Stirring in a nitrogen atmosphere was continued for 2 h at room temperature. Then the solvent was removed in vacuo. A solution of the residue in CH_2Cl_2 was washed with 1 N HCl and with brine and subsequently dried over Na_2SO_4. The residue obtained by evaporation of the solvent was subjected to HPLC (1:1 (v/v) hexane/CH_2Cl_2) to give **17** in 79% (1.25 g, oil) yield, which was homogeneous by TLC (R_f 0.55, CH_2Cl_2): high-resolution mass spectrum, exact mass calcd for $C_{22}H_{24}N_2O_3S$ m/e 396.1507, found 396.1497; UV (methanol) λ_{max} 220, 288, 298 nm; ^1H N mR δ 8.2 (br s, 1 H, indole NH), 7.2 (s, 5 H, C_6H_5), 7.6–6.9 (m, 4 H, indole C(4)–C(7)H), 5.25 (s, 2 H, $CH_2C_6H_5$), 4.2 (s, 2 H, indole C(3)–CH_2–), 4.15 (q, 2 H, OCH_2CH_3), 2.7 (q, 2 H, SCH_2CH_3), 1.2 (t, 3 H, OCH_2CH_3), 1.2 (t, 3 H, SCH_2CH_3).

Ethyl α-((*E*)-Benzyloximino)-β-(indol-3-yl)propanoate (18). Raney nickel catalyst (Merck-Schuchard, Darmstadt, FRG) was added portionwise to a solution of **17** (1 mmol, 396 mg) in ethanol (5 mL), which was stirred at room temperature under an atmosphere of nitrogen. The addition of the catlayst was stopped upon completion of the reaction, which was monitored by TLC (R_f 0.5, CH_2Cl_2). The reaction mixture was then filtered, and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL), washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave **18** (306 mg, oil) in 91% yield, which was homogeneous on TLC (R_f 0.6, CH_2Cl_2): high-resolution mass spectrum, exact mass calcd for $C_{20}H_{20}N_2O_3$ m/e 336.1474, found 336.1487; UV (methanol) λ_{max} 220, 280, 288 nm; ^1H NMR δ 8.1 (br s, 1 H, NH), 7.7–7.0 (m, 4 H, indole C(4)–C(7)H), 7.25 (s, 5 H, C_6H_5), 6.9 (d, 1 H, indole C(2)H), 5.3 (s, 2 H, $CH_2C_6H_5$), 4.2 (q, 2 H, OCH_2CH_3), 4.05 (s, 2 H, indole C(3) CH_2), 1.2 (t, 3 H, OCH_2CH_3).

Ethyl α-(Benzyloxamino)-β-(indol-3-yl)propanoate (19). A solution of HCl in ethanol (5 mL of a 7 N solution) was added to a stirred solution of **18** (0.45 mmol, 150 mg) and trimethylamine borohydride complex (Aldrich Chemical Co., 0.9 mmol 66 mg) in ethanol (5 mL) at room temperature. Stirring was continued for 24 h at room temperature. The mixture was then concentrated to dryness in vacuo and the residue positioned between CH_2Cl_2 and water. The organic layer was washed twice with water, dried over Na_2SO_4, and then concentrated in vacuo. The residue was subjected to HPLC (eluent CH_2Cl_2) to yield 98 mg (65%, oil) of **19**, which was homogeneous on TLC (R_f 0.2, CH_2Cl_2). The ^1H NMR spectrum is identical with that of the product obtained from **20** (Scheme III).[1]

3-(Methylsulfinyl)indole. To a stirred and cooled (0 °C) solution of the thioether **8**[6] (5 mmol, 815 mg) in acetonitrile (10 mL) was added dropwise a solution of sodium metaperiodate (5 mmol, 1070 mg) in water (10 mL). Stirring of the reaction mixture was continued at room temperature until completion of the reaction (ca. 3 h) as was monitored by TLC (R_f 0.25, 4:96 (v/v) MeOH/CH_2Cl_2). The precipitate consisting of sodium iodate was removed by filtration, and CH_2Cl_2 was added to the filtrate. The organic layer was washed with brine and dried with Na_2SO_4. Evaporation of the solvent in vacuo and recrystallization from CH_2Cl_2/*n*-hexane gave the product in 91% (814 mg) yield: mp 117–120 °C; high-resolution mass spectrum, exact mass calcd for C_9H_9NOS m/e 179.0405, found 179.0400; UV (methanol) λ_{max} 210, 265, 276, 282 nm; ^1H NMR δ 10 (br s, 1 H, NH), 7.9–6.9 (m, 5 H, indole C(2)H, C(4)–C(7)H), 2.9 (s, 3 H, $-SOCH_3$). Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.15; H, 5.06; N, 7.70.

3-(Ethylsulfinyl)indole. This compound was prepared from **9**[6] (5 mmol, 885 mg) and sodium metaperiodate (5 mmol, 1070 mg) as described for 3-(methylsulfinyl)indole. It was obtained in 87% (840 mg) yield: mp 142–143 °C dec (CH_2Cl_2/hexane); high-resolution mass spectrum, exact mass calcd for $C_{10}H_{11}NOS$ m/e = 193.0561, found 193.0550; UV (methanol) λ_{max} 210, 265, 276, 282 nm; ^1H NMR δ 10 (br s, 1 H, NH), 7.9–6.7 (m, 5 H, indole C(2)H, C(4)–C(7)H), 3.15 (q, 2 H, $SOCH_2$), 1.05 (t, 3 H, $SOCH_2CH_3$). Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25. Found: C, 62.11; H, 5.72; N, 7.22.

Registry No. **5**, 73472-94-3; **6**, 87497-88-9; **8**, 40015-10-9; **9**, 1484-16-8; **13**, 87843-25-2; **14**, 87843-26-3; **16**, 87843-27-4; **17**, 87843-28-5; **18**, 87843-29-6; **19**, 81095-85-4; 3-(methylsulfinyl)indole, 86925-06-6; 3-(ethylsulfinyl)indole, 87843-30-9; benzyl bromide, 100-39-0.

Synthesis of the Enantiomeric Forms of α- and β-Alkoxy Carbonyl Compounds from the (2*S*,3*R*)-2,3-Diol Prepared in Fermenting Bakers' Yeast from α-Methylcinnamaldehyde

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One of the major problems faced in the use of components of the set of readily available, optically active products produced by Nature ("pool of chirality"[1]) as starting materials in the synthesis of enantiomerically pure forms of natural products is that most of these materials are usually accessible in only one enantiomeric form. Attempts to overcome this drawback involve, amongst others, the chemical conversion of abundant natural products into the unnatural form of structurally related materials (e.g., natural tartaric acid into unnatural malic acid[2]), the production of the enantiomeric forms of a chiral synthon by microbial transformulations of nonconventional substrates using microorganisms acting on the same substrate with opposite stereochemistry (e.g., (*R*)- and (*S*)-3-hydroxybutyrate from ethyl 3-oxobutyrate using *Geotrichum candidum* and bakers' yeast, respectively[3]), and preparation of the two enantiomers from suitably functionalized chiral synthons (e.g., the conversion of (*S*)-3-hydroxy-2-methylpropionic acid into (*R*)- and (*S*)-3-*tert*-butoxy-2-methyl-1-propanol[4]).

In this context we report now the preparation of the chiral carbonyl compounds 14–17 and of their enantiomers from the (2*S*,3*R*)-2,3-diol **1**, obtained from fermenting bakers' yeast and α-methylcinnamaldehyde.[5] The procedure takes advantage of the possibility of preparing regioselectively from **1** the 2- and 3-*O*-tosylates **2** and **4**, from which the enantiomeric epoxides **5** and **6** are obtained. To this end, the diol **1**, reacted with 1 mol equiv of 4-toluenesulfonyl chloride in CH_2Cl_2–pyridine, afforded the 2-*O*-tosylate **2** in high yield. ^1H NMR studies on **1** and **2** support the regiospecificity of the reaction: the H-2 signal is shifted from δ 4.08 in **1** to δ 4.75 in **2**. Compound **2** gave rise on basic treatment to the (2*R*,3*R*)-2,3-epoxide **5**. The same epoxide **5** was obtained when the diol **1** was treated with 4-toluenesulfonyl chloride, 1,2-dimethoxyethane, and KOH,[6] thus indicating the regiospecificity of this one-pot conversion of **1** to **5**. On reaction with diisobutylaluminum hydride in THF at −50 °C or with $LiAlH_4$ in diethyl ether at O °C, compound **5** gave rise to the alcohol **7**, which converted, in turn, to the *O*-benzyl ether **8** in ca. 70% overall yield. The latter material on

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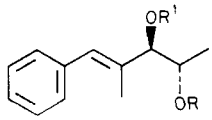
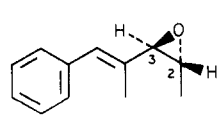


1, R = R¹ = H
2, R = Ts; R¹ = H
3, R = COC_6H_5; R¹ = H
4, R = COC_6H_5; R¹ = Ts



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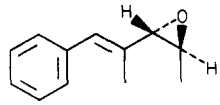
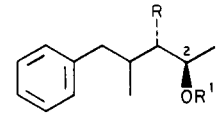


6

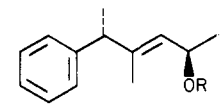
ozonolysis in CH_2Cl_2 at −40 °C and treatment with 1 mol equiv of $(C_6H_5)_3P$ afforded benzaldehyde and (4*R*)-4-(benzyloxy)pentan-2-one (**15**), easily separated by SiO_2 column chromatography.

(3*R*,4*R*)-3-Methyl-4-(benzyloxy)pentan-2-one (**16**) was obtained from **5** in the following way. Addition of an excess of Me_2CuLi in Et_2O at −30 °C to **5** gave rise to the products of α and γ attack, **9** and **12**, respectively, separated by SiO_3 column chromatography in ca. 1:3 ratio. Compound **9** was benzylated to **10** and ozonized, as above, to afford the required (3*R*,4*R*)-3-methyl-4-(benzyloxy)-pentan-2-one (**16**). The product of γ addition, **12**, once benzylated to **13**, was ozonized to give, in the usual way, (3*S*)-3-phenylbutan-2-one (**14**), $[\alpha]^{20}_D$ + 340° (*c* 1, benzene) (lit.[7] $[\alpha]^{10}_D$ +368°), ca. 90% pure by GLC, and *O*-benzyllactaldehyde (**17**), a sample of which, purified by bulb-to-bulb distillation, showed $[\alpha]^{20}_D$ + 60° (*c* 1, $CHCl_3$). The absolute configuration and the optical purity at position 2 of **13** were determined as follows. Ozonolysis of **13** in methanol at −70 °C and $NaBH_4$ reduction afforded, in addition to 3-phenylbutan-2-ol, alcohol **18** with $[\alpha]^{20}_D$ −47° (*c* 1, $CHCl_3$). This was assigned the *R* absolute configuration because identical material obtained from (2*S*)-4-phenylbut-3-en-2-ol[8] via similar reaction sequence showed $[\alpha]^{20}_D$ +42°. The optical purity of the alcohols so obtained was determined by conversion to the corresponding esters with (+)-2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid [(+)-MTPA].[9] ^1H NMR studies on these derivatives indicated that the parent alcohols were enantiomers. The most significant difference in the NMR spectra is in the $CHCH_3$ absorption: δ 1.21 in the derivative of **18** and δ 1.19 in the product formed from the *S* enantiomer. The ee was ca. 95%. These results allow us to assign the *R* absolute configuration depicted in **17** to *O*-benzyllactaldehyde obtained from **13**.

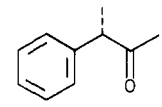
Access to the (2*S*,3*S*)-2,3-epoxide **6** from **1** involved the 2-*O*-benzoate **3**, obtained from **1** on treatment with 1 mol equiv of benzoyl chloride in CH_3Cl_2–pyridine. Compound **3** is obtained in ca. 75% yield and was easily separated from some 3-*O*-benzoate. When reacted with a large excess of 4-toluenesulfonyl chloride in pyridine product **3** afforded the unstable derivative **4**. Crude product **4**, treated with NaOH in ethylene glycol–water, gave rise to the epoxide **6**, in ca. 55% yield. The latter material, on $LiAlH_4$ reduction, afforded the enantiomer of **7**. In order to determine the optical purity of the latter material and of **7**, previously prepared from **5**, these two alcohols were converted into the (+)-MTPA esters. ^1H NMR studies on the latter derivatives indicated that the alcohols were optically pure and enantiomers. The main difference in the spectra is in the C-4 methyl absorption: at δ 2.5 in **11** and δ 2.45 in the product derived from the epoxide **6**. Reaction of Me_2CuLi with **6** afforded the 2*S*,3*R* and the 2*S*,5*R* enantiomers of **9** and **12**, respectively, in 85% yield. From the latter materials, as indicated above, the 3*S*,4*S* enantiomer of **16**, $[\alpha]^{20}_D$ +28.2°, the *R* enantiomer of **14**, $[\alpha]^{20}_D$ −350°, and the 2*S* enantiomer of **18**, $[\alpha]^{20}_D$ +43°, obtained by reduction of the intermediate *O*-benzyllactaldehyde, were prepared. Similarly, (4*S*)-4-(benzyloxy)pentan-2-one, $[\alpha]^{20}_D$ +19.5°, was obtained from the product of hydride opening of **6**.



7, R = R¹ = H
8, R = H; R¹ = $CH_2C_6H_5$
9, R = Me; R¹ = H
10, R = Me; R¹ = $CH_2C_6H_5$
11, R = H; R¹ = $COC(CF_3)(OMe)C_6H_5$



12, R = H
13, R = $CH_2C_6H_5$



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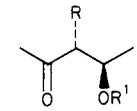
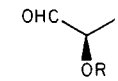
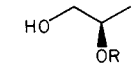


15, R = H; R¹ = $CH_2C_6H_5$
16, R = Me; R¹ = $CH_2C_6H_5$



17, R = $CH_2C_6H_5$



18, R = $CH_2C_6H_5$

The chiral carbonyl compound obtained in the two enantiomeric forms through unexceptional steps from readily available **1** might be a useful starting material in the synthesis of fragments of naturally occurring polyhydroxy derivatives, taking advantage of known methods for stereocontrolled chain elongation through nucleophilic additions to carbonyl carbons.[10] The significance of the transformations reported above is further supported by the fact that the diol prepared in fermenting bakers's yeast from cinnamaldehyde (**1**, bearing H instead of Me in position 4) gives rise to the 2-*O*-tosylate and to regioisomeric 2- and 3-*O*-benzoates. By repeating the reaction sequences mentioned above for the derivatives of **4**, on the latter regioselectively functionalized substances it should be possible to have access to the aldehydic analogues of the methyl ketones **14**–**16** and to their enantiomers. Recently,[11] the framework of (2*S*,3*S*)-2-methyl-3-hydroxybutyraldehyde, one of the products hopefully obtainable through the above procedures, has been constructed from D-glucose and incorporated into the side chain of (+)-pseudomonate C.

Experimental Section

^1H NMR spectra were recorded at 90 MHz. Chemical shifts are in ppm from $SiMe_4$ as internal standard. Flash chromatography was performed with Merck silica gel (0.040–0.069 mm) and TLC with Merck HF_{254} silica gel. GLC analysis was performed on a DANI 3800 gas chromatograph, equipped with a FID detector; carrier N_2, 25 mL/min, on 2-m Pyrex columns, i.d. 2 mm packed with 10% UCC W-982 silicone on Chromosorb W A.W. and 5% Sp 1000 on 100/120 Supelcoport. Organic solutions were

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dried with Na_2SO_4 and evaporated at the water pump at 50–60 °C.

(2*R*,3*R*)-2,3-Epoxy-4-methyl-5-phenylpent-4-ene (5). To a stirred solution of 19.2 g (0.1 mol) of (2*S*,3*R*)-2,3-dihydroxy-4-methyl-5-phenylpent-4-ene (**1**)[5c] in 200 mL of CH_2Cl_2 containing 50 mL of dry pyridine is added dropwise at 0 °C a solution of 19 g (0.1 mol) of 4-toluenesulfonyl chloride in 50 mL of CH_2Cl_2. After stirring overnight, the reaction mixture is washed with 0.1 N HCl (2 × 100 mL), water, and 3% $NaHCO_3$ (50 mL). The residue obtained upon evaporation of the solvent is chromatographed on a column with 350 g of SiO_2, eluting with hexane–ethyl acetate (70:30) the 2-*O*-tosylate **2**: 28 g (81%) of a thick oil, which solidified on standing, $[\alpha]^{20}_D$ −15.4° (*c* 1, EtOH), and ca. 2 g of unreacted starting material. To a stirred solution of 28 g (0.08 mol) of **2** in 100 mL of ethylene glycol and 100 mL of water at 0 °C is added dropwise 100 mL of 2.5 N NaOH. After ca. 30 min the cooling bath is removed and the reaction mixture is kept at room temperature for 3 h. The cloudy reaction mixture is extracted with Et_2O (3 × 100 mL). On evaporation the organic phase afforded **5**: 11 g (71%), 97% pure by GLC. An analytical sample, obtained by bulb-to-bulb distillation (oven temperature 70–80 °C (0.1 mmHg)) showed the following $[\alpha]^{20}_D$ +130° (*c* 1, EtOH); ^1H NMR ($CDCl_3$) δ 7.4–7.2 (5 H, Ph), 6.6 (1 H, s, H-5), 3.2 (1 H, H-3, $J_{2,3}$ = 2.0 Hz), 3.0 (1 H, H-2, $J_{H,Me}$ = 5 Hz), 1.72 (3 H, s, 4-Me), 1.35 (3 H, d, $CHCH_3$). Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.66; H, 8.02.

(2*R*)-2-(Benzyloxy)-4-methyl-5-phenylpent-4-ene (8). A solution of 8.7 g (0.05 mol) of the epoxide **5** in 25 mL of dry THF is added dropwise under stirring at −50 °C to 160 mL of 0.5 M diisobutylaluminum hydride in hexane–THF. After 3 h, 50 mL of a 1:1 mixture of MeOH–acetone is added, and the precipitate that separates within a few hours is filtered and washed with methanol. The organic phase, diluted with 200 mL of ethyl acetate, is washed with 15% NaCl in water (3 × 100 mL). The residue obtained upon evaporation of the solvent is chromatographed on 200 g of SiO_2, obtaining with 30% ethyl acetate in hexane oily **7**: 6.9 g (80%); $[\alpha]^{20}_D$ +3° (*c* 1, EtOH); ^1H NMR ($CDCl_3$) δ 7.4–7.15 (5 H, Ph), 6.4 (1 H, s, H-5), 4.05 (1 H, m, H-2), 2.3 (2 H, d, H-3), 1.9 (3 H, s, 4-CH_3), 1.25 (3 H, d, $CHCH_3$); 96% pure by GLC. Product **7** (6.4 g, 0.036 mol) in 15 mL of dry DMF is added dropwise under stirring to 1.2 g (0.05 mol) of NaH in 10 mL of dry DMF. The reaction mixture is stirred under N_2 for 3 h at 40 °C. Therefore, 5 g (0.04 mol) of benzyl chloride in 10 mL of DMF is added. After 2 h, the reaction mixture is treated carefully with 10 mL of MeOH and poured into ice–water. The reaction mixture is extracted with 1:1 ethyl acetate–hexane (3 × 100 mL), and the organic phase is washed with water (2 × 100 mL) and evaporated. The residue is chromatographed in a column, using 150 g of SiO_2 and product **8** is eluted with hexane–ethyl acetate (8:2): 8 g (83%); $[\alpha]^{20}_D$ +6.9° (*c* 1, EtOH); ^1H NMR ($CDCl_3$) δ 7.5–7.1 (10 H, 2 Ph), 6.35 (1 H, s, H-5), 4.55 (2 H, 2 d, CH_2Ph), 3.75 (1 H, m, H-2), 2.6–2.2 (2 H, m, H-3), 1.85 (3 H, s, 4-CH_3), 1.22 (3 H, d, $CHCH_3$). Anal. Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.33. Found: C, 85.76; H, 8.29.

(4*R*)-4-(Benzyloxy)pentan-2-one (15). Ozonized oxygen is passed through a solution of 5.2 g (0.02 mol) of **8** in 30 mL of dry CH_2Cl_2 at −40 °C. At the end of the absortion, N_2 is flushed through, and, subsequently, 5.2 g (0.02 mol) of $(C_6H_5)_3P$ in 15 mL of CH_2Cl_2 is added. The reaction mixture is kept at 25 °C for 3 h and then concentrated at the water pump. The oily residue is taken up with 1:1 Et_2O–petroleum ether (30–40 °C) (ca. 80 mL) and left at 0 °C overnight. The precipitate is filtered and washed with ether, and the residue obtained upon evaporation of the solvent is chromatographed on a column with 150 g of SiO_2, eluting benzaldehyde and (4*R*)-4-(benzyloxy)pentan-2-one (**15**) with inceasing amounts of ethyl acetate in hexane: 2.8 g (78%); $[\alpha]^{20}_D$ −20.3° (*c* 1, EtOH), purified by bulb-to-bulb distillation (oven temperature, 150 °C (20 mmHg)); ^1H NMR ($CDCl_3$) δ 7.3 (5 H, Ph), 4.5 (2 H, 2 d, CH_2Ph), 4.2–3.8 (1 H, m, H-4), 2.9–2.2 (2 H, o, H-3), 2.1 (3 H, s, $COCH_3$), 1.19 (3 H, d, $CHCH_3$).

(2*R*,3*S*)-2-Hydroxy-3,4-dimethyl-5-phenylpent-4-ene (9) and (2*R*,5*R*)-2-Hydroxy-4-methyl-5-phenylhexane (12). A solution of 8.7 g (0.05 mol) of epoxide **5** is added dropwise under N_2 to 100 mL of 1 M Me_2CuLi (prepared from solid CuI (Fluka) in ether and 1.6 M MeLi (Fluka) at 0 °C for 45 min) with stirring at −30 °C, using ether as the solvent. After 3 h the temperature is raised to 0 °C and the reaction mixture is so kept overnight. Thereafter, 20 mL of a saturated solution of NH_4Cl is added, and the organic phase is separated, washed with water (2 × 50 mL), dried, and taken to dryness. The residue is chromatographed in a column with 200 g of SiO_2, obtaining with increasing amounts of ethyl acetate in hexane oily **9**: 2.14 g (22%); $[\alpha]^{20}_D$ −13.6° (*c* 1, EtOH); ^1H NMR ($CDCl_3$) δ 7.3 (5 H, Ph), 6.45 (1 H, s, H-5), 3.75 (1 H, m, H-2), 2.25 (1 H, m, H-3), 1.85 (3 H, s, 4-CH_3), 1.55 (1 H, s, OH), 1.5–1 (6 H, 2 d, 2 $CHCH_3$). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.01; H, 9.46. Subsequently eluted in oily **12**: 6.5 g (68%); $[\alpha]^{20}_D$ +47.5° (*c* 1, EtOH); ^1H NMR ($CDCl_3$) δ 7.35 (5 H, s, Ph), 4.5 (2 H, 2 d, CH_2Ph), 3.75 (1 H, m, H-2), 2.75 (1 H, m, H-3), 2.15 (3 H, s, $COCH_3$), 1.25–0.95 (6 H, 2 d, 2 $CHCH_3$); 94% pure by GLC.

(3*S*)-3-Phenylbutan-2-one (14) and (*R*)-*O*-Benzyllactaldehyde (17). The alcohol **12** is converted, according to the procedure reported above, into the *O*-benzyl derivative **13**, oil (90%), $[\alpha]^{20}_D$ +48° (*c* 1, EtOH), ozonized, in turn, as indicated above, to afford, after SiO_2 column chromatographic separation, (3*S*)-3-phenylbutan-2-one (**14**) (78%), $[\alpha]^{20}_D$ +340° (*c* 1, benzene), and (*R*)-*O*-benzyllactaldehyde (**17**) (60%), $[\alpha]^{20}_D$ +60° (*c* 1, $CHCl_3$), once purified by bulb-to-bulb distillation (oven temperature, 100–120 °C (8 mmHg)); ^1H NMR ($CDCl_3$) δ 9.7 (1 H, CHO), 7.35 (5 H, s, Ph), 4.65 (2 H, s, CH_2Ph), 3.9 (1 H, m, H-2), 1.35 (3 H, d, $CHCH_3$).

(2*S*,3*R*)-2-(Benzyloxy)-3-hydroxy-4-methyl-5-phenylpent-4-ene (3). To a stirred solution of 19.2 g (0.1 mol) of **1** in 200 mL of CH_2Cl_2 and 50 mL of dry pyridine is added dropwise at 0 °C 14 g (0.1 mol) of benzoyl chloride in 50 mL of CH_2Cl_2. After 16 h the reaction mixture is washed with cold 1 N HCl (3 × 100 mL), water, and, finally, 3% $NaHCO_3$ (50 mL). The residue obtained upon evaporation of the solvent is chromatographed on a column with 250 g of SiO_2, eluting with increasing amonts of ethyl acetate in hexane the 2-*O*-benzoate **3**: 22.2 g (75%); $[\alpha]2^0_D$ +86.7° (*c* 1, EtOH); ^1H NMR ($CDCl_3$) δ 8.1–7.1 (10 H, 2 Ph), 6.6 (1 H, s, H-5), 5.35 (1 H, m, H-2), 4.35 (1 H, d, H-3), 2.45 (1 H, s, OH), 1.9 (3 H, s, 4-CH_3), 1.4 (3 H, d, $CHCH_3$).

(2*S*,3*S*)-2,3-Epoxy-4-methyl-5-phenylpent-4-ene (6). To a solution of the monobenzoate **3** (22 g, 0.074 mol) in 250 mL of dry pyridine is added at −10 °C 70 g (0.37 mol) of 4-toluenesulfonyl chloride. The reaction mixture is kept at room temperature for 5 days and then poured into ice–water. The mixture is extracted with CH_2Cl_2 (3 × 150 mL), and the organic phase is washed with cold 3% HCl (2 × 50 mL), water, and 3% $NaHCO_3$ (2 × 50 mL). The solvent is evaporated to leave product **4**: 26 g (80%) of a thick oil, which decomposes on standing; ^1H NMR ($CDCl_3$) δ 8.2–7.2 (14 H, 3 Ph), 6.7 (1 H, s, H-5), 5.45 (1 H, m, H-2), 4.65 (1 H, d, H-3), 2.3 (3 H, s, $C_6H_4CH_3$), 1.9 (3 H, s, 4-CH_3), 1.55 (3 H, d, $CHCH_3$). A solution of 26 g (0.055 mol) of the latter material in 150 mL of ethylene glycol and 50 mL of water is treated at 0 °C with 100 mL of 2.5 N NaOH. After 10 min, the reaction mixture is slowly heated up to 40 °C for 3 h. The cooled reaction mixture is extracted with 1:1 hexane–Et_2O (3 × 100 mL) and the organic phase is washed with water (2 × 100 mL). The residue obtained upon evaporation of the solvent is chromatographed on SiO_2 to give product **6**: 5.3 g (55%); $[\alpha]^{20}_D$ −126° (*c* 1, EtOH).

(+)-2-Methoxy-2-(trifluoromethyl)-2-phenylacetic Acid Esters of (*R*)- and (*S*)-2-Hydroxy-4-methyl-5-phenylpent-4-ene. The epoxide **6** on $LiAlH_4$ reduction afforded (2*S*)-2-hydroxy-4-methyl-5-phenylpent-4-ene, $[\alpha]^{20}_D$ −2.9° (*c* 1, EtOH), in a way similar to that followed in the conversion of **5** to **7**. The two enantiomeric alcohols are converted to the (+)-MTPA esters, purified by SiO_2 column chromatography. The ester of the *S* enantiomer showed the following: ^1H NMR ($CDCl_3$) δ 7.6–7.1 (10 H, 2 Ph), 6.25 (1 H, s, H-5), 5.45 (1 H, m, H-2), 3.55 (3 H, s, OCH_3), 2.45 (2 H, t, H-3), 1.85 (3 H, s, 4-CH_3), 1.4 (3 H, d, $CHCH_3$); the ester from the *R* enantiomer, δ 7.6–7.1, 6.35, 5,45, 3.55, 2.5, 1.95, 1.35.

(*R*)-2-(Benzyloxy)propanol (18) and Its *S* Enantiomer. A sample of **13** is ozonized in MeOH at −70 °C and the crude reaction mixture is reduced with excess $NaBH_4$ to give product **18** after dilution with water, extraction with ether, and vacuum distillation of the residue obtained upon evaporation of the solvent: $[\alpha]^{20}_D$ −47 °C (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.35 (5 H, Ph), 4.55 (2 H, 2 d, CH_2Ph), 3.8–3.4 (3 H, m, CH_2OH + CHO), 1.2 (3 H, d, $CHCH_3$). The same material obtained from the epoxide **6**

showed $[\alpha]^{20}_D$ +43°. The two alcohols were converted into the esters with (+)-MTPA. In the derivative from the *R* alcohol, the CH_3CH doublet adsorbs at δ, 1.21 whereas in the derivative obtained from the *S* enantiomer it adsorbs at δ 1.19.

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Registry No. 1, 87900-45-6; 2, 87841-57-4; 3, 87841-58-5; 4, 87841-59-6; 5, 87841-60-9; 6, 87841-61-0; (*R*)-7, 87900-46-7; (*S*)-7, 87900-47-8; (*S*)-7 (+)-MTPA ester, 87841-72-3; 8, 87841-62-1; 9, 87841-63-2; 10, 87841-64-3; 11, 87841-65-4; 12, 87841-66-5; 13, 87841-67-6; 14, 23406-52-2; 15, 87841-68-7; 16, 87841-69-8; 17, 81445-45-6; (*R*)-18, 87037-69-2; (*S*)-18, 33106-64-8; (*R*)-18 (+)-MTPA ester, 87841-70-1; (*S*)-18 (+)-MTPA ester, 87841-71-2; (+)-2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid, 20445-31-2.

Reaction of Substituted *N*-Methylbenzimidoyl Chlorides with Pyrrole-2-acetate Esters

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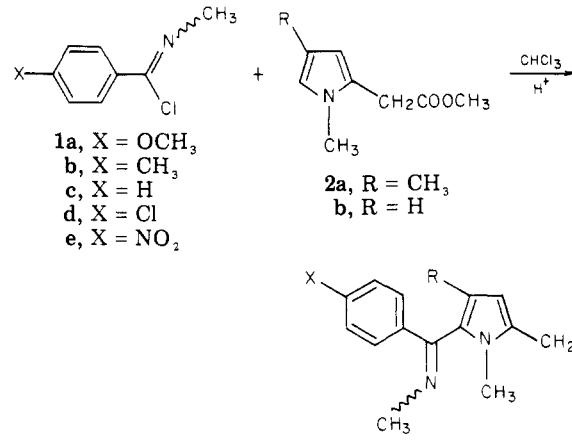
This paper expands the scope of the Vilsmeier–Haack reaction. Stable ketimines are isolated from the reaction of benzimidoyl chlorides with pyrrole derivatives.

The classical Vilsmeier–Haack reaction is the formylation of electron-rich aromatic or heterocyclic compounds or compounds containing activated double bonds, using disubstituted formamides activated by phosphoryl chloride.[1] The term "Vilsmeier reagent" is now often used to denote an amide derivative activated by any one of a number of inorganic or organic acid halides.[2] Depending upon the structure of the Vilsmeier reagent, the products isolated are usually ketones or aldehydes. An exception to this generalization is the Bischler–Napieralski reaction.[3]

Results

The scope of the Vilsmeier–Haack reaction has been extended with the discovery that isolable ketimines are produced in the acid-catalyzed condensation[5] of *N*-methylbenzimidoyl chlorides, **1a–e**, with pyrroleacetates, as shown in Scheme I and Table I. In the absence of added acid catalysts,[6] little or no condensation was observed even at reflux in toluene.

Scheme I



1a, X = OCH_3
b, X = CH_3
c, X = H
d, X = Cl
e, X = NO_2

2a, R = CH_3
b, R = H

3a, X = OCH_3, R = CH_3
b, X = CH_3; R = CH_3
c, X = H; R = CH_3
d, X = Cl; R = CH_3
e, X = NO_2; R = CH_3
f, X = CH_3; R = H

Table I. Summary of Yield and Physical Constant Data[c]

compd	mp (bp, mmHg), °C	% yield isolated	% yield (GLC)[a]
1a	(75-80, 0.1)	76	
1b	(57, 0.1)	80	
1c	(80-90, 0.1)	91	
1d	(125, 15)	83	
1e	67-73	98	
3a	123-129 dec[b]	64	(82.4)
3b	119-124 dec[b]	61	(82.4)
3c	145-147 dec[b]	61	(87.1)
3d	168-171 dec[b]	69	(86.0)
3e	108 dec[b]	65	(92.8)
3f	138-143 dec[b]	30	(39)

[a] GLC yields (using dodecane as internal standard) are not corrected for recovered pyrrole. In all cases, the yield is essentially quantitative when corrected for recovered pyrrole. [b] Isolated as a perchlorate salt. [c] Satisfactory analyses (±0.2% for C, H, N, and Cl) were reported for compounds **3a–f**.

Kinetic data generated to date indicate that unlike the Vilsmeier–Haack reaction of *N*,*N*-disubstituted benzamides,[7] this reaction is not first order in pyrrole, acid halide, or acid. However, the relative order of reactivity of imidoyl chlorides **1a–e** with **2a** is the same as that reported in the Vilsmeier–Haack aroylation of pyrroles. In both reactions, electron-withdrawing groups on the phenyl ring increase the rate of the condensation, while electron-donating groups decrease the rate relative to the unsubstituted case. The half-life values for the reactions of imidoyl halides **1a–d** with pyrrole **2a** when [1] = [**2a**] = 0.17 M and the initial [chlorosulfuric acid] = 1.7×10^{-2} M at 22 °C in chloroform were found to be 20, 13, 8.5, and 6.25 h, respectively. Under the above conditions, the reaction of **1e** with **2a** never proceeded to the point where half of the pyrrole was consumed but stopped at about 38% conversion to products. When [**1e**] = 1.5 M and [**2a**] = 0.35 M, the reaction half-life was 1.38 h.

Irreversibility of product formation was demonstrated by crossover experiments. In the first experiment, pure ketimine **3b** (as its hydrochloride salt) was treated with

(1) A. Vilsmeier and A. Haack, *Chem. Ber.*, **60**, 119 (1927).
(2) For a review of the Vilsmeier–Haack reaction, see: S. Seshadri, *J. Sci. Ind. Res.*, **32**(3), 128 (1973).
(3) The Bischler–Napieralski reaction is an intramolecular Vilsmeier–Haack reaction that leads to dihydroisoquinoline derivatives. Recent modifications of this reaction have used trifluoroacetic anhydride or trifluoromethanesulfonyl anhydride[4a] as activating reagents. Isolated and purified *N*-(2-phenethyl)benzimidoyl chlorides have been shown to cyclize in the presence of Lewis acids.[4b]
(4) (a) S. Nagubandi and G. Fodor, *Heterocycles*, **15**, 165 (1981); (b) S. Nagubandi and G. Fodor, *J. Heterocycl. Chem.*, **17**, 1457 (1980).
(5) The ketimines prepared in this study were surprisingly stable to both acid and base hydrolysis. In most cases, the ketimine may be hydrolyzed to the corresponding ketone in aqueous methanol containing an eightfold excess of sodium acetate in 60–65% yield. Alternatively, the ketimine may be alkylated with dimethyl sulfate and then hydrolyzed with aqueous methanolic sodium bicarbonate in about 75% yield.
(6) Suitable acid catalysts are protic acids, e.g., chlorosulfuric acid and hydrochloric acid. Some imidoyl halides condense with pyrroleacetates in the presence of diethylaluminum chloride. The effect of other Lewis acids has not been studied in detail. For convenience, all work reported in this paper was done with use of chlorosulfuric acid as the catalyst.
(7) (a) J. White and G. McGillivray, *J. Chem. Soc., Perkin Trans. 2*, 259 (1982); (b) *ibid.*, 943 (1979); (c) J. White and G. McGillivray, *J. Org. Chem.*, **42**, 4248 (1977).

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