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On the Mode of Baker's Yeast Reduction of Methyl Substituted Arylalkyl Gamma and Delta Keto Acids. Synthesis of Cis - (+) - Rose Oxide.

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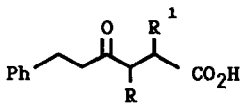
Abstract. Baker's yeast reduction of methyl substituted γ-and δ-keto acids **1-6** *proceeds in a mode depending upon subtle substrate structural modifications; it affords γ-lactones of modest ee and de values and highly functionalized, enantiomerically pure δ-lactones, such as* **13** *from which cis-(+)-rose oxide* **23a** *has been prepared.*

The structural requirements of non-conventional multifunctional carbonyl compounds in baker's yeast reduction, and the mode of their transformation, are still often unpredictable despite extensive studies in this field.[1,2] This unpredictability is due to the complexity of the enzymatic system of baker's yeast which can transform structurally similar substrates in different ways. A pertinent example is found in the yeast transformation of the methyl (and ethyl) substituted arylalkyl γ- and δ-keto acids **1-6** in which the behaviour of the yeast seems to be influenced by even slight substrate structural modifications. However, yeast treatment of **1-6** provides enantiomerically pure educts of synthetic significance, e.g. lactone **13** in the preparation of cis-(+)-rose oxide **23a**, together with mixtures of diastereoisomers of modest optical purity.

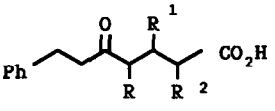
Baker's yeast reduction of γ- and δ-keto acids.

The keto acids **1-6** were prepared from methylsuccinic, methylglutaric and glutaric anhydrides via the mono methyl ester chlorides, and the corresponding arylalkyl Grignard reagents according to literature procedures.[3] Products **1** and **2** were used as the regioisomer mixture. The timecourse of the yeast reduction of **1** (GLC) indicates that the transformation of the two isomers takes place at a similar rate, lactones **7-10** being formed at ca. 50% conversion in 21:28:20:24 ratio. Column chromatography allowed the

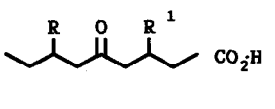
isolation of 7, 8 and a mixture of 9 and 10. The structural assignment was made by NMR. 7 and 8 showed ^{13}C methyl signal resonances at 16.62 and 13.43 ppm, respectively. The methyl group cis to the vicinal substituent at C-4 is expected to resonate at higher fields than that of the trans oriented group because of the mutual γ gauche effect of the substituents. Structures 9 and 10 were assigned from NOE experiments. In the case of the cis isomer 9 the irradiation of proton H-4 significantly enhanced the signal of H-2, but this effect was not observed for the trans isomer 10.



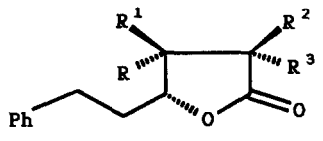
1 R,R^1= H,Me



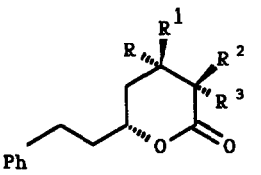
2 R,R^2= H,Me; R^1=H
3 R^1= Me; R=R^2= H
4 R=R^2= H; R^1= Et



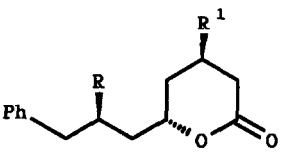
5 R= H; R^1= Me
6 R= Me; R^1= H



7 R=R^2=R^3=H; R^1= Me
8 R= Me; R^1=R^2=R^3=H
9 R=R^1=R^2=H; R^3= Me
10 R=R^1=R^3=H; R^2= Me



11 R=R^1=R^3=H; R^2= Me
12 R=R^1=R^2=H; R^3= Me
13 R=R^2=R^3=H; R^1= Me
14 R= Me; R^1=R^2=R^3=H
15 R=R^2=R^3=H; R^1= Et



16 R=H; R^1= Me
17 R= Me; R^1=H

The enantiomeric excess values (Table) of 7, 8, 9 and 10 were respectively 59%, 54%, 57% and 72%, as determined by NMR studies in the presence of Eu(hfc)$_3$ and GLC analysis on a chiral capillary column.[4] The modest ee and de values of lactones 7-10 discouraged us from making a time consuming chemical correlation to determine their absolute configuration. The (R) absolute configuration depicted in the structural formulas 7-10 was assigned by analogy with the product of the yeast reduction of unsubstituted 1 (R=R^1=H).[5] Reduction of 1 with sodium borohydride in ethanol gave a diastereoisomer distribution similar to that observed with baker's yeast.

Yeast treatment of the phenethyl δ-keto acids 2-4 resulted in quite different substrate specificity and enantioselectivity. In the case of the 1:1 isomer mixture 2 baker's yeast reduced only the 2-substituted isomer; GLC analysis indicated that the derived lactones 11 and 12 are formed in a constant 1:1 ratio. At the end of the reaction, isomerically pure unreacted 4-methyl-5-oxo-7-phenylheptanoic acid was obtained together with 11 and 12. Under the same fermentation conditions the δ-keto acid 3 affords, at the end of the reaction, lactones 13 and 14 in 87:13 ratio. Structures were

assigned from the vicinal coupling constants of the ring protons or from NOE experiments. The irradiation of proton H-5 produced enhancements of ca. 5% on H-2 of **12** and of ca. 2% on the Me-3 group of **13** indicating a cis and a trans relationship, respectively, of the ring substituents for these compounds. The ee values determined through the usual NMR method were 100% for compounds **11-14** (Table).

TABLE. ee values and optical rotations[a] of lactones **7-17** obtained in yeast reduction of keto acids **1-6**, determined by NMR studies in presence of $Eu(hfc)_3$.

Lactone	ee values	signals observed major[b]	minor(δ)[c]	$[\alpha]_D^{20}$
7	0.59	1.53 (d, Me-3)	1.54(0.01)	+15.2°
8	0.54	1.55 (d, Me-3)	1.56(0.01)	+2.4°
9	0.59	4.53 (m, H-4)	4.54(0,01)	
10	0.72	1.57 (d, Me-2)	1.59(0.02)	
11	1.0	2.03 (d, Me-4)	2.04(0.01)	
12	1.0	1.79 (d, Me-4)	1.80(0.01)	
13	1.0	3.55 (dd, H-2)	3.58(0.03)	+76.2°
14	1.0	3.65 (dd, H-2)	3.57(0.08)	
15	1.0	3.52 (dd, H-2)	3.55(0.03	
16	1.0	3.37 (dd, H-2)	3.34(0.03)	+46.8°[d]
17	1.0	1.32 (d, Me-7)	1.34(0,02)	+28.4°[e]

[a] c 1 in $CHCl_3$. [b] Signal (δ) of the major enantiomer upon addition of $Eu(hfc)_3$. [c] Signal (δ) of the minor enantiomer or taken from the racemic mixture upon addition of $Eu(hfc)_3$; the difference in chemical shift between the signals of the enantiomeric species is shown in brackets. [d]Diastereoisomeric mixture 88:12 [e]Diastereoisomeric mixture 82:18.

The recovered unreacted keto acid **3**, transformed into the methyl ester, was shown by NMR to contain ca. 70% of a single enantiomer. The major diastereoisomer obtained by reduction of **3** was assigned the (3R,5R) configuration **13** on the basis of the following experiments: yeast reduction of enantiomerically pure (3R) 3-methyl-5-oxo-7-phenylheptanoic acid, prepared[3] from (3R) methyl hydrogen 3-methylglutarate,[6] affords lactone **13** as the sole transformation product in ca. 80% yield. Similarly the reduction of the 3-ethyl 5-keto acid **4** by baker's yeast gives rise to a 9:1 diastereoisomer mixture, the main product being lactone **15**. Both materials were enantiomerically pure, but even after a long incubation time the yield was only 20%.

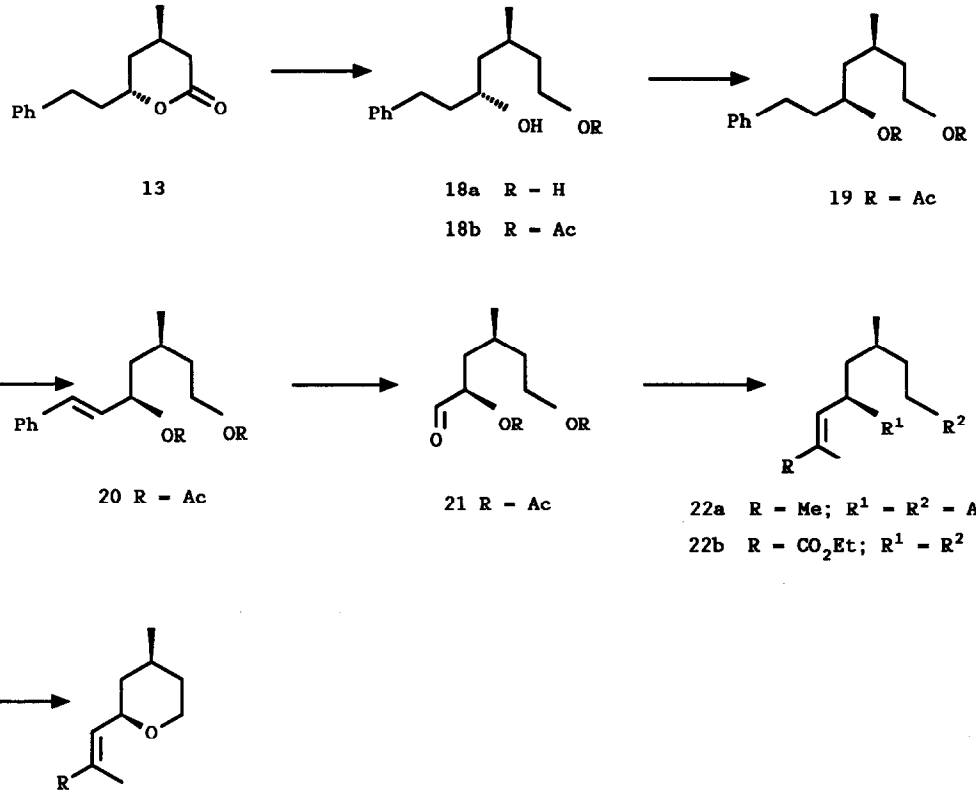
Yeast treatment of the isomeric 3-and 7-methyl substituted 5-oxo-8-phenyloctanoic acids **5** and **6** bearing, like **3**, a methyl substituent in 1,3 relationship with the carbonyl carbon, affords reduction materials in which lactones **16** and **17** are respectively in 88:12 and 82:18 ratios with their diastereoisomers. Lactone **16**, enantiomerically pure on the basis of the above NMR method (Table), was tentatively

assigned the depicted (3R,5R) stereochemistry. This assignment was made in the light of the observation that on adding $Eu(hfc)_3$ lactone **16** behaves like (3R,5R) **13**, whose absolute configuration has already been unambiguously established. The (7R) configuration of the methyl bearing carbon of lactone **17** was assigned after observing that the methyl ester of the keto acid **6** surviving the yeast reduction possessed the (7S) absolute configuration, a conclusion drawn by comparing it with an authentic sample prepared[3] from (2S) 2-methyl-3-phenylpropan-1-ol[7] via the corresponding bromide. The two products showed negligeable optical rotation, but NMR studies in the presence of $Eu(hfc)_3$ showed that they possessed the same absolute configuration. The (R) configuration of **17** at position 5 was assigned only by analogy with **13**. $NaBH_4$ reduction of the above keto acids produces lactones in ca. 1:1 diastereoisomeric ratio.

Thus from our studies it emerges that the baker's yeast reduction of the methyl substituted γ-keto acids is different from that of δ-keto acids. Whereas 2- and 3-methyl substituted 4-keto acids **1** are readily susceptible to yeast, giving reduction products of similar ee and de values, the δ-keto acid **2** bearing the methyl substituent adjacent to the carbonyl carbon is not reduced at all. Conversely, the isomer in which the methyl substituent is alpha to the carboxyl group is readily reduced at a similar rate, affording diastereoisomeric lactones. More importantly, all the substrates of this series, bearing methyl (and ethyl) substituents in 1,3 relationship with the carbonyl carbon (and with the carboxyl group), afford enantiomerically pure reduction products, highly enriched in diastereoisomers with identically configurated alkyl substituents and syn to the newly formed carbinol.

Synthesis of cis-(+)-rose oxide.

Yeast generated lactone **13** contains some structural features which make it of potential interest as a chiral starting material. Simple functional group manipulations of **13**[5] can provide the chiral framework of (protected) 2,6-dihydroxy-4-methylhexanal, which is of potential interest for the synthesis of terpenoid compounds.[8] Thus we used product **13** as the starting material for the synthesis of cis-(+)-rose oxide **23a**, the unnatural enantiomeric form of a flavouring material of practical interest.[9,10] In the light of the today's interest in the sensory evaluation of both enantiomeric forms of aromas we undertook the synthesis of the unnatural form of cis-rose oxide.[11] Syntheses of cis-(+)-rose oxide are terpenoid-based,[12] the notable exception being the one using D-glucose as starting material.[13] The conversion of **13** into **23a** proceeded (Scheme) through **18-22** and required the inversion of the configuration at position 5 in order to assess the (2R) configuration of cis-(+)-rose oxide **23a**. This inversion was achieved by converting monoacetate **18b** (obtained from diol **18a**, the lithium aluminum hydride reduction product of **13**, by the action of vinyl acetate in the presence of lipase from *Candida cylindracea*) into diacetate **19** by treating them with acetic acid under Mitsunobu esterification.[14]



13

18a R = H
18b R = Ac

19 R = Ac

20 R = Ac

21 R = Ac

22a R = Me; R^1 = R^2 = Ac
22b R = CO_2Et; R^1 = R^2 = Ac

23a R = Me
23b R = COOMe
23c R = CH_2OH
23d R = CH_2Br

SCHEME

The (2R,4S) aldehyde **21** was obtained via **20** and ozonolysis.[5] The Wittig reaction of **21** with isopropylidene-triphenylphosphorane[15] gave diacetate **22a**, in varying yields. Nevertheless, basic hydrolysis of **22a** followed by regioselective monotosylation and base-catalyzed ring closure led to cis-(+)-rose oxide **23a**. Therefore the synthesis of **23a** from **21** was accomplished more efficently through **22b**. Basic hydrolysis and diazomethane treatment of **22** afforded the methyl ester **22c**, yielding, in turn, via regioselective monotosylation and basic treatment, **23b**. From this material, cis-(+)-rose oxide **23a** (97% by GLC, $[\alpha]_D^{20}$ +54°. (Lit.[9,10] for the (-)-enantiomer, -58.1° and -41.5°)) was obtained routinely in ca. 15% overall yield from **13**.

Thus, although some limitations have been shown of the yeast transformation of

non-conventional substrates, our results have highlighted their usefulness. Such transformations provide a source of chiral educts complementary to the "pool of chirality" for starting materials[16] for synthesis, and are relevant in organic synthesis due to the potentially high selectivity of enzymatic reactions.

Acknowledgement. We thank Mrs. Rosanna Bernardi for analytical assistance and Dr. Massimo Barbeni (San Giorgio Flavors) for an authentic sample of cis-(-)-rose oxide. This work was financially supported by Progetto Chimica Fine II.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were acquired on Bruker CXP 300 or AC 250 spectrometers unless otherwise indicated. Chemical shifts are reported in ppm (δ) from internal Me_4Si and coupling constants in Hz. The ^1H NOE were determined by using the monodimensional difference spectroscopy technique; 2-4 experiments were performed with a selective irradiation of different protons and then subtracted from a control spectrum (off resonance irradiation). All the volatile materials mentioned in this paper were submitted to GLC-linear retention index analysis which was performed on a Hewlett-Packard 5890 gas chromatograph equipped with two fused silica capillary columns (DB-1 and DB-1701, J & W, 30 m x 0.25 mm id), mounted in the same injector port, and two flame ionisation detectors. Injector (split ratio 50:1) and detector (FID) point heaters were 280 and 300 °C, respectively. Helium carrier gas was used (1 cm^3 min^{-1}) and the temperature program was 50 °C for 3 min, followed by increases of 5 °C min^{-1} to 285 °C for the remainder of the run. The double column signals were recorded simultaneously and elaborated on a Hewlett-Packard 5895A GC-workstation connected with the gas chromatograph. Linear retention indices of peaks, referred to n-alkanes, were calculated and compared with those of authentic standards chromatographed under identical conditions on DB-1 and DB-1701 columns. Chiral analyses were carried out on a Perkin-Elmer 8500 gas chromatograph, equipped with a Megadex-1 column (permethylated beta cyclodextrine coated fused silica capillary column, 25 m x 0.25 mm id) and flame ionization detector. Injector (split 50:1). Temperature: 240 °C. Detector temp.: 250 °C. Helium was used as carrier gas at a flow of 1 cm^3 min^{-1}, followed by increases of 1 °C min^{-1} to 200 °C.

Synthesis of the precursors. Racemic keto acids **1-6** were prepared in 60-70% by alkaline hydrolysis of the methyl ester prepared from the anhydrides, according to lit.[3] procedures. Diazomethane treatment of the acids gave back the methyl esters.

Methyl 2(3)-methyl-4-oxo-6-phenylhexanoate.- Oil, δ_H ($CDCl_3$)(mixture ca. 2:1 of the two isomers, signals not assigned) 1.10 and 1.20 (3H, d, Me, J(Me,$H_{2(3)}$) 6.5 Hz), 2.28-3.08 (7H, m, H-2(3), CH_2-2(3), CH_2-5 and CH_2-6), 3.67 and 3.69 (3H, s, OMe groups), 7.15-7.35 (5H, m, C_6H_5), (Found: C, 71.9; H, 7.68. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74%).

Methyl 2(4)-methyl-5-oxo-7-phenylheptanoate.- Oil, δ_H ($CDCl_3$) (mixture ca. 1:1 of the two isomers, signals not assigned) 1.05 and 1.15 (3 H, d, Me-2(4), J(Me,$H_{2(4)}$) 6.5 Hz), 1.50-2.90 (8 H, m, H-2(4), CH_2-3, CH_2-4(2), CH_2-6 and CH_2-7), 3.68 (3H, s, OMe), 7.10-7.32 (5 H, m, C_6H_5) (Found: C, 72.41; H, 8.09. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%).

4-methyl-5-oxo-7-phenylheptanoic acid.- (Recovered from yeast treatment of **2**). Oil, δ_H($CDCl_3$) 1.07 (3 H, d, Me-4, J(Me,H_4) 6.5 Hz), 1.55-2.97 (9 H, m, CH_2-2, CH_2-3, H-4, CH_2-6 and CH_2-7), 7.11-7.36 (5 H, m, C_6H_5), 8.00 (1 H, s broad, COOH).

Methyl 3-methyl-5-oxo-7-phenylheptanoate. Oil, δ_H ($CDCl_3$) 0.94 (3 H, d, Me-3, J(Me,H_3) 6.5 Hz), 2.12-2.95 (9 H, m, CH_2-2, H-3, CH_2-4, CH_2-6 and CH_2-7), 3.66 (3 H, s, OMe), 7.13-7.26 (5 H, m,C_6H_5) (Found: C, 72.53; H, 8.14. $C_{15}H_{18}O_3$ requires C, 72.55; H, 8.12%).

Methyl (3S) 3-methyl-5-oxo-7-phenylheptanoate (from the diazomethane treatment of the acid recovered from the yeast reduction of **3**).The ee value was determined by observing the OMe signal upon addition of Eu(hfc)$_3$, δ_{OMe} 5.37 (64%) and 5.41 (36%).

Methyl (3R) 3-methyl-5-oxo-7-phenylheptanoate (from (3*R*) methyl hydrogen 3-methylglutarate[6]). $[\alpha]_D^{20}$ +3.43° (*c* 1, $CHCl_3$).

Methyl 3-ethyl-5-oxo-7-phenylheptanoate. Oil, δ_H ($CDCl_3$) 0.86 (3 H, t, CH_2CH_3, $J(CH_2,CH_3)$ 7.0 Hz), 1.34 (2 H, dq, CH_2CH_3, $J(CH_2,CH_3)$ 6.6 Hz), 2.22-2.93 (9 H, m, CH_2-2, H-3, CH_2-4, CH_2-6 and CH_2-7), 3.65 (3 H, s, OMe), 7.14-7.34 (5 H, m, C_6H_5) (Found: C, 73.64; H, 7.65. $C_{16}H_{20}O_3$ requires C, 73.82; H, 7.74%).

Methyl 3-methyl-5-oxo-8-phenyloctanoate. Oil, δ_H ($CDCl_3$) 0.98 (3 H, d, Me, $J(Me,H_3)$ 6.5 Hz), 1.82-2.68 (11 H, m, CH_2-2, H-3, CH_2-4, CH_2-6, CH_2-7 and CH_2-8), 3.64 (3 H, s, OMe), 7.10-7.36 (5 H, m, C_6H_5). (Found: C, 73.91; H, 7.68. $C_{16}H_{20}O_3$ requires C, 73.82; H, 7.74%).

Methyl 7-methyl-5-oxo-8-phenyloctanoate. Oil, δ_H ($CDCl_3$) 0.90 (3 H,d, Me-7, $J(Me,H_7)$ 6.7 Hz) 1.80-2.60 (11 H, m, CH_2-2, CH_2-3, CH_2-4, CH_2-6, H-7 and CH_2-8), 3.65 (3 H,s, OMe,) 7.12-7.32 (5 H, m, C_6H_5) (Found: C, 73.72; H, 7.59. $C_{16}H_{20}O_3$ requires C, 73.82; H, 7.74%).

Methyl (7S) 7-methyl-5-oxo-8-phenyloctanoate (from (2*S*) 1-bromo-2-methyl-3-phenylpropane[7] and from diazomethane treatment of acid **6** surviving the yeast reduction). On addition of Eu(hfc)$_3$ the signal of the Me-7 group is split, δ_{Me} 1.55 (46%) and 1.50 (54%).

Yeast reduction. A suspension of 2.5 kg of baker's yeast and 2.0 kg of D-glucose in 7.5 L of tap water was stirred for 30 min at 32 °C. A solution of keto acids (150 mmol) in 20 cm^3 ethanol was then added. After 16 h at room temperature 1.0 kg of Celite was added and the reaction mixture was filtered, washing the Celite pad with 2 L of ethyl acetate. The filtrate was adjusted to pH 4 with 2N HCl and extracted twice with 2 L portions of ethyl acetate. The organic layer was dried over sodium sulfate and the solvent was evaporated under reduced pressure. The residue was taken up with 300 mL of diethyl ether and extracted three times with 200 cm^3 portions of cold 3% sodium hydrogen carbonate. The residue obtained upon evaporation of the dried organic phase was chromatographed with hexane-ethyl acetate on 350 g of silica gel, giving the lactones 7-17 in 20-40% yield. The alkaline aqueous phase was acidified and extracted three times with 200 cm^3 portions of ethyl acetate. Upon evaporation of the dried solution unreacted acids are recovered. The acidic fraction, when required, was methylated upon treatment with ethereal diazomethane solution.

Reduction products. *(3S,4R) 3-methyl-6-phenyl-γ-hexanolide* **7**.- Oil, $\delta_H(CDCl_3)$ 1.11(3 H, d, Me-3, $J(Me,H_3)$ 7.0 Hz), 1.72-2.08 (2 H, m, CH_2-5), 2.12-2.32 (2H, m, H-2 and H-3), 2.60-2.97 (3 H, m, H-2' and CH_2-6), 4.01 (1 H, m, H-4), 7.14-7.34 (5 H, m, C_6H_5), $\delta_C(CDCl_3)$ 17.2 (Me-3), 32.0, 35.7 and 37.0 (three methylene carbons), 36.0 (C-3), 86.2 (C-4), 126.1, 128.4 and 140.9 (aromatic carbons), 176.4 (C-1) (Found: C, 76.53; H, 7.81. $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90%).

(3R,4R) 3-methyl-6-phenyl-γ-hexanolide **8**.- Oil, $\delta_H(CDCl_3)$ 1.01 (3 H, d, Me-3, $J(Me,H_3)$ 7.0 Hz), 1.70-2.08 (2 H, m, CH_2-5), 2.20 (1 H, dd, H-2, $J(H_2,H_{2'})$ 16.8, $J(H_2,H_3)$ 3.7 Hz), 2.58 (1 H, m, H-3), 2.68 (1 H, dd, H-2', $J(H_{2'},H_3)$ 8.0 Hz), 2.65-3.95 (2 H, m, CH_2-6), 4.42 (1 H, ddd, H-4, $J(H_3,H_4)$ 6.0, $J(H_4,H_{5,5'})$ 4.0 and 10.0 Hz), 7.18-7.35 (5 H, m, C_6H_5). $\delta_C(CDCl_3)$ 13.9 (Me-3), 31.9, 32.1 and 37.4 (three methylene carbons), 32.9 (C-3), 82.4 (C-4), 126.2, 128.5 and 140.9 (aromatic carbons), 176.4 (C-1) (Found: C, 76.61; H, 7.77. $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90%).

(2R,4R) and (2S,4R) 2-methyl-6-phenyl-γ-hexanolide **9** *and* **10**.- Oil, (Found: C, 76.67; H, 7.85. $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90%). The NMR signals of the inseparable mixture of **9** and **10** are partially resolved and the two diastereoisomers can be recognized. **9**.- $\delta_H(C_6D_6)$ 0.97 (3 H, d, Me-2, $J(Me,H_2)$ 7.3 Hz), 0.79 (1 H, d, H-3, $J(H_3,H_{3'})$ 12.5, $J(H_3,H_2)$ 12.5, $J(H_3,H_4)$ 10.5 Hz), 1.35-1.70 (3 H, m, H-3' and CH_2-5), 1.91 (1 H, m, H-2, $J(H_2,H_{3'})$ 9.0 Hz), 2.33-2,40 (2 H, m, CH_2-7), 3.62 (1 H, m, H-4), 6.95-7.21 (5 H, m, C_6H_5). **10**.- $\delta_H(C_6D_6)$ 0.90 (3 H, d, Me-2, $J(Me,H_2)$ 7.3 Hz), 1.05-1.70 (4 H, m, CH_2-3 and CH_2-5), 2.08 (1 H, m, H-2, $J(H_2,H_{3,3'})$ 7.5 and 9.0 Hz), 2.33-2.40 (2 H, m, CH_2-7), 3.86 (1 H, m, H-4), 6.95-7.21 (5 H, m, C_6H_5).

(2R,5R) and (2S,5R) 2-methyl-7-phenyl-δ-heptanolide **11** *and* **12**.- Oil, $\delta_H(CDCl_3$, mixture ca. 1:1 of **11** and **12**) 1.22 (3 H, d, Me-2 of **12**, $J(Me,H_2)$ 6.7 Hz), 1.31 (3 H, d, Me-2 of **11**, $J(Me,H_2)$ 7.0 Hz), 1.50-2.15 (6 H, m, CH_2-3, CH_2-4 and CH_2-6 of **11** and **12**),

2.46 (1 H, m, H-2 of **11**, $J(H_2,H_{3,3'})$ 6.0 and 10.0 Hz), 2.57 (1 H, m, H-2 of **12**, $J(H_2,H_{3,3'})$ 8.0 and 10.0 Hz), 2.60-2.90 (2 H, m, CH_2-7 of **11** and **12**), 4.20-4.35 (1 H, m, H-5 of **11** and **12**), 7.13-7.35 (5 H, m, C_6H_5) (Found: C, 77.08; H, 8.26. $C_{14}H_{18}O_2$ requires C, 77.03; H, 8.31%).

(3R,5R) and (3S,5R) 3-methyl-7-phenyl-δ-heptanolide **13** *and* **14**.- Oil, (Found: C, 77.14; H, 8.11. $C_{14}H_{18}O_2$ requires C, 77.03; H, 8.31%). δ_H of **13** (C_6D_6, 600 MHz) 0.49 (3 H, d, Me-3, $J(Me,H_3)$ 6.5 Hz), 0.79 (1 H, ddd, H-4, $J(H_4,H_3)$ 6.0, $J(H_4,H_{4'})$ 14.0, $J(H_4,H_5)$ 4.2 Hz), 1.11 (1 H, ddd, H-4', $J(H_{4'},H_5)$ 9.0, $J(H_{4'},H_3)$ 7.0 Hz), 1.46 (1 H, m, H-3), 1.39 (1 H, m, H-6), 1.61 (1 H, dd, H-2, $J(H_2,H_{2'})$ 16.0, $J(H_2,H_3)$ 9.5 Hz), 1.68 (1 H, m, H-6'), 2.17 (1 H, dd, H-2', $J(H_{2'},H_3)$ 6.0 Hz), 2.46-2.68 (2 H, m, CH_2-7), 3.80 (1 H, m, H-5), 7.05-7.20 (5 H, m, C_6H_5). δ_H of **14** (C_6D_6, 600 MHz) 0.46 (3 H, d, Me-3, $J(Me,H_3)$ 6.5 Hz), 0.46 (1 H, dt, H-4', $J(H_{4'},H_4)$ 14.0, $J(H_{4'},H_3)$ 11.5, $J(_{4'},H_5)$ 11.5 Hz), 0.96 (1 H, dddd, H-4, $J(H_4,H_3)$ 4.0, $J(H_4,H_5)$ 2.9, $J(H_{4'},H_2)$ 2.0 Hz), 1.10-1.50 (3 H, m, H-3 and CH_2-6), 1.55 (1 H, dd, H-2', $J(H_{2'},H_2)$ 17.2, $J(H_{2'},H_3)$ 11.0 Hz), 2.25 (1 H, ddd, H-2, $J(H_2,H_3)$ 6.0, $J(H_2,H_4)$ 2.0 Hz), 3.56 (1 H, m, H-5), 7.04-7.20 (5 H, m, C_6H_5).

(3R,5R) 3-ethyl-7-phenyl-δ-heptanolide **15**.- Oil, δ_H ($CDCl_3$) 0.92 (3 H, t, CH_2CH_3, $J(CH_2,CH_3)$ 7.0 Hz), 1.30-2.10 (7 H, m,H-3, CH_2-4, CH_2-6 and CH_2CH_3), 2.16 (1 H, dd, H-2, $J(H_2,H_{2'})$ 16.0, $J(H_2,H_3)$ 10.0 Hz), 2.60 (1 H, dd, H-2', $J(H_{2'},H_3)$ 5.0 Hz), 2.65-2.97 (2 H, m, CH_2-7), 4.32 (1 H, m, H-5), 7.13-7.36 (5 H, m,C_6H_5) (Found: C, 77.60; H, 8.59. $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68%).

(3R,5R) 3-methyl-8-phenyl-δ-octanolide **16**.- Oil, $\delta_H(C_6D_6)$ 0.49 (3 H, d, Me-3, $J(Me,H_3)$ 7.0 Hz), 0.78 (1 H, ddd, H-4, $J(H_4,H_{4'})$ 14.0, $J(H_4,H_3)$ 6.0, $J(H_4,H_5)$ 4.0 Hz), 1.08 (1 H, ddd, H-4', $J(H_{4'},H_3)$ 6.5, $J(H_{4'},H_5)$ 9.0 Hz), 1.07-1.76 (7 H, m, H-3, CH_2-6, CH_2-7 and CH_2-8), 1.65 (1 H, dd, H-2, $J(H_2,H_{2'})$ 15.6, $J(H_2,H_3)$ 9.5 Hz), 2.18 (1 H, dd, H-2', $J(H_{2'},H_3)$ 5.6 Hz), 2.42 (2 H,m, CH_2-8); 3.75 (1 H, m, H-5), 7.03-7.25 (5 H, m, C_6H_5) (Found: C, 77.47; H, 8.61. $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68%).

(5R,7R) 7-methyl-8-phenyl-δ-octanolide **17**.- Oil, $\delta_H(CDCl_3)$ 0.92 (3 H, d, Me-7, $J(Me,H_7)$ 7.0 Hz), 1.12-2.70 (11 H, m, CH_2-2, CH_2-3, CH_2-4, CH_2-6, H-7 and CH_2-8), 4.37 (1 H, m, H-5), 7.12-7.35 (5 H, m, C_6H_5) (Found: C, 77.58; H, 8.70. $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68%).

Synthesis of cis-(+)-rose oxide.

(3R,5R)3-methyl-7-phenyl- heptane-1,5-diol **18a**.- A solution of the lactone **13** (22 g,100 mmol) in 30 cm^3 of dry THF was added to a boiling THF (150 cm^3) suspension of $LiAlH_4$ (7 g, 184.4 mmol) under nitrogen. After refluxing for 4 h, the reaction mixture was quenched by sequential addition of ethyl acetate, a saturated solution of potassium sodium tartrate and water. The organic layer was separated, dried over sodium sulfate and the solvent evaporated under reduced pressure. The crude residue was purified by chromatography (AcOEt/hexane 65/35) to give diol **18a** in 85% yield. $\delta_H(CDCl_3)$ 0.91 (3 H, d, Me-3, $J(Me,H_3)$ 6.5 Hz), 1.12-1.94 (7 H, m, CH_2-2, H-3, CH_2-4 and CH_2-6), 2.18 (2 H, s broad, OH-1 and OH-5), 2.71 (2 H, m, CH_2-7), 3.60-3.80 (3 H, m, H-5 and CH_2-1), 7.12-7.34 (5 H,m, C_6H_5), $[\alpha]_D^{20}$ -1.5°(c 1, $CHCl_3$) (Found: C, 75.60; H, 9.89. $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97%).

Mono acetate **18b**.- The diol **18a** (16.6 g, 75 mmol) in 150 cm^3 of benzene-hexane (1:1) was treated at room temperature with vinyl acetate (13.4 cm^3, 216.5 mmol) and 3 g of lipase from *Candida cylindracea*[17] (Fluka). After 3 h stirring, the reaction mixture was filtered and the solvent evaporated under reduced pressure. The crude product was purified by chromatography (hexane/ethyl acetate 8/2) to give **18b** in 85% yield. Oil, $[\alpha]_D^{20}$ +4.2°(c 1, $CHCl_3$), $\delta_H(CDCl3)$ 0.94 (3 H, d, Me-3, $J(Me,H_3)$ 6.5 Hz), 1.35-1.89 (7 H, m, CH_2-2, H-3, CH_2-4 and CH_2-6), 1.51 (1 H, s broad, OH), 2.04 (3 H, s, COMe), 2.74 (2 H, m, CH_2-7), 3.74 (1 H, m, H-5), 4.10 (2 H, m, CH_2-1), 7.14-7.35 (5 H, m, C_6H_5) (Found: C, 72.61; H, 9.02. $C_{16}H_{24}O_3$ requires C, 72.69; H, 9.15%).

(3R,5S) 3-methyl-7-phenyl-1,5-diacetoxyheptane **19**.- A solution of triphenylphosphine (26.2 g, 100 mmol) and monoacetate **18b** (26.4 g, 100 mmol) in 120 cm^3 of ether was added slowly to a solution of diisopropylazodicarboxylate (20.2 g, 100 mmol) and acetic acid (7.2 g, 120 mmol) in 120 cm^3 of ether at room temperature. After 16 h the precipitate was removed by filtration and the residue obtained upon evaporation of the solvent was chromatographed (AcOEt-hexane) to give **19** in 88% yield. Oil, $[\alpha]_D^{20}$ +24° (c 1, $CHCl_3$), $\delta_H(CDCl_3)$ 0.93 (3 H, d, Me-3, $J(Me,H_3)$ 6.5 Hz), 1.22-2.02 (7 H, m, CH_2-2, H-3, CH_2-4 and CH_2-6), 2.03 (3 H, s, COMe), 2.04 (3 H, s, COMe), 2.64 (2 H, m, CH_2-7),

4.92 (2 H, m, CH_2-1), 5.06 (1 H, m, H-5), 7.10-7.32 (C_6H_5) (Found: C, 70.43; H, 8.49. $C_{18}H_{26}O_4$ requires C, 70.56; H, 8.55%).

(3R,5S) 3-methyl-7-phenyl-1,5-diacetoxyhept-6-ene **20**.- Diacetate **19** (15.3 g, 50 mmol) in 70 cm^3 of carbon tetrachloride was treated with N-bromosuccinimide (13.5 g, 75 mmol) and a trace amount of perbenzoic acid. The reaction mixture was refluxed for 1 h, then filtered and the solvent evaporated under reduced pressure. The crude bromo derivative was dissolved in 150 cm^3 of chloroform and treated with DBU (15.2 g, 100 mmol). After refluxing for 3 h, the reaction mixture was cooled and treated with 2N HCl until pH 5. The organic layer was washed with water and brine. The residue obtained upon evaporation of the solvent was chromatographed (AcOEt/hexane 3/7) to give **20** in 85% yield. Oil, $[\alpha]_D^{20}$ +70° (c 1, $CHCl_3$), $\delta_H(CDCl_3)$ 0.98 (3 H, d, Me-3, J(Me,H_3) 6.4 Hz), 1,42-1.90 (5 H, m, CH_2-2, H-3, and CH_2-4), 2.00 (3 H, s, COMe), 2.06 (3 H,s, COMe), 4.12 (2 H, m, CH_2-1), 5.52 (1 H, m, H-5), 6.11 (1 H, dd, H-6, J(H_6,H_7) 7.0, J(H_7,H_8) 15.0 Hz), 6.61 (1 H, d, H-7), 7.21-7.42 (5H, m, C_6H_5) (Found: C, 71.07; H, 7.89. $C_{18}H_{24}O_4$ requires C, 71.02; H, 7.95%).

(2R,4S) 4-methyl-2,6-diacetoxyhexanal **21**.- The unsaturated diacetyl derivative **20** (12.16 g, 40 mmol) in 80 cm^3 of dichloromethane/ methanol 4/1 was ozonized at -78°C until the reaction was complete. Nitrogen was fluxed through for 20 min and at the same temperature solid triphenylphosphine (10.5 g, 40 mmol) was added in portions. The reaction mixture was evaporated under vacuum at 30-40 °C and the residue taken up with ether-petr.ether to precipitate triphenylphosphine oxide. The oily residue obtained upon evaporation of the solvent was chromatographed with increasing amounts of AcOEt in hexane, obtaining benzaldehyde and the aldehyde **21** in 78% yield. Oil, $[\alpha]_D^{20}$ +28.5° (c 1, $CHCl_3$), $\delta_H(CDCl_3)$ 0.98 (3 H, d, Me-4, J(Me,H_4) 6.4 Hz), 1.52-1.75 (5 H, m, CH_2-3,, H-4, and CH_2-5), 4.11 (2 H, m, CH_2-6), 5.07 (1 H, dd, H-2, J(H_2,$H_{3,3'}$) 3.3 and 10.0 Hz), 9.51 (1 H, s, CHO).

Ethyl (4R,6S) 2,6-dimethyl-4,8-diacetoxyoct-2-enoate **22b**.- A solution of aldehyde **21** (6.9 g, 30 mmol)and (carbethoxyethylidene)- triphenylphosphorane (10.86 g, 30 mmol) in 60 cm^3 of benzene is refluxed 14 h. The solution was evaporated and after precipitation of triphenylphosphine oxide with ether-petr./ether the oily residue was chromatographed (AcOEt/hexane 30/70) to give **22b** in 83% yield. Oil, $[\alpha]_D^{20}$ +12.9° (c 1, $CHCl_3$), δ_H(CDCl3) 0.98 (3 H, d, Me-6, J(Me,H_6) 6.5 Hz), 1.30 (3 H, t, CH_2CH_3, J(CH_2,CH_3) 7.0 Hz), 1.24-1.88 (5 H, m, CH_2-5, H-6 and CH_2-7), 1.94 (3 H, d, Me-2, J(Me,H_3) 1.5 Hz), 2.04 (3 H, s, COMe), 2.06 (3 H,s, COMe), 4.10 (2 H,m, H-8), 4.20 (2 H, q, CH_2CH_3), 5.62 (1 H, td, H-4, J(H_4,$H_{5,5'}$) 4.5 and 9.0 Hz), 6.53 (1 H, dq, H-3, J(H_3,H_4) 9.0 Hz) (Found: C, 61.21; H, 8.38. $C_{16}H_{26}O_6$ requires C, 61.13; H, 8.34%).

Methyl ester **23b**. Ester **22b** (7.85 g, 25 mmol) was refluxed 3 h in 100 cm^3 of 2N NaOH and 100 cm^3 of ethanol. The solution was concentrated to small volume and the acidified mixture was extracted three times with ethyl acetate (100 cm^3). The residue dissolved in ether was transformed, upon treatment with diazomethane,into the dihydroxy methyl ester quantitatively. The residue (4.8 g, 22 mmol) in 60 cm^3 of dichloromethane and 10 cm^3 of dry pyridine was treated at 0 °C with p-toluenesulfonyl chloride (4.2 g, 22 mmol) for 16 h. The reaction mixture was washed with cold 3% HCl and water, dried and evaporated. The residue was chromatographed (AcOEt/hexane 1/1) to give the 8-p-toluenesulfonate in 90% yield as thick oil. $[\alpha]_D^{20}$ +8° (c 1, $CHCl_3$), $\delta_H(CDCl_3)$ 0.91 (3 H, d, Me-6,J(Me,H_6) 6.5 Hz), 1.11-1.76 (6 H, m, CH_2-5, H-6, CH_2-7 and OH), 1.85 (3 H, d, Me-2, J(Me,H_3) 1.5 Hz), 2.45 (3 H, s, *para* methyl group), 3.75 (3 H,s, OMe), 4.00-4.15 (2 H, m, CH_2-8), 4.51 (1 H, td broadened due to the OH coupling, H-4, J(H_4,$H_{5,5'}$) 8.9 and 4.0 Hz), 6.61 (1 H, dq, H-3, JH_3,H_4) 8.9 hz), 7.35 and 7.779 (4 H, m, aromatic protons). The above material (7 g, 19 mmol) in 20 cm^3 of methanol was added to a solution of sodium (1.15 g, 50 mmol) in 40 cm^3 of methanol. After 3 h the reaction was completed (TLC). The reaction mixture was concentrated to small volume, diluted with ether and washed with cold 3% HCl. Chromatography of the residue afforded the cyclic ester **23b** in 82% yield. Oil, $[\alpha]_D^{20}$ +39.9° (c 1, CHC13), $\delta_H(CDCl_3)$ 0.99 (3 H, d, Me-4, J(Me,H_4) 6.5 Hz), 1.00-1.80 (5 H, m, CH_2-3, H-4 and CH_2-5), 1.88(3 H, d, Me-8, J(Me,H_7)1.5 Hz), 3.48 (1 H, ddd, H-6ax, J(H_{6ax},H_{6eq}) 11.5, J(H_{6ax},H_{5ax}) 12.5, J(H_{6ax},H_{5eq}) 2.0 Hz), 3.74 (3 H, s, OMe), 4.02 (1 H, ddd, H-6eq, J(H_{6eq},H_{5ax}) 2.7, J(H_{6eq},H_{5eq}) 1.5 Hz), 4.13 (1 H, ddd, H-2, J(H_2,H_{3ax}) 11.5, J(H_2,H_{3eq}) 2.5 Hz), 6.67 (1 H, dq, H-7, J(H_2,H_7) 8.0 Hz) (Found: C, 66.56; H, 9.05. $C_{11}H_{18}O_3$ requires C, 66.64; H, 9.15%)

Cis-(+)-rose oxide **23a**.- The ester **23b**(3 g, 15 mmol) in 10 cm^3 of THF was added to a boiling suspension of LiAlH4 in THF. After 3 h reflux, the usual work up afforded carbinol **23c** in 90% yield. Oil, $[\alpha]_D^{20}$ +59.2° (c 1, $CHCl_3$), δ_H(CDCl3) 0.95 (3 H, d,

Me-4, J(Me,H_4) 6.5 Hz), 0.98-1.70 (5 H, m, CH_2-3. H-4 and CH_2-5), 1.71 (3 H, d, Me-8, J(Me,H_7) 1.5 Hz), 1.90 (1 H, s broad, OH), 3.48 (1 H, ddd, H-6ax, J(H_{6ax},H_{6eq}) 11.5, J(H_{6ax},H_{5ax}) 12.5, J(H_{6ax},H_{5eq}) 2.4 Hz), 4.00 (2 H, s, CH_2OH), 3.95-4.10 (2 H, m, H-2 and H-6eq), 5.43 (1 H, dq, H-7, J(H_2,H_7) 8.0 Hz) (Found: C, 70.43; H, 10.53. $C_{10}H_{18}O_2$ requires C, 70.54; H, 10.66%). Carbinol **23c** (1.7 g, 10 mmol) and triphenylphosphine (2.6 g, 10 mmol) in 20 cm^3 of dichloromethane were treated below 30 °C with N-bromosuccinimide (1.77 g, 10 mmol). After 3 h the reaction mixture was evaporated and the residue was taken up with ether/petr. ether. The solid was filtered off and the residue chromatographed (AcOEt/hexane 25/75) to give **23d** in 88% yield. Oil, $[\alpha]_D^{20}$ +65.2° (c 1, CHCl3), δ_H(CDCl3) 0.95 (3 H, d, Me-4, J(Me,H_4) 6.4 Hz), 0.95-1.70 (5 H, m, CH_2-3, H-4 and CH_2-5), 1.82 (3 H, d, Me-8, J(Me,H_7) 1.1 Hz), 3.45 (1 H, ddd, H-6ax, J(H_{6ax},H_{6eq}) 11.4, J(H_{6ax},H_{5ax}) 12.0, J(H_{6ax},H_{5eq}) 2.1 Hz), 3.93 (2 H, s, CH_2Br), 3.93-4.05 (2 H, m, H-6eq and H-2), 5.57 (1 H,dq, H-7). The latter material (1.74 g, 7.5 mmol) in 10 cm^3 THF was added to $LiAlH_4$ (0.3 g, 7.5 mmol) in 10 cm^3 THF. After 6 h reflux, the reaction mixture was treated with AcOEt, sat. soln. of potassium sodium tartrate and water. The organic phase is separated and the aqueous phase further extracted with ether. The washed and dried combined organic extract was carefully evaporated (30 cm Vigroux) and the residue distilled (bulb-to-bulb at the water pump, oven temp. 100 C) to give cis-(+)-rose oxide **23a** in 75% yield, 97% by GLC. $[\alpha]_D^{20}$ +54° (c 1, $CHCl_3$), δ_H($CDCl_3$) 0.93 (3 H, d, Me-4, J(Me,H_4) 6.5 Hz), 0.95-1.70 (5 H, m, CH_2-3, H-4 and CH_2-5), 1.68 (3 H, d, Me-8, J(Me,H_7) 1.5 Hz), 1.71 (3 H, d, Me-8, J(Me,H_7) 1.5 Hz), 3.45 (1 H, ddd, H-6ax, J(H_{6ax},H_{6eq}) 11.2 , J(H_{6ax},H_{5ax}) 12.4, J(H_{6ax},H_{5eq}) 2.2 Hz), 3.96 (2 H, m, H-6eq and H-2), 5.15 (1 H, dqq, H-7, J(H_7,H_2) 8.0 Hz).

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