residue was passed through a Florisil (60–200 mesh) column using 20% ether–hexane as eluent to remove Pd-containing compounds, if any. The product obtained after evaporation of the solvents was purified by chromatography on a silica gel column (60–200 mesh) using 2% ether–hexane as eluent. Concentration under reduced pressure afforded 0.63 g (3.45 mmol, 69% yield) of the title compound: IR (neat) 2230 (s), 1651 (m), 1207 (m) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.8–1.0 (distorted t, 3 H), 1.1–1.5 (m, 6 H), 1.6 (s, 3 H), 1.8–2.1 (m, 2 H), 2.5–2.9 (m, 2 H), 3.50 (s, 3 H), 3.58 (s, 3 H), 4.2–4.5 (m, 1 H), 4.55–4.85 (m, 1 H), 5.0–5.25 (t, J = 7 Hz, 1 H), 5.85 (d, J = 6 Hz, 1 H, for the 1*Z*,4*E* isomer), 6.32 (d, J = 12.5 Hz, 1 H, for the 1*E*,4*E* isomer); MS (CI), m/e 182 ($M^{+\cdot}$). Anal. Calcd for $C_{12}H_{22}O$: C, 79.05; H, 12.17. Found: C, 78.78; H, 12.34. The ratio of the *E* and *Z* isomers calculated by the ratio of the areas of the doublets at 6.32 and 5.85 ppm was 67:33. The GLC yield of this compound estimated against *n*-hexadecane as an internal standard was 92%.

(*E*)-5-Methyl-4-decenal. This compound was prepared in 85% yield by treating (4*E*)-5-methyl-1-methoxy-1,4-decadiene with dilute HCl in acetone–H_2O (4:1) for 4 h at refluxing temperature: IR (neat) 2718 (m), 1725 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 (t, 3 H), 1.1–1.5 (m, 6 H), 1.60 (s, 3 H), 1.7–2.1 (m, 2 H), 2.1–2.5 (m, 4 H), 5.0–5.3 (m, 1 H), 9.72 (s, 1 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.00, 14.91, 19.89, 21.55, 26.59, 30.51, 38.63, 43.02, 120.82, 136.29, 201.54.

1-Methoxy-3-phenylpropene. To 1.67 mL (5 mmol) of phenylmagnesium bromide (3 M in diethyl ether) was added a solution of zinc chloride (0.68 g, 5 mmol) in 10 mL of THF at 0 °C. The mixture was stirred at room temperature for 0.5 h and then added to a mixture of acrolein dimethyl acetal (0.51 g, 0.6 mL, 5 mmol) and $Pd(PPh_3)_4$ (0.28 g, 0.25 mmol) in 10 mL of THF. The reaction mixture was worked up in a manner similar to that described above and purified by chromatography on a silica gel column (60–200 mesh) using 0.5% ether–hexane as the eluent. Concentration provided 0.52 g (3.5 mmol, 70% yield) of the title compound: IR (neat) 1651 (s), 1598 (w), 1210 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 3.2 (d, J = 9 Hz, 2 H), 3.42 (s, 3 H), 3.52 (s, 3 H), 4.4–4.6 (m, 1 H), 4.7–5.0 (m, 1 H), 5.8–5.9 (d, J = 6 Hz, 1 H, for the *Z* isomer), 6.35 (d, J = 12.5 Hz, 1 H, for the *Z* isomer), 7.0–7.3 (br s, 5 H); MS (CI), m/e 148 ($M^{+\cdot}$). The ratio of the *E* and *Z* isomers determined by the areas of the doublets for the corresponding 1-alkenyl protons was 71:29. The major resonances observed in the ^{13}C NMR ($CDCl_3$, Me_4Si) were at δ 34.07, 55.76, 101.91, 125.72, 125.97, 128.32 (2), and 148.18. Minor resonances were observed at δ 30.21, 59.43; 105.58, 141.71, and 146.67.

1-Methoxy-3-phenyl-1-hexene. This compound was prepared in 44% isolated yield by the reaction of phenylzinc chloride with the dimethyl acetal of (*E*)-2-hexenal in the presence of 5 mol % of $Pd(PPh_3)_4$ in a manner analogous to that described for the preparation of 1-methoxy-3-phenylpropene: IR (neat) 1648 (s), 1601 (w), 1204 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.75–1.1 (distorted t, 3 H), 1.0–1.85 (m, 4 H), 3.0–3.3 (m, 1 H), 3.42 (s, 3 H), 3.49 (s, 3 H), 4.4–4.6 (m, 1 H), 4.75–5.0 (m, 1 H), 5.88 (d, J = 6 Hz, 1 H, for the *Z* isomer), 6.32 (d, J = 12.5 Hz, 1 H, for the *E* isomer), 7.1–7.4 (m, 5 H); MS (CI), m/e 190 ($M^{+\cdot}$). Ratio of the *E* and *Z* isomers determined by the ratio of the areas of the doublets at 6.32 and 5.88 ppm was 76:24.

Ethyl 3-Phenylpropanoate. To 3.3 mL (10 mmol) of phenylmagnesium bromide (3 M in diethyl ether) was added a solution of zinc chloride (1.36 g, 10 mmol) in 30 mL of THF at 0 °C. The mixture was stirred at room temperature for 0.5 h and then added to a mixture of ethyl orthoacrylate (2.6 g, 15 mmol) and $Pd(PPh_3)_4$ (0.57 g, 0.5 mmol) in 30 mL of THF. To this was added HMPA (2.68 g, 2.6 mL, 15 mmol), and the reaction mixture was stirred at room temperature for 12 h and poured onto ice-cold 3 N HCl. The aqueous layer was extracted with ether. The combined organic layers were washed successively with aqueous $NaHCO_3$ and water, dried over $MgSO_4$, concentrated, and then passed through a Florisil (60–200 mesh) column using 30% ether–hexane as eluent. Evaporation of solvents followed by distillation provided 1.32 g (7.4 mmol, 74% yield) of the title compound: bp 130–133 °C (17 mm); IR (neat) 1730 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.16 (t, J = 7 Hz, 3 H), 2.4–2.7 (m, 2 H), 2.75–3.0 (m, 2 H), 4.05 (q, J = 7 Hz, 2 H), 7.05–7.3 (m, 5 H).

Ethyl (*E*)-5-Methyl-4-decenoate. To a solution of zirconocene dichloride (0.12 g, 0.4 mmol) in 8 mL of dry 1,2-dichloroethane was added 1-heptyne (0.19 g, 2 mmol).[13] The mixture was cooled to 0 °C and trimethylalane (0.29 g, 0.38 mL, 4 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature, and then a solution of anhydrous $ZnCl_2$ (0.27 g, 2 mmol) was added to it. The mixture thus obtained was then added to a mixture of ethyl orthoacrylate (0.52 g, 3 mmol), $Pd(PPh_3)_4$ (0.12 g, 0.1 mmol), and HMPA (0.54 g, 0.5 mL, 3 mmol). After being stirred at room temperature for 6 h, the reaction mixture was slowly poured onto a 1:1 mixture of ice-cold aqueous NH_4Cl and 3 N HCl. The mixture was stirred at room temperature for 1 h, and the layers were separated. The aqueous layer was extracted with ether, and the combined organic layers were washed successively with $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated. The product was passed through a Florisil (60–200 mesh) column (60:40 hexane:ether) to remove palladium residues, if any, and the solvents were evaporated. Distillation provided 0.21 g (1 mmol, 50% yield) of the title compound: bp 75–79 °C (0.3 mm); IR (neat) 1728 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.75–1.0 (distorted t, 3 H), 1.1–1.5 (m, 9 H), 1.60 (s, 3 H), 1.7–2.5 (m, 6 H), 3.95–4.25 (q, J = 7 Hz, 2 H), 4.9–5.2 (m, 1 H). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.46; H, 11.52. The GLC yield of the compound estimated against *n*-nonane used as an internal standard was 60%. The GLC trace of the reaction product before purification also showed the formation of another unidentified product, the retention time of which corresponded to the product of disubstitution.

Acknowledgment. We thank the National Institutes of Health for support of this work. We also thank Engelhard Industries and Ethyl Corporation for providing us with valuable chemicals.

Registry No. **4**, 6044-68-4; **5**, 18318-83-7; **6**, 42216-96-6; (1*E*,4*E*)-$CH_3(CH_2)_4C(CH_3)$=$CHCH_2CH$=$CHOMe$, 97614-16-9; (1*Z*,4*E*)-$CH_3(CH_2)_4C(CH_3)$=$CHCH_2CH$=$CHOMe$, 97614-17-0; $(C_5H_5)_2ZrCl_2$, 1291-32-3; $(PPh_3)_4Pd$, 14221-01-3; (*E*)-$CH_3(CH_2)_4C(CH_3)$=$CH(CH_2)_2CHO$, 97614-18-1; (*E*)-$PhCH_2CH$=$CHOMe$, 60053-38-5; (*Z*)-$PhCH_2CH$=$CHOMe$, 60053-39-6; PhZnCl, 28557-00-8; (*E*)-$CH_3(CH_2)_2CH(Ph)CH$=$CHOMe$, 97614-19-2; (*Z*)-$CH_3(CH_2)_2CH(Ph)CH$=$CHOMe$, 97614-20-5; $Ph(CH_2)_2C(U)OEt$, 2021-28-5; (*E*)-$CH_3(CH_2)_4C(CH_3)$=$CH(CH_2)_2C(O)OEt$, 97614-21-6; ethyl orthopropionate, 115-80-0; 1-heptyne, 628-71-7; trimethylalane, 75-24-1.

Mild Hydrogen-Transfer Reductions Using Sodium Hypophosphite

Stephen K. Boyer,* Joseph Bach, Joseph McKenna, and Erick Jagdmann, Jr.

Technical Operations Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, New Jersey 07901

Received July 12, 1984

Phosphinic acid and sodium hypophosphite (NaH_2PO_2) are known to be effective reagents for the transfer hydrogenation of certain functional groups in the presence of an appropriate catalyst. In this way various olefins,[1] alkynes,[2] nitriles,[3] nitroaromatics,[4] and 1,4-benzoquinones[5] have been reduced under relatively mild reaction conditions. However, the reduction of other functional groups such as ketones, aldehydes, azides, epoxides, *N*-oxides, and the hydrogenolysis of halides or of benzylic protecting

(1) Bakulina, G. V.; Erafeev, B. V. *Chem. Abstr.* **1975**, *83*, 1468375; **1975**, *83*, 192490*f*; **1972**, *77*, 101050 m.
(2) Johnstone, R. A. W.; Wilby, A. H. *Tetrahedron* **1981**, *37*, 3667.
(3) Beckeberg, O. G.; Staskun, B. *J. Org. Chem.* **1962**, *27*, 3461.
(4) Entwistle, I. D.; Jackson, A. E.; Johnstone, R. A. W.; Telford, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 443.
(5) Entwistle, I. D.; Johnstone, R. A. W.; Telford, R. P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 117.

0022-3263/85/1950-3408$01.50/0

Chart I. Sodium Hypophosphite Hydrogenation of Isolated Carbonyls, Olefins, *N*-Oxides, Azides, and Epoxides

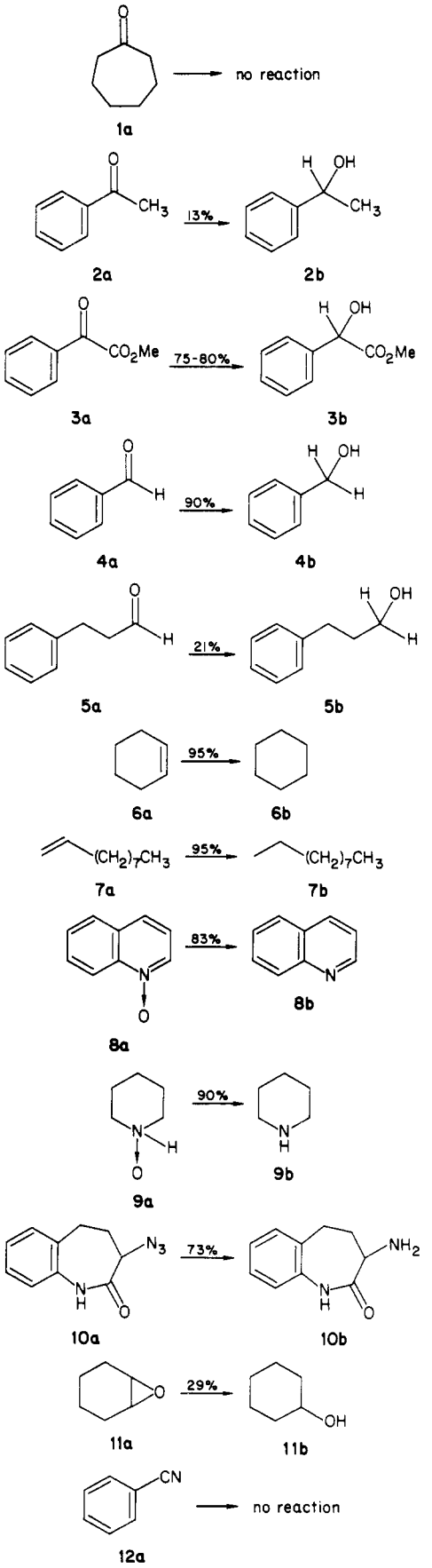
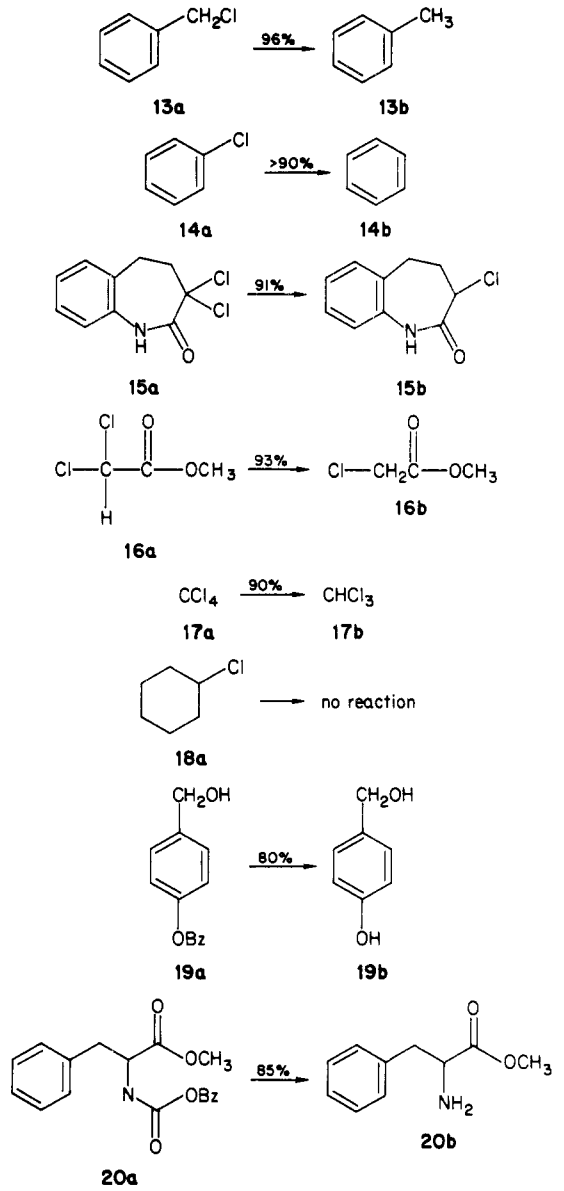


Chart II. Hydrogenolyses with Sodium Hypophosphite



groups have been largely unexplored. In addition, no extensive study has been made of the functional group selectivity of this method. We wish to report the results of our investigation on the scope and limitations of this seldom-used but very practical and useful reducing agent.

We first carried out a systematic examination in which sodium hypophosphite was used to reduce several isolated functional groups in simple model systems, then attempted to examine selectivity in polyfunctional systems. In a typical experiment, 10 mmol of substrate was dissolved in ca. 25 mL of tetrahydrofuran (THF) and treated with sodium carbonate (ca. 1.17 g, 11 mmol), followed by a catalytic amount of palladium on carbon (ca. 200 mg). A solution of sodium hypophosphite monohydrate (ca. 11 mmol) in 4–6 mL of water was added dropwise over 10–15 min to the rapidly stirred mixture, and gas evolution was observed. In some cases, the reaction mixtures were warmed to 50–65 °C. The reaction was monitored by gas chromatography (or HPLC) to determine the extent of reaction, and more sodium carbonate and sodium hypophosphite was introduced when necessary. The solution was then diluted with ether and filtered and the aqueous layer extracted several times with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated in

vacuo to afford crude product, which was purified (as appropriate). In some cases THF could be replaced with any of several other organic solvents or with glacial acetic acid/sodium acetate in order to obtain nearly anhydrous conditions.

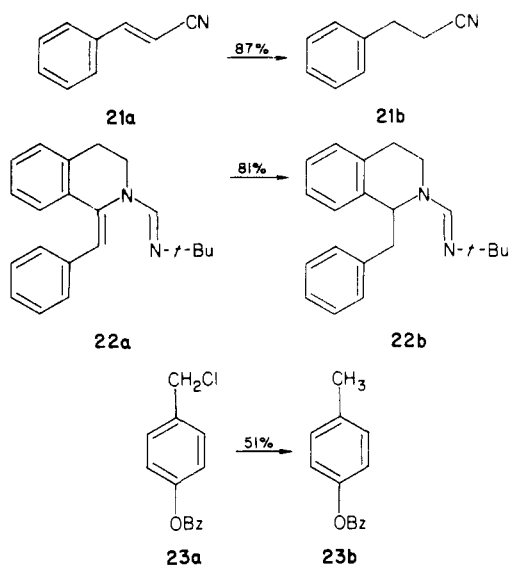
Chart I includes certain isolated functional groups (ketones, aldehydes, olefins, *N*-oxides, azides, epoxides, and nitriles) which were subjected to sodium hypophosphite reduction under standard conditions. Unactivated ketones such as cycloheptanone (**1a**) were completely unreactive even under prolonged reflux (ca. 48 h). Acetophenone (**2b**) reacted slowly, affording only about 13% alcohol after 48 h reflux, and activated keto esters such as **3a** were smoothly reduced in high yield after only a few hours. Benzaldehyde (**4a**) was reduced in 48 h with an excess of sodium hypophosphite at reflux, to yield >90% benzyl alcohol (GC yield, internal standard). However, aliphatic aldehydes like **5a** were reduced very slowly, yielding only ca. 21% of alcohol **5b** after 62 h at 65 °C.

Both cyclic and acyclic alkenes were smoothly reduced to alkanes at room temperature in high yield (cf. **6a** → **6b**; **7a** → **7b**). Aromatic and aliphatic *N*-oxides **8a** and **9a** behaved similarly and afforded **8b** **9b**, respectively. Quinoline *N*-oxide (**8a**) furnished quinoline (**8b**) in nearly 83% yield free of inorganic contaminants, which would ordinarily complicate this deoxygenation when performed with PPh_3. Likewise, morpholine *N*-oxide (**9a**) was converted to morpholine (**9b**). Aliphatic azides such as **10a**[6] could be reduced to amine (**10b**) in fair yields, while epoxides and isolated nitriles appeared to be quite unreactive. Epoxide **11a** afforded only ca. 29% alcohol after 48 h at 65 °C. Nitrile **12** was unreactive.

The results of several hydrogenolysis experiments are summarized in Chart II. Benzylic chlorides such as **13a** as well as aromatic chlorides like **14a** were cleanly reduced to the corresponding hydrocarbons in yields of greater than 90%.[7,8] Selective monohydrogenolysis of polyhalogenated compounds are usually difficult to achieve. However, by carrying out the reactions in acetic acid with sodium acetate, the geminal dichloro lactam[6] **15a**, methyl dichloroacetate (**16a**), and carbon tetrachloride (**17a**) were all smoothly converted to the monodehalogenated products. A 91% isolated yield of **15b** from **15a** was achieved by using sodium acetate/acetic acid to neutralize any HCl released during the course of the reaction. Similarly high yields were obtained in the case of **16a** and **17a**. Due to the volatility of the products, however, yields of **16b** and **17b** had to be determined by GC comparison to internal standards. Unactivated alkyl halides such as chlorocyclohexane (**18**) could not be reduced by this method.[9]

Sodium hypophosphite was quite effective in removing *O*-benzyl ethers. *p*-(Benzyloxy)benzyl alcohol (**19a**) was converted to the debenzylated product **19b** in 81% yield.

Chart III



Nonaromatic benzyloxy groups were also studied. Thus, carbamate **20a** was deprotected to methyl phenylalaninate **20b** in ca. 85% yield.

In some polyfunctional molecules we were able to achieve selective reduction, but for the most part our results seemed to parallel those obtained from catalytic hydrogenation. Chart III lists some of the systems that were investigated.

Cinnamonitrile (**21a**) was selectively reduced to dihydrocinnamonitrile **21b** in 87% isolated yield with sodium hypophosphite and 5% palladium on carbon. Beckeberg and Staskun,[3] however, obtained only cinnamaldehyde from cinnamonitrile in ca. 20% yield using sodium hypophosphite and Raney nickel and observed no concomitant alkene reduction. We have observed little or no reduction of carbon–nitrogen double bonds. Formamidines like **22a**[10] were inert, and most imines and oximes were simply hydrolyzed to carbonyls. Thus **22a** reacted selectively at the carbon–carbon double bond as was the case for catalytic hydrogenation. However, under similar conditions, *p*-Benzoxybenzyl chloride **23a** gave a mixture of *p*-cresol and *p*-benzoxy toluene. Attempts to use only 1 equiv of hypophosphite in order to achieve selectivity was unsuccessful since dechlorinated benzyl ether was isolated in 51% yield.

In conclusion, it is hoped that the above examples of mild hydrogen transfer reductions using sodium hypophosphite will serve as a convenient alternative to conventional methods of hydrogenation. The cost does not appear to be particularly prohibitive, and our results indicate that this is suitable for scale-up, especially in light of the relatively slow release of hydrogen, and the fact that the hydrogen source (the hypophosphite solution) can be easily regulated and that it offers the opportunity to easily follow the reaction by chromatography. We have scaled some of these reactions up to 1000-gal equipment, encountering few problems and without any substantial loss of yields. Further results of our continuing efforts in this area will be reported later.

Experimental Section

The physical data were obtained as follows: melting points in a Thomas-Hoover melting-point apparatus (uncorrected); IR

(6) Prepared according to the general procedure of: Watthey, J. W. H. U. S. Patent 4 410 520.

(7) After this paper was submitted for publication, a report entitled "Reduction of Carbon–Carbon Double Bonds and Hydrogenolysis by Sodium Hypophosphite" was published.[8] These authors reported selective reduction of olefins in the presence of aromatic halides (eg., *p*-chlorocinnamic acid) and they stated that halogens substituted on aromatic nuclei were not affected by this [NaH_2PO_2/Pd–C] system. In our hands, when *p*-chlorocinnamic acid was reduced with excess sodium hypophosphite (>3 equiv) under prolonged conditions (~24 h 50 °C) this too underwent hydrogenolysis to afford hydrocinnamic acid in ~70% isolated yield. Under milder conditions (1 equiv, 1.5 h) only *p*-chlorohydrocinnamic acid and unreacted starting material were observed.

(8) Sala, R.; Doria, G.; Passcerotti, C. *Tetrahedron Lett.* **1984**, *4565*.

(9) It appears that groups which stabilize radicals or anions are necessary to achieve hydrogenolysis. The lack of reactivity of unactivated alkyl halides is consistent with earlier reports, for example: Pandeny, P.; Purkayastha, M. L. *Synthesis* **1982**, 876.

(10) Prepared according to the general procedure of: Meyers, A. I.; Hellring, S.; Tenhowe, W. *Tetrahedron Lett.* **1981**, 5115.

spectra on a Perkin-Elmer 521; mass spectra on an AEI MS 902 by direct insertion; NMR spectra on a Varian A-60 using Me_4Si as an internal standard. The following abbreviations are used: (br) broad, (w) weak, (ex) exchangeable with D_2O, (s) singlet, (t) triplet, (q) quartet, (m) multiplet.

The following procedures are illustrative of the reductions carried out.

DL-**Mandelic Acid Methyl Ester (3b).** To a solution of methyl phenylglyoxalate (**3a**) (1.6 g, 10 mmol) in THF (25 mL) was added potassium carbonate (2 g, 14 mmol) and Pd/C (5%, 50:50 water wet, 300 mg). The stirring mixture was heated to reflux, and a solution of sodium hypophosphite (2 g, 18 mmol) in water (20 mL) was added dropwise. The reaction mixture was stirred overnight, and the next day, a TLC analysis (70:20:10 toluene/CH_2Cl_2/EtOAc) showed the reaction to be complete. The reaction mixture was cooled and filtered and the filtrate diluted with diethyl ether. The organic layer was separated, washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated to yield DL-mandelic acid methyl ester (**3b**) ~1.2 g (~75%), mp 53–54 °C. The product could be recrystallized from cyclohexane to yield material which was identical (IR, NMR, mp) with an authentic reference standard: IR (CH_2Cl_2) 3550 (br), 3080, 1740 (s) cm^{-1}; NMR ($CDCl_3$) δ 7.4 (s, 5, Ar), 4.3 (Ab q, 1, CH), 3.7 (s, 3, OCH_3).

3-Chloro-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one (15b). A mixture of the dichloro lactam **15a**[6] (20 g, 0.087 mol), Pd/C (10%, 1.2 g), sodium acetate (20 g, 0.24 mol), and sodium hypophosphite (9.2 g, 0.244 mol) in glacial acetic acid (200 mL) was heated to 56 °C for 24 h. The reaction mixture was filtered and the filtrate concentrated to a residue; water (200 mL) was added, and this was stirred as the product precipitated out. The product **15b** was filtered, washed with water, and dried in vacuum to yield 15.1 g (~89% 1st crop), mp 164–167 °C.; this material contained ~1.7% lactam which was completely reduced and no detectable starting material: NMR ($CDCl_3$) δ 8.8 (m, 4, Ar), 4.5 (m, 1, CH), 2.8–2.5 (m, 4, aliphatics).

Acknowledgment. We thank Drs. B. Ganem and S. Hanessian for their helpful consultation and encouragement in this work. Also, we would like to acknowledge the help of the members of the Analytical Services Group: Ruth Behnke (NMR), Natalie Cahoon, Mike Hatolski (IR, UV), Magda Brzechffa (MS), and G. Robertson and R. Oeckinghaus (microanalyses).

Registry No. **1a**, 38743-17-8; **2a**, 98-86-2; **2b**, 98-85-1; **3a**, 1603-79-8; **3b**, 4358-88-7; **4a**, 100-52-7; **4b**, 100-51-6; **5a**, 104-53-0; **5b**, 122-97-4; **6a**, 110-83-8; **6b**, 110-82-7; **7a**, 872-05-9; **7b**, 124-18-5; **8a**, 1613-37-2; **8b**, 91-22-5; **9a**, 23162-18-7; **9b**, 110-89-4; **10a**, 86499-24-3; **10b**, 86499-35-6; **11a**, 286-20-4; **11b**, 108-93-0; **12a**, 100-47-0; **13a**, 100-44-7; **13b**, 108-88-3; **14a**, 108-90-7; **14b**, 71-43-2; **15a**, 86499-22-1; **15b**, 86499-23-2; **16a**, 116-54-1; **16b**, 96-34-4; **17a**, 56-23-5; **17b**, 67-66-3; **18a**, 542-18-7; **19a**, 836-43-1; **19b**, 623-05-2; **20a**, 32563-40-9; **20b**, 15028-44-1; **21a**, 4360-47-8; **21b**, 645-59-0; **22a**, 97351-55-8; **22b**, 81763-85-1; **23a**, 836-42-0; **23b**, 834-25-3; sodium hypophosphite, 7681-53-0.

Microbial Reduction of Prochiral 2,2-Disubstituted 1,3-Cycloheptanediones

Dee W. Brooks,*† Hormoz Mazdiyasni, and Peter Sallay

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

Received January 30, 1985

We have pursued a research program directed toward applying the ability of enzymes to make prochiral distinctions as a useful element of synthetic strategy to obtain optically pure intermediates for the total synthesis of natural products. Asymmetric microbial reduction with common bakers' yeast (*Saccharomyces cerevisiae*) of 2,2-disubstituted 1,3-cyclopentane- and 1,3-cyclohexanediones has proved to be a synthetically useful method.[1] We have further examined the scope and generality of yeast-mediated reductions of medium sized (seven-, eight-, and nine-membered) diones and herein report these results.

The 2-methyl 1,3-diones **3**, **6**, and **9** were prepared by applying the method reported for **3**, by Okamura,[2] as outlined in Scheme I.

Treatment of the 2-methyl diones **3**, **6**, and **9** with 1 N NaOH (1 equiv) followed by 3-bromopropene (10 equiv) at 25 °C for 64 h gave the allyl diones **15** (60%), **30** (50%), and **35** (50%). Reaction of **3** with 3-chloropropyne (5 equiv) and triethylamine (10 equiv) at reflux for 24 h gave **20** (65%). Similar treatment of **3** with 3-chloro-2-methylpropene gave **25** (75%). Hydrogenation of **15** with PtO_2 catalyst at 1 atm in ethanol for 2 h at 25 °C gave **10** (98%).

The diones **10**, **15**, **20**, **25**, **30**, and **35** were subjected to microbial reduction with bakers' yeast and the results are summarized in Table I. The enantiomeric composition of the chiral ketols produced by yeast reduction was determined by analysis and comparison of the ^1H NMR (470 MHz) of the corresponding (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters[3] with those derived from the racemic ketols prepared by reduction with $NaBH_4$ (1 equiv, 0.1 M in ethanol, 0 °C, 3 h). In each case the singlets of the 2-methyl group and the methine proton α to the MTPA derivatized hydroxyl group were clearly resolved. In all cases the ketols generated by yeast reduction were found to have >98% enantiomeric excess.[4] The assignment of structure and absolute configuration for the chiral cycloheptanoids was established by comparison of the ^1H NMR spectra of the propyl (+)-MTPA esters **11** and **13** of known absolute configuration which were peviously reported[1c] with the same propyl (+)-MTPA esters derived from catalytic hydrogenation of the (+)-MTPA esters of **16**, **21**, and **23** obtained by yeast reduction. The structure of the microbial ketol products derived from diones **25** and **30** were not proven but assigned on the basis of comparison of their spectral data with those of the analogous (+)-MTPA esters of the correlated products.

The medium-size rings are not as efficiently reduced by bakers' yeast as the five- or six-membered diones.[1] Substrates **20** and **25** provide synthetically useful conversions to novel chiral functionalized cycloheptanoids. In each case the ketols derived by yeast reduction were >98% enantiomerically pure regardless of the conversion efficiency. Attempts to optimize the fermentation conditions to provide better conversions were not carried out.

The completely opposite stereoselectivity in the yeast reduction of the propyl dione **10** (entry 1) vs. the allyl dione **15** (entry 3) and the lack of stereoselectivity for the methylallyl dione **25** (entry 7) is very interesting. The stereoselectivity of the yeast reduction closely parallels that of the $NaBH_4$ reduction of these substrates.[6] Microbial

†Current address: Department 47K AP10, Abbott Laboratories, Abbott Park, IL 60064.

(1) (a) Brooks, D. W.; Grothaus, P. G.; Irwin, W. L. *J. Org. Chem.* **1982**, *47*, 2820. (b) Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, H. *J. Am. Chem. Soc.* **1983**, *105*, 4472. (c) Brooks, D. W.; Mazdiyasni, H.; Chakrabarti, S. *Tetrahedron Lett.* **1984**, 1241.

(2) Lewicka-Piekut, S.; Okamura, W. H. *Synth. Commun.* **1980**, *10*, 415.

(3) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(4) A control experiment established a practical limit of detection of 1.5% of a MTPA diastereomer in a mixture by ^1H NMR at 470 MHz.

(5) The use of MTPA derivatives for assignment of absolute configurations has been reported, see: (a) Dale, J. A.; Mosher, A. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.

0022-3263/85/1950-3411$01.50/0