (*R*,*R*)-hydrobenzoin (96% ee)[171] could be obtained by using *Saccharomyces montanus*,[170] *Rhodotorula glutinis*,[170] or *Candida macerans*,[171] respectively. In contrast to these findings with **222**,[169] it is of interest to note that furil (**224**) was very quickly reduced via furoin (**225**) into hydrofuroin (**226**).[172] Similarly, **227** and **228** have been reduced by BY to result in formation of **232**.[173] 1-Phenyl-1,2-propanedione (**229**) (Scheme 52) was reduced by BY at pH 5 to (*S*)-(−)-2-hydroxy-1-phenyl-1-propanone (**230**) whereas at pH >5 **230** together with the direduction product **231** were obtained. A possible explanation is depicted in the Scheme 52.[120]

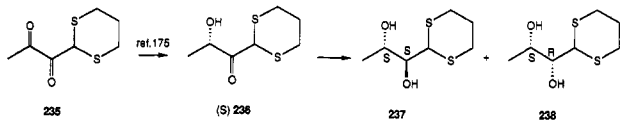
Although 1,2-diketones are good substrates for BY, the selectivity of the reductions is rather low. Introduction of a bulky sulfur-containing moiety (which can easily be removed) is an effective way to stereochemically control these reductions (cf. II.B.4.). Thus, 1-(phenylthio)-2,3-butanedione (**233**) gave mainly (2*S*,3*S*)-1-(phenylthio)-2,3-butanediol (**234**) (anti:syn = 86:14 with a total yield of 66%).[174]

Similarly, 1-(1,3-dithian-2-yl)-1,2-propanedione (**235**) (Scheme 53) gave upon BY reduction after 2 h 60% of (*S*)-1-(1,3-dithian-2-yl)-2-hydroxy-1-propanone (**236**) whereas prolonged reaction time afforded the product of a direduction, (1*S*,2*S*)-**237**, with an ee of 97%; 5% of the syn-configured product **238** could be detected. The large difference between the reduction rates of the two carbonyl groups was attributed to the bulkiness around them. In comparison, reduction of **235** with diisobutylaluminum hydride (−90 °C) gave 74% of a

SCHEME 52



SCHEME 53



mixture of **238** and **237** (syn:anti = 89:11); $ZnBH_4$ (−90 °C) afforded 58% of the mixture of **238** and **237** (syn:anti = 86:16).[175]

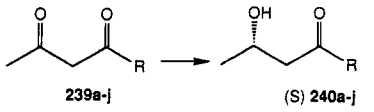
b. 1,3- and 1,4-Diketones. Similarly, reductions of acyclic 1,3-diketones have been attempted, but the results obtained were not satisfying. Thus, 2,4-pentanedione was hydrogenated only slowly and incompletely by fermenting yeast.[176] A comparative study for the reduction of different 2,4-diones **239a–j** (Scheme 54) showed for the reduction by BY excellent ee values with predominant formation of (*S*)-**240a–j**; only monoreduction was observed.[177-181] Reduction by the yeastlike fungus *Geotrichum candidum* or by *Aspergillus niger*, however, proceeded much faster and resulted for **239a,b,h,i** products of opposite configuration.

Analogue **241** (Scheme 55) was easily reduced within 3 days by BY (Hirondelle) in quantitative yield but only with low ee (30%) to (*R*)-**242**.[177] Reduction of the more lipophilic **243** gave after 100% conversion a 33:67 mixture of ketols **244** and **245**, each exhibiting an ee of 98%.[180]

For the 3-methyl-branched compound **246** an 80:20 mixture of the *syn*-(3*R*,4*S*)-**247** and *anti*-(3*S*,4*S*)-**248** isomers was isolated in 30% yield (Scheme 56). This result suggests that there is high enantiofacial selectivity in reduction of the enantiotopic carbonyl groups but low diastereofacial selectivity since (3*R*)- and (3*S*)-methyl ketols were obtained.[180,182a]

4-Methylheptane-3,5-dione (**249**) was found to be reduced only by *Geotrichum candidum*[182b] to yield

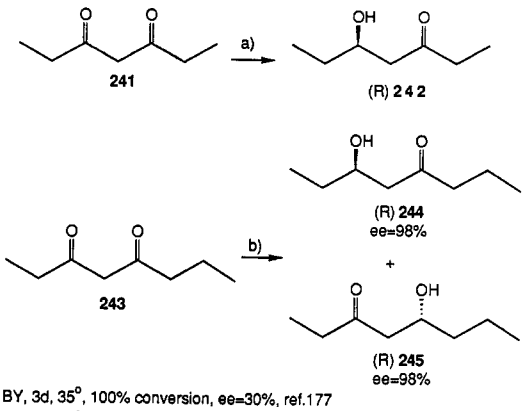
SCHEME 54



	R	t[d]	y[%]	ee[%]	ref.
a	CH_3	6	90	>99	177,180
		2	18	>99	179
b	C_2H_5	3	100	>99	177,180
		2	48	97	179
c	n-C_3H_7	2	62	94	179
d	n-C_4H_9	2	42	>99	179
e	n-C_5H_{11}	2	25	96	179
f	n-C_8H_{17}	2	23	97	179
g	i-C_3H_7	2	24	92	179
h	C_6H_5	2	21	94	179
		6	33	98	181
		3	90	98	180[a]
i	$C(CH_2)_3CH{=}CH_2$	3	100	>99	177,180
j	$(CH_2)_3R^1$	2	n.r.	97.5	178

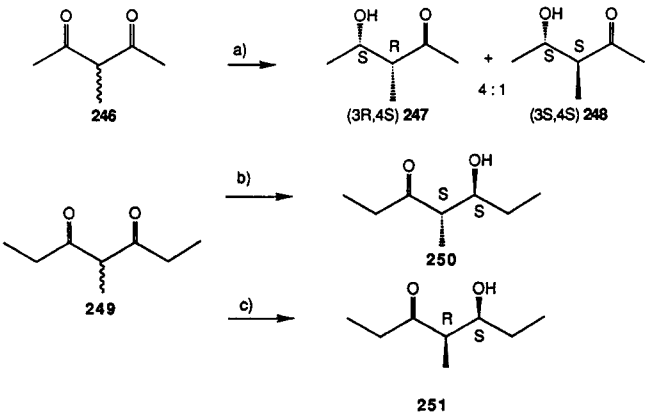
a) mixture of 2-hydroxy- and 4-hydroxyketone 85:15 R^1=

SCHEME 55

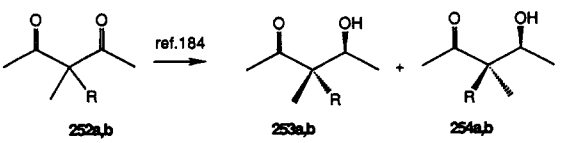


a) BY, 3d, 35°, 100% conversion, ee=30%, ref.177
b) BY, 3d, 35°, 100% conversion, ref.180

SCHEME 56



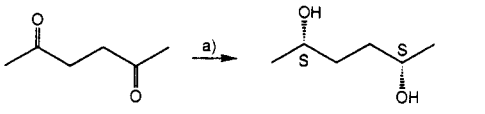
a) BY, 6d, 35°, 30%, ee=95%, ref.177,180
b) Geotrichum candidum, aerobic; c) anaerobic



a $R = CH_2CH{=}CH_2$
b $R = CH_2C(CH_3){=}CH_2$

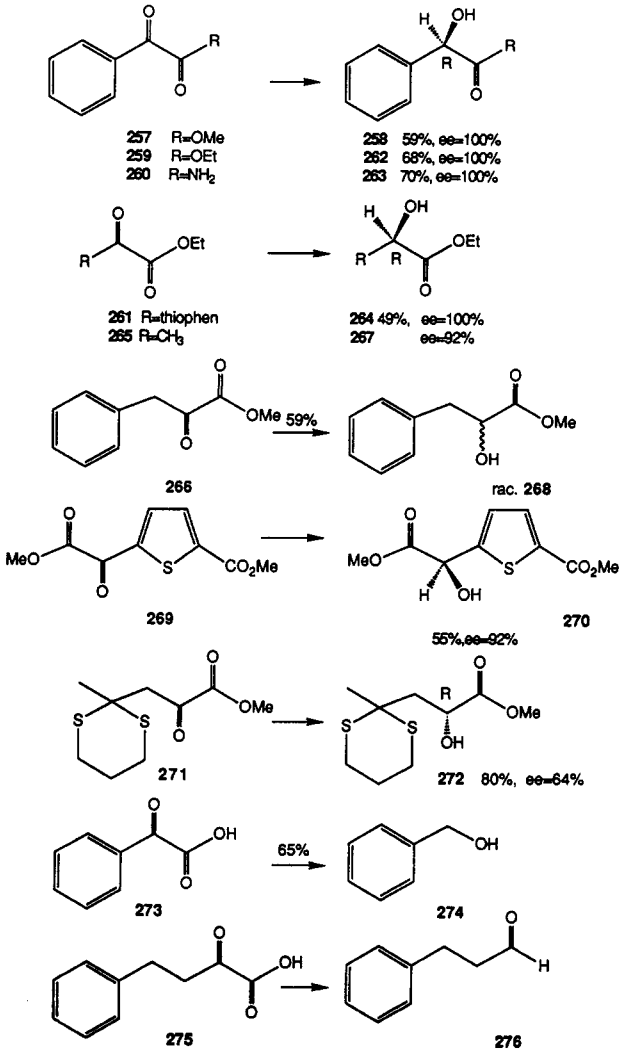
under aerobic conditions (4*S*,5*S*)-4-methyl-5-hydroxyheptan-3-one (**250**) or the 4*R*,5*S* stereoisomer **251** under anaerobic conditions.[182b] The reduction by BY failed.

SCHEME 57



a) BY (Budweiser), 144h, ref.185a, 185b

SCHEME 58



251 (contaminated with 0.5% of **250**) was found to be the aggregation pheromone sitophilure of the rice weevil *Sitophilus oryzae* L. and the maize weevil *Sitophilus zeamais* Motsch.[183]

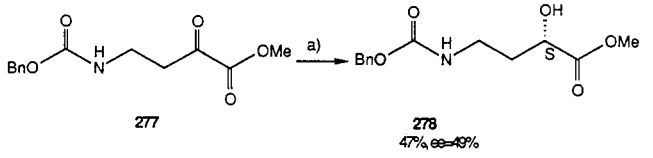
Yeast reduction of the 1,3-diketones **252a,b** bearing a quaternary carbon atom proceeded well and provided mixtures of diastereomeric ketols **253a,b** and **254a,b** with >98% enantiomeric purity.[184]

In contrast to the exclusive monoreduction of these 1,3-diketones, 2,5-hexanedione (**255**) (Scheme 57) was cleanly reduced to (2*S*,5*S*)-hexane-2,5-diol (**256**).[185a] HPLC analysis indicated the presence of *S,S*, *R,S*, and *R,R* diols in the ratio 49.8:1.04:1 (96% ee, 2% meso). This was upgraded to >98% ee and <1% meso by recrystallization.[185b]

D. Reduction of α-Keto Esters

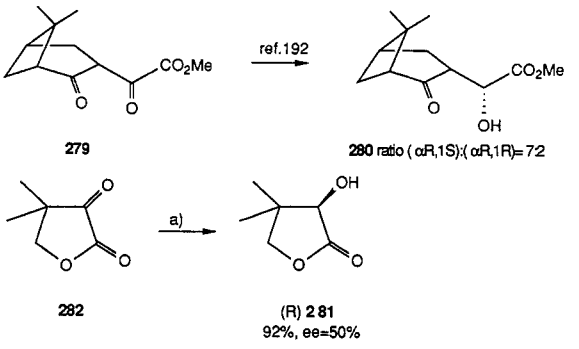
Although there are not as many examples as for the reduction of β-keto esters, α-keto esters have also been

SCHEME 59



a) BY, 12h, r.t., ref.187

SCHEME 60



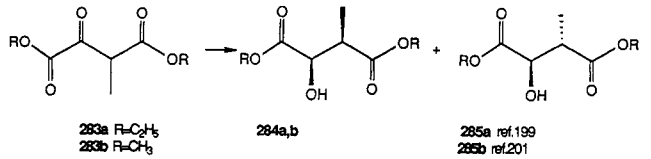
a) BY, 4h, 42%, ref.197, pH=3.2-3.5, aerated, 24h, 30°, ref.193

successfully reduced by BY. 2-Oxo-2-arylacetic acid derivatives **257**, **259**,[186,187] **260**,[186] and **261**[186] (Scheme 58) gave optically pure α-hydroxy acid derivatives **258**, **262**,[186,187] **263**,[186] and **264**,[186] respectively. The 2-oxoalkanoic esters **265** and **266** produced alcohols **267** (92% ee) and **268**; the latter product was found to racemize under the reaction conditions.[186] Ethyl pyruvate (**265**) is reduced to (*R*)-ethyl lactate[186] whereas pyruvate is reduced by purified yeast alcohol dehydrogenase in the presence of NADH into (*S*)-lactate.[188] The thiophene derivative **269** was reduced in fair yield to the corresponding alcohol **270**, a precursor in the synthesis of daucic acid, present in wheat, sugar beet, and sunflower.[189] Batyl alcohol, the key intermediate for the preparation of platelet activating factor, was synthesized from the keto ester **271**, which gave on BY treatment the corresponding (*R*)-(+)-alcohol **272** in high yield (80%), but only with a moderate ee of 64%. Use of *Saccharomyces cerevisiae* Kisato improved the ee (89%), although the yield dropped significantly (22%). The highest ee (99%) but very low yield (15%) were finally achieved, however, with *Torulopsis sp.* Jyozokyokai 17,[190] keto acid **273**, however, decarboxylated under the same conditions to give 65% of benzyl alcohol (**274**),[76] whereas **275** afforded aldehyde **276**.[191] **277** (Scheme 59) yielded after 12-h incubation with fermenting BY 47% of (*S*)-**278** (49% ee), which served as a precursor for the synthesis of the antibiotic butirosin.[187]

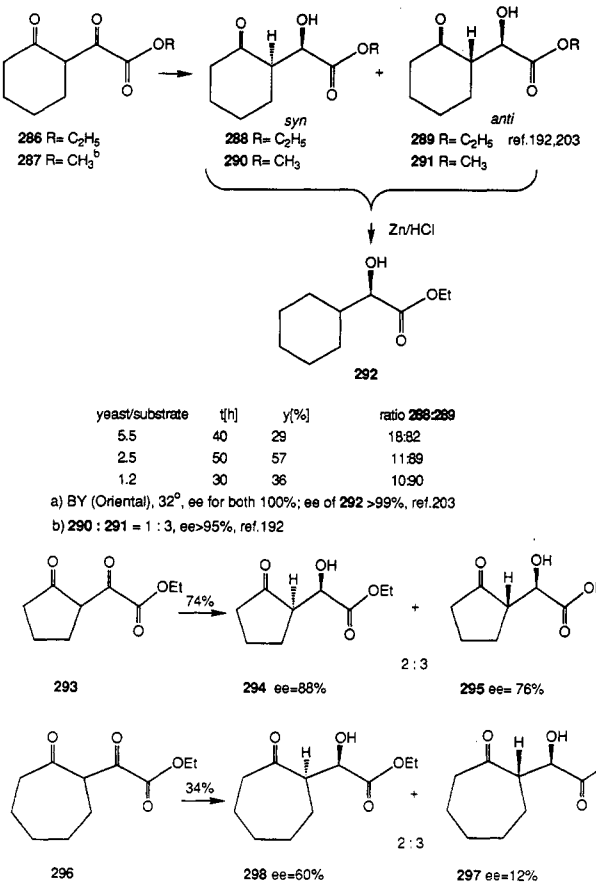
Regiodifferentation has been achieved for the bicyclic educt **279** (Scheme 60), affording upon reduction a 7:2 mixture of diastereomers **280**.[192]

The synthesis of enantiomerically pure (*R*)-pantolactone (**281**) was achieved via enantiospecific reduction of ketopantolactone (**282**). Among a broad variety of microorganisms[193] highest optical and chemical yields have been reported with *Rhodoturula minuta*,[194] *Candida parapsilosis* and *Aspergillus niger*,[195] or *Byssochlamys fulva*[196] whereas the BY (Fleischmann's, Red Star, or Anheuser-Busch) mediated reduction gave low yields[197] or low ee values.[193] In addition, a 2-ketopan-

SCHEME 61



SCHEME 62



yeast/substrate	t[h]	y[%]	ratio 288:289
5.5	40	29	18:82
2.5	50	57	11:89
1.2	30	36	10:90

a) BY (Oriental), 32°, ee for both 100%; ee of **292** >99%, ref.203
b) **290** : **291** = 1 : 3, ee>95%, ref.192

tolactone reductase (optimum pH 7) and a 2-ketopantoic acid reductase (optimum pH 5) have been isolated from baker's yeast.[198]

E. Reduction of α,γ-Diketo Ester and Keto α,γ-Diester

Diethyl 2-methyl-3-oxosuccinate (**283a**) (Scheme 61) gave a 43:57 mixture of *syn*-(2*R*,3*R*)-**284a** (79% ee) and *anti*-(2*S*,3*R*)-**285a** (31% ee). Higher ee's were obtained by use of *Candida albicans* instead of BY.[199] It was shown that formation of **284** decreases with increasing substrate concentration.

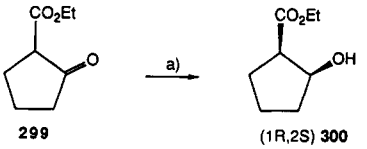
Low ee values (of 65 and 20%, respectively) were obtained for the reduction (57% yield) of dimethyl 2-methyl-3-oxosuccinate (**283b**), affording an inseparable mixture[200] of dimethyl 2-methylmalates[201] **284b** and **285b** in a ratio of 53:47. A lower yield (22%) but a better ratio (**284b**:**285b** = 64:36) and higher ee values (95% and 58%[202]) were obtained with *Candida albicans*.

Several diketo esters of differing structural type have been reduced by BY. Optically pure (*R*)-(−)-hexahydromandelic acid has been synthesized by reduction of the cyclohexanone derivatives **286** and **287** under fermenting conditions (Scheme 62). Mixtures of *syn*-**288** and *anti*-**289** or of **290** and **291** (1:3, ee = 95% for both components) were obtained, which gave on subsequent treatment with Zn/HCl the optically pure (*R*)-(−)-hexahydromandelic ester **292** with an ee >99%.[192,203]

It was found for **286** that the ratio of syn to anti depended on the relative amount of BY to substrate. The chemical yield and the anti selectivity increased as the ratio of the amount of yeast was decreased. No higher yield or better diastereoselectivity was obtained with immobilized yeast.[203]

The cyclopentanone analogue **293** gave higher yields (74%) of **294** and **295** (in a ratio of 2:3) although with reduced enantiomeric excess. With the cycloheptanone **296** both yields and ee's dropped. Only 34% of **297** (12% ee) and **298** (60%) were obtained (**297**:**298** = 3:2).[192]

SCHEME 63



a) 80%, de=100%, ee= 100%; ref. 186, n.d., de=60%, ee= n.d.; ref.206

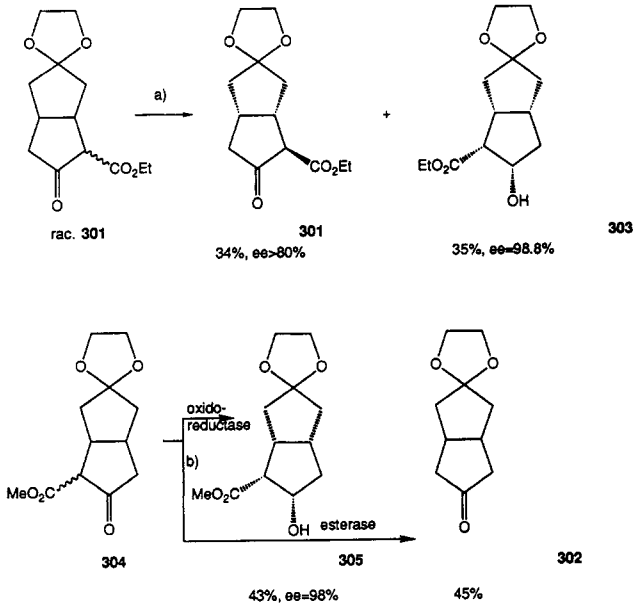
F. Reduction of β-Keto Esters

1. β-Keto Esters with the Keto Group Being Part of the Ring

The enantioselectivity of the reduction of cyclic keto esters seems to be higher than that of open-chain β-keto esters substituted at C-2 (cf. F.2., Scheme 69).[204,205] There are several examples of the reduction of cyclic β-keto esters by BY. Thus, reduction of **299** (Scheme 63) is performed in 80% yield, leading to a de of 100% of *cis*-**300**;[186] in another experiment,[206] **300** was obtained with a de of 60%. These reductions with BY produce 2-hydroxy esters of predominant 1*R*,2*S* configuration. In general, *Saccharomyces cerevisiae* gives for these types of compounds often mixtures of optically pure diastereomeric hydroxy esters, predominantly of 2*S* configuration, whereas mold strains often exhibit a very high dia- and enantioselection and give only *one* optically pure cis or trans stereoisomer.[206]

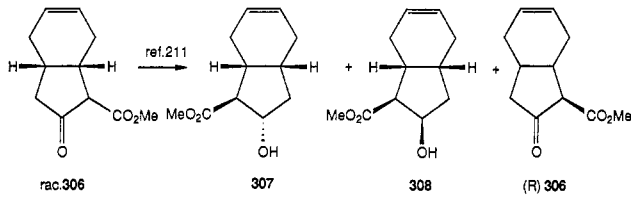
The 1*R*,5*S* enantiomer of racemic methyl (±)-3-oxo-7,7-(ethylenedioxy)bicyclo[3.3.0]octane-2-carboxylate (**304**) was reduced in high optical purity to the methyl (1*R*,2*R*,3*S*,5*S*) 3-hydroxy-7,7-(ethylenedioxy)bicyclo-[3.3.0]octane-2-carboxylate (**305**), whereas the 1*S*,5*R* enantiomer of **304** gave achiral **302** (Scheme 64). Formation of the latter can be explained by a hydrolysis of (1*S*,5*R*)-**304** followed by a subsequent decarboxylation of the proposed intermediate β-keto acid.[207] These transformations can be regarded as a simultaneous dual kinetic resolution performed by two different enzymes of BY. Mori et al.[208] found the reaction of **301** with fresh BY (Oriental) to proceed smoothly and to give (+)-**301** in 34% yield (ee > 80%) together with 35% of *cis*-**303** (ee = 98.8%). In comparison, dry BY gave **301** in 61.8% ee. *Saccharomyces bailii* yielded **301** of 92–94% ee, but its use was more time-consuming due to the necessity of performing a precultivation of the microorganism.[209] In addition, BY was found to remove the acetal group under fermenting conditions.[209]

SCHEME 64



a) BY, 30°C, 24h, pH=7; ref.208,209
b) BY, ref.207

SCHEME 65



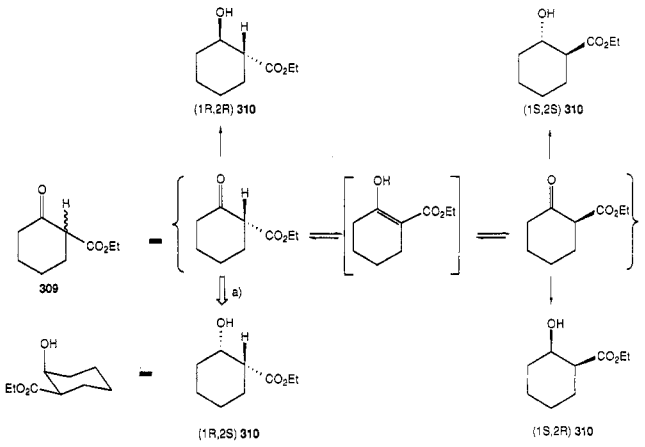
303 is an important precursor for the synthesis of pentalenolactone E, a sesquiterpene antibiotic isolated from cultures of *Streptomyces* 4C5319.[210] Enantiomerically pure **301** could be transformed into (+)-carba-PGI_2 (carbaprostaglandin). The reduction of racemic methyl 8-oxobicyclo[4.3.0]non-3-ene-7-carboxylate (*rac*-**306**) (Scheme 65) afforded only the trans isomer **307** although in low yield, but ee > 99% and 40% of starting material exhibiting an ee of 27% could be recovered whereas *Kloeckera saturnus* gave both cis and trans isomers (**307**:**308** = 73:27, ee (**307**) = 99%, ee (**308**) = 99%) and the recovered starting material (*R*)-**306** in high optical purity (ee = 96%).[211]

The reduction of 6-membered cyclic β-keto esters is more widespread. Reduction of the simplest compound of this class, racemic **309**, was performed by BY (Scheme 66)[186,206,212a,b] in 65–85% yield and resulted in formation of ethyl (+)-(1*R*,2*S*)-2-hydroxycyclohexanecarboxylate (**310**) in 86% ee[213] or with an ee of 96–99%[206,212a] and a diastereoselection giving rise to a de of 76%,[206] 86%,[212b] or 99%.[212a] One of the possible diastereomers (of cis configuration) was produced in excess—a fact that was due to an equilibrium by enolization (with concomitant racemization) of the educt followed by kinetic resolution.

The allyl-branched derivative **311** (Scheme 67) was found to be a less suitable substrate for BY. It was reduced only to an extent of about 10% to (1*S*,2*S*)-**312**, and 20% of starting material was recovered, comprising an ee of approximately 27%.[213]

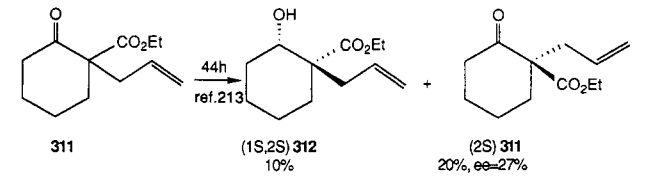
Reduction of racemic ethyl 2-oxo-4,4-(ethylenedioxy)cyclohexanecarboxylate (**313**) (Scheme 68) by BY

SCHEME 66

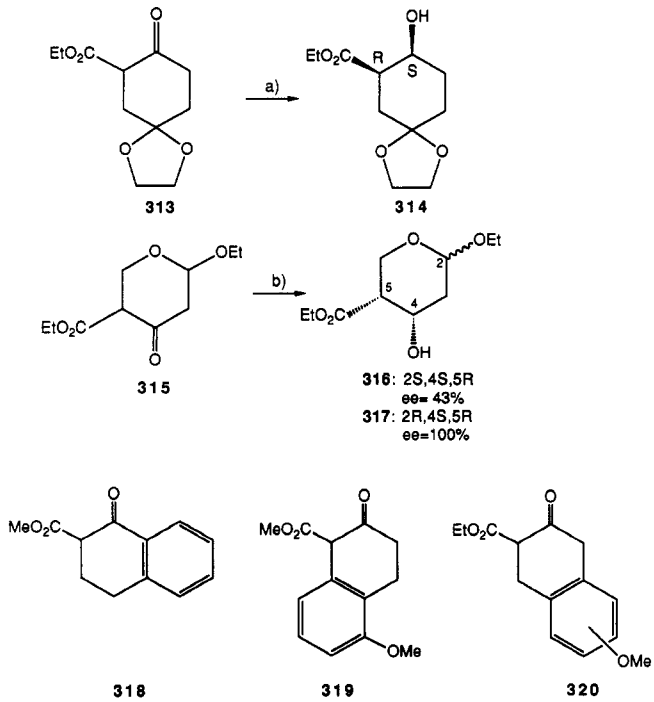


a) BY, 65-85%, r.t., ee=86-99%, ref.186,206,212,213

SCHEME 67



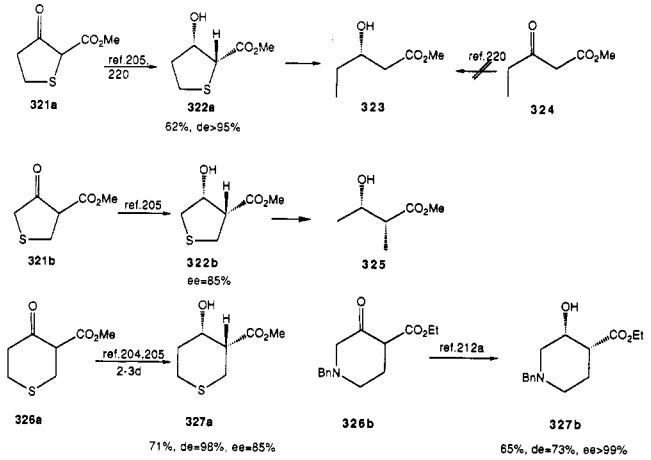
SCHEME 68



a) 74-86%, 30°C, 12h, aeration, ee=98.4%, recovered ca. 15%; ref.212,214,215
b) 81%, 1h, 30°C, pH=8, Triton X, ref.219

afforded in 74% yield the corresponding ethyl (1*R*,2*S*)-4,4-(ethylenedioxy)-2-hydroxycyclohexanecarboxylate (**314**),[214,215] which was used[215] for the synthesis of sporogen-AO-1, a sporogenic sesquiterpene from *Aspergillus oryzae*.[210,216–218] The aerated fermentative reduction of **315** afforded a mixture of diastereomers **316** and **317** in a ratio of 63:27. Interestingly, (2*S*,4*S*,5*R*)-**316** was obtained only with an ee of 43% whereas the minor (2*R*,4*S*,5*R*)-**317** was found to exhibit an ee of 100%. Both *Saccharomyces bailii* and *Pichia*

SCHEME 69



terricola were found to be unsuitable for this reduction of **315**.[219]

Several benzo-annelated oxo esters, e.g., of type **318–320**, were successfully reduced to their corresponding cis hydroxy esters under "starving conditions" in fair to excellent yield, de, and ee.[212a]

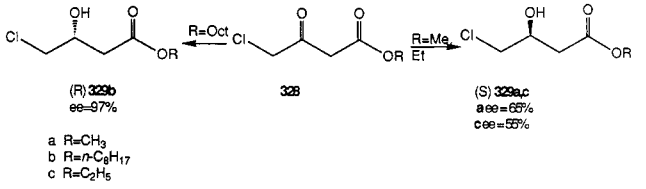
The reduction of such cyclic β-keto esters can be extended to 5- and 6-membered rings containing one additional ring heteroatom instead of a carbon. Reduction of methyl tetrahydro-3-oxothiophene-2-carboxylate (**321a**) (Scheme 69) yielded in high diastereomeric excess (>95%) the corresponding (2*R*,3*S*)-3-hydroxy derivative **322a**.[205] **322a** afforded upon treatment with Raney nickel (3*S*)-**323**, which cannot be obtained by BY reduction of the keto ester **324**.[220]

Similarly, **321b** gave with an ee of 85% **322b**;[205] the analogous reduction of the methyl thiacyclohexanone-2-carboxylate (**326a**) is the key step in a synthesis of (4*RS*,6*S*,7*S*)-serricornine, a pheromone of the cigarette beetle.[205] **327a** is obtained in 98% diastereomeric purity, 85% ee, and a yield of 71%.[204] No higher ee was obtained for this transformation with the corresponding acid instead of the ester or by working in a more diluted solution.[204] The piperidone derivative **326b** afforded **327b** in 65% yield (de = 73%, ee > 95%).[212a]

2. Aliphatic Keto Esters

a. General Remarks. Reductions of β-keto esters by BY are well documented and have been reviewed recently.[26,55,56,221-223] The general feature for these reductions is for most cases well explained by Prelog's rule.[30] When an exception to this rule is found, it is generally assumed that an enzyme system other than alcohol dehydrogenase is used for "anomalous" biohydrogenation.[224] Since discussions of stereochemistry in terms of involved enzymes have already taken place,[55] this will be omitted here. However, it was established that the absolute configuration and the optical purity of the products depend strongly both upon the nature and the size of the substituents adjacent to the carbonyl group and of the ester moiety but also—in some instances—upon the substrate concentration,[225] the pH,[226a] the concentration of glucose,[226b] and the cultivation conditions of the yeast.[227] Thus, low concentrations of substrate often give better enantiospecificity because at low concentrations specificity is determined by the relative V_{max}/K_m, while at higher concentrations

SCHEME 70



it is the relative V_{max} that determines specificity. The stereochemistry of the reduction can be influenced to some extent by the addition of certain α,β-unsaturated carbonyl compounds. These additives tend to shift the stereochemistry to the production of the D-hydroxy ester.[226b]

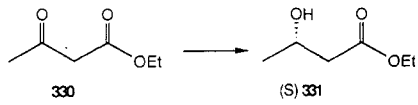
The changes in the stereochemical course caused by different physiological states of the yeast cells (e.g., glucose-grown versus methanol-grown cells) are probably due to the induction of different oxidoreductases.[227,228] A simulation for quantitative mathematical treatment of the kinetics of competing enzymes as for the reduction of **328** (Scheme 70) has been performed.[229] The low ee's obtained for several educts have very often to be explained by invoking the participation within the reduction process of two or more different enzymes[228a,b,230] acting with opposite stereochemistry. It was the merit of C. J. Sih to establish that the stereochemistry of BY reductions of β-keto carbonyl compounds may be influenced by substituents at both ends of the molecule by the action of different oxidoreductases operating with different rates.[29,228b] Thus, the preferred substrates for the enzymes leading to *R*-type products are those with a large hydrophobic substituent at position C-4 whereas enzymes yielding *S*-type products should prefer substrates bearing large hydrophobic ester moieties.[226,228b]

Three oxidoreductases capable of actively reducing β-keto esters have been isolated from the cytosolic fraction of Red-Star BY. These enzymes of molecular weight 2 400 000 (a fatty acid synthetase), 74 000 (the L enzyme, leading to carbinols of L configuration), and 38 000 (the D enzyme) were purified to homogeneity, and their respective Michaelis constants and turnover numbers were measured.[228b]

Sih and co-workers[29,228b,231] investigated the BY reduction of γ-chloroacetoacetates **328** (Scheme 70) in more detail. It was shown that the stereochemical course for this reduction can quite efficiently be altered by changing the size of the ester grouping. No significant difference in the *rates* of the reductions were observed for educts containing esters up to eight carbons, whereas the C_{16} ester was not reduced at all. The methyl ester **328a** was reduced to (*S*)-**329a** with an ee (*S*) of 65% whereas the octyl ester **328b** was reduced to the *R* enantiomer **329b** in high yield (70%) and with an excellent ee (*R*) of 97%.[29,230] The reduction of **328c** gave (*S*)-**329c**, although with low yield (30%) and low ee (50–60%).[232] It is of interest to note that there was a change in the stereochemistry of the carbinols derived from the butyl and the pentyl esters.[29]

b. Reduction of Ethyl Acetoacetate. The simplest case, the reduction of ethyl acetoacetate (**330**) (Scheme 71) to the corresponding (*S*)-hydroxybutanoate **331** has been performed many times although with differing yields and ee's.[76,136,225,233-240] **331** has been starting material for many syntheses: e.g. for the main com-

SCHEME 71



330 (S) 331

Reduction of **330**

yield [%]	ee [%]	ref.	yield [%]	ee [%]	ref.
54	92	233	n.r.	90	236
57	84	234	59-76	85	237
n.r.	88	241	67	86	84
36	97	243	70	94	238
n.r.	90	245	32	96	239
64	>97	246	60-80	>98	225
56	82	248	80	n.r.	76
n.r.	95	250	66	77	136
64	>97	235	62	95	240

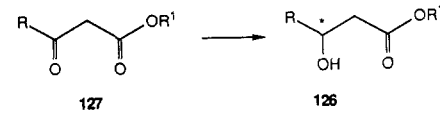
ponent of the cephalic segregation of *Andrena wilkella*, 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane,[241] for phorancantholides,[242] for (*S*)-(−)-citronellol,[241] for (6*R*,11*R*,12*R*,14*R*)-colletodial (a metabolite of the plant pathogen *Colletotrichum capsici*),[243] for the carbapenem thienamycin,[244,245] for the C-2–C-5 building block of griseoviridin,[246,247] for (*S*)-2-methyloxetane,[248] for 2-methyl-1,7-dioxaspiro[5.6]dodecane (the volatile secretion from the mandibular glands of *Andrena haemorrha* F.),[249] for (2*R*,5*S*)-2-methylhexanolide,[250] for (3*S*,11*S*)-3,11-dimethyl-2-nonacosanone (the sexual pheromone of the German cockroach),[250] for serricornin,[250] for (*S*)-(+)-sulcatol,[84] and for the synthesis of nystatin[251] and amphothericin B.[251] Unfortunately, an unacceptable broad bias for the quoted optical rotations of **331** is found, and the reported ee values determined by NMR vary from 70% to >97%.[248]

It was shown that this reduction strongly depends on the reducing conditions. Thus, replacement of the carbon source in the medium by other nutrients (fructose, (*R*)-lactate, (*S*)-lactate, acetate, glycerol, mannitol, glucuronolactone) showed that only glucuronolactone completed the conversion of **330**. "Best conditions" were claimed to be "starving conditions":[212a] a 4-day treatment of the yeast with 5% ethanol prior to the addition of **330**.[238] Another group claimed that interrupting the fermentation after 4 h will lead to 94–96% pure material.[84] Several of the results obtained for this reduction are summarized in Scheme 71, although some of the procedures given seem not to be reproducible with respect to yield and/or ee. The activating effect of allylic alcohol has been demonstrated.[136]

Leuenberger et al.[252] have investigated this reduction very carefully under controlled conditions even on a large industrial scale, and these authors found a decrease of optical purity with increasing concentration of the educt (up to 1 g/L for ee = 95–97%, 20 g/L for ee = 58%). Performing the reduction with *Geotrichum candidum* led to (*R*)-**331** in 36% yield and 90% ee. The latter reduction was found to depend strongly on the physiological state of the cells.[252] The reduction of **330** by many other microorganisms has been compared and investigated.[67,68]

c. Reduction of Alkyl-Substituted β-Keto Esters. Some reductions of β-keto esters are worthwhile to comment on in more detail. The results for "simple" alkyl-substituted β-keto esters[29,136,186,224-227,235,236,239,253-258] are summarized in Scheme 72. It seems noteworthy that while acetoacetates were reduced predominantly to (*S*)-3-hydroxybutanoates, β-ketovalerates (and all other β-ketoalkanoates **127** with R > CH_3) gave predominantly their respective (*R*)-3-hydroxyalkanoates

SCHEME 72

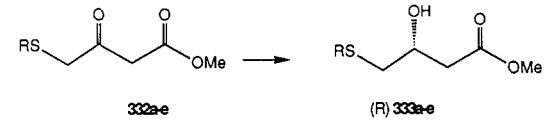


127 126

R	R^1	y [%]	conf.	ee [%]	ref.
CH_3	CH_3	23	*S*	87	253
CH_3	n-C_4H_9	58	*S*	90	254
CH_3	t-C_4H_9	61	*S*	85	254
		45	*S*	77	239
C_2H_5	CH_3	60-80	*R*	5	225
		47	*R*	54	227
		56	*R*	96	136[a]
C_2H_5	C_2H_5	67	*R*	40	236[b]
C_6H_5	C_2H_5	70	*S*	100[c]	224, 186
C_2H_5	C_8H_{17}	75	*R*	95	255
		67	*R*	100	29
C_3H_7	C_8H_{17}	12	*S*	71	29
C_4H_9	C_2H_5	32	*R*	90-99	236, 256
$CH_2CH_2CH=CH_2$	H	35	*R*	99	257
n-$C_{15}H_{31}$	K	40	*R*	98	258[a]
$CH_2CH_2CH=CH_2$	K	38	*R*	>99	239
"	CH_3	30	*R*	92	239
"	C_2H_5	54	*R*	80	239
"	t-C_4H_9	66	*R*	81	239
$CH_2CH_2C(CH_3)=CH_2$	K	55	*R*	>99	239
"	CH_3	18	*R*	67	239
"	C_2H_5	15	*R*	18	239
"	t-C_4H_9	0	-	-	239
$CH_2CH_2CH=C(CH_3)_2$	K	59	*R*	>99	239
"	CH_3	73	*R*	92	239
"	C_2H_5	12	*R*	50	239
"	t-C_4H_9	0	-	-	239

[a] on addition of 1g/L of allylic alcohol; without activator an ee of 59% was reported;[136] [b] 18h, room temperature; material of higher enantiomeric purity was obtained by acidic depolymerization of natural heteropolymer $[R\text{-}CH(OH)\text{-}CH_2\text{-}C(=O)]_nOH$ with R: 20% Et, 80% Me 254; [c] at high yeast:substance ratio.

SCHEME 73



332a-e (R) 333a-e

entry	R	y [%][a] (*R*)-333	ee [%][a] (*R*)-333	y [%][b] (*S*)-333	ee [%][b] (*S*)-333
a	C_2H_5	55	70	41	85
b	n-C_3H_7	49	65	36	85
c	n-C_4H_9	67	70	53	80
d	n-C_5H_{11}	30	58	28	85
e	p-Cl-C_6H_4	40	50	30	80
f	C_6H_5	42	73	50	50

a) by redn. using SC NCYC1765
b) -"- candida guilliermondi

126. A better access to (*R*)-3-hydroxybutanoate was found by the reduction of ethyl acetoacetate with *Thermoanaerobium brockii*.[259]

d. Reduction of δ-Heteroatomic Substituted β-Keto Esters. The reduction of δ-thio-substituted keto esters **332a–e** (Scheme 73) with *Saccharomyces cerevisiae* (NCYC1765) afforded the corresponding hydroxy esters (*R*)-**333a–e**[260] whereas upon treatment with *Candida guilliermondi* (*S*)-**333a–e** could be obtained.[260]

The results for reduction of β-keto esters[136,224-226,232,239,260-262] containing a further heteroatom-substituted moiety attached to C-4 are summarized in Scheme 74.

Dramatic differences in the reduction of **334q** (Scheme 74) (to yield **335q**) have been found that were related to the incubation conditions in general and the yeast to substrate ratio in particular. Addition of **334q** as an ethanolic solution over 6 h to a suspension of yeast (38 g/mmol of **334q**) afforded (*R*)-**335q** after 1 day of incubation with 71% ee and 73% yield. The stereo-

SCHEME 74

334a-r 335a-r

R = heterosubstituted

entry	R	R'	y [%]	conf.	ee [%]	ref.
a	$-CH_2Cl$	CH_3	60-80	*R*	[a]	225, 232
			60	*R*	70	260
b	$-CH_2Cl$	C_2H_5	60-80	*R*	50-60	232, 136
			30	*S*	[b]	225
c	$-CH_2-Br$	C_2H_5	40-50	*S*	100[c]	226
d	$-CH_2-Br$	$CH_2-C_6H_5$	40-50	*S*	100[d]	226
e	$-CH_2-Br$	C_3H_7	40-50	*S*	100[d]	226
f	$-CH_2-Br$	C_7H_{15}	40-50	*S*	100[d]	226
g	$-CH_2-Br$	C_8H_{17}	40-40	*S*	100[d]	226
h	$-CCl_3$	C_2H_5	70	*S*	84-88	261
i	$-CF_3$	C_2H_5	75	*R*	49-51	261[e]
j	$-CH_2-N_3$	C_2H_5	70-80	*R*	80	226[f]
k	$-CH_2-N_3$	$CH_2-C_6H_5$	70-80	*R*	95	226[f]
l	$-CH_2-N_3$	$CH_2CH_2-C_6H_5$	70-80	*R*	95	226[f]
m	$-CH_2-N_3$	$(CH_2)_6-C_6H_5$	70-80	*R*	100	226[f]
n	$-CH_2-N_3$	$(CH_2)_7-C_6H_5$	70-80	*R*	100	226[f]
o	$-CH_2-O-t-C_4H_9$	CH_3	72	*R*	97	262
p	$-CH_2-O-t-C_4H_9$	C_2H_5	70	*R*	82	262
q	$-CH_2OCH_2-C_6H_5$	C_2H_5	73	*R*	71	224[g]
			58	*R*	56	262
				S	48	224[h]
r	$-(CH_2)_3-O-CH_2-C_6H_5$	K	51	*R*	>99	239[i]

[a] the ee was shown to depend on the concentration of the educt: 10 mM gave 31 % ee, 20 mM gave 12% ee.[225]; [b] the ee was shown to depend on the concentration of the educt; 10 mM concentration of educt afforded product of 42 % ee whereas 20 mM gave 27% ee and 50 mM only 15% ee.[225]; [c] at pH=8; with pH=6 an ee of 60% was achieved; [d] at pH=8; [e] at a concentration of 15g/L of educt, 30°, 44h; 2 recrystallizations of the 3,5-dinitrobenzoate afforded product with ee>98%; data reported in refs. 263, 264 are erroneous.[261]; [f] at pH=7.5-8; [g] educt was added as a solution in EtOH during 6h; 1d,38 g yeast per mmol of educt. [h] educt added at once, 6d; 0.75 g yeast per mmol of educt; [i] the corresponding derivatives with R'=Me, Et, or *t*-Bu gave no reaction at all.[239]

SCHEME 75

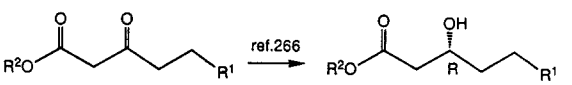
336a-m 337a-m

entry	R	y [%]	config.	ee[%]	ref.
a	$O-CH_3$	58;65	n.r;*R*	30;60	265, 266
b	$O-C_2H_5$	60	*S*	56	265
c	$O-i-C_3H_5$	40	*S*	34	265
d	$O-n-C_4H_9$	55	*S*	70	265
e	$O-CH_2CH(CH_3)_2$	70	*S*	90	265
f	$O-n-C_5H_{11}$	40	*S*	92	265
g	$O-CH_2CH_2CH(CH_3)_2$	35	*S*	54	265
h	$O-CH_2C(CH_3)_3$	35	*S*	96	265
i	$O-C_6H_{13}$	10	*S*	96	265
j	$O-C_8H_{17}$	0	-	--	265
k	OK	10	*S*	n.r.	265
l	$S-C_4H_9$	40	*S*	68	265
m	$S-CH_2CH(CH_3)_2$	30	*S*	74	265

chemical outcome of this reduction is reversed when **334q** is added at once and only 0.75 g/mmol of yeast is added. After 6 days of incubation (*S*)-**335q** is obtained with 48% ee.[224]

Enantioselectivity of the yeast-mediated reduction of 5-(benzyloxy)-3-oxopentanoate esters **336a–m** (Scheme 75)[265,266] was influenced by changes in the ester alkoxy group in a way that the enantioselectivity increases with increasing chain length for the *n*-alkyl esters. However, the amount of conversion of substrate to product **337a–m** decreased with increasing chain length. For branched hydrocarbon groups, there seems

SCHEME 76

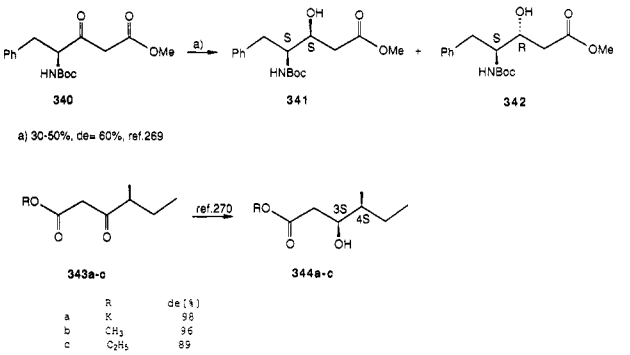


338a-n 339a-n

entry	R^1	R^2	y [%]	config.	ee [%] of **339**	ref
a	OCH_3	CH_3	11	*S*	33.3	266
b	OCH_3	C_2H_5	41	*S*	66.1	266
c	OCH_3	C_3H_7	40	*S*	80.0	266
d	OCH_3	C_4H_9	48	*S*	82.1	266
e	OCH_3	C_5H_{11}	26	*S*	80.2	266
f	OCH_3	C_6H_{13}	15	*S*	76.7	266
g	OCH_3	C_7H_{15}	9	*S*	71.4	266
h	OH	C_4H_9	33	*S*	79.8	266
i	OH	C_5H_{11}	59	*S*	86.7	266
j	OH	C_6H_{13}	3	*S*	77.8	266
k	$O(CH_2)_2Si(CH_3)_3$	CH_3	41	*R*	33.3	266
l	SCH_3	CH_3	28	*S*	20.0	266
m	SC_6H_5	CH_3	88	*R*	41.2	266
			42	*R*	73.0	260
			32	*R*	88	267
			36	*S*	65	268[a]
n	SC_6H_5	K	8	*S*	100	268[b]

[a] using *Saccharomyces SCNCYC240*; [b] isolated as methylester

SCHEME 77



340 341 342

a) 30-50%, de= 60%, ref.269

343a-c 344a-c

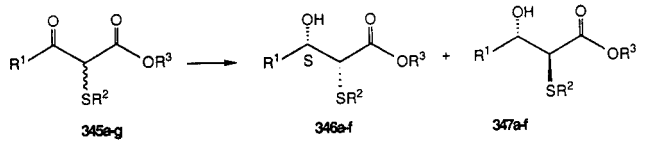
	R	de[%]
a	K	98
b	CH_3	96
c	C_2H_5	89

to be an optimum of enantioselectivity with one methylene group spacer before branching but this trend seems unclear. A change of the electronic environment with thioesters (entries l, m) had little effect, and no change in the enantioselectivity of this reduction was observed.[265]

For **338a–g** (Scheme 76) both enantiomer ratio and the chemical yield increased on going from the methyl ester (entry a) to the butyl ester (entry d) and then fell off toward the heptyl ester (entry g). The esters with yet a smaller and more hydrophilic OH group (entries h–j) exhibited a similar trend, but in this series the maximum was obtained in the reaction of the pentyl ester (entry i). These results[266] are in contrast to the results obtained by Sih et al.[29,231] on the reduction of **328**. In this case, the preferred enantiomer has the same configuration when R^1 is sufficiently large in both series.[266] The results for **338m** are somewhat controversial[260,266–268] with respect to yield and ee. Use of *Candida guilliermondi* (NCYC973 or NCYC1399) for some of these educts gave predominantly (*S*)-**339** in comparable yields and ee values between 83 and 90%.[260]

e. β-Keto Ester with an Additional Center of Chirality. An additional center of chirality in the side chain as in **340** (Scheme 77) gave upon treatment with BY 30–50% of (3*S*,4*S*)-**341** (major) and (3*R*,4*S*)-**342** (minor); the de of 60% could be improved either by 2-fold recrystallization (de = 99%) or by use of *Hansenula anomala* to yield (3*S*,4*S*)-**341** with de = 92% whereas *Candida boidini* gave predominantly

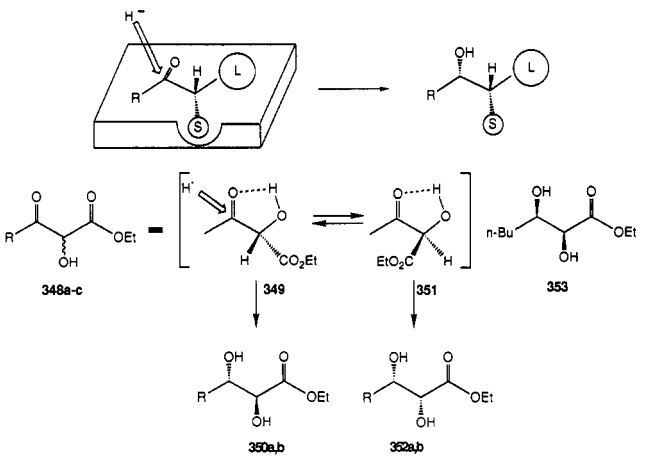
SCHEME 78



345a-g 346a-f 347a-f

entry	R^1	R^2	R^3	y [%] of **346**	y [%] of **347**
a	CH_3	CH_3	CH_3	52	20
b	CH_3	CH_3	C_2H_5	37	25
c	CH_3	CH_3	$C(CH_3)_3$	31	44
d	CH_3	C_6H_5	CH_3	33	7
e	CH_3	C_6H_5	C_2H_5	36	13
f	C_2H_5	CH_3	C_2H_5	21	23
g	$CH_2CH_2OCH_2$-C_6H_5	C_6H_5	$C(CH_3)_3$	decomposition	

SCHEME 79



348a-c 349 351 353 350a,b 352a,b

R	y[%] of 350 : 352
a CH_3	55 : 13
b C_2H_5	62 : 11
c n-C_4H_9	48 : 12 of **353**

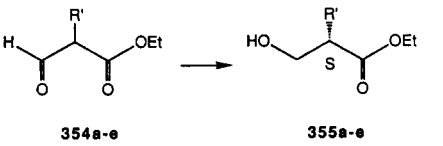
ref 272

(3*R*,4*S*)-**342** with 90% de.[269] Similarly, reduction of **343a–c** gave **344a–c** although with low yields but excellent de values.[270]

f. α-Substituted β-Keto Ester. The reduction of α-thio-substituted β-keto esters **345a–g** (Scheme 78) has been suggested as an alternative to the reduction of β-keto esters **127**[271] since α-sulfenyl esters **346** or **347** can smoothly be desulfenylated by oxidation (*m*-chloroperbenzoic acid, dichloromethane, −78 °C, followed by treatment with amalgamated aluminum). The yields of **346** and **347** are fair, but ee values >96% were found for all compounds investigated. Although these reactions yielded both *syn*-**346** and *anti*-**347**, it should be noted that the *S* configuration in the C-3 position was exclusively obtained in all cases.[271]

For the reduction of the α-hydroxy keto esters **348a–c** a mechanism as depicted in Scheme 79 has been proposed[272] to explain the predominant formation of 2*S*,3*S* isomers. If BY prefers *re* face reduction by the Prelog rule, reduction of **349** to form a 5-membered ring with a hydrogen bond between the 2-hydroxy and the carbonyl oxygen at C-3 with less hindered *re* face site to give the 2*S*,3*S* products **350** is more favorable than that of **351** to give 2*R*,3*S* products **352**. An equilibrium between **349** and **351** is possible as well as degradation of the 2*R* isomer by BY to cause the predominant formation of the 2*S*,3*S* isomers.[272] From **348c** (2*S*,3*R*)-**353** is formed. Chiral (2*S*,3*S*)- and (2*R*,3*S*)-2,3-dihydroxybutanoic acids have been shown to be versatile key intermediates in a variety of natural product syntheses.[273–281]

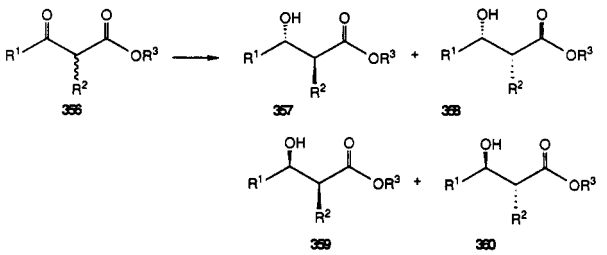
SCHEME 80



354a-e 355a-e

entry	R'	y [%]	ee [%]	ref
a	CH_3	70–80	60–65	282
b	CH_2CH_3	88	91	238, 282
c	$CH(CH_3)_2$	50–70	60	238, 282
d	CH_2-C_6H_5	50–70	46	282
e	C_6H_5	50–70	83	282

SCHEME 81



356 357 358 359 360

R^1	R^2	R^3	y [%] of **357**	y [%] of **358**	ee [%] of **357**	ee [%] of **358**	ref.
CH_3	CH_3	CH_3	13	58	100	100	283
CH_3	CH_3	C_2H_5	16	49	100	100	283, 285, 286 291, 292
CH_3	CH_3	t-C_4H_9	18	22	100	100	283
CH_3	CH_3	$CH_2CH(CH_3)_2$	10	46	100	100	283
CH_3	CH_3	n-C_5H_{11}	11	59	100	100	283
CH_3	CH_3	n-C_8H_{17}	4	78	100	100	283
CH_3	Cl	C_2H_5	34	34	100	n.r.	290
CH_3	CH_3	$CH_2C_6H_5$	30	15	97	84	284[a]

R^1	R^2	R^3	y[%] of **357**	y[%] of **358**	ee[%] of **357**	ee[%] of **358**	ref.
CH_3	CH_2CH=CH_2	C_2H_5	63	21	100	70	285, 286
CH_3	CH_2-C_6H_5	C_2H_5	15	7	100	85	285
$CH_2OCH_2C_6H_5$	CH_3	CH_3	45	5	6	68	288

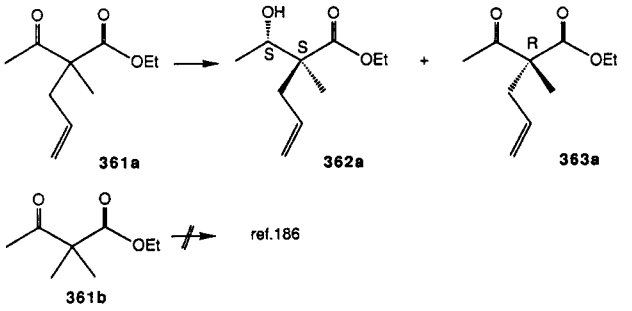
R^1	R^2	R^3	y [%] of **358**	y [%] of **360**	ee [%] of **358**	ee [%] of **360**	ref.
$CH_2OCH_2C_6H_5$	CH_3	C_2H_5	25	21	36	24	288[b]
$CH_2OCH_2C_6H_5$	CH_3	i-C_3H_7	15	49	96	50	288
CH=CH-C_6H_5	CH_3	CH_3	7	-	95	-	289[c]

[a] better yields were obtained with *Candida albicans* (92%, *syn/anti*-ratio 26/74 with ee's of 97 and 95% , respectively, highest *syn/anti*-ratio 94/6 (ee 97% and 87%) with *Rhodotorula glutinis*, highest ee-values (99%, 99%) with *Pichia farinosa* (*syn/anti* = 50/50). [b] to obtain the different stereoisomers with higher ee values, *Rhodotorula mucilaginosa*, *Curvularia minuta* and *Geotrichum candidum* have been used[288]; [c] use of *Candida albicans* gave 35% of **359** with 97% ee.

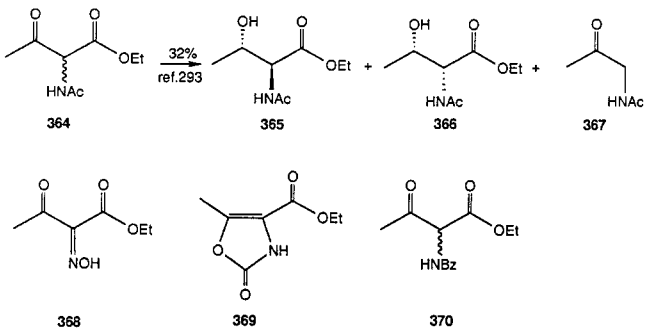
A general model for predicting the diastereoselectivity in yeast reductions has been suggested[228b] following similar reasoning as in the formulation of Prelog's rule. Thus, size and hydrophobicity of the α-substituent are compared to that of the ester ligand. Such microbiological reductions allow the production predominantly of a single diastereoisomer; these reductions are at the same time both enantioselective and stereospecific.[53b] This model explains the high syn/anti selectivity observed for the reduction of α-substituted β-keto esters.[228b]

g. Reduction of Formyl Derivatives. Although of great synthetic potential, the reduction of formyl derivatives **354a–e** (Scheme 80) has only scarcely been performed;[238,282] however, **355a–e** were obtained in 70–83% yield and ee values ranging from 46 to 91%. As exemplified by **355a** the ee could improved to 100%

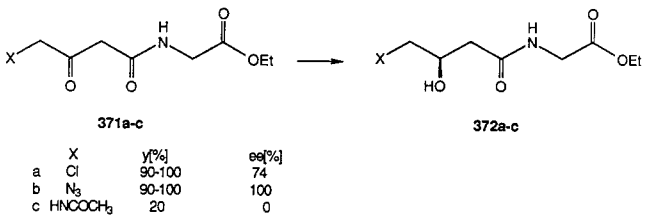
SCHEME 82



SCHEME 83

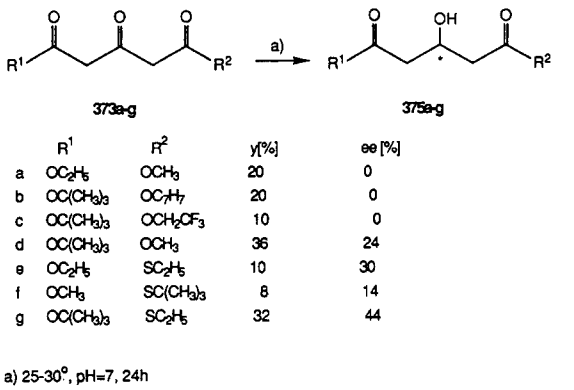


SCHEME 84



	X	y[%]	ee[%]
a	Cl	90-100	74
b	N_3	90-100	100
c	$HNCOCH_3$	20	0

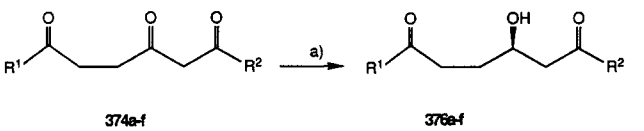
SCHEME 85



	R^1	R^2	y[%]	ee [%]
a	OC_2H_5	OCH_3	20	0
b	$OC(CH_3)_3$	OC_7H_7	20	0
c	$OC(CH_3)_3$	OCH_2CF_3	10	0
d	$OC(CH_3)_3$	OCH_3	36	24
e	OC_2H_5	SC_2H_5	10	30
f	OCH_3	$SC(CH_3)_3$	8	14
g	$OC(CH_3)_3$	SC_2H_5	32	44

a) 25-30°, pH=7, 24h

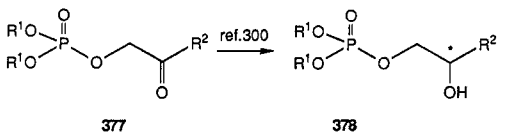
SCHEME 86



	R^1	R^2	y [%]	ee [%]
a	OCH_3	OCH_3	19	48
b	OC_7H_7	OCH_3	24	2
c	OCH_3	SC_2H_5	56	4
d	$OC(CH_3)_3$	OCH_3	26	30 (S)
e	OCH_3	$OC(CH_3)_3$	29	66
f	$OC(CH_3)_3$	SC_2H_5	26	84 (S)

a)25-30°, pH=7, 24h

SCHEME 87



by 6-fold recrystallization of the corresponding 3,5-dinitrobenzoate (yield 40%).[282]

h. Miscellaneous Aliphatic β-Keto Esters. β-Ketobutanoates **356** (Scheme 81) substituted at the α-position[283-290] have been reduced and afforded compounds **357–360**.

Introduction of a quaternary carbon as in **361a** (Scheme 82) afforded upon BY reduction (*S,S*)-**362a** (20%, ee = 100%) and 38% of (*R*)-**363a** of 28% ee,[285,286] whereas 2,2-dimethylacetoacetate **361b** was not reduced at all.[186]

During an L-threonine synthesis, **364** (Scheme 83) was reduced in 32% yield, leading to the diastereomers **365** and **366** in a ratio of 60:40; in addition, 5% of **367** (as a product of hydrolysis and decarboxylation) was identified. Better yields than with BY were obtained with *Saccharomyces rouxii* (60%). No reaction was observed for compounds **368–370**;[293] contrary, other oximes have already successfully been reduced.[163]

BY reduction of 4-substituted 3-oxobutanamides **371a–c** (Scheme 84) gave **372a–c**.[294]

The enantioselectivity of the BY-mediated reduction of prochiral 3-ketoglutarates **373a–g** (Scheme 85) and 3-ketoadipates (Scheme 86) **374a–f** to the corresponding 3-hydroxy esters **375a–g** and **376a–f**, respectively, was influenced by the simple differences in the ester group,[295] but for **373a–g** no readily differentiation (by changing in the size of the ester group) was found. For the reduction of **374f**, the best result with 84% ee was obtained.[294] Enantiomerically enriched 3-hydroxyglutarates have been synthesized by hydrolysis of the corresponding diesters with the esterase from porcine liver,[296,297] α-chymotrypsin,[298] and *Arthrobacter*[299] and *Acinebacter sp.*[299]

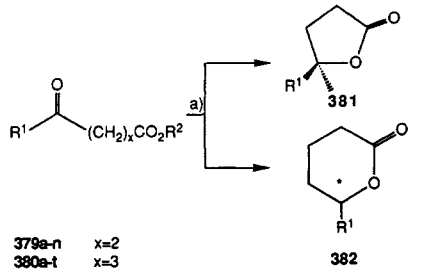
The heteroanalogous keto esters **377** (R^1 and R^2 alkyl substituents) (Scheme 87) have been reduced by BY to yield the corresponding β-hydroxy phosphates **378**.[300] The reactions proceeded well, but due to partial racemization the optical purities of the products were low (0–52%).

G. Reduction of γ- and δ-Keto Acids and Esters

BY reduction of keto acids or esters **379** or **380** (Scheme 88) affords the corresponding γ- or δ-lactones **381** or **382**, respectively. Some of these lactones are insect pheromones. As for the esters it was supposed that first the ester is hydrolyzed by some nonspecific esterase(s) to the corresponding acid, which is the true substrate for the bioreduction.[224] In addition, it was suggested[301] that the acids are not reduced as such but that their corresponding CoA thioesters are.

Reduction of the simplest compound, namely ethyl levulinate (**379a**, R^1 = Me), proceeded only to a modest extent under a variety of conditions. Approximately 70–85% of starting material was recovered after 48 h of incubation and 10–15% of the reduction product was obtained, which gave on chemical cyclization (*S*)-**381a**.[224] Reduction of an ethanolic solution of potassium 4-oxo-4-phenylbutanoate (**379n**, R^1 = Ph) yielded

SCHEME 88



a) ref.224

Reduction of **379**

entry	R^1	R^2	y [%]	t [h]	ee	conf.	ref
a	CH_3	C_2H_5	0				302
			10-15	48	n.r.	*S*	224
b	CH_3	H	10	24	46	*S*	306
c	CH_3	CH_3	30	24	85.6	*S*	306
d	C_2H_5	H	16	24	>98	*R*	306
e	C_2H_5	CH_3	44	24	83	*R*	302,308
f	C_3H_7	H	39	24	>98	*R*	306
g	C_4H_9	H	44	24	>98	*R*	302,306
h	C_5H_{11}	H	77-82	24	>99	*R*	302-306
i	C_6H_{13}	H	85	24	>99	*R*	303,304
j	C_7H_{15}	H	72-90	24	>99	*R*	302-306
k	C_8H_{17}	H	60-71	24	>99	*R*	302,303
							304,306
l	C_8H_{17}	CH_3	41	24	94	*R*	305
m	$C_{11}H_{23}$	K	50	48	>98	*R*	302
n	C_6H_5	K	31	160	>95	*S*	224

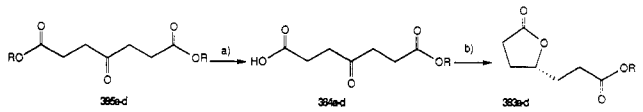
reduction of **380**

entry	R^1	R^2	y [%]	t [h]	ee/de	conf.	ref
a	CH_3	H	0	48			302
b	CH_3	C_2H_5	0	48			302
c	C_2H_5	H	6	48	>98	*R*	302
d	C_2H_5	C_2H_5	11	48	>98	*R*	302
e	C_3H_7	H	13-30	24	83	*R*	224,303
			54-67	48	>98	*R*	302,304
f	C_3H_7	C_2H_5	58	48	>98	*R*	302
g	C_4H_9	H	35	24	95	*R*	224
			55-68	48	>98	*R*	303,304
h	C_4H_9	K	67	24	98	*R*	307
i	C_4H_9	C_2H_5	71	48	>98	*R*	302
j	C_5H_{11}	H	30-47	24	>98	*R*	224,303
			45-75	48	>98	*R*	224,303
k	C_6H_{13}	H	30	24	>98	*R*	224
			63	24	>98	*R*	303,304
l	C_7H_{15}	H	35-56	24	>98	*R*	224,
							303,304
m	C_8H_{17}	H	54	48	>98	*R*	302
n	C_8H_{17}	K	54	48	>98	*R*	307
o	C_8H_{17}	C_2H_5	21	48	>98	*R*	302
p	$C_{11}H_{23}$	CH_3	29	24	57	*R*	305
q	$C_{11}H_{23}$	H	40	48	>98	*R*	302
			40	48	39	*R*	309
r	$C_{11}H_{23}$	K	40	48	>98	*R*	302
s	$C_{11}H_{23}$	C_2H_5	0	48			302
t	$C_{13}H_{27}$	K	17	48	>98	*R*	302

31% **381n** (with an ee > 95%) after 7 days.[224] It appears noteworthy that longer chain alkyl-substituted 4-oxocarboxylates **379**[302-305] gave better yields and higher ee values (in favor of *R*-configured products) as compared to derivatives possessing short alkyl groups.[306] 4-Oxo-3-methyloctanoate gave a mixture of cis-4*R* (major, ee > 99%) and trans-4*R* (minor, ee > 92%) substituted 3-methyl lactones.[306]

For **380f** a more detailed investigation has been undertaken,[302] and it was revealed that the optical purity of **382f** is always >98% irrespective of conditions used. It must be noted that the results obtained in this investigation[302,307] are controversial to previous results.[308] The yields observed indicate that 5.5 g of dry yeast/mol of substrate was sufficient while smaller amounts were insufficient due to poisoning of the yeast[302] and larger amounts of yeast gave lower yields due to trapping of the keto acid by the yeast within the first 6-h period of the reaction.[302] As an alternative for the preparation

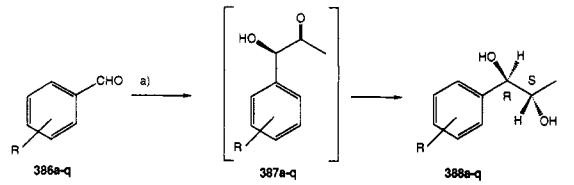
SCHEME 89



R	y[%]	ee[%]
a CH_3	25	>98
b C_2H_5	54	98
c nC_3H_7	45	98
d nC_4H_9	43	98

a) *Pseudomonas diminuta*
b) BY, 30°, 1d, pH=6.8, ref.310

SCHEME 90



a) dry yeast (Oriental), r. t., 3.5 h, ref.320

	R	yield [%]	ee[%]	*anti/syn*
a	H	30	97	97/3
b	*p*-OCH_3	22	97	97/3
c	*p*-CH_3	28	99	98/2
d	*p*-Cl	27	98	98/2
e	*p*-F	26	97	97/3
f	*o*-CH_3	7	97	99/1
g	*o*-Cl	32	97	99/1
h	*o*-F	31	97	99/1
i	*m*-F	30	97	93/7
j	*o*-CF_3	---		
k	*m*-CF_3	---		
l	*p*-CF_3	---		

	R	ref.
m	*o*-$CH_3OC_6H_4$	317
n	*m*-HOC_6H_4	318
o	*p*-HOC_6H_4	318
p	3-CH_3O, 4-HOC_6H_3	319
q	(3,4-OCH_2O)-C_6H_3	319

for entry **a** see ref. 313,321,326; for entry **b** and **g**: see ref. 317; for entry **c** and **f** see ref.322; for entry **d**, **e**,**h**-**l** see ref. 320

of **382f**, the use of an acylase from *Aspergillus sp.* has been proposed.[309]

It seems noteworthy that the material deficit and hence the yield seem to depend upon the length of the alkyl chain whereas the pH was not found to be critical as long as it was kept between 4.7 and 7.0.[302] This is in good accord with the reported value of pH 5 for the reduction of **380c**.[301] Generally, δ-keto acids are more rapidly reduced than the corresponding δ-keto esters. Retardation in the reduction of the long-chain alkyl keto esters was assumed to arise from their low solubility.[302]

Optically active (*R*)-(+)-(γ-butyrolactonyl)-propionates **383a–d** (Scheme 89) were prepared by reducing 3-ketoheptane-1,5-dicarboxylic monoesters **384**. Whereas diesters **385a–d** were hydrolyzed to **384** with *Pseudomonas diminuta* (IFO13181) as the best microorganism for partial hydrolysis of compounds of such type, **384a–d** were reduced to **383a–d** with fermenting BY in large-scale quantities, fair yields, and excellent ee. The yeast cells could be employed repeatedly several times for the reductions.[310]

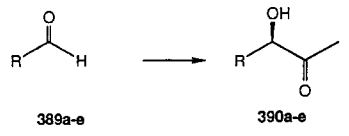
III. C–C Bond-Forming and -Breaking Reactions

A. α,β-Unsaturated Systems

1. Acyloin-Type Condensations and Reductions of α,β-Unsaturated Compounds

First reports on this condensation reaction have been published 60 years ago by von Liebig (for the reaction of furfural),[311] and later Neuberg[312,313] and Dirscherl[314] investigated this type of reaction for benzaldehyde (**386a**) (Scheme 90) in more detail. Broader synthetic applications[315] have been brought about by Fuganti and

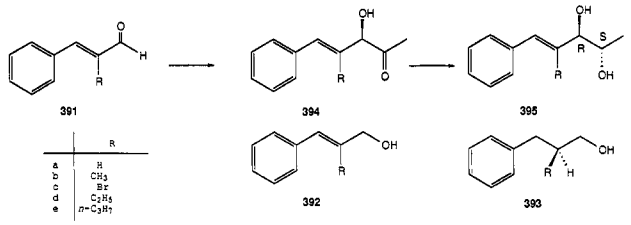
SCHEME 91



389a-e 390a-e

	R	ref.
a	CH_3	324,325,326
b	$(CH_3)_2CH$	327
c	n-C_4H_9	328
d	n-C_7H_{15}	329
e	n-$C_{12}H_{25}$	329

SCHEME 92



co-workers since the mid-1970s.[316] The results for substituted benzaldehyde derivatives **386b–q** (leading via **387b–q** to products **388b–q**) are summarized in Scheme 90.[317-322] Mainly, formation of *anti*-1-aryl-1,2-dihydroxypropanes **388a–q** has been observed.[320]

The acyloin-type condensation[323] of benzaldehyde (**386a**) found its industrial application very early in the synthesis of D-(−)-ephedrine, thus being one of the first industrial processes combining microbiological and chemical synthesis.[321] These investigations have been extended to aldehydes **389a–e**, leading to products **390a–e** (Scheme 91).[313,317,318,322-329]

This reaction type can be considered the result of two subsequent transformations: Addition of a C_2 unit equivalent of acetaldehyde in statu nascendi by means of 2-(α-hydroxyethyl)thiamine pyrophosphate onto the *si* face of the carbonyl group to form (*R*)-α-hydroxy ketones.[330,331] Subsequent reduction of this intermediate on the *re* face by (an) alcohol dehydrogenase(s) results in the formation of predominantly anti-configured diols.

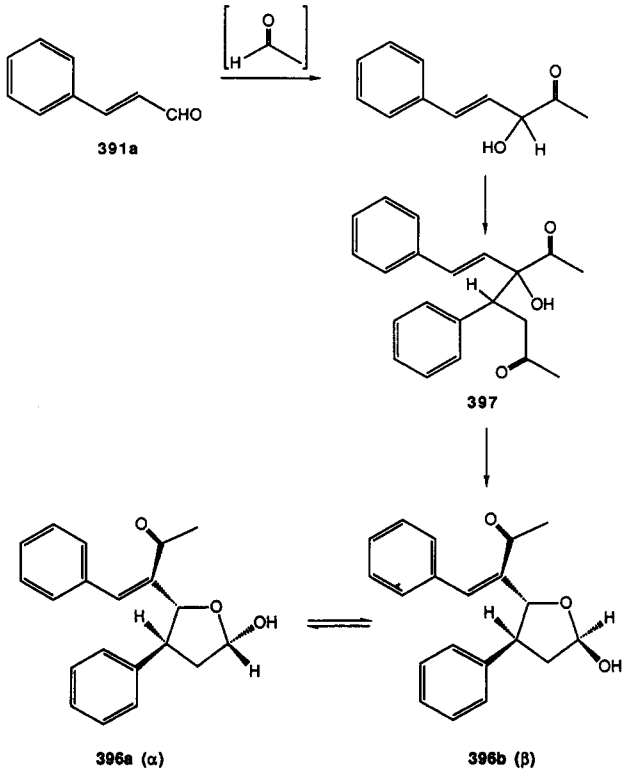
The reaction sequence was found to be dependent on pH. In acidic medium, the formation of ketols predominates whereas under neutral or basic conditions (optimum pH 9.5) only diols were observed.[320]

In addition, it seems noteworthy that upon addition of salicylaldehyde the fermentation immediately stops;[329,332,333] this result has been interpreted in terms of toxicity. The highest cell toxicity in the aliphatic series has been found for heptanal.[329]

There are some severe limitations for this reactions: Whereas a broad structural tolerance for the first aldehyde to be used in the enzymic system is found, only acetaldehyde is accepted as the second terminus. With other aldehydes (e.g., propion- or butyraldehyde), no incorporation of these added aldehydes could be found.[334] The other limitation investigated in more detail[316] in the case of α,β-unsaturated carbonyl compounds,[315] e.g., cinnamaldehyde (**391a**) (Scheme 92), is that the acyloin condensation is dominated by simple biohydrogenation leading to the corresponding alcohols **392** and **393** (70–75%) instead of a chain extension reaction leading to **394** (25–30%).[191]

Compounds **394** and **395** have successfully been used for the synthesis of deoxy sugar analogues,[273-277,331,335,336]

SCHEME 93



391a 397 396a (α) 396b (β)

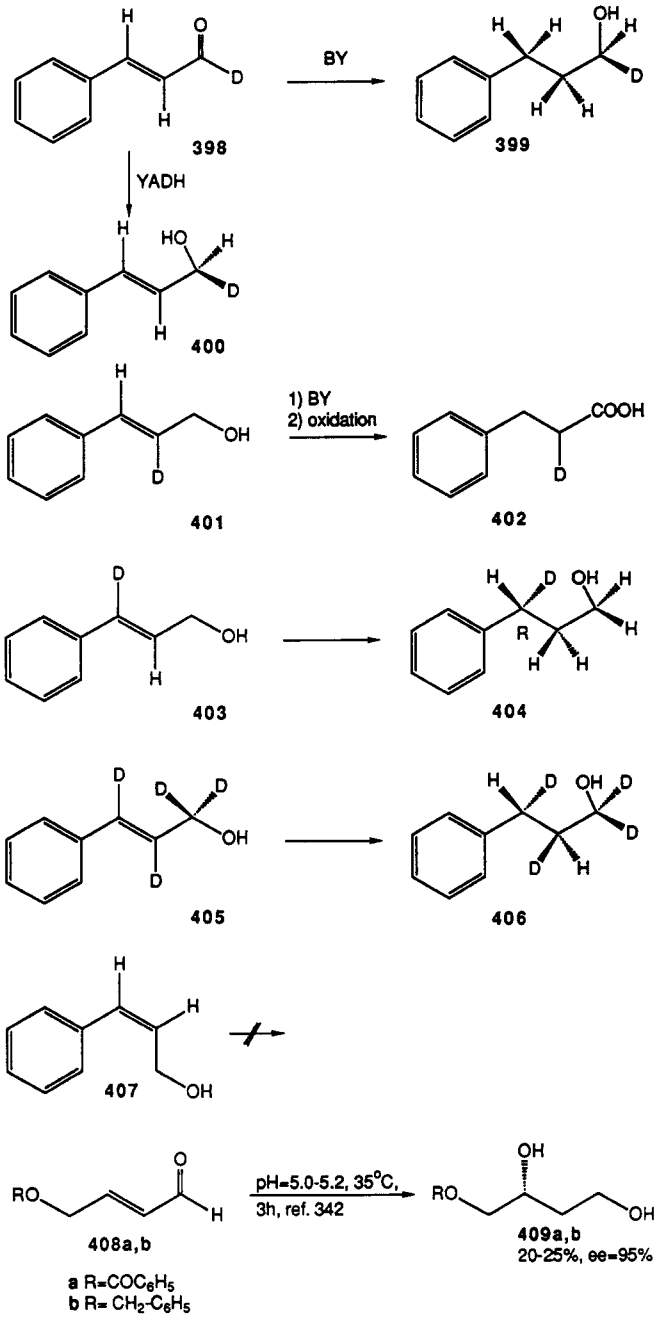
LTB_4 intermediates,[279] D-(−)-*allo*-muscarine,[337] (+)-*exo*-brevicomin,[256,277] hexanolides,[278,281] octanolides,[277] frontalin, and other pheromones.[338]

Reaction of **391d** and **391e** afforded under these conditions **392d,e** and **393d,e**.[274,330] Small amounts of **391a** were converted into **396**[273] (Scheme 93). As shown by NMR studies,[339] **396a** (possessing α-configuration when regarded as a substituted furanoid carbohydrate) underwent mutarotational isomerism, reaching an equilibrium value of about 60% α-anomer after 1 day. Intermediate **397** is expected to arise upon Michael addition of the anion derived from the α-ketol from cinnamaldehyde and a molecule of cinnamaldehyde followed by ring closure to yield **396**.[339] It is noteworthy that no analogous byproduct of this type was formed from **391b**.

A further application of the enzymic acyloin-type condensation to mono- and sesquiterpenes has been reported by *Diplodia gossypina* and *Corynespora cassicola* for the synthesis of norterpenes.[340] A similar reaction of 3,4-dimethoxybenzaldehyde has been reported with use of *Aerobacter aerogenes* instead of BY.[319]

Since the acyloin condensation reaction was found to be followed more or less always by reduction of the carbonyl and/or the C–C double bond, some deuteration studies have been performed (Scheme 94) in order to establish the stereochemical course of the reduction of α,β-unsaturated carbonyl compounds.[341] Thus, [^{2}H]formyl-labeled **398** gave (1*S*)-3-phenyl[1-^{2}H]-propanol (**399**), whereas treatment of **398** with purified yeast alcohol dehydrogenase afforded **400**. Analogue **401** gave upon treatment with BY followed by CrO_3 oxidation **402** without any loss of deuterium. From **403** was obtained (3*R*)-[^{2}H]-**404**. [1,1,2,3-$^2H_4$]Cinnamyl alcohol (**405**) afforded (1*S*,2*S*,3*R*)-3-Ph [1,2,3-$^2H_3$]-**406**;[341] (*Z*)-cinnamyl alcohol (**407**), however, was re-

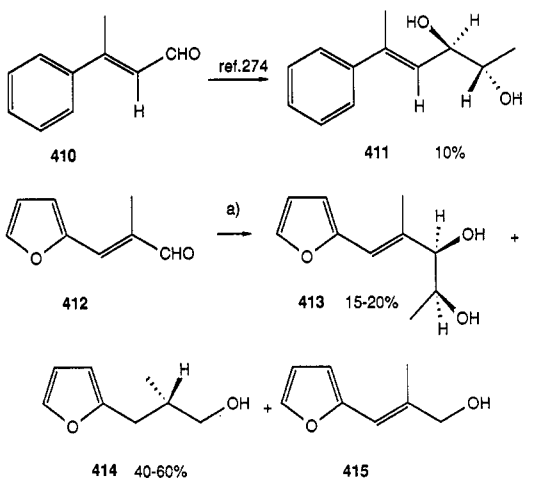
SCHEME 94



covered unchanged from the reaction mixture.[341] These results indicate a formal anti stereospecific addition of hydrogen across the double bond; this reduction is the result of an introduction of a *pro-R* hydrogen substituent at position 1. Deuterium labeling has also been used to get first insights for the analogous water addition and transformation of **408a,b** into (*R*)-**409a,b** in approximately 25% yield and proceeding with 90–95% ee for the products.[342]

Many different α,β-unsaturated carbonyl compounds have been used for this kind of BY-mediated C–C bond formation. **410** (Scheme 95) gave 10% of **411** (conjectural stereochemical assignment).[274] Enantiomerically pure vitamin E has been synthesized in a convergent manner from a single precursor, α-methyl-β-2-furylacrolein (**412**), which gave upon BY-mediated acyloin condensation followed by reduction diol **413** in 15–20% yield. Yields of 40–60% of reduction product **414** and traces of unsaturated alcohol **415** were also isolated.[343]

SCHEME 95



a) 6-8h, r.t., 15-20%, ref.343

BY treatment of a 1:1 mixture of (*Z*)- and (*E*)-3-methyl-5-phenyl-2,4-penta-2,4-dien-1-ol (**416**) (Scheme 96) afforded ca. 10% of desired **417** and a 6:4 mixture of isomers **418**.[274] *E*-Configured **419** gave 15% of **420**, which was further transformed into 2,6-dideoxy-3-*C*-methyl-L-*arabino*-hexopyranose (olivomycose, **421**), thus ascertaining the stereochemical assignments for **420**.[274]

The same group also used **419** and (*Z*)-**416** as starting materials for another synthesis of α-tocopherol. Thus, **419** gave 87% of **422** whereas BY treatment of (*Z*)-**416** gave an inseparable mixture of **423** and (*Z*)-**418**.[344]

Reduction of **424** under modified conditions afforded 15–20% of 4-phenylbut-3-en-2-ol (**425**) (Scheme 97) of 90% ee, a valuable starting material for the synthesis of (*S*)-*O*-benzyllactaldehyde.[345] **425** was found to be contaminated with 5–10% of inseparable **426**.[345]

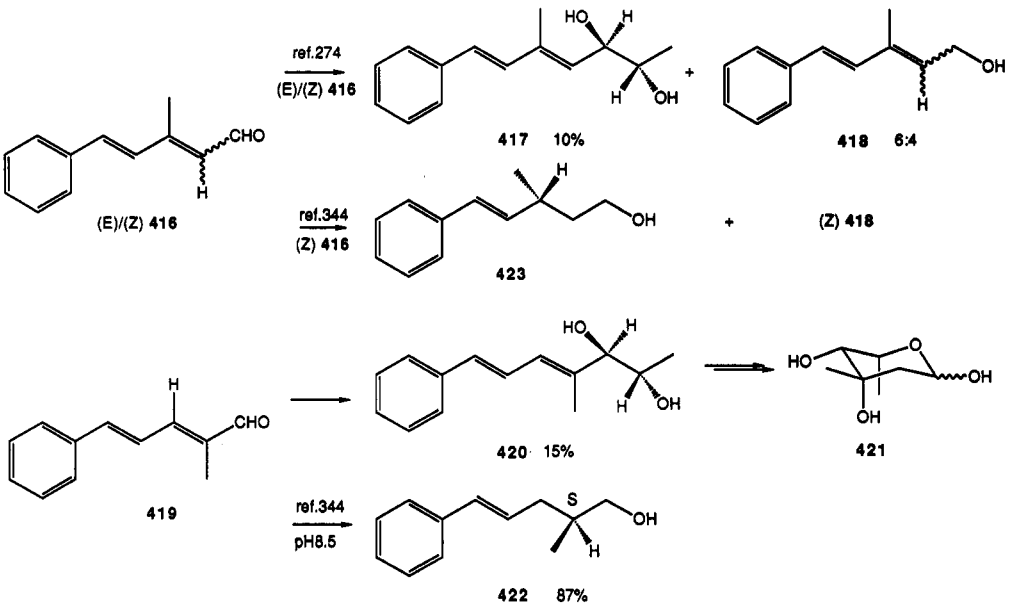
α,β-Unsaturated ketone **427** gave upon reduction with fermenting BY 12% of (*S*)-**428** of ca. 95% ee and 1.5% of **429**. Reduction of **430** with fermenting *Saccharomyces cerevisiae* or resting cells of *Saccharomyces fermentati* gave different results; the former yielded racemic **431**, the latter (*S*)-**431** of ca. 50% ee. Reduction of **432** gave only 4% of **433** (ee 95%) and 1% of **434**.[346] The absolute stereochemistry of these products has not been determined.

It seems that the condensing enzyme(s) are very specific whereas the substrate specificity of the subsequent reduction step is not so restricted. Thus, the racemic and synthetically prepared hydroxy ketones **435a–d** (Scheme 98) (all of them *not* formed by BY-mediated acyloin-type condensation) were clearly reduced by BY under usual conditions. **435a** gave 70–80% of a 6:4 mixture of (2*S*,3*R*)-**436a** and (2*S*,3*S*)-**437a**. The same is true for **435b** (leading to products **436b** and **437b**) whereas **435c,d** gave only 20% of anti-configured **436c,d** accompanied by about 10% of the corresponding syn isomers **437c** and **d**, respectively.[334]

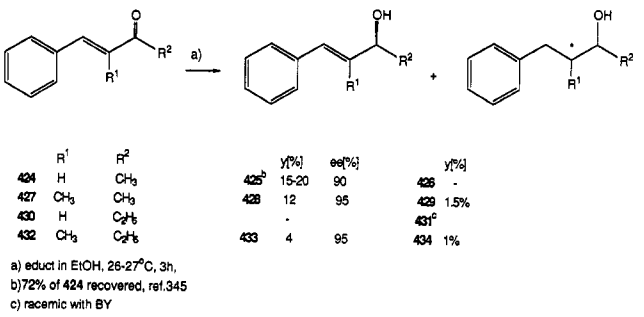
Reduction of **438** gave 70% of a 6:4 mixture of (2*S*,3*R*)-**439** and the syn analogue (*R*,*R*)-**437b**.[330] The latter is the enantiomer of (*S*,*S*)-**437b** (obtained by BY reduction of **435b**).[334]

Branched hydroxy ketones of similar type were also submitted to BY reduction. Thus, **440** (Scheme 99) gave 80% of a 1:1 mixture of **441** and **442** whereas upon reduction of **443** excess (4*S*)-**443** and 15[336]–20%[334] of

SCHEME 96



SCHEME 97



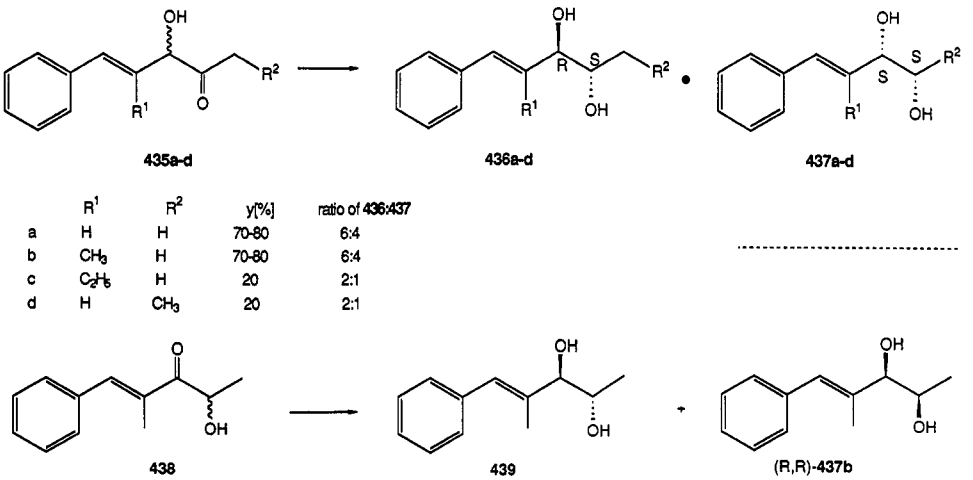
(3*S*,4*R*)-**444** were obtained.[336]

Some conclusions can be drawn from these experiments. For **435a,b** and **440** the hydride addition to the carbonyl grouping occurred on the *re* face regardless of the configuration of the adjacent center. For **435c,d** and **443**, however, only the *R* enantiomers were reduced to a significant extent.[330] In contrast to **435a,b** and to **440** for **438** hydride addition took place onto the *si* face irrespective of the configuration of the adjacent center. Chain elongation (as in **443** as compared to **440**) resulted in decreased yields.[334]

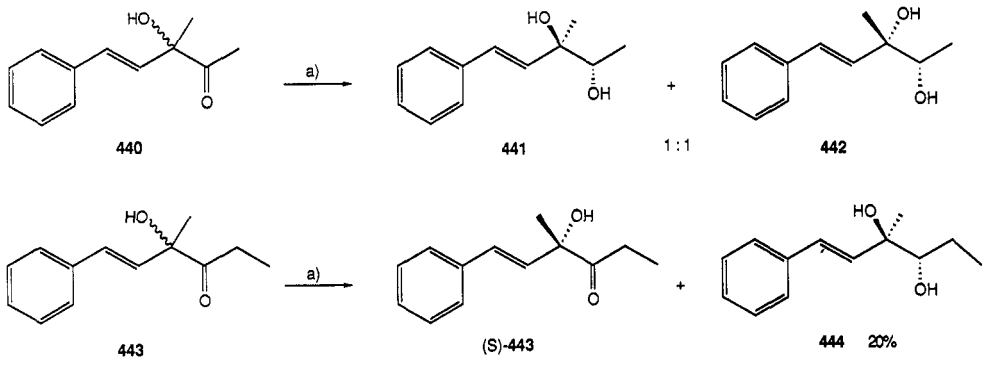
Direction of the stereocontrol of the reduction was performed for **445**–**447** (Scheme 100). **445** gave 20% of **448** in enantiomerically pure form, and 30–40% of 4*S*-configured starting material (of 90% ee) could be recovered;[347] **446** gave mainly (3*S*,4*R*)-**449** with 50% ee. Reduction of **447** resulted in predominant formation of (3*R*,4*S*)-**450**. For **447** the hydrogen addition occurred preferentially on the *si* face. The stereochemical course of these reactions parallels[331] the mode of reduction of 4-heterosubstituted 3-oxobutanoate esters by yeast (due to its five-membered acetal in 1,3-relationship to the carbonyl group).[331]

Similarly, **451** was reduced in about 20% yield to **452**, and 10% of **453** and 70% of starting material could be recovered. While (2*S*,4*S*,5*R*)-**452** served as a valuable starting material for the synthesis of 4-deoxy-D-*lyxo*-hexopyranose, (2*R*,4*S*,5*R*)-**453** was used for the preparation of 2,3-di-*O*-acetyl-4-deoxy-D-*lyxo*(L-*ribo*)-hexopyranose; **454** gave upon reduction 20% of **455**.[348] Apparently for this compound the absolute configuration at C-3 determined which of the components of the racemic mixture is accepted as a substrate for reduction by the enzyme(s) at C-5. (2*R*,3*R*,6*R*)-**454** was not reduced by this system.[348]

SCHEME 98



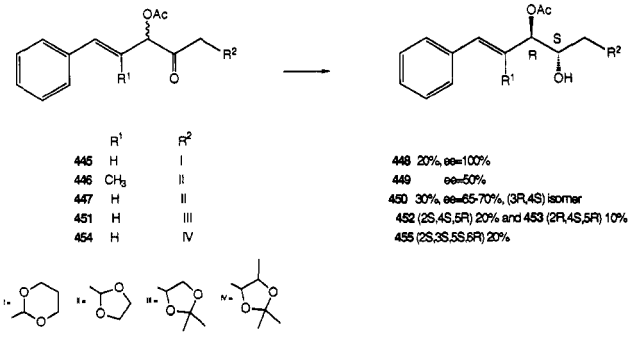
SCHEME 99



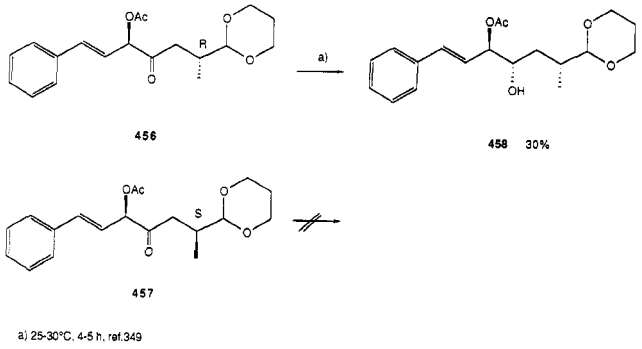
ref. 330,334,336

a) BY; educt in EtOH; 25°;12h;

SCHEME 100



SCHEME 101



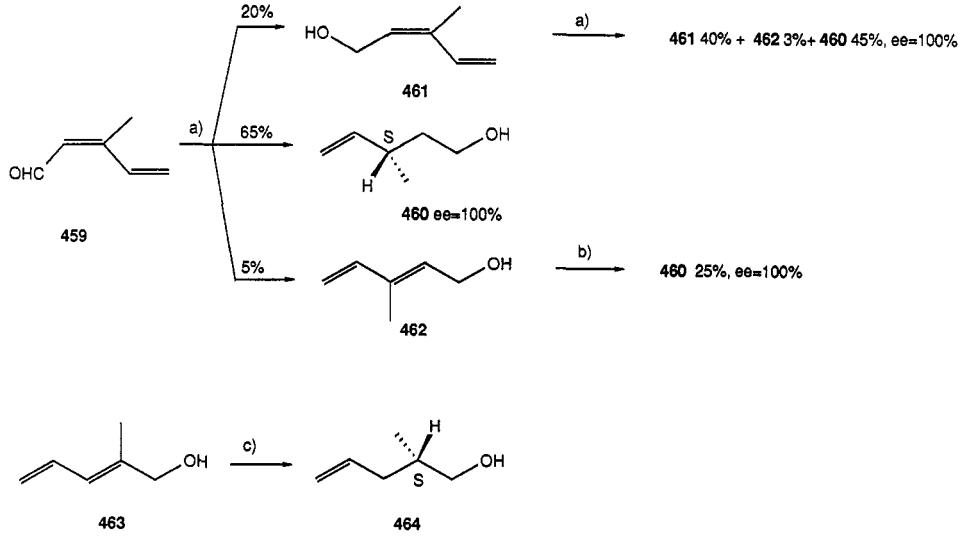
a) 25-30°C, 4-5 h, ref.349

The same phenomenon was observed when the structural analogues (2*RS*,5*RS*)-**456** and (2*SR*,5*RS*)-**457** were treated with BY (Scheme 101). Only (2*RS*,5*RS*)-**456** gave 30% of (2*R*,4*S*,5*R*)-**458**—an intermediate in the synthesis of (−)-α-multistriatin. (2*SR*,5*RS*)-**457** gave no reaction at all.[349] It appears that the yeast's enzyme(s) involved in the reduction of these α-acetoxycarbonyl compounds are quite sensitive to the stereochemistry of remote (here β) centers. Hydrogen addition onto the carbonyl grouping occurred from the *re* face of the 5*R* or 6*R* enantiomer, but of the two diastereomers the one with a (2*R*)-methyl group was reduced at much higher rate.[348,349]

The reduction of (*Z*)-3-methyl-2,4-pentadienal (**459**) (Scheme 102) gave after 10 days of reaction with BY 65% of (*S*)-3-methyl-4-penten-1-ol (**460**), 20% of (*Z*)-3-methyl-2,4-pentadienol (**461**), and 5% of (*E*)-**462** whereas reduction of **461** afforded after 10 days 40% of recovered starting material, 45% of **460**, and 3% of (*E*)-**462**, which upon further BY reduction at pH 8 for another 10 days gave 25% of enantiomerically pure (*S*)-**460**.[350]

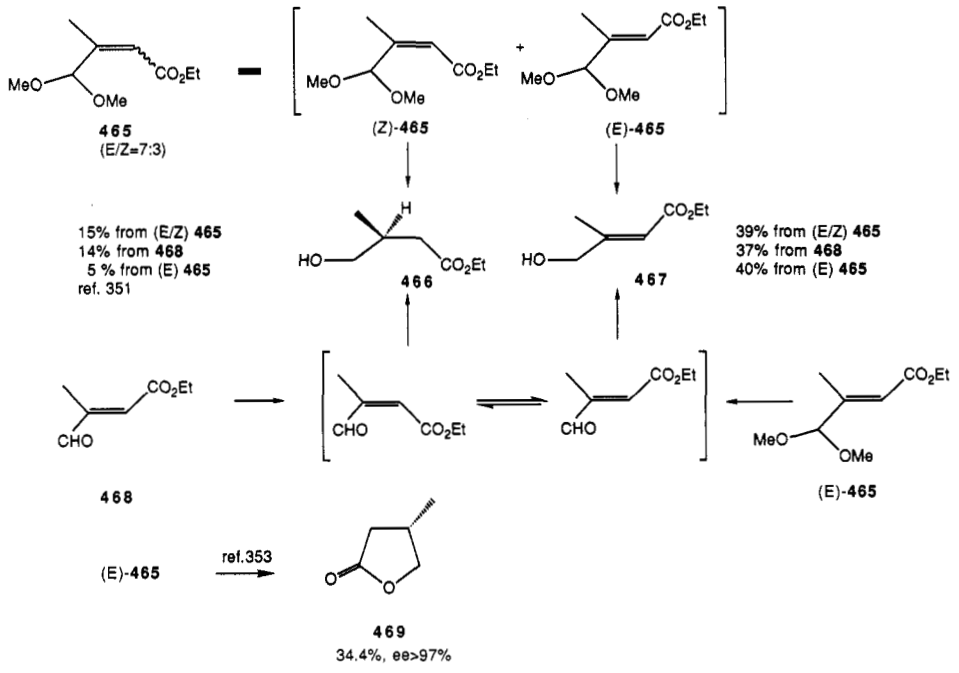
The structural analogue **463** afforded 30% of enantiomerically pure (*S*)-2-methyl-4-penten-1-ol (**464**) under similar conditions.[350] It was established for all of these transformations that only the double bond con-

SCHEME 102

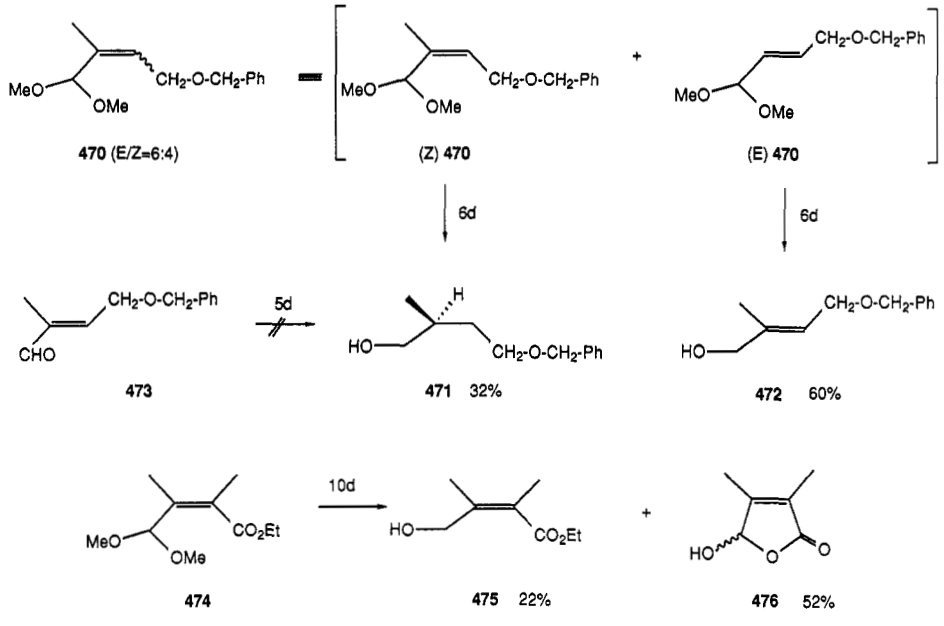


a)BY, 10d, ref.350;
b) 32°C, 10d, pH=8, 80% completion of the reaction
c) 32°C, pH=8, 7d, **463** in EtOH, 30%, ee=100%, ref.350

SCHEME 103



SCHEME 104



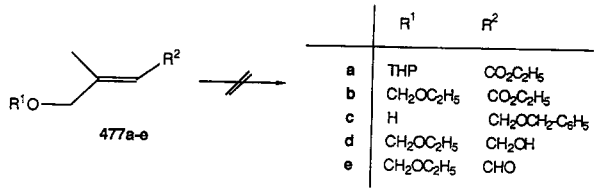
tiguous to the alcoholic or aldehydic function is hydrogenated by BY.[350]

Reduction of the acetal-masked aldehyde but no reduction of the ester moiety were observed for a *Z*/*E* mixture of ethyl 4,4-dimethoxy-3-methylcrotonate (**465**) (Scheme 103). Thus, **465** (*E*:*Z* = 7:3) gave 15% of **466** and 39% of (*E*)-**467**,[351] a valuable synthon for the synthesis of cholesterol derivatives.[352] The *Z* isomer **465** was the best substrate for this biohydrogenation. The acetal group, however, is not completely equivalent to the aldehyde group, since slow hydrolysis of (*Z*)-**465** allowed the isomerization to the (*E*)-aldehyde ester, which was reduced to the corresponding (*E*)-alcohol more rapidly than any possible isomerization. Slow addition of aldehyde **468** to BY afforded within 1 day 37% of **467** and 14% of **466**. With the acetal group the formation of the unsaturated hydroxy ester **467** is favored over formation of the saturated product.[351] If **467** was subjected to a further subsequent BY reduction, it was recovered unchanged. Similarly (*E*)-**465** afforded upon aerobic reduction within 56 h at 30 °C and pH 3–4 a mixture of **466** (49.2%, ee > 97%) and **467** (46.9%). Approximately 2–5% of (*S*)-3-methyl-γ-butyrolactone (**469**) was formed during the reaction and could be obtained from **466** by acidic workup (34.4%, ee > 97%).[353]

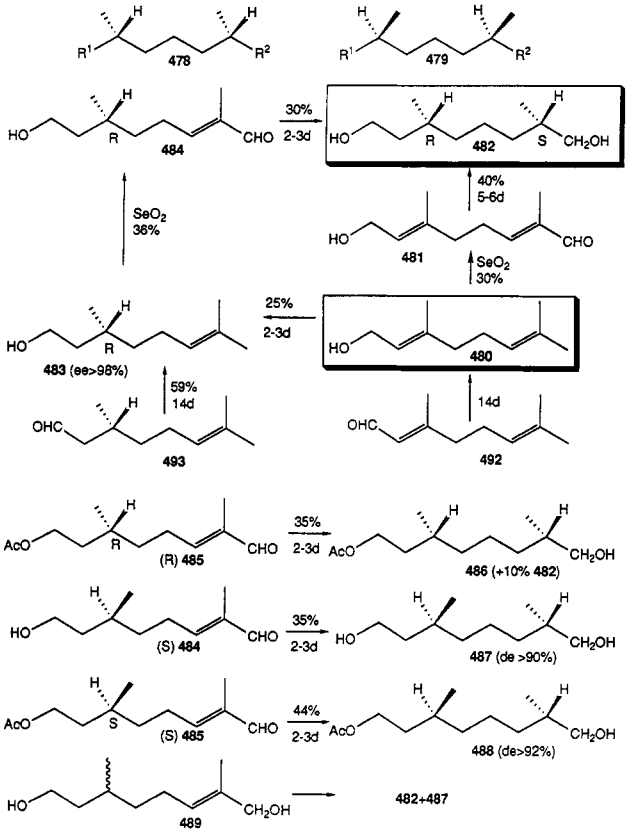
Treatment of the analogue **470** (*E*:*Z* = 6:4) (Scheme 104) showed that (*Z*)-**470** or its equivalent aldehyde was the substrate for the biohydrogenation to yield **471** in 32% yield, whereas (*E*)-**470** was only hydrolyzed and reduced to the corresponding alcohol **472** (60%). No reaction was observed for **473**. **474** gave after 10 days 22% of **475** and 52% of lactone **476**.

The inability to biohydrogenate the respective *E* isomers seems not to be a general rule since such transformations are known to proceed with structural analogues.[354] Furthermore, no reaction upon BY

SCHEME 105



SCHEME 106



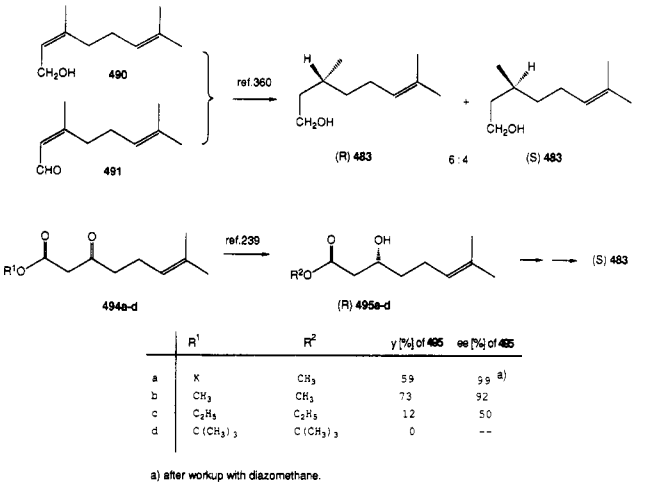
treatment was observed for **477a–e** (Scheme 105) differing in the O substituent R^1 or in R^2. This may be attributed to a too dramatic change in the electronic and stereochemical demand of the biohydrogenation.[351]

A noteworthy access to the valuable C_{10}-synthons for building up molecules containing the 1,5-dimethylated acyclic units **478** or **479** has been reported (Scheme 106).[354] These units are present in tocopherol, phylloquinones, insect pheromones,[355-358] and the marine sponge sesquiterpenoid fasciculatin.[359]

Thus, in a very elegant way geraniol, 3,7-dimethyl-2,6-octadien-1-ol (**480**), was oxidized to the aldehyde **481**, which gave by a one-pot double hydrogenation diastereomerically pure **482**. The same compound was prepared by BY hydrogenation of **480** to afford enantiomerically pure (*R*)-citronellol ((*R*)-**483**),[354,360] which was oxidized to (*R*)-**484**; (*R*)-**484** gave on subsequent BY treatment again **482**. In a similar way and with comparable yields (*R*)-**485**, (*S*)-**484**, and (*S*)-**485** were hydrogenated to afford **486–488**, respectively.[354]

Racemic **489** afforded an equimolar mixture of diastereomers **482** and **487**. It was shown that introduction of the asymmetric center at C-2 is highly stereoselective and the same absolute configuration at C-2 resulted when starting from both (*R*)- or (*S*)-citronellol (**483**). Both (*R*)-**483** and (*S*)-**483** were precursors for the

SCHEME 107



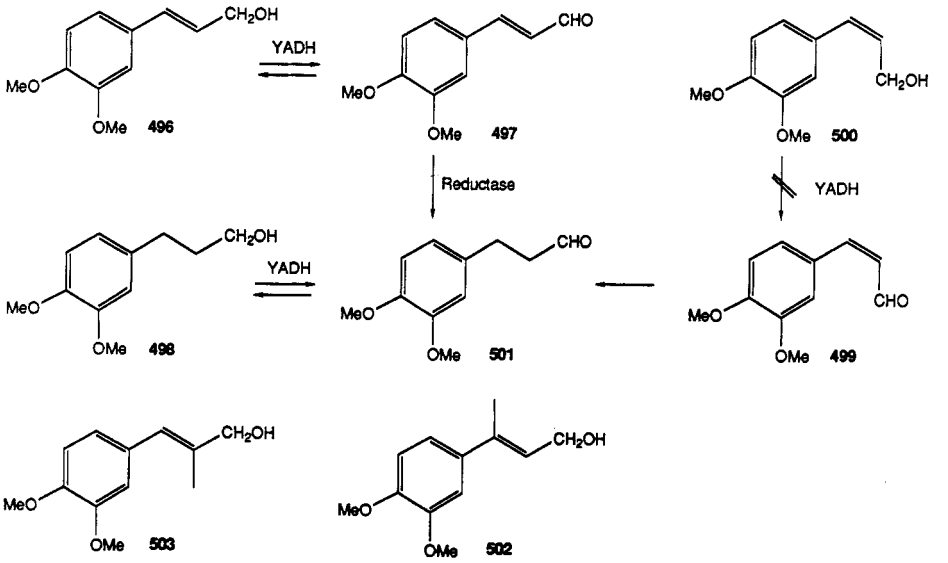
preparation of (*R*)- or (*S*)-**484**. No epimerization took place at C-6 of the α,β-unsaturated aldehydes or alcohols during microbial reduction.[354] It is interesting to note that nerol (**490**) and neral (**491**) (Scheme 107) each afforded a mixture of the two enantiomers of citronellol with a ratio of (*R*)-**483** to (*S*)-**483** of 6:4. This is due to a potential *Z*/*E* isomerization of neral (**491**), which appears to be an obligatory intermediate in the BY-mediated conversion of nerol into citronellol.[360] The same *R* to *S* ratio was found for the reduction performed with *Beauvaria sulfurescens*.[361]

Even the starting materials for these syntheses have been prepared by BY-mediated biohydrogenations or reductions. Thus, **492** (Scheme 106) gave on BY treatment[362] for 2 weeks **480**, and **493** afforded under similar conditions 59% of (*R*)-**483**.[363] BY reduction[239] of the β-keto ester **494a–d** gave (*R*)-**495a–d**, which were successfully transformed into (*S*)-**483** (Scheme 107).[364] The intermediates of this elegant approach to chiral C_{10} synthons have been used for the synthesis of natural (*E*)-(7*R*,11*R*)-phytol.[354]

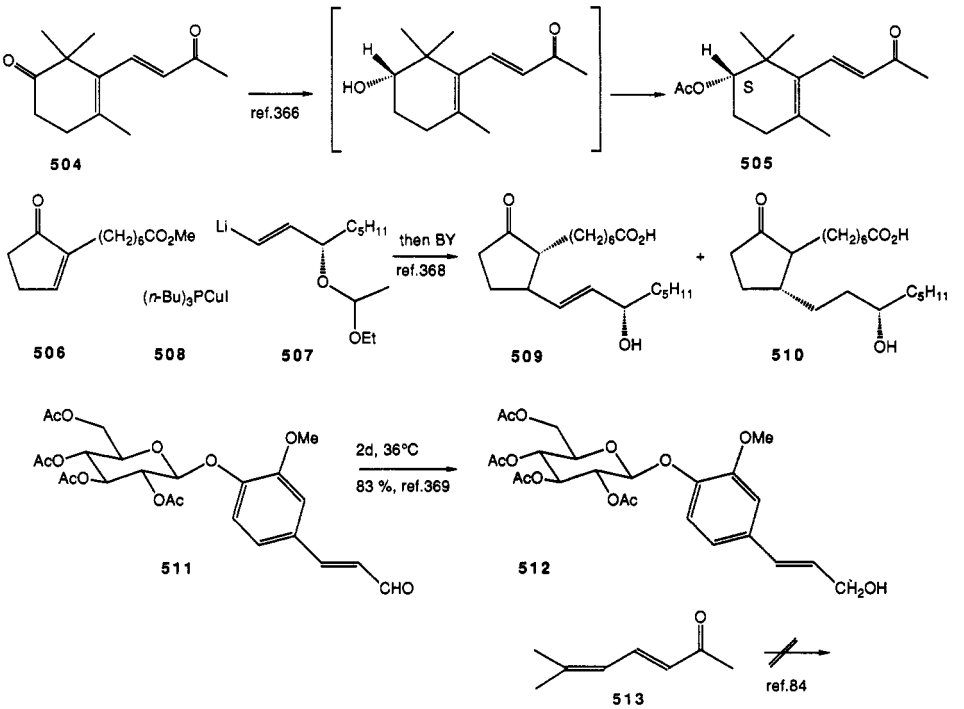
Reduction of α,β-unsaturated alcohols was investigated in more detail for substituted cinnamyl alcohols.[365] It was shown that the reduction of **496** (Scheme 108) proceeded through the corresponding aldehyde **497** to yield finally **498**. In analogy to the decarboxylation of (*E*)-cinnamic acid (cf. III.A.b), only (*E*)-cinnamyl alcohol but not the *Z* type was reduced. Since (*Z*)-3′,4′-dimethoxycinnamylaldehyde (**499**)—which could not be obtained from **500**—was rapidly reduced to **501**, it was concluded that in this two-step enzymic system consisting of one (or two) alcohol dehydrogenases and a reductase it is the alcohol dehydrogenase showing a specificity with respect to *E* versus *Z* configuration.[365] Gramatica and co-workers observed that an inductive alcohol dehydrogenase (ADH-II, of ethanol-grown cells) showed the same specificity toward the double-bond configuration as the constitutional dehydrogenase ADH-I. Although no (*Z*)-alcohol was reduced by ethanol-grown cells, these cells were able to reduce the (*E*)-alcohol faster than glucose-grown cells.[365] The same results were found for cell homogenates, thus allowing a more direct comparison between ADH-I and ADH-II. A blockage of the reductase but not of the alcohol dehydrogenase was established for **502** but not for **503**.[365]

Slower reaction as compared to α,β-unsaturated aldehydes or alcohols or even no reaction at all was ob-

SCHEME 108



SCHEME 109

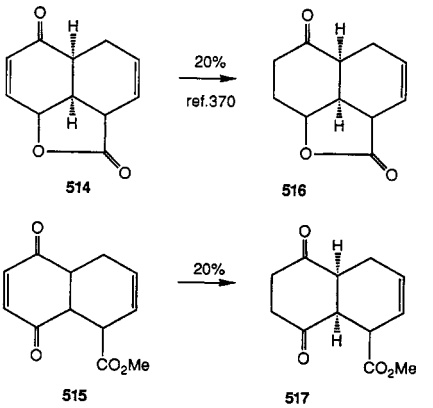


served for α,β-unsaturated ketones. Thus, no reaction of α,β-unsaturated ketone **504** could be achieved (Scheme 109). Instead, reduction of the cyclic keto function occurred; subsequent acetylation afforded (*S*)-**505** in 60% yield.[366] **505** is a valuable building block for the synthesis of carotenoids with a 2-hydroxylated β-ring.[367] Side-chain reduction but no reduction of the cyclanone were found during the synthesis of prostaglandins. Thus, reaction of cyclopentanone **506** with **507** and **508** followed by hydrolysis and subsequent BY treatment gave a mixture of unsaturated **509** and saturated **510**.[368]

Upon reduction of glycoside **511**, 83% of tetra-*O*-acetylconiferin (**512**) was obtained.[369] Interestingly, no deacetylations were found to occur during this transformation. No reaction occurred with **513**.[84]

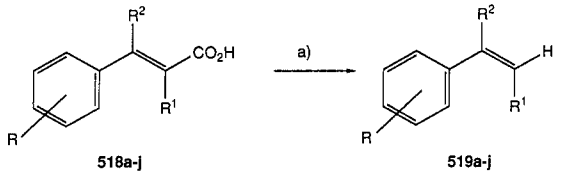
In addition, Woodward's lactone (**514**) (Scheme 110) and the analogue **515** have been reduced in about 20%

SCHEME 110



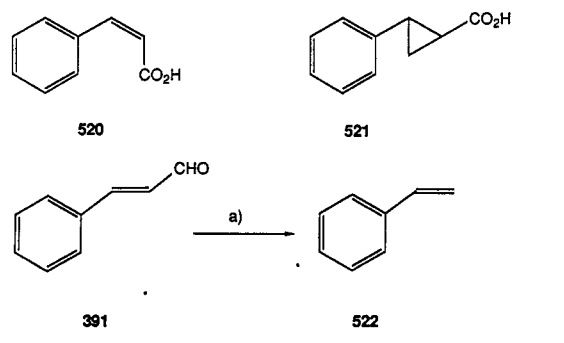
yield to give **516** and **517**, respectively.[370] Further examples for the reduction of C=C double bonds are

SCHEME 111



a) 24h, pH=4-5, ref.371

No	R	R^1	R^2	reaction
a	H	H	H	-
b	3,4-dihydroxy	H	H	-
c	3,4-methylenedioxy	H	H	-
d	4-hydroxy	H	H	+
e	4-methoxy	H	H	+
f	4-hydroxy-3-methoxy	H	H	+
g	3,4-dimethoxy	H	H	+
h	3,4-dimethoxy	CH_3	H	+
i	3,4-dimethoxy	H	CH_3	+
j	3,4-dimethoxy	CH_2CH_3	H	+



a) for conditions, cf ref. 374

found in Schemes 48, 92, 95, 97, 120, and 123.

2. Decarboxylations

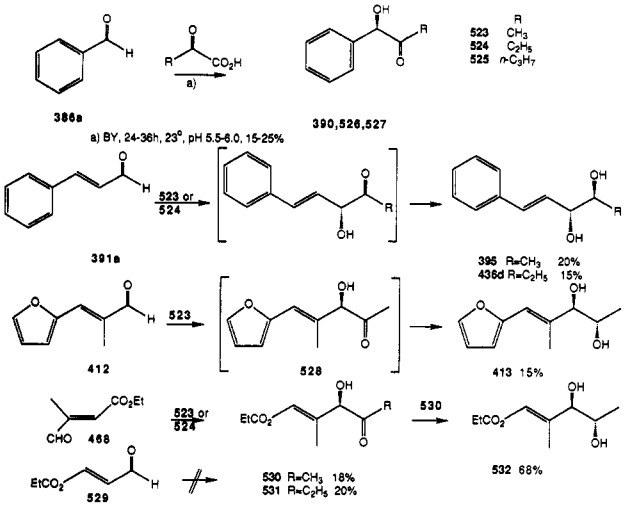
The decarboxylation of substituted cinnamic acids **518a–j** by BY has been investigated extensively by Gramatica et al.[371] and as shown by NMR investigation of deuterated compounds to proceed with retention of configuration to yield **519d–j** (Scheme 111). The results obtained for BY parallel earlier findings obtained for *Bacillus pumillus*.[372] Thus, to account for the overall stereochemistry, it has been suggested that a syn-1,2-Michael-type addition has been followed by an anti-1,2-decarboxylative elimination.

The *E* configuration of the double bond is necessary since neither **520**—for geometric reasons—nor **521**—for electronic and/or geometrical reasons—was reduced at all. This pronounced enzymic specificity with respect to the double bond might also be due to a conformational effect at the transition-state level of the decarboxylation step.[373] The presence of remote hydroxy or methoxy groups in the aromatic ring seems to be necessary for attachment to the enzyme.[371]

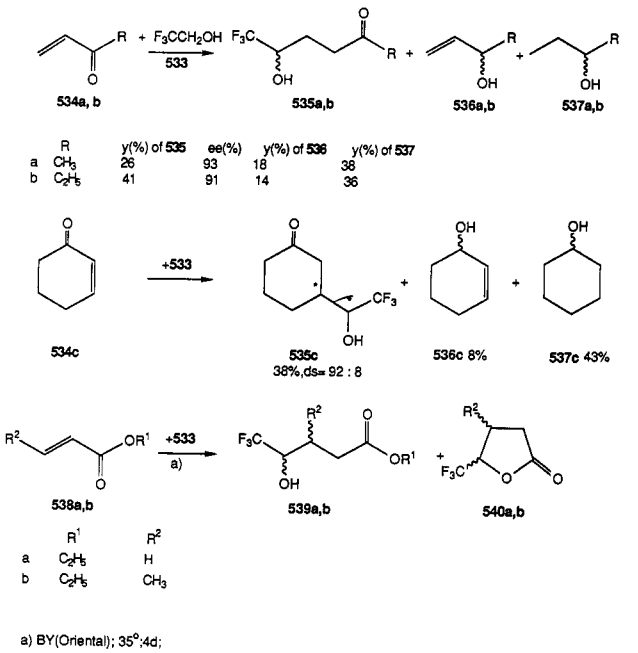
Similar to the decarboxylation of aromatic α,β-unsaturated carboxylic acids upon treatment with BY, there is one report describing the transformation of (*E*)-cinnamylaldehyde (**391**) to styrene (**522**) by means of *Saccharomyces cerevisiae* SC3212[374] instead of its reduction to cinnamyl alcohol.[191]

Recently, decarboxylative incorporation of linear C_3, C_4, and C_5 α-oxo acids into (*R*)-α-hydroxy ketones was accomplished when benzaldehyde was incubated with BY.[375]

SCHEME 112



SCHEME 113



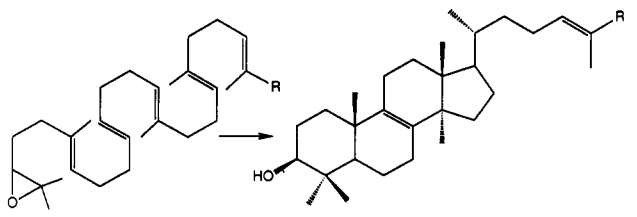
a) BY(Oriental); 35°;4d;

Thus, BY-mediated reaction of benzaldehyde (**386a**) (Scheme 112) with **523–525** afforded 15–20% of **390**, **526**, and **527**, respectively. Similarly, cinnamyl aldehyde (**391a**) afforded 20% of **395** or 15% of **436d** on incubation with **523** or **524**, respectively. The furyl derivative **412** gave **528**, which afforded on subsequent BY reduction 15% of **413**; **529** gave no reaction at all whereas **468** yielded 18–20% of **530** and **531**, respectively, the former of which was reduced by BY to optically pure **532** in 68% yield.[375]

B. Miscellaneous C–C Bond-Forming Reactions

C–C bond formation has been reported to occur during the reaction of 2,2,2-trifluoroethanol (**533**) (Scheme 113) with α,β-unsaturated ketones **534a–c**. Products **535a–c** are the results of a conjugate 1,4-addition, although obtained in lower yield (26–41%) but with high ee (91–93%) or de (92:8). These reactions were accompanied by a reduction process, thus yielding **536a–c** and **537a–c**. The α,β-unsaturated esters **538a,b** gave products **539a,b**, which lactonized very easily to **540a,b**. In addition, it was found that the reduction of

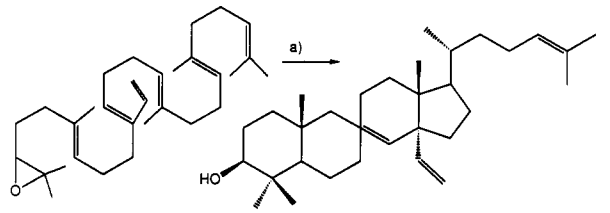
SCHEME 114



541a,b 542a,b

	R	y[%]	t[h]
a	CO_2CH_3	62	28
b	CH_3	84	12

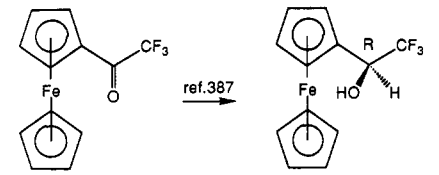
activation of BY: 25 g BY, pH 7.4, irradiated ultrasonically 0°, 2h, ref.377a



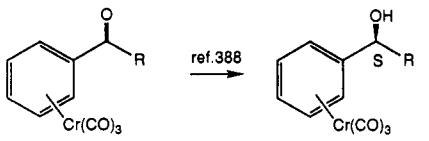
(+/-)-541c (-)-542c

a) 23°, 48h, 62% conversion, ref. 377b

SCHEME 115



543 544
90.5%, ee>90%



545a,b 546a,b

	R	y[%]	ee[%]
a	CH_3	96	99
b	C_2H_5	20	87

educts **534** and **538** is slower if **533** is absent.[376]

Cyclization of **541a** to **542a** (Scheme 114) by an osterol cyclase was achieved in an enantioselective manner by treatment of **541a** with ultrasonically activated BY. Similarly, 2,3-oxidosqualene (**541b**) gave lanosterol (**542b**) in 83% yield whereas using unstimulated BY only 19% of product could be obtained. It was shown[377a] that the cyclase operates only on the *S* enantiomer of the racemic starting material.

On examination of the time course dependence of sterol production on ultrasound, it was shown that for incubations conducted with whole cells there was a significant increase in sterol formation when cells were first sonicated for at least 0.5 h, reaching maximum conversion efficiency at 2 h of sonication.[377a] Since a cell-free cyclase system was unaffected and was completely insensitive to ultrasound irradiation, it was suggested that the ultrasound effect is more likely associated either with facilitating substrate diffusion by removing the obstructing outer membrane (rather than activating the cyclase) or by liberating membrane-associated sterol-carrier protein factors.[377a] A vinyl group rearrangement was observed in the BY oxidosqualene–lanosterol cyclase mediated cyclization of racemic squalendoid **541c** to afford (–)-**542c**.[377b] However, an attempt to apply this cyclization method to an isomeric substrate possessing a vinyl appendage at C-15 in the squalene backbone was not successful.[377b] In addition, imidazo-fused quinazolinones have been prepared from *N*-(allylcarbamoyl)anthranilonitriles by BY-mediated cyclization.[377c]

IV. Reduction of Organometallic Compounds

Although the reduction of porphyrins and hemoglobins[378-380] by BY is long known, there are only a few works dealing with inorganic material[381-384] and with the reduction of metal-containing organic molecules or organometallic species. The first reports[385] on that topic described the reduction of ferrocenyl-type molecules.[386] Thus, **543** (Scheme 115) gave on treatment with BY 90.5% of (*R*)-**544** (ee > 90%).[387] It is also possible to reduce aryl ketone–$Cr(CO)_3$ complexes **545a,b** with BY.[388] This reaction seems to be dependent on the bulkiness of the substituents since reduction of **545a** afforded **546a** within 1 day, **545b** gave **546b** within 2 weeks, but 2,4,6-trimethylacetophenone–$Cr(CO)_3$ or acetophenone–$Cr(CO)_2$–PPh_3 gave no reaction at all. Reduction of racemic indanone–$Cr(CO)_3$ (*rac*-**547**) (Scheme 116) afforded a mixture of alcohols (*S*)-*endo*-**548** (47%, ee = 51%) and (*S*)-*exo*-**549** (5%, ee = 71%) together with unreacted starting material **547** (48%, 25% ee).[388]

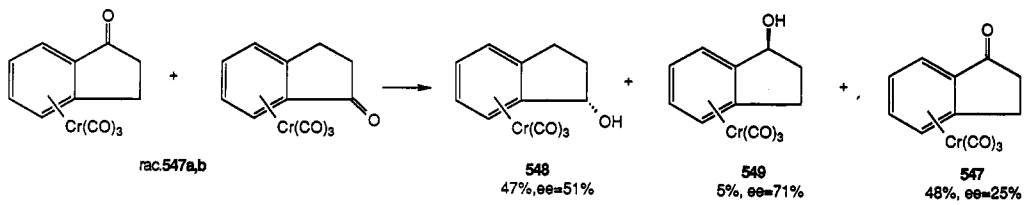
Similarly, enantioselective microbial resolution of the planar chiral metallocenic aldehyde **550** (Scheme 117) afforded after 55% conversion (+)-(1*R*)-tricarbonyl[2-methoxy-1-(hydroxymethyl)phenyl]chromium ((*R*)-**551**) in 49% yield (66% ee) and the optically active starting material (*S*)-**550** (45%, ee = 81%).[389]

V. Reduction of Fluorine-Containing Compounds

A. Ketones

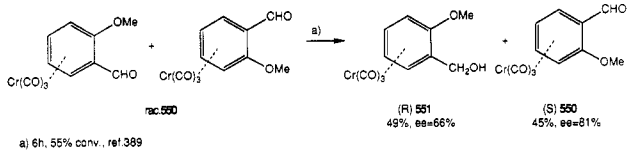
Fluorine-containing compounds are only scarcely found in nature.[107,390] Nevertheless, due to their potential use as drugs and valuable tools for metabolic studies, the number of syntheses of mono- and polyfluorinated natural product analogues has increased

SCHEME 116



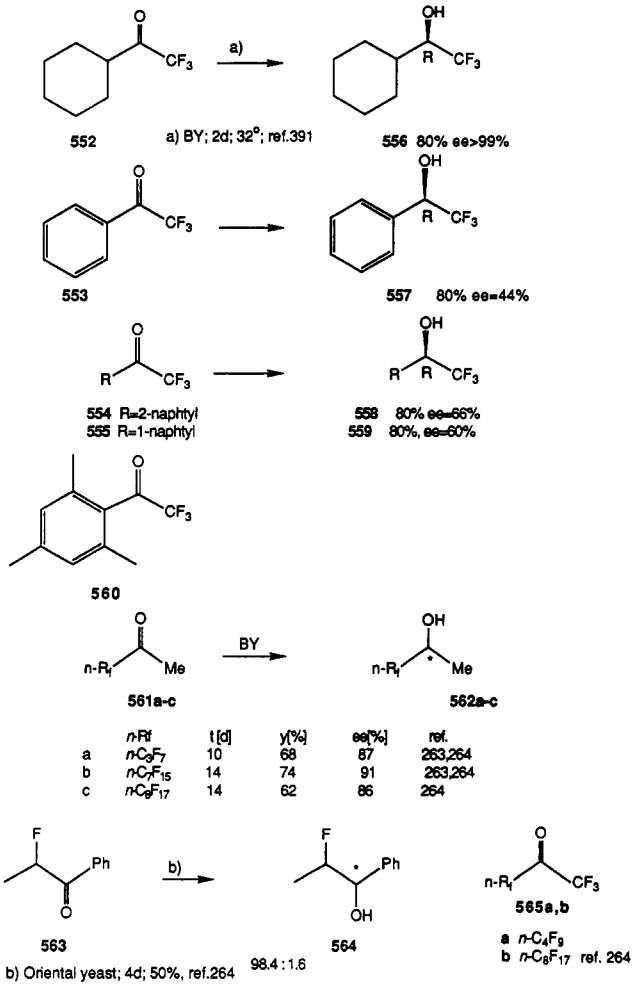
rac.547a,b 548 47%,ee=51% 549 5%, ee=71% 547 48%, ee=25%

SCHEME 117



a) 6h, 55% conv., ref.389

SCHEME 118



	n-Rf	t [d]	y[%]	ee[%]	ref.
a	nC_6F_7	10	68	87	263,264
b	nC_7F_{15}	14	74	91	263,264
c	nC_8F_{17}	14	62	86	264

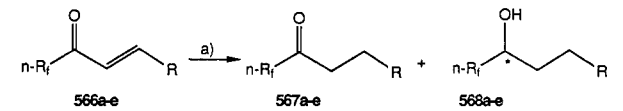
b) Oriental yeast; 4d; 50%, ref.264

tremendously within the last 10 years. Recently, the reduction of such compounds by means of enzymic or microbial systems has gained much interest as tools for the preparation of enantiomerically pure fluorinated compounds. The trifluoromethyl ketones **552–555** (Scheme 118) were reduced in good yield to the corresponding (*R*)-carbinols **556–559**, respectively,[391] but no reduction was observed for **560**.[391]

561a–c gave after a quite long reaction time of 10–14 days between 62 and 74% of (–)-**562a–c**; the absolute configuration of these compounds has not been determined. Although the reactions were inconvenient to handle, particularly in the case of compounds with long perfluoroalkyl chains, the optical purity of the products was high.[263,264] (–)-**563** gave in 50% yield a 98.4:1.6 mixture of diastereomers **564**. Bis(perfluoroalkyl) ketones were strongly resistant to the action of yeast; thus, trifluoromethyl-substituted ketones **565a,b** gave no reaction at all within 7 days.[264]

Further examples have been provided,[64] and it was shown that the stereochemistry of the reduction and the ee value can be rationalized due to steric effects of the adjacent groups rather than to electronic effects.

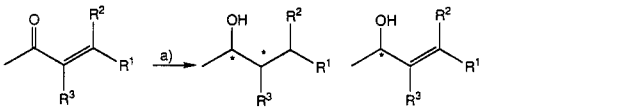
SCHEME 119



	R_f	R	y[%]of 567	y[%] of 568	ee[%] of 568
a	CF_3	C_6H_5	74	5	81
b	C_2F_5	C_6H_5	68	6	77
c	nC_6F_9	C_6H_5	77	3	78
d	CF_3	CH_3	46	7	85
e	C_2F_5	CH_3	42	9	89

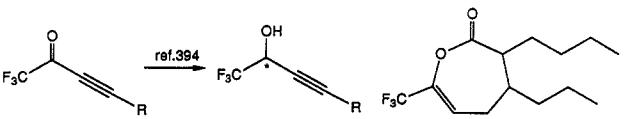
a) Oriental, 10d, 30-35°, ref.392

SCHEME 120



	R^1	R^2	R^3	t [d]	y[%]of 571	y[%] of 570	ds of 571	ee[%] of 570
a	CF_3	H	F	2	4	81	-	86
				10	67	7	81/19	-
b	CF_3	CH_3	H	2	6	64	-	88
				10	46	5	76/24	-
c	C_2F_5	H	F	2	3	78	-	90
				10	51	6	83/17	-
d	H	H	CF_3	2	2	69	-	93
				10	51	3	84/16	-

a) BY (Oriental); 30-35°; ref. 392,393



	R	ee[%]
a	C_6H_5	46
b	nC_3H_7	82
c	nC_4H_9	53

Trifluoromethyl ketones are faster reduced than the corresponding methyl ketones but slower than their bromomethyl analogues.[64] Differences were encountered for the reduction with or without addition of carbohydrates.

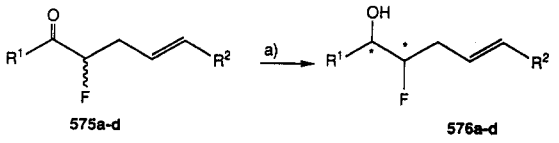
Investigations on the reduction of these fluorinated carbonyl compounds were extended to unsaturated analogues. Thus, compounds **566a–e** (Scheme 119) gave within 10 day of reaction **567a–e** (major) and **568a–e** was found as a minor byproduct although of high optical purity; the absolute stereochemistry of the products has not been established.[392,393]

When the reductions were applied to ketones **569a–d** (Scheme 120) containing a perfluoroalkyl group attached on the carbon–carbon double bond, BY was found to reduce these particular ketones, producing first the optically active carbinols **570a–d**; diastereomers **571a–d** were obtained after incubation for 10 days.[392,393] These results seem to indicate that the C=O group of fluoroalkenyl ketones is more easily reduced than the C=C bond with actively fermenting BY.[392]

Fluoroalkynones **572a–c** have been reduced by BY to give fluoroalkynols **573a–c**; (*E*)-fluoroalkenones and fluoroalkanones were observed as the byproducts. Interestingly enough, for the reduction of **572b,c**, **574** was obtained in 18–21% yield.[394]

The olefinic α-fluoroolefins **575a–d** (Scheme 121) gave in 38–64% yield mixtures of diastereomers **576a–d** without any reduction of the C=C double bond. The respective diastereomeric ratio was determined by ap-

SCHEME 121



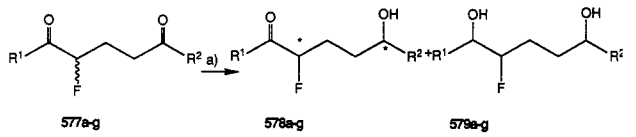
575a-d 576a-d

a) BY(Oriental); 35°; pH 7.3; ref.395

	R^1	R^2	y[%]	threo/erythro	ee[%][a]
a	CH_3	H	58	72/28	86/76
b	C_2H_5	H	64	68/32	75/54
c	n-C_3H_7	H	38	56/44	79/45
d	n-C_4H_9	H	42	58/42	64/47

[a] of threo and erythro compound, respectively.

SCHEME 122



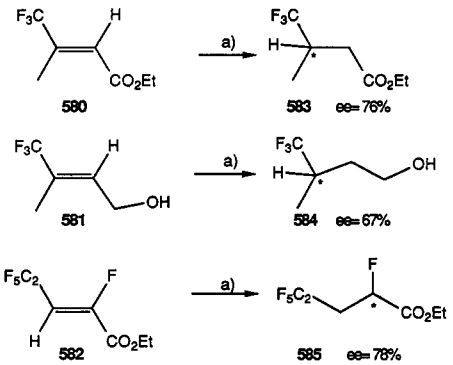
577a-g 578a-g 579a-g

a) BY(Oriental); 35°; pH 7.3; ref. 395

	R^1	R^2	t[d]	y[%] of 578	y[%] of 579	ee[%] of 578[a]
a	CH_3	CH_3	1	61	4	73/27
			5	2	65	
b	CH_3	C_2H_5	1	58	2	66/34
			5	5	49	
c	C_2H_5	CH_3	1	62	7	68/32
			5	2	57	
d	C_2H_5	C_2H_5	1	54	5	58/42
			5	7	51	
e	n-C_3H_7	CH_3	1	48	16	71/29
			5	6	52	
f	n-C_3H_7	C_2H_5	1	51	8	63/37
			5	6	46	
g	n-C_4H_9	CH_3	1	62	2	55/45
			5	4	48	

a) of the corresponding stereoisomers, whose configuration was not assigned

SCHEME 123



580 583 ee=76%

581 584 ee=67%

582 585 ee=78%

a) BY; 7d; ref. 263

plication of ^{19}F NMR spectroscopy.[395]

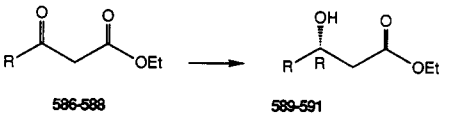
Fluorinated 1,5-diketones **577a–g** (Scheme 122) gave after a 1-day lasting reduction mainly the products of a monoreduction remote of the fluorine substituent **578a–g**, whereas on prolonged reaction time (5 days) the corresponding diols **579a–g** were obtained.[395]

Clean reduction of the double bond even occurred with compounds **580–582** (Scheme 123) after 7-day incubation with fermenting BY and gave products **583–585**, respectively.[263]

B. Keto Esters

Reduction of polyfluorinated β-keto esters **586–588** (Scheme 124) gave the desired reduction products

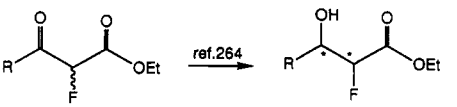
SCHEME 124



586-588 589-591

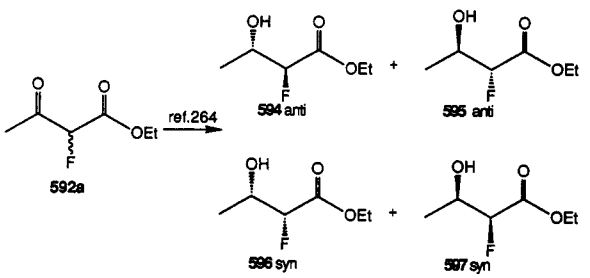
products 589-591

	R	y[%]	ee[%]	ref.
586	CF_3	75	49-51	261,263,264
587	C_2F_5	87	94	263,264
588	n-C_7F_{15}	86	93	264



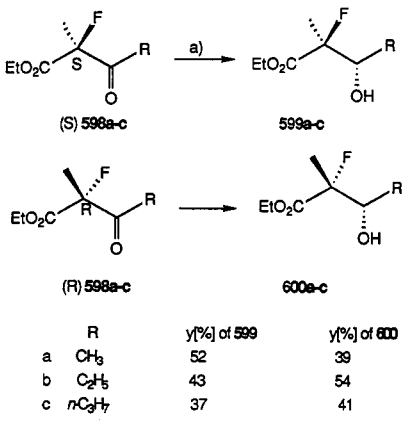
592a-d 593a-d

	R	t[d]	y[%]	syn/anti
a	CH_3	5	78	81/19
b	C_2H_5	5	69	78/22
c	n-C_3H_7	7	74	84/16
d	n-C_5H_{11}	7	71	82/18



592a 594 anti 595 anti 596 syn 597 syn

SCHEME 125



(S) 598a-c 599a-c

(R) 598a-c 600a-c

	R	y[%] of 599	y[%] of 600
a	CH_3	52	39
b	C_2H_5	43	54
c	n-C_3H_7	37	41

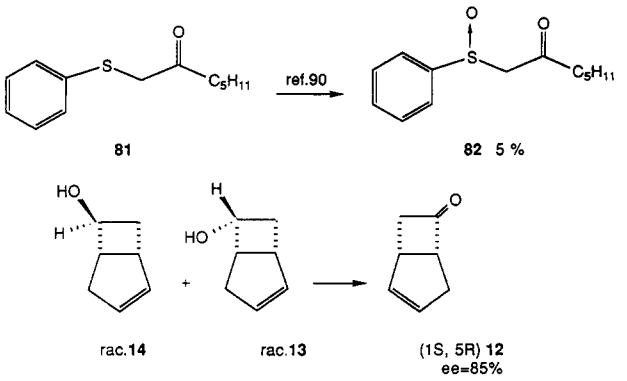
a) BY(Oriental); 35°; 3d; ref. 396

589–591 in good yields.[261,263,264] Previously reported optical purities[263,264] for **589** are in contrast to more recent findings.[261] With lower yields, but still with a fair diastereomeric ratio, monofluorinated compounds **592a–d** were reduced to afford mixtures of diastereomers **593a–d**.[264]

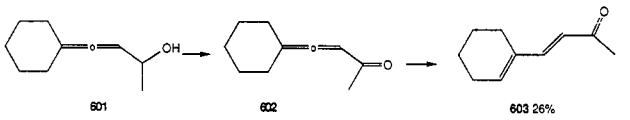
Reduction of the racemic monofluorinated ethyl acetoacetate **592a** (giving rise to the four products **594–597**) was investigated in more detail by extensive NMR studies. The ratio of syn (**596** + **597**) to anti (**594** to **595**) was 81:19 with **596**:**597** = 4:96 corresponding to an ee of 92%, whereas the ratio between the anti-configured products **594** and **595** was determined to be 28:72 corresponding to a significantly lower ee of 44%.[264]

Reduction of the optically active (*S*)-α-fluoro-α-methyl-β-keto esters (*S*)-**598a–c** (Scheme 125) gave *anti*-β-hydroxy esters **599a–c** (ee > 99%) while (*R*)-

SCHEME 126



SCHEME 127



598a–c were reduced to give *syn*-β-hydroxy esters **600a–c** (ee > 98%).[396]

VI. Oxidations

Oxidations by means of BY have scarcely been described in the literature obviously due to two reasons: On the one hand, the microbiological oxidation of alkanols to alkanones is not of very great interest except were polyols are to be selectively oxidized since chemical methods are often adequate.[32] On the other hand, the oxidational capabilities of BY seem to be very limited.[397] For example, chiral sulfoxidation became an important tool in organic synthesis and many fungi including *Aspergillus niger* and *Rhizopus arrhizus* and fungi from the *Penicillium* and *Rhodotorula* species as well as bacteria were used for these oxidations, but there are no examples performed by BY.[398] It seems there is only one oxidation at a sulfur substituent known, namely the oxidation of **81** to racemic **82** (Scheme 126), which proceeded in only about 5% yield.[90]

Due to these reasons, only a few examples can be provided. Thus, a 1:5 mixture of racemic 6-*exo*-bicyclo[3.2.0]hept-2-en-6-ol (**14**) and 6-*endo*-bicyclo[3.2.0]-hept-2-en-6-ol (**13**) was treated with BY for 4 days at pH 6 to give (1*S*,5*R*)-**12** in 85% optical purity; **13** was recovered in 90% optical purity.[45,399]

Finally, α-allenic alcohol **601** (Scheme 127) was oxidized to **602**, which underwent an isomerization of the allenic moiety. Thus, 26% of **603** was obtained and 72% of the starting material could be recovered.[400]

VII. Hydrolyses of Esters

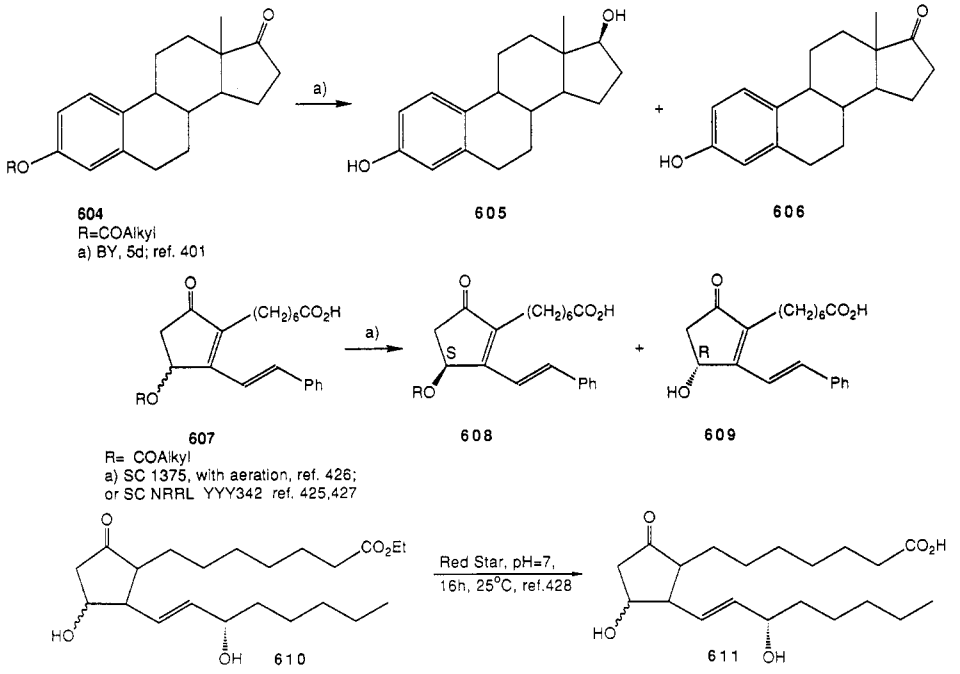
A. General Remarks

Although discovered inadvertently as an undesired side reaction,[401] the deacylations have only recently been a focus of thorough studies. These deacylations have been regarded for a longer period of time just as simple and more or less useless reactions happening only to annoy chemists and to complicate the workup procedure. The first report of such hydrolyses was given by Mamoli[401] in the steroid field. Esters **604** (Scheme 128) gave upon treatment with BY mainly **605** as products both of a reduction at position C-17 and a hydrolysis at position C-3. As byproduct, **606** was observed.[401]

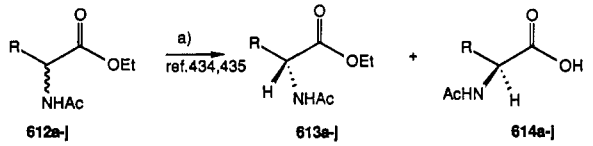
Several groups investigated the enzymes involved in hydrolysis reactions. A very comprehensive review on proteinases[402,403] has been published recently,[404] and it has been shown that all compartments of the cells are possible locations for these enzymes. Enzymes characterized as esterases have been isolated from *Saccharomyces cerevisiae*,[405–409] and their hydrolytic as well as their synthesizing activities have been probed.[405,410–414] In addition, phospholipase,[415–417] lipase,[415,418,419] tributyrinase,[420,421] and triacylglycerol–lipase activities[419,422–425] have been detected and investigated.

Such hydrolysis reactions were found to be very suitable in the synthesis of prostaglandins and their

SCHEME 128

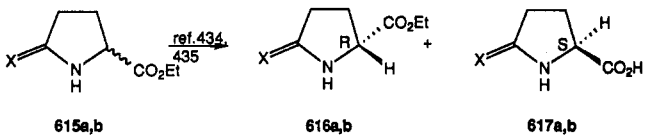


SCHEME 129



612a-j 613a-j 614a-j

	R	y[%] of 613	ee[%] of 613	cond.
a	CH_3	47	100	an
b	C_2H_5	48	96	an
c	$i\text{-}C_3H_7$	75	13	an
c	$i\text{-}C_3H_7$	38	80	ae
d	$i\text{-}C_4H_9$	48	92	an
e	$CH_2C_6H_5$	38	>97	an
f	CH_2CO_2Et	49	86	an
g	$(CH_2)_2CO_2Et$	46	89	an
h	$(CH_2)_4NHAc$	0[c]	-	an
i	CH_2OAc	37	43	an
i	CH_2OAc	36	47	ae
j	$CH(OAc)CH_3$	64	3	an



615a,b 616a,b 617a,b

	X	y[%]	ee[%]
a	H_2	10	25
b	O	59	0

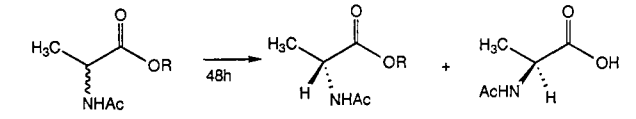
a) SC Hansen 48h, r.t.
b) an= anaerob, ae=aerob
c) 94% of starting material recovered

precursors. Thus, esters of racemic 7-(2-*trans*-styryl-3-hydroxy-5-oxocyclopentenyl)heptanoic acid (**607**) were stereoselectively hydrolyzed by fermenting BY during 120 h to yield **608** and **609**,[426,427] but no ee values have been reported. Ester cleavage has been reported for **610** to yield **611**[428] and other prostaglandin precursors.[429-431] An excellent approach for the mathematical treatment of such biochemical kinetic resolutions of enantiomers has been proposed by Sih et al.[431b]

B. Esters of Amino Acids

Although the enzymic de-N-acetylation of racemic *N*-acetyl amino acids by an aminoacylase (E.C. 3.5.1.14) from pork kidney[432,433] has gained high industrial potential, the hydrolytic abilities of BY have also been used for the synthesis of amino acid derivatives. Thus, racemic esters of *N*-acetyl amino acids **612a–j** (Scheme 129) were hydrolyzed by BY (*Saccharomyces cerevisiae* Hansen) to yield the unreacted D-configured esters **613a–j**; acids **614a–k** were not isolated.[434] Generally the ee's were high for educts containing unbranched alkyl or arylalkyl substituents (e.g., **613a,b,d,e**), but the reactions were inhibited by a branching in the β-position, thus resulting in high recovery rates and therefore low ee values (e.g., **613c,j**); a substituent in the γ-position showed no effect, whereas introduction of additional polar groups as in **612h–j** lowered the ee of the obtained products. Ethyl 3-(*N*-acetylamino)butanoate was a nonsubstrate for the insertion of an additional CH_2 group between the center of chirality and the ester moiety. Enzymic regioselection, however, was found for diesters **612f,g**; only the ester moiety α to the center of chirality was hydrolyzed. The cyclic derivatives

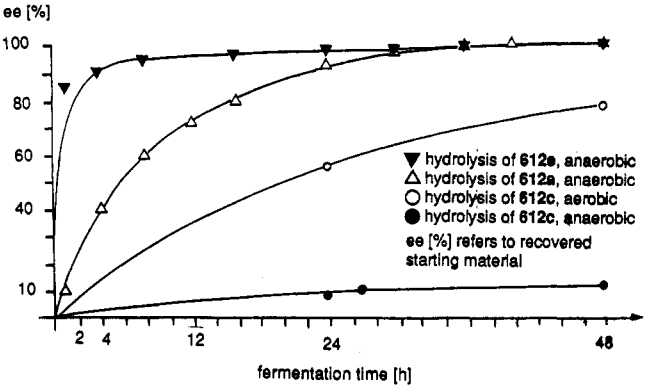
SCHEME 130



618a-h 619a-h 614a

	R	y[%] of 619	ee[%] of 619
a	CH_3	33	88
b	C_2H_5	47	>99
c	$n\text{-}C_3H_7$	35	>99
d	$i\text{-}C_3H_7$	40	96
e	$n\text{-}C_4H_9$	36	98
f	$n\text{-}C_8H_{17}$	25	97
g	$CH_2C_6H_5$	43	>99
h	C_6H_{11}	27	>99
i	$C(CH_3)_3$	recov. 80% of 618i	

SCHEME 131



615a,b gave **616a,b** with low or no ee at all. **617** was not isolated.[434,435]

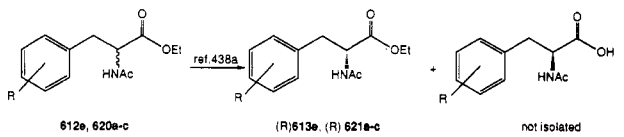
Variation of the alcohol part R of **618a–h** (to yield products **619a–h** whereas **614a** was not isolated) (Scheme 130) showed little or no influence on the course of hydrolysis. No reaction, however, was obtained for *tert*-butyl ester **618i**.

The course of hydrolysis has been investigated for **612a,c,e** in more detail, and its time dependency is depicted in Scheme 131.

By use of the quadruple-mutant *ABYS1* (from the wild type *X2 180-1A*) deficient of four vacuolar peptidases, i.e., the nonspecific proteinases *yscA* and *yscB* and the nonspecific carboxypeptidases *yscY* and *yscS*, and due to the close analogy of the hydrolytic behavior with α-chymotrypsin, the active enzyme for these hydrolyses was supposed to be an nonspecific carboxylester hydrolase (E.C. 3.1.1.1, optimum pH 8) rather than a lipase, esterase, or phospholipase.[434]

As an alternative to the use of fresh baker's yeast, the use of acetone-dried powders[323,436] has been suggested. It was shown that these powders remained active for several months. The presence of nicotinamide during the process of crushing the yeast for providing a cell-free preparation having high fermentative power appears necessary. Alternatively, lyophilized yeast has been prepared and found to offer several advantages as compared to the use of viable cells or acetone-dried powders. It is easily accessible and a ratio of educt to yeast (ca. 1:1.5, w/w) allows the reactions to be performed in a convenient manner. Since no metabolism is detected as long as no carbohydrates are supplied, both working up of the reaction mixture and easy monitoring (e.g., by use of a pH-stat) are facilitated. In addition, reductions of carbonyl groups are suppressed. The hydrolytic activity is fully maintained and was

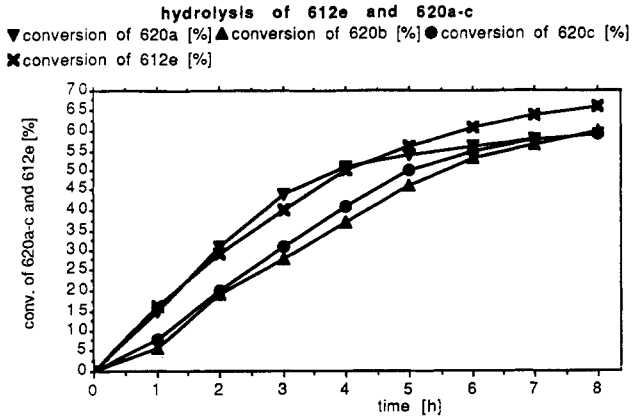
SCHEME 132



612e, 620a-c (R)613e, (R) 621a-c not isolated

R	educt	y[%]	ee[%]	config.
H	612e	42	>96	R
o-F	620a	40	>96	R
m-F	620b	38	>96	R
p-F	620c	43	>96	R

SCHEME 133



shown to remain stable for several months when stored at 0–4 °C.[437]

As shown for the hydrolysis of **612e** and the fluorinated analogues **620a–c** (Scheme 132), the reaction stopped at about 50% conversion (Scheme 133) and thus allowed very easily the isolation of the D-configured esters (*R*)-**613e**[434] and (*R*)-**621a–c** in about 40% yield.[438a] Very recently, the enantioselective hydrolysis of methyl esters of racemic *N*-acetyl-α-amino acids by BY (*Saccharomyces cerevisiae* NCIM3044) in reverse micellar suspension has been reported.[438b]

C. Other α-Substituted Carboxylic Esters

It seems noteworthy in this context that racemic α-substituted carboxylic esters other than amino acid esters gave in general bad results.

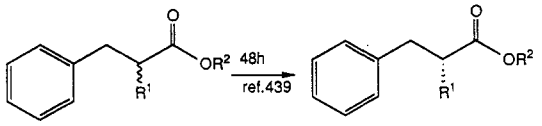
Thus, hydrolysis of **622a–c** (Scheme 134) resulted in low yields and low ee's of products **623a–c**. Hydrolysis of **622d** afforded 40% of (*R*)-**623d** with low ee (15%) and 15% of (*R*)-**622d** (ee = 60%). The low ee may be due to racemization during the reaction (pH 4). An excellent ee of 99%, however, could be achieved for (*R*)-**622d** (31% yield) by use of the lipase of *Candida cylindracea* for the hydrolysis step.[439]

Racemic **624** was hydrolyzed under aerobic conditions with both moderate yield and ee to afford (*S*)-**624** (40% yield, 35% ee). For racemic **625** the cleavage occurred also at the benzoate, and therefore (*S*)-**625** was obtained although in moderate yield (27%) but fair ee (79%).[439]

D. Acyloxy Esters and Lactones

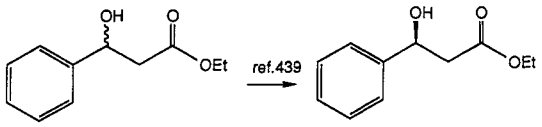
Studies were extended to acyloxy carboxylic acid esters **626a–k** (Scheme 135). No dramatic differences in the ee values of the products could be observed with use of either viable cells or lyophilized yeast although the ee values were slightly better with lyophilized cells due to facile and appropriate monitoring of the reaction

SCHEME 134

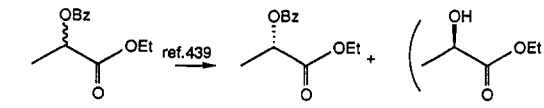


rac.622a-d 623a-d

	R^1	R^2	y[%]	ee[%]	conf.of 623	cond.
a	OH	C_2H_5	25	21	R	an
b	OH	n-C_8H_{17}	12	37	R	an
			17	40	R	ae
c	CH_3	C_2H_5	10	8	S	an
d	OC(=O)CH_3	C_2H_5	40	15	R	ae

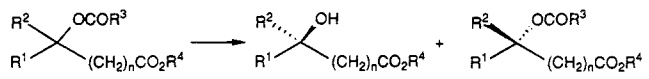


rac.624 (S) 624 (R) acid not isolated
40%, ee=35% aerob



rac. 625 (S) 625
27%, ee=79%

SCHEME 135



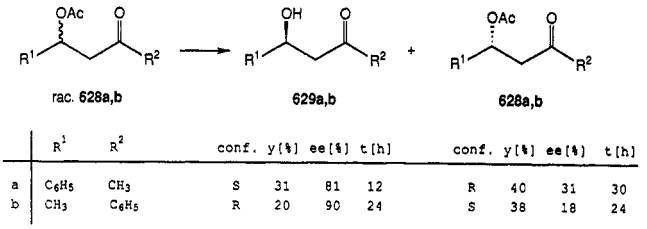
626a-k (S) 627a-k (R) 626a-k

	R^1	R^2	R^3	R^4	n	y[%] ee[%] of (R) 626	y[%] ee[%] of (S) 627
a	n-C_5H_{11}	H	CH_3	C_2H_5	1	non substrate	
b	C_6H_{11}	H	CH_3	C_2H_5	1	-"-	
c	HC≡C	H	CH_3	C_2H_5	1	>97	91
d	C_6H_5	H	CH_3	C_2H_5	1	25 79	21 85
e	CH_2-C_6H_5	H	CH_3	C_2H_5	1	30 <10	17 97
f	(E) PhHC=CH	H	CH_3	C_2H_5	1	67 33	18 91
g	C_6H_5	H	CH_3	C_2H_5	0	<10	<10
h	C_6H_5	H	CH_3	C_2H_5	2	non substrate	
i	C_6H_5	CH_3	CH_3	C_2H_5	1	-"-	
j	C_6H_5	H	nC_3H_7	C_2H_5	1	-"-	
k	C_6H_5	H	CH_3	nC_8H_{17}	1	-"-	

by means of a pH-stat. For example, racemic **626d** afforded after 24 h under fermenting conditions 43% of (*S*)-**627d** (ee = 76%) whereas prolonged reaction time (48 h) allowed the isolation of (*R*)-**626d** (26% yield, 72% ee). Similar results were obtained with lyophilized yeast: (*S*)-**627d** was shown to exhibit an ee of 85%, and for (*R*)-**626d** an ee of 79% was reported. Enantiomerically pure (*R*)-**627d** was obtained by using the lipase from *Pseudomonas sp.* No hydrolysis was observed for butyrate **626j**,[434] a finding that is in good accord with the reported resistance of butyrates upon hydrolysis by yeasts.[407] The recovered octyl ester **626k** (11% after 48 h) showed no optical rotation; no reaction was observed for **626i** either.[439]

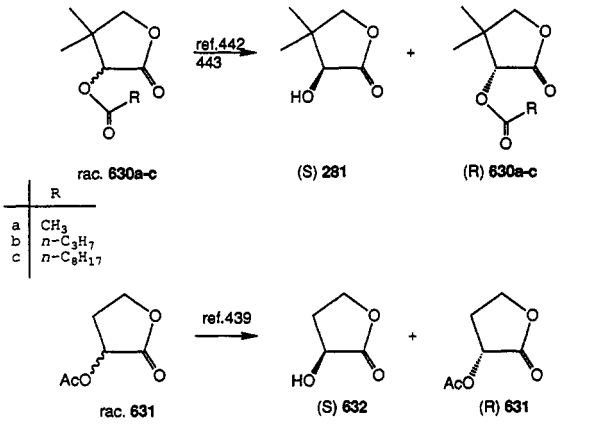
Racemic **626e** afforded 17% of **627e** (97% ee after 20 h), and 30% of unreacted (nearly) racemic starting material was recovered. (*E*)-Ethyl 3-acetoxy-5-phenylpent-5-enoate (**626f**) afforded 18% of **627f** with 91% ee after 24 h. Stopping the hydrolysis after 12 h

SCHEME 136



	R^1	R^2	conf.	y[%]	ee[%]	t[h]	conf.	y[%]	ee[%]	t[h]
a	C_6H_5	CH_3	S	31	81	12	R	40	31	30
b	CH_3	C_6H_5	R	20	90	24	S	38	18	24

SCHEME 137



afforded 67% of starting material (33% ee). **627f** is a valuable starting material for the synthesis of an inhibitor of 3-hydroxy-3-methylglutaric acid CoA-reductase.[440] The *n*-pentyl and cyclohexyl analogues **626a,b** were found to be nonsubstrates for yeast (*Saccharomyces cerevisiae* Hansen) mediated hydrolyses.[439] These results show that enantioselective hydrolysis is achieved only when the acetoxy moiety is located in β-position to the carboxylate and that the asymmetric center has to bear an unsaturated substituent since simple aliphatic groups of similar size are not sufficient for an effective hydrolysis.[441]

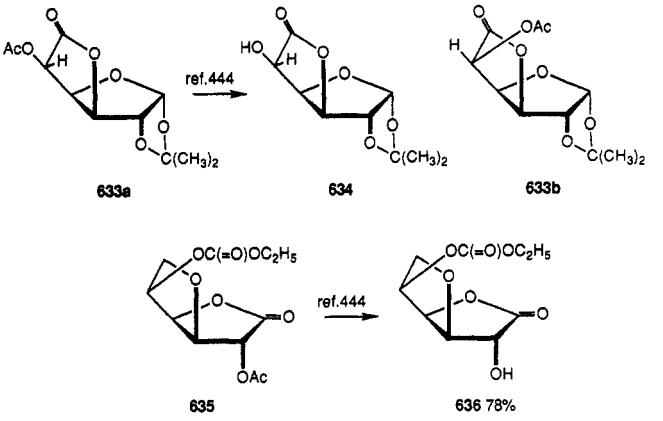
The structural analogues **628a,b** (Scheme 136) were hydrolyzed, and this resulted in the formation of (*S*)-**629a** and (*R*)-**629b** of 81% and 90% ee (isolated after 40% conversion) and of (*R*)-**628a** (31% ee) and (*S*)-**628b** (18% ee), respectively.

Regio- and enantiodifferentiation of the enzymes in yeast cells can be used for the selective hydrolysis of 2-*O*-acyl lactones. Thus, 2-*O*-acetylpantoyllactone (**630a**) (Scheme 137) gave with fermenting BY under anaerobic conditions (48 h) or with lyophilized BY 28% of (*S*)-**281** (86% ee) and 35% of (*R*)-**630a**.[442] No dependency of the ee from the length of the acyl chain was observed (85% versus 81% from **630b** or **630c**), whereas the conversion rate decreased for the butyrate but increased for the octanoate.[443] It is of interest to note that only the lipase from *Aspergillus sp.* exhibited the same enantioselectivity as compared to BY, thus allowing isolation of 32% of (*S*)-**281** (ee = 61%) and 32% of (*R*)-**630** (96% ee). No conversions were achieved with other commercially available enzymes (e.g., the lipases from *Candida cylindracea*, *Pseudomonas sp.*, porcine pancreas, or α-chymotrypsin).[439,442]

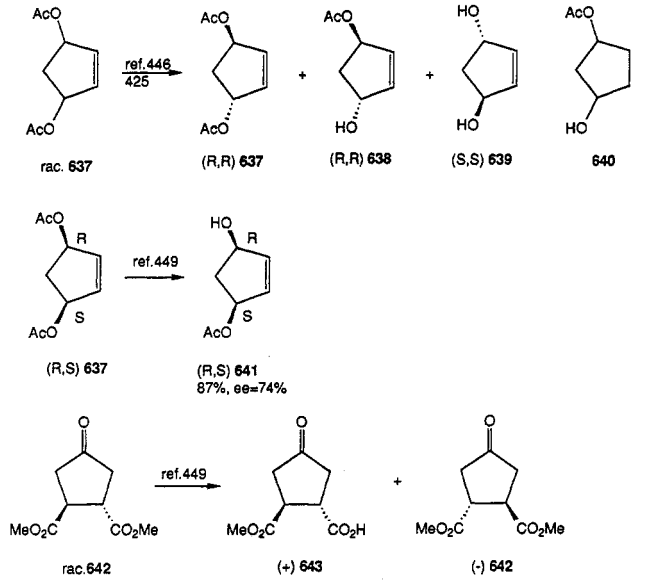
For comparison, the analogue *rac*-**631** however, gave upon hydrolysis with BY under anaerobic fermentative conditions only 14% of (*S*)-**632** and 25% of (*R*)-**631** (70% ee).[439]

Similarly, the deacetylation of carbohydrate-derived α-acetoxy lactone **633a** (Scheme 138) afforded **634**,

SCHEME 138



SCHEME 139

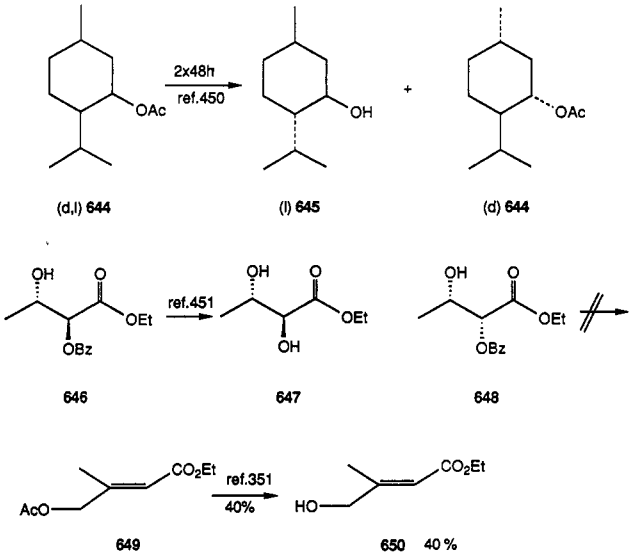


whereas **633b** was not affected by lyophilized BY but by several enzymes.[444] By means of this educt enantioselectivity, mixtures of epimers **633a** and **633b** could be separated very easily. The anhydro sugar **635** was deacetylated by the same procedure within 15 h to yield **636**; unfortunately, this method was not extendible to the regioselective deacetylation of peracetylated carbohydrate-derived lactones[444] or anhydro sugars.[445]

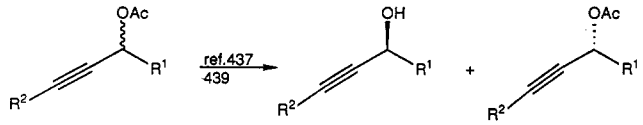
A further application for these regioselective hydrolyses was performed for the diacetylated cyclopentene derivative racemic **637** (Scheme 139), which gave a mixture of (*R,R*)-**637**, (*R,R*)-**638**, and (*S,S*)-**639**.[446] It was found[425] for a 1:1 mixture of *cis*- and *trans*-**637** that the meso compound *cis*-**637** was more rapidly hydrolyzed than *trans*-**637**. The highest ee values for (*R,R*)-**637** (93%) and (*R,R*)-**638** (90%) were obtained after 48 h, whereas the ee for (*S,S*)-**639** dropped with prolonged reaction time (32% after 17 h, 10% after 48 h).[425] As a byproduct due to the action of (a) reductase(s) **640** was obtained. Since these compounds are valuable starting materials for the synthesis of optically active prostaglandins, alternative enzymic approaches have been reported.[425,447] BY treatment of (*R,S*)-**637** afforded in 87% chemical yield (*R,S*)-**641** of 74% ee.[448]

Similarly, (±)-*trans*-3,4-bis(methoxycarbonyl)cyclopentanone (**642**) was hydrolyzed to yield (+)-**643** and (−)-**642** although with low chemical yield (25%) and low ee (30%); better results could be achieved with *Candida*

SCHEME 140



SCHEME 141



	R^1	R^2	652 y[%]	652 ee[%]	652 t[h]	651 y[%]	651 ee[%]	651 t[h]
a	$CH_2CH(CH_3)_2$	H	22	91	24	19	72	35
b	$CH_2CH(CH_3)_2$	CH_3	10	94	24	56	<10	24
c	nC_5H_{11}	H	29	>97	26	21	74	48
d	nC_7H_{15}	H	7	91	24	36	18	18
e	$CH_2CH{=}CH_2$	H	10	95	9	33	35	18
f	CH_2CO_2Et	H	37	91	18	40	>97	15
g	C_6H_5	H	14	86	9	45	64	17
h	$(CH_3)C{=}CHC_2H_5$	H	66	87	23	42	37	35

humicola CCY29-11-1 (ee > 99%).[449]

Although with low rate of hydrolysis (14% with *Saccharomyces cerevisiae* var. ellipsoideus, 41.8% with *Rhodotorula mucilaginosa*, ee = 99.2%), *dl*-menthyl acetate (**644**) (Scheme 140) was hydrolyzed; it was found that *l*-menthylacetate was preferentially hydrolyzed to form *l*-menthol (**645**).[450] The rate of hydrolysis and the ee values dropped on increasing of the acyl moiety. No hydrolysis occurred with isomenthylacetate by yeasts (but by bacteria and other fungi); citronellol isolated from microbial hydrolysis of *dl*-citronellyl acetate was optically inactive.[450]

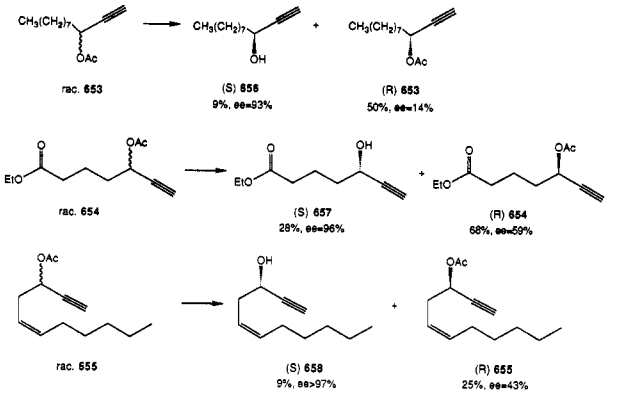
Hydrolysis[451] of *anti*-**646** yielded **647** (but no saponification of *syn*-**648** occurred); the hydrolysis of **649** gave 40% of **650**.[351]

E. Alkynol Acetates

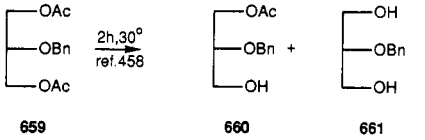
Chiral propargylic alcohols have gained importance in the synthesis of natural products. Both enantiomers of optically active 1-alkyn-3-ols of high optical purity can be obtained by resolution of their corresponding racemic acetates by use of lyophilized BY.[437]

Previously, enantioselective hydrolyses of such compounds have been performed with selected microorganisms that may not be cultivated without sterile fermentation equipment, e.g., *Bacillus subtilis*,[452-455] *Brevibacterium ammoniagenes*,[456] and *Rhizopus nigricans*.[457] Thus, *rac*-**651a–h** (Scheme 141) afforded on

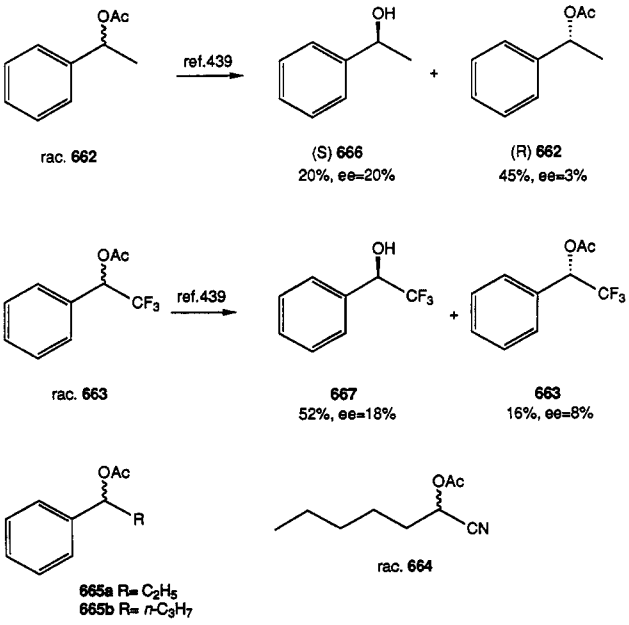
SCHEME 142



SCHEME 143



SCHEME 144



treatment with lyophilized BY[437,439] **652a–h** in high optical purity.

Racemic alkynol acetates **653–655** (Scheme 142), which are precursors for the synthesis of leukotrienes, were hydrolyzed in an enantioselective manner by means of lyophilized BY. Thus, *rac*-**653** afforded (*S*)-**656** (93% ee) and (*R*)-**653** (14% ee), **654** gave (*S*)-**657** (96% ee), and **655** was hydrolyzed to yield (*S*)-**658** (>97% ee).[439]

From these results it becomes clear that replacement of the acetylenic hydrogen by a methyl group shows a dramatic decrease in the speed of hydrolysis, making a conversion of 60% inaccomplishable. An unsubstituted CH_2 unit adjacent to the asymmetric center is necessary for a high degree of enantioselection.[437]

F. Miscellaneous Hydrolyses

1,3-Di-*O*-acetyl-2-*O*-benzylglycerol (**659**) (Scheme 143) gave upon hydrolysis with BY[458] 29% of **660** and 1% of completely deacetylated **661**. The ee of **660** was low

(32.7%) but could be improved on use of enzymes.[458-460]

Similar low ee values have been obtained for the hydrolyses of racemic **662–664** and **665a,b** (Scheme 144).[439]

Contrary to bacteria and several yeast strains,[461,462] *Saccharomyces cerevisiae* neither had the ability to utilize lactams nor was able to hydrolyze them.[462] On the other hand, extracts from disintegrated BY cells found an application in the hydrolysis of several amino acid naphthylamides.[463] Very recently *dl*-3-acetylazetidinone derivatives have been reduced by BY without affecting the lactam moiety.[464]

VIII. Immobilized Baker's Yeast

A. General Remarks

Biotransformations with immobilized yeast cells are attractive due to several reasons although the catalytic activity of the cells is generally reduced when compared to the same amount of cells in solution. This loss of activity is caused by an additional permeability barrier[26] introduced by the carrier material and due to some cell damage occurring during the immobilization. Four major categories for immobilization of microorganisms in general and of baker's yeast in particular can be recognized in analogy to the immobilization of enzymes.[465]

(*i*) *Immobilization by physical or chemical adsorption*: surface adsorption to a water-insoluble, solid support, e.g., a metal oxide, DEAE-cellulose, or an ion-exchange resin.

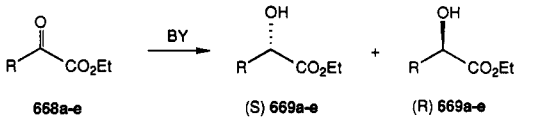
(*ii*) *Cell aggregation of the microorganism*: physical or chemical (e.g., glutaraldehyde) cross-linking.

(*iii*) *Covalent attachment to a carrier material*: e.g., carboxymethyl cellulose.

(*iv*) *Microorganism entrapment in a gel or a membrane or within microcapsules*: applicable in industrial and laboratory use (urethane, cellulose, agar, alginate, collagen, chitosan, κ-carrageenan, and polyacrylamide have been used as polymerous porous networks for entrapment).

Beside enhancing the operational stability of yeast by immobilization, easier isolation of the products is provided. In addition, reuse of the catalyst is often possible. Due not only to minimal inhibitory influences but also to high cell population, product formation rates are usually high.[466] Continuous operation is performed easily since the immobilized cells are easily removed from the reaction medium and can repeatedly be used although with deceasing activity of the immobilized cells. In contrast to enzyme immobilization, a required coenzyme is supplied and regenerated within the intact cell.[14] Comparative studies between "free" yeast and immobilized yeast cells have only scarcely been performed. Some differences in stereoselectivity and yield, however, have been observed depending on the kind of immobilization. This observation seems reasonable since immobilized yeast cells (either gel entrapped or adsorbed on various carriers) exhibit altered physiological, morphological, and metabolic properties.[467] Significant differences in kinetics, growths, and DNA/RNA and protein content of *Saccharomyces cerevisiae* adsorbed on gelatin-coated glass beads were reported.[468,469] It seems therefore that immobilization affects the cells in several aspects simultaneously and

SCHEME 145



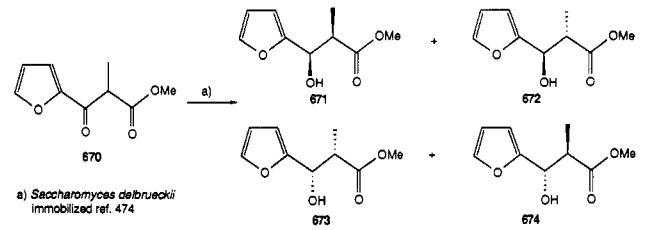
668a-e (S) **669a-e** (R) **669a-e**

R= (CH_3)-$(CH_2)_n$-

n	educt[a]	free BY product ee /y [%]/[%]	imm.BY (water) product ee /y [%]/[%]	imm. BY (hexane) product ee /y [%]/[%]
0	**668a**	(*S*)-**669a** 91/47	(*S*)-**669a** 87/43	(*S*)-**669a** 94/33
1	**668b**	(*S*)-**669b** 77/42	(*S*)-**669b** 66/42	(*S*)-**669b** 36/28
2	**668c**	(*S*)-**669c** 31/36	(*S*)-**669c** 39/36	(*S*)-**669c** 32/27
3	**668d**	(*S*)-**669d** 50/29	(*S*)-**669d** 78/20	(*R*)-**669d** 47/41
4	**668e**	(*S*)-**669e** 30/23	(*S*)-**669e** 63/31	(*R*)-**669e** 54/36
mean time of reaction [h]		5	6	24-72

[a] taken from ref. 473

SCHEME 146



Course of reduction of **670** in dependance of prepolymer used for immobilization (*Saccharomyces delbrueckii*).[474]

prepolymer	yield[a] [%]	671 ee[%]	672 ee[%]	673 ee[%]	674 ee[%]	ratio *syn/anti*
none	43	90	91	--	--	39/61
PU-6[b]	33	56	74	--	--	41/59
ENT-4000[c]	64	--	--	81	57	50/50

[a] total yield; [b] immobilization with urethane; [c] immobilization with a photon crosslinkable prepolymer.

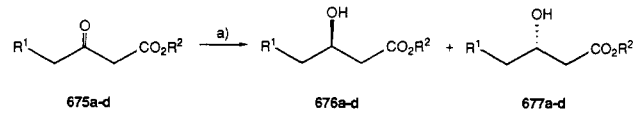
that the combination of these effects imposes stresses on the metabolic behavior.[470] Among these effects are found diffusional limitations (leading to partitioning of hydrophobic material, reduced oxygen concentration, and oxygen-transfer rates[471]) as well as the creation of microenvironmental effects such as reduced water activity and high cell concentrations. As shown for polyacrylamide–hydrazide-entrapped cells of *Saccharomyces cerevisiae*, even the tolerance to ethanol and ethylene glycol was increased.[472]

B. Examples for the Use of Immobilized Baker's Yeast

Ethyl 2-oxoalkanoates **668a–e** (Scheme 145) have been reduced by free BY in water and by immobilized yeast (using a polyurethane prepolymer) either in water or in hexane.[473] Some marked differences in the stereochemical control of these reactions have been elaborated obviously due to the effects of changes in the reaction conditions at the surface of the yeast (as evidenced by scanning electron microscopy the yeast cells are tightly surrounded by the polymer) or due to a change in the concentrations of the respective substrates.

In some cases, as for the reduction of **670** (Scheme 146) with *Saccharomyces delbrueckii*, the stereochemistry is affected by the used prepolymer. Thus, differing amounts of products **671–674** are obtained depending

SCHEME 147



675a-d 676a-d 677a-d

	R^1	R^2
a	Cl	C_2H_5
b	Cl	CH_3
c	CH_3	CH_3
d	H	C_2H_5

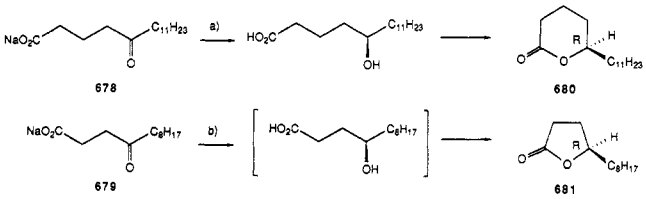
a) BY, 60-80%, ref.225

Entrapment dependend reduction of ß-keto-esters.[225]

educt	entrapment	product	ee [%]	conc.of educt [mmol]
a	free BY	**677a**	42	10
a	free BY	**677a**	27	20
a	free BY	**677a**	15	50
a	ALG[a]	**677a**	16	20
a	CAR[b]	**677a**	11	20
a	PAA[c]	**677a**	3	10
a	PU[d]	**676a**	82	10
a	PU	**676a**	82	50
b	free BY	**677b**	31	10
b	free BY	**677b**	12	20
b	ALG	**677b**	10	20
b	PU	**676b**	90	20
c	free BY	**676c**	5	20
c	ALG	**676c**	17	20
c	PU	**676c**	86	20
d	free BY	**677d**	>98	20
d	ALG	**677d**	92	20
d	PU	**677d**	60	20

[a] entrapment in calcium alginate; [b] entrapment in carrageenan [477]; [c] entrapment in polyacrylamide [480]; [d] entrapment in polyurethane.[481]

SCHEME 148



678 679 680 681

a) 6g κ-carrageenan/4g BY, 30°C, 48h, 32%; b) 30°C, 48h, 26%, ref.482

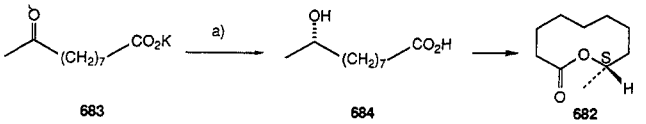
on the used prepolymer.[477-481] The use of a water-miscible organic solvent (DMSO, THF, or 1,4-dioxane) or nonpolar organic solvents saturated with water was shown to deactivate the immobilized cells.[474] No reaction was observed with *Saccharomyces cerevisiae*.[475,476]

The use of calcium alginate[477] or κ-carrageenan[478] has been shown to be unsuitable for the reduction of **668a-e** since a certain amount of water oozed from such gels during the reaction. For the reduction of **675a-d**, this seems to be insignificant with respect to the optical purity.[225] For **676a-d** and **677a-d** (Scheme 147), the ee of each alcohol was unaffected by the substrate concentration in the reduction by polyurethane-entrapped BY whereas the ee value was susceptible to the concentration in the reduction by free BY.

κ-Carrageenan-immobilized BY was taken for the reductive lactonization of **678** and **679** (Scheme 148) used for the synthesis[482] of (*R*)-5-hexadecanolide ((*R*)-**680**), the pheromone component isolated from the heads of the queens of the oriental hornet, *Vespa orientalis*,[483] and of (*R*)-4-dodecanolide ((*R*)-**681**), the defensive secretion from pygidial glands of rove beetles, *Bledus mandibularis* and *Bledus spectabilis*, respectively.[484] These reductions employing immobilized BY gave lower yields as compared with the analogous reduction with "free" BY[485] (Scheme 148).

It is of interest to note that in the synthesis[486] of phorancolide I (**682**) (Scheme 149) the reduction of **683** by κ-carrageenan-immobilized BY with the first use of

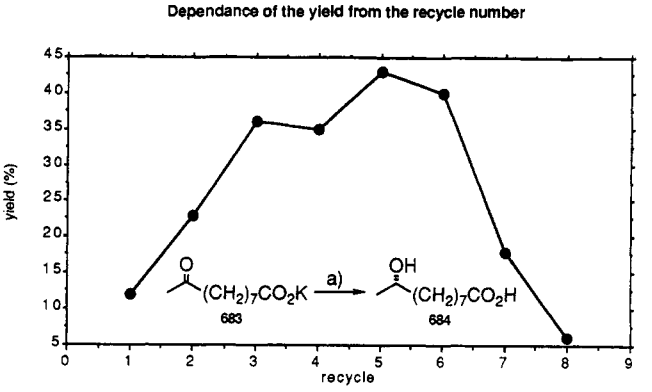
SCHEME 149



683 684 682

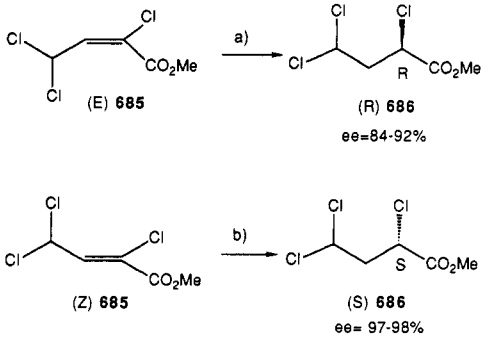
a) immobilized BY, 48 h, 35°C, ref.486

SCHEME 150

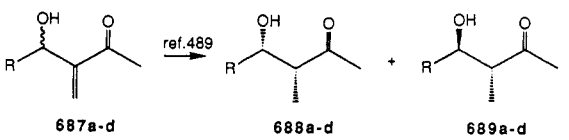


a)IBY: ee=96%, ref.486
fresh BY: 36%, ee=92%

SCHEME 151



a) i)Ca-alginate immobilized BY, 32°C, 30h, pH 7 to 5, 65% ii) CH_2N_2
b) 60%, ref.487.

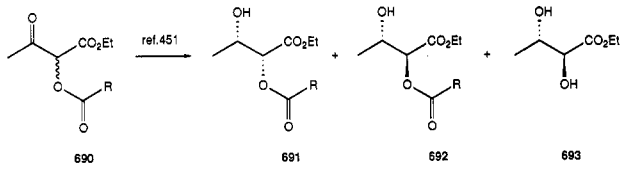


	R	y[%]	ratio**688:689**	ee[%] of **688**	ee[%] of **689**
a	C_2H_5	61	53:47	98	98
b	*n*-C_3H_7	64	42:58	98	72
c	*n*-C_4H_9	56	33:67	98	67
d	*n*-C_5H_{11}	72	36:64	98	69

the catalyst gave a lower yield of (*S*)-**684** (12%), whereas a maximum yield of 43% was obtained after the fifth use (Scheme 150). In addition, the immobilized BY could be stored in an aqueous solution of KCl for 6 months at 0–5 °C. The optical purity of **684** was constant within experimental error throughout the use of the catalyst but only slightly superior than that obtained by the use of free BY.

Sodium alginate/$CaCl_2$ immobilized BY[477] has been applied for the highly stereocontrolled synthesis of D- and L-armentomycin.[487] L-Armentomycin, (*S*)-2-amino-4,4-dichlorobutanoic acid, is known as a naturally occurring antibiotic from the culture broth of *Strep-*

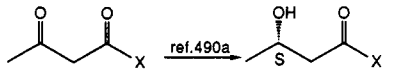
SCHEME 152



690a: R= CH_3; 690b: R= C_6H_5

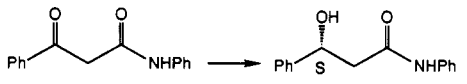
	yeast	t [h]	y[%]	691 : 692 : 693 [%]
a	free BY	48	45	28:16:54
a	imm. BY	12	37	19:58:23
a	imm. BY	43	49	18:26:56
a	imm. BY	53	58	18:19:63
b	free BY	23	61	14:86:0
b	imm BY	21	70	6:94:0
b	immBY (at pH=7)	21	62	51:49:0

SCHEME 153



	X	condition *	y[%]	ee[%]
a	NHEt	BY (dry / fresh)	0	-
		dry BY (alginate)	9	90-95
b	NHPh	BY (fresh)	11	n.r.
		SC H194	48	>90
		dry BY (alginate)	36	>95
		fresh -"-	21	>98
		dry BY (polyurethane)	28	84

* 7d, 30°



tomyces armentosus var. armentosus.[488] The remarkable feature of this reduction is the highly effective stereochemical control for each geometrical isomer ((*Z*)- or (*E*)-**685**) to produce precursors of L-armentomycin ((*S*)-**686**) or its D enantiomer ((*R*)-**686**) (Scheme 151).

The lower stereoselectivity for the reduction of the *E* isomer ((*E*)-**685**) to *R*-configured **686** as compared to the reduction of (*Z*)-**685** to (*S*)-**686** reflects the enantioselectivity of the involved yeast reductase(s), since both (*E*)- and (*Z*)-**685** were found to be stable under reaction conditions.[487] Although immobilization of BY in calcium alginate gels represents an extremely economical method, the half-lifetime of such a preparation seems to be limited to several weeks.[477]

Examples for the reduction of α-methylene-branched carbonyl compounds by alginate-immobilized BY have been provided. Thus, **687a–d** afforded *syn*-(3*R*)-**688a–d** and *anti*-(3*R*)-**689a–d**. The methylene group was reduced in all cases whereas no reduction of the carbonyl group took place.[489]

The use of calcium alginate gel immobilized BY was shown to improve the anti selectivity as well as the total yield of the reduction products for some β-keto esters. Thus, **690** (Scheme 152) gave on treatment with BY or immobilized BY syn-configured **691** and the anti-configured compounds **692** and **693**; the ee of each of the products was higher than 95%.[451] From the data provided in Scheme 152 it can be seen that only the anti-configured product **692** is hydrolyzed by BY to yield **693**.[451]

The reductions of **694** and **696** (Scheme 153) were achieved to yield the corresponding (3*S*)-hydroxy compounds **695** and **697**, respectively.[490a] While in the case of substrate **694a** no reduction occurred using dry or fresh BY, alginate-immobilized BY afforded 9% conversion and **695a** was shown to possess an ee of 90–95%. As for **694b**, *Saccharomyces cerevisiae* (H-194) gave a yield of 48% of **695b** showing an ee of >90%, treatment with fresh BY afforded only 11% of the product, but alginate-immobilized BY again gave 21–36% yield (ee 95–98%).[186,490a]

Recently, the reduction of β-keto esters with BY immobilized by magnesium alginate has been introduced as exemplified for the reduction of methyl 3-oxopentanoates to yield predominantly (*S*)-hydroxy esters (i.e., L-configured), whereas under "normal" reaction conditions the (*R*)-hydroxy ester is obtained.[490b]

IX. Miscellaneous Reactions

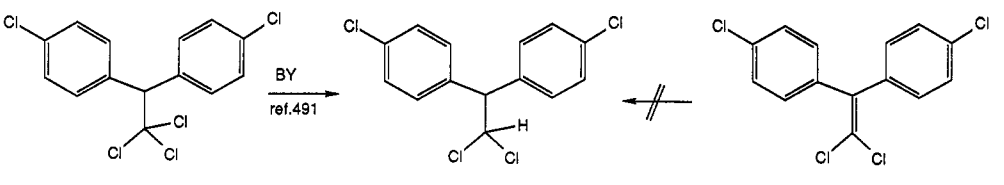
Of importance in environmental chemistry are attempts to probe the yeast-mediated abilities of degradation of pesticides as exemplified in the transformation of DDT (**698**) (Scheme 154) into (1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane) (DDD, **699**) by reductive dechlorination of the former. DDE (**700**) gave upon treatment with BY no **699**.[491]

Contrary, reduction of (*Z*)-3-chloro-3-alken-2-ones **701a–c** (Scheme 155) with fermenting BY proceeded well and afforded optically active α-chloro ketones **702a–c**, which were reduced on further treatment with BY to optically pure chlorohydrins **703a–c** and **704a–c**. It was shown that the reduction of the double bond was fast—independent of the length of the carbon chain—while the reduction of the C=O bond is retarded as the carbon chain length increases.[492]

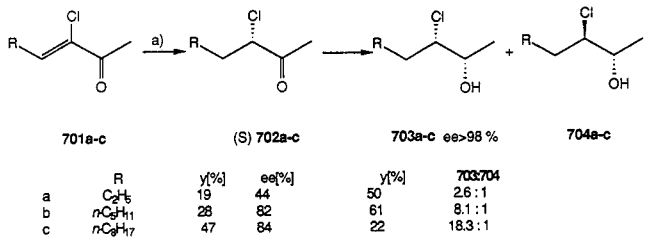
Phosphorylations[16,53a,54] by means of BY have been reported very early. Thus, nucleoside 5′-phosphates,[493–500] galactose 1-phosphate,[501] glucose and fructose 1,6-diphosphate[502] as well as 2-deoxyglucose 1,6-diphosphate[503] and 2- or 3-phosphoglycerates[504–506] have been prepared.

The reduction of galactose to dulcitol[507] as well as the cleavage of glycoside aesculin (**705**) (Scheme 156) to yield the phenolic aglycon aesculetin (**706**)[54] have been reported; on treatment of amygdalin (**707**) with BY, both glycosidic bonds were cleaved.[54]

SCHEME 154



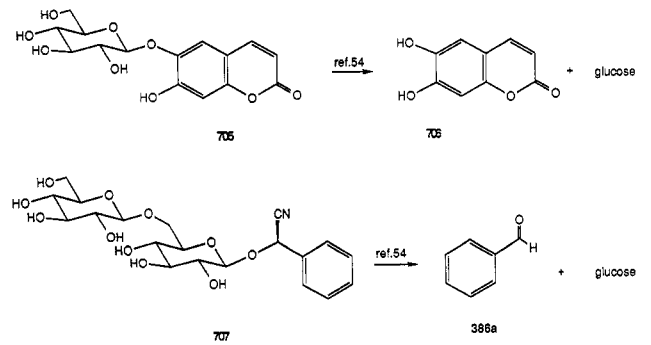
SCHEME 155



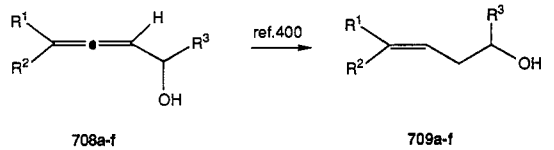
	R	y[%]	ee[%]	y[%]	703:704
a	C_2H_5	19	44	50	2.6:1
b	nC_5H_{11}	28	82	61	8.1:1
c	nC_9H_{17}	47	84	22	18.3:1

a) 33°, pH=7, ref.492

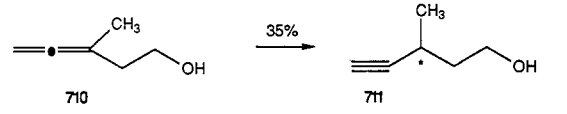
SCHEME 156



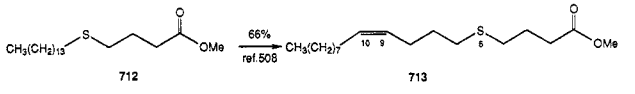
SCHEME 157



	R^1	R^2	R^3	t[d]	y[%]708:709
a	CH_3	C_2H_5	H	2	2 80
b	CH_3	CH_3	H	2	25 65
c	CH_3	H	H	2	20 70
d		C_5H_{10}	H	2	30 55
e	CH_3	C_2H_5	CH_3	3	20 55
f	CH_3	CH_3	CH_3	5.5	35 50
g	CH_3	H	CH_3	no reaction	



SCHEME 158



Of special interest is the reduction of α-allenic alcohols **708a–f** (Scheme 157), which gave the corresponding β-ethylenic alcohols **709a–f** whereas β-allenic alcohol **710** afforded 35% of γ-acetylenic alcohol **711**.[400]

There are many examples of BY-mediated hydrogenations of alkenes to yield the corresponding alkanes, but there seems to be only one example of the reverse process. Thus, methyl 5-thiastereate (**712**) (Scheme 158) afforded upon BY (SC NRC2335) treatment methyl 5-thiaoleate (**713**) in 66% yield. In addition, it was shown that addition of **712** changed the fatty acid profile of the cell extracts dramatically although no observable effect on the growth of the yeast cells could be detected.[508]

Abbreviations Used

BY, baker's yeast; IBY, immobilized baker's yeast; ee, enantiomeric excess; de, diastereomeric excess.

X. References

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