Substrate Modification as a Means of Enhancing the Enantioselectivity of Microbial Reductions of β-Keto Esters. An (*R*)- or (*S*)-1,3,5-Trihydroxypentane Synthon

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The enantioselectivity of yeast-mediated reduction of 5-(benzyloxy)-3-oxopentanoate esters can be optimized by simple selection of a suitable ester alkoxy group. The resulting chiral 5-(benzyloxy)-3-hydroxypentanoates with >95% ee can serve as either an (*R*)- or (*S*)-1,3,5-trihydroxypentane synthon for asymmetric syntheses. The synthesis of a key optically active intermediate for (*S*)-(−)-lipoic acid is provided as an example.

The discovery and development of enzyme-catalyzed processes to accomplish asymmetric syntheses of optically pure synthetic intermediates is an alternative complementary strategy to methods involving resolution of racemates, chiral pool templates, and asymmetric synthetic reagents.[1] Asymmetric microbial reduction of the carbonyl group by common bakers' yeast (*Saccharomyces cerevisiae*) has gained widespread popularity as a method to obtain optically active secondary hydroxy compounds.[2] β-Keto esters appear to be a rather general substrate for yeast-mediated reduction; however, the yield and optical purity of the 3-hydroxy ester products are often variable.[3] This can be a result of competing enzymes present in the microorganism, generating products of opposite configuration at different rates or a single oxidoreductase acting with poor enantioselectivity for that substrate.[4] Another general disadvantage of enzymatic transformations, from a synthetic viewpoint, is that the enantioselective outcome of the reaction (*R* or *S*) cannot be readily controlled, as the corresponding antipodal enzyme is not available. A typical procedure in developing applications of microbial systems in synthesis is to screen numerous organisms to identify those that might effect a desired transformation with respect to yield and enantioselectivity.[5] This approach might not have broad appeal in a synthetic laboratory. Yeast-mediated reductions would be generally more useful to synthetic chemists if there were simple "chemical" means to optimize and control the stereochemical outcome.

Our approach has been to study applications of bakers' yeast since it is readily available, easily manipulated, and contains a variety of enzymes capable of reducing carbonyl-containing substrates. Chemical modification of the substrate can be the major variable used to optimize the yield and optical purity of the product(s) of yeast-mediated reduction. Enantioselective control can be accomplished by designing the substrate such that the enantiomer produced can be readily converted synthetically to the other enantiomer.

During our investigation two significant reports on a similar theme have been reported. Hirama and co-workers[6] studied 6-alkoxy-3-oxohexanoates and found that yeast-mediated reduction of the potassium carboxylate salt provided complete enantioselectivity. Sih and co-workers[7] discovered a reversal of enantioselectivity from *S* (ee = 0.65) to *R* (ee = 0.97) in yeast-mediated reduction of 4-chloro-3-oxopentanoates which was controlled by the size of a homologous series of C1 to C12 *n*-alkyl esters. They also provided evidence for the existence of at least two active oxidoreductases in yeast for the 4-chloro-3-oxopentanoate substrates.

We have previously reported the ability of bakers' yeast to distinguish differences in the ester groups of prochiral 3-oxoglutarate and 3-oxoadipate esters providing the corresponding 3-hydroxy esters with optical purities ranging from 0 to 80% depending on the respective ester groups present in the substrate.[8] A logical extension of this preliminary work was to study yeast-mediated reduction of 5-alkoxy-3-oxopentanoate esters **2a–k** where the choice of ester group and/or the 5-alkoxy group might be used to "fine tune" the enantioselectivity of the microbial reduction of the carbonyl group to provide an optically pure 5-alkoxy-3-hydroxypentanoate ester.

A series of such substrates were examined, and the results of this study clearly demonstrate the ability to optimize the optical purity of products resulting from yeast-mediated reductions of β-keto esters by simple modification of the ester group employed. Furthermore, the optically active 5-alkoxy-3-oxypentanoate ester can serve as a useful intermediate in asymmetric syntheses of natural products as either an (*R*)- or (*S*)-1,3,5-trihydroxypentane synthon, as will be briefly illustrated.

Results and Discussion

Yeast-Mediated Reduction of 5-(Benzyloxy)-3-oxo-

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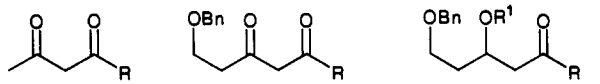
Table I. Yeast Reduction of 5-Alkoxy-3-oxopentanoates

entry	substrate	R	product, % yield[a]	enantiomeric composition	predominate configuration
1	**2a**	OCH_3	**3a**, 65	**4a** 65:35	–
2	**2b**	OCH_2CH_3	**3b**, 60	**4b** 78:22	–
3	**2c**	$OCH(CH_3)_2$	**3c**, 40	**4c** 67:33	–
4	**2d**	$OCH_2CH_2CH_2CH_3$	**3d**, 55	**4d** 85:15	*S*
5	**2e**	$SCH_2CH_2CH_2CH_3$	**3e**, 40	**4e** 84:16	–
6	**2f**	$OCH_2CH(CH_3)_2$	**3f**, 70	**4f** 95:05	*S*
7	**2g**	$SCH_2CH(CH_3)_2$	**3g**, 30	**4g** 87:13	–
8	**2h**	$OCH_2(CH_2)_3CH_3$	**3h**, 40	**4h** 96:04	*S*
9	**2i**	$OCH_2CH_2CH(CH_3)_2$	**3i**, 35	**4i** 77:23	*S*
10	**2j**	$OCH_2C(CH_3)_3$	**3j**, 35	**4j** 98:02	*S*
11	**2k**	$OCH_2(CH_2)_4CH_3$	**3k**, 10	**4k** 98:02	*S*
12	**2l**	$OCH_2(CH_2)_6CH_3$	**3l**, 0		
13	**2m**	O^-K^+	**3m**, 10		

[a] Yield is reported as percent of product isolated *not* substracting recovered starting material, which was the balance of mass in most cases. The conditions of the yeast-mediated reductions were performed simply as described in the Experimental Section, and attempts to optimize various parameters such as temperature, pH, and added nutrients to improve substrate conversion to product were not examined.

pentanoate Esters. A series of 5-(benzyloxy)-3-oxopentanoate esters **2a–k** were prepared by alkylation of the



1a–k **2a–k** **3a–k**, R^1 = H; **4a–k**, R^1 = (–)-MTPA; **5a–k**, R^1 = TBDPSi

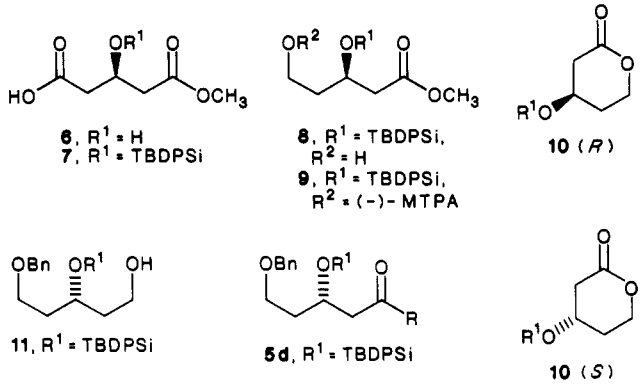
dianion of the corresponding 3-oxobutanoate esters **1a–k**[9] with benzyl chloromethyl ether. Incubation of these substrates with bakers' yeast at 30 °C for 16 h followed by extraction with dichloromethane and purification by chromatography on silica gel provided the corresponding 5-(benzyloxy)-3-hydroxypentanoate esters **3a–k**.

Reduction of the same substrates **2a–k** with $NaBH_4$ provided the corresponding racemic hydroxy esters **3a–k** as standards. The 3-hydroxy esters **3a–k** from the yeast and $NaBH_4$ reductions were converted to the respective (–)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA)[10] derivatives **4a–k**, and the enantiomeric excess was analyzed by ^1H and ^{19}F NMR spectroscopy.[11] The results of the stereoselective outcome of the yeast-mediated reductions are summarized in Table I.

Determination of Absolute Configuration. The absolute configuration of the microbial products **3a–k** was determined as follows. As a correlation standard, 3(*R*)-((*tert*-butyldiphenylsilyl)oxy)valerolactone (**10**) was prepared as follows. Chymotrypsin-catalyzed hydrolysis of dimethyl 3-hydroxyglutarate[12] and subsequent silyl ether protection provided **7** with known *R* configuration. Reduction of **7** with borane–THF followed by aqueous base and then acid treatment provided the reference (*R*)-lactone **10R**, $[\alpha]_D$ +9.2° (*c* 7.69, $CHCl_3$). The enantiomeric purity of this standard was evaluated by conversion of the hydroxy intermediate **8** to the corresponding (+)-MTPA ester. The ^1H NMR at 470 MHz clearly resolved the methyl ester signals at 3.52 and 3.51 (9:1), respectively, which translates to an enantiomeric excess of 80% of the *R* configuration.[13]

Synthesis of the corresponding lactone from the yeast product **3d** was accomplished by silylation to provide **5d**, which upon treatment with *N*-bromosuccinimide in refluxing tetrachloromethane under a sunlamp followed by quenching in water and extraction with dichloromethane gave benzaldehyde and 3-((*tert*-butyldiphenylsilyl)oxy)-valerolactone (**10S**), $[\alpha]_D$ –10.2° (*c* 2.32, $CHCl_3$). The major enantiomer of the yeast product **3d** was thus established as having the *S* configuration.

The correlated yeast product **5d** was reduced with $LiBH_4$ to provide a common chiral intermediate, **11**, which was



6, R^1 = H; **7**, R^1 = TBDPSi; **8**, R^1 = TBDPSi, R^2 = H; **9**, R^1 = TBDPSi, R^2 = (–)-MTPA; **10** (*R*)

11, R^1 = TBDPSi; **5d**, R^1 = TBDPSi; **10** (*S*)

used to correlate the other silylated yeast products in a similar fashion. The major enantiomer produced by the microbial reduction was consistently of the *S* configuration for the examples studied. No reversal of enantioselectivity was observed in this series, in contrast to that observed for 4-chloro-3-oxopentanoates by Sih and co-workers.[7] To investigate the possible involvement of two oxidoreductases of opposite enantioselectivity, we evaluated the effect of substrate concentration on the stereochemical outcome of the yeast reduction of **2f** at four concentrations: 0.056 M, 0.028 M (the standard concentration used for the results listed in Table I), 0.007 M, and 0.0018 M. Over this range of concentration the enantiomeric composition of the (–)-MTPA derivatized reduction product **4f** remained constant at 95% *S*: 5% *R* (±2%). In another experiment the potassium carboxylate salt **2m** was reduced by bakers'

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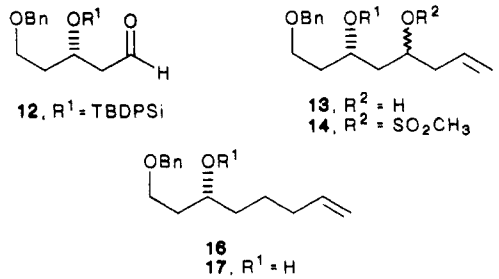
yeast with less than 10% conversion to the corresponding hydroxyacid **3m** over a 24-h period.

Control of Enantioselectivity of Yeast Reduction of β-Keto Esters by Changing the Ester Group. The enantioselectivity of yeast-mediated reduction of 5-(benzyloxy)-3-oxopentanoate esters was influenced by small changes in the ester alkoxy group. The trends that can be discerned from these results are that enantioselectivity increases with increasing chain length for *n*-alkyl esters. However, the amount of conversion of substrate to product, under the standard fermentation conditions, decreased with increasing length of the *n*-alkyl chain as shown for methyl, ethyl, butyl, hexyl, and octyl esters (entries 1, 2, 4, 8, 11, and 12). For branched hydrocarbon groups, the trend is less clear, but there seems to be an optimum enantioselectivity with one methylene group spacer before branching; compare *tert*-butyl with neopentyl (entries 3 and 10) and isoamyl with isobutyl (entries 9 and 6). A change of the electronic environment with thiol esters as in *n*-BuS **2e** and *i*-BuS **2g** had little effect. The isobutyl ester **2f** (entry 6) provided good conversion to product and synthetically useful enantiomeric excess.

This study demonstrates the utility of adjusting substrate substituents in a systematic manner in order to obtain improved enantiomeric excess in the products derived from yeast-mediated reductions of β-keto esters. For example, using this approach, we were able to increase the enantiomeric composition of yeast-mediated reduction products from 65% *S*:35% *R* for the methyl ester (entry 1) to greater than 98% *S*:2% *R* for the neopentyl ester (entry 10).

A Useful Chiral 1,3,5-Trihydroxypentane Synthon. A chiral, differentially protected 1,3,5-trihydroxypentane synthon, **11**, was prepared from the yeast reduction product **3f** by silylation and subsequent reduction with $LiBH_4$ as mentioned previously in the correlation of absolute configuration. This compound is a useful, new optically active intermediate for asymmetric syntheses. By appropriate chemical manipulation of either terminus, the hydroxy group or the benzyloxy group, this intermediate can serve as a (*R*)- or (*S*)-3-hydroxypentanoid synthon. It also provides an alternative to similar chiral intermediates derived by enzymatic hydrolysis of dimethyl 3-hydroxyglutarate, a reaction which is difficult to conduct on a large scale. The yeast-mediated reduction can be scaled up with simple equipment which provides vigorous stirring open to the air.

To demonstrate an application of the chiral intermediate **11**, we have prepared (*R*)-8-(benzyloxy)-6-hydroxy-1-octene (**17**), which was first synthesized by Golding and co-



workers[14] from (*S*)-malic acid and used as a key intermediate in their total synthesis of (*S*)-(−)-lipoic acid (unnatural enantiomer). This intermediate was readily prepared from our yeast-derived intermediate **11** as follows. Oxidation of **11** with bipyridinium chlorochromate[15] provided the aldehyde **12**, which was treated with allylmagnesium bromide, resulting in formation of an epimeric mixture of alcohols **13** which were converted to the corresponding iodides **15** by displacement of the mesylates **14** with LiI. Treatment of the iodides **15** with *n*-C_4H_9SnH[16] provided **16** and cleavage of the silyl ether gave the desired intermediate (*R*)-8-(benzyloxy)-6-hydroxy-1-octene (**17**).

Conclusion

This work provides another example of extending the scope and application of enzyme-catalyzed transformations in organic syntheses by simple substrate optimization to provide improved optical purity of the desired products. In addition, by incorporating prochiral elements into the design of a substrate which can be interconverted by chemical methods after the asymmetric microbial transformation, the chemist is not limited by the enantioselective outcome of the enzymatic transformation, as the other enantiomer can be accessed by subsequent chemical transformations. In the present case, the ester alkoxy group of the β-keto ester substrate is used to optimize the optical purity of the microbial product. The ester group and the benzyloxy group serve as the prochiral elements which an be chemically interconverted to provide both *R* or *S* antipodes of chiral intermediates derived from the yeast products **3** for asymmetric synthetic applications. The chiral building block **11** and derivatives thereof should prove useful in asymmetric syntheses of natural products especially those derived from the polyketide biosynthetic pathway.

Experimental Section

All experiments requiring anhydrous conditions were conducted under a dry nitrogen atmosphere. Reactions were performed at room temperature unless indicated otherwise and with stirring by using a magnetically driven stir bar. Reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel 60 F-254 plates (0.25 mm). The plates were visualized by spraying or dipping with a *p*-anisaldehyde solution (1350 mL of ethanol, 50 mL of concentrated H_2SO_4, 15 mL of glacial acetic acid, 37 mL of *p*-anisaldehyde) followed by heating the plate (125–150 °C). Chromatography was performed with 230–400-mesh silica gel. Solvents were evaporated on a rotary evaporator at aspirator pressure (ca. 20 mm). Nuclear magnetic resonance (NMR) spectra were acquired on a Perkin-Elmer R-32 90-MHz NMR, Nicolet 470-MHz NMR, or General Electric QE-300-MHz NMR for proton and a Varian XL-200 or QE-300 for carbon. Chemical shifts are reported in ppm downfield relative to tetramethylsilane as standard.

Representative Dianion Alkylation Procedure. Isobutyl 5-(Benzyloxy)-3-oxopentanoate (2f). To 3.2 g (106 mmol) of NaH (80% in mineral oil) was added 10 mL of dry hexane under a nitrogen atmosphere. The mixture was stirred briefly and allowed to settle, and the hexane was carefully decanted off to remove most of the mineral oil. The NaH was then suspended in 100 mL of dry THF and with stirring at 0 °C a solution of 15.8 g (100 mmol) of isobutyl acetoacetate in 20 mL of THF was added dropwise over 0.5 h. The mixture was stirred for 0.5 h after the addition and then cooled to −25 °C, and 42 mL (110 mmol) of a solution of *n*-butyllithium (2.6 M in hexane) was added dropwise over 15 min. The mixture was stirred for 0.5 h after the addition, and then a solution of 17 g (110 mmol) of benzyl chloromethyl ether in 10 mL of THF was added slowly. The mixture was stirred at −25 °C for 1 h, and then 100 mL of cold 1 N HCl was added slowly, followed by 100 mL of dichloromethane. The phases were

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separated, and the aqueous layer was extracted again with 100 mL of dichloromethane. The combined organic extract was dried over $MgSO_4$, filtered, and evaporated, and the crude product was purified by chromatography (silica gel, 25% ether in hexane) to provide 19.5 g of **2f** (70% yield): ^1H NMR ($CDCl_3$, 300 MHz) 0.92 (6 H, d, J = 7 Hz), 1.94 (1 H, m), 2.84 (2 H, t, J = 7 Hz), 3.51 (2 H, s), 3.76 (2 H, t, J = 6 Hz), 3.91 (2 H, d, J = 7 Hz), 4.51 (2 H, s), 7.33 (5 H, m).

Representative Bakers' Yeast Reduction. Isobutyl 5-(Benzyloxy)-3-hydroxypentanoate (3f). To a mixture of 250 mL of H_2O, 25 g of sucrose, and 1 g of yeast extract at 35 °C with rapid stirring open to the air was added 25 g of dry active bakers' yeast (Fleischmanns). After stirring for 0.5 h, 2 g (7 mmol) of **2f** was added dropwise. The mixture was stirred vigorously for 20 h, after which 250 mL of dichloromethane was added. Stirring was continued for 2 h, then 20 g of Celite filter aid was added, and the mixture was filtered through a sintered funnel. The solids were washed with dichloromethane (2 × 100 mL), the combined filtrate was transferred to a separatory funnel, and the organic phase was collected, dried over $MgSO_4$, filtered, and evaporated to give 1.5 g of crude **3f** (78% yield), which could be used directly in the next step. Purification of a 0.3-g portion by chromatography (silica gel, 50% ether in hexane) gave 0.27 g of pure **3f**: ^1H NMR ($CDCl_3$, 300 MHz) 0.93 (6 H, d, J = 7 Hz), 1.81 (2 H, m), 1.94 (1 H, m), 2.52 (2 H, d, J = 6 Hz), 3.39 (1 H, d, J = 3 Hz, OH), 3.68 (2 H, m), 3.89 (2 H, d, J = 7 Hz), 4.25 (1 H, m), 4.52 (2 H, s), 7.33 (5 H, m).

5-(Benzyloxy)-3-((*tert*-butyldiphenylsilyl)oxy)pentanol (11). To a solution of 1.2 g of crude **3f** in 20 mL of dichloromethane was added 1.4 g (20 mmol) of imidazole, 50 mg of 4-(dimethylamino)pyridine, and 1.5 g (5.5 mmol) of *tert*-butylchlorodiphenylsilane. The mixture was stirred for 16 h, after which 50 mL of dichloromethane was added followed by 25 mL of 1 N HCl. The organic phase was collected, washed with aqueous saturated NaCl, dried over $MgSO_4$, filtered, and evaporated to provide crude **5f**.

This product was dissolved in 40 mL of THF, and 2 mL of 2 M $LiBH_4$ in THF was added. The mixture was heated at 60 °C under nitrogen for 24 h. The mixture was cooled to 5 °C, 10 mL of H_2O was added slowly, and then the pH of the mixture was adjusted to 2 with 1 N HCl. The mixture was extracted with ether (2 × 50 mL), the organic extract was washed with aqueous saturated NaCl, dried over $MgSO_4$, filtered, and evaporated, and the crude product was purified by chromatography (silica gel, 50% ether in hexane) to give 1.25 g of 11 (66% yield): ^1H NMR ($CDCl_3$, 90 MHz) 1.06 (9 H, s, 3 CH_3), 1.6–2.0 (4 H, m, 2 CH_2), 2.8 (1 H, s, OH), 3.45 (2 H, td, J = 6 Hz, 2 Hz, OCH_2), 3.70 (2 H, t, J = 6 Hz, OCH_2), 4.15 (1 H, m, CHOSi), 4.35 (2 H, s, $OCH_2C_6H_5$), 7.35–7.9 (15 H, m, 3 C_6H_5); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 19.3 (C), 27.01 (3 CH_3), 36.36 (CH_2), 38.52 (CH_2), 59.58 (OCH_2), 66.76 (OCH_2), 69.89 (CHOSi), 72.72 ($OCH_2C_6H_5$), 127.48 (2 CH), 127.54 (2 CH), 127.59 (2 CH), 127.63 (2 CH), 128.28 (CH), 129.72 (2 CH), 133.77 (C), 133.92 (C), 135.91 (4 CH), 138.27 (C); IR (thin film) (cm^{-1}) 3400, 3050, 2925, 2850; MS (CI), $M^+ + H^+$ 449; $[\alpha]_D$ +11.6° (c 4.3, $CHCl_3$). Anal. Calcd for $C_{28}H_{36}O_3Si$: C, 74.96; H, 8.09. Found: C, 75.08; H, 7.94.

(*R*)-3-Hydroxypentanedioic Acid, Monomethyl Ester (6). To a solution of 5.0 g (28.4 mmol) of 3-hydroxypentanedioic acid, dimethyl ester, in 85 mL of pH 6.7 buffer was added 2.5 g of α-chymotrypsin (Sigma Chemical Co.), and the mixture was stirred for 72 h at room temperature, after which the mixture was acidified to pH 3 with 1 M HCl. The solvent was evaporated, and the residue was extracted with ether (3 × 100 mL). Evaporation of the ether afforded 3.9 g of **6** (84% yield) which was used directly in the next step.

(*R*)-((3-*tert*-Butyldiphenylsilyl)oxy)pentanedioic Acid, Monomethyl Ester (7). To a solution of 2.42 g (14.2 mmol) of **6** in 70 mL of dichloromethane was added 3.56 g (32.2 mmol) of imidazole, 0.18 g of 4-dimethylaminopyridine, and 8.54 mL (32.8 mmol) of *tert*-butylchlorodiphenylsilane, and the mixture was stirred for 12 h at room temperature, after which 50 mL of dichloromethane and 50 mL of 1 M HCl were added. The organic phase was separated and evaporated, and the residue was treated with 15 mL of 1 M NaOH in 50 mL of *tert*-butyl alcohol at 60 °C for 1 h. The solvent was evaporated at reduced pressure, the residue was suspended in 50 mL of H_2O, and the pH was adjusted to 10 with 1 N KOH. The mixture was extracted with 100 mL of ether to remove noncarboxylic impurities. The ether layer was washed with 2 × 25 mL of H_2O, and the aqueous fractions were combined, the pH was adjusted to 2 with 1 N HCl, and the desired product was extracted with 3 × 100 mL of ether. This combined ether extract was dried over $MgSO_4$, filtered, and evaporated, and the residue was chromatographed (silica gel, 10% ether in dichloromethane) to give 5.18 g of **7** (87% yield): ^1H NMR ($CDCl_3$, 470 MHz) 1.0 (9 H, s, 3 CH_3), 2.53–2.66 (4 H, m), 3.55 (3 H, s, OCH_3), 4.5 (1 H, m, CHOSi), 7.35–7.66 (10 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 19.2 (C), 26.8 (3 CH_3), 41.5 (2 CH_2), 51.5 (OCH_3), 66.9 (CHOSi), 127.6 (4 CH), 129.8 (2 CH), 133.2 (2 C), 135.8 (2 CH), 171 (COOH), 177 ($COOCH_3$).

(*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-5-hydroxypentanoic Acid, Methyl Ester (8). To a solution of 1.0 g (2.5 mmol) of **7R** in 5 mL of THF was added 7.5 mL of a 0.3 M solution of BH_3–THF. After the mixture had been stirred for 2 h, 10 mL of saturated aqueous K_2CO_3 was added and the mixture stirred for 0.5 h. The product was extracted with 50 mL of ether, dried over $MgSO_4$, filtered, and evaporated, and the crude product was purified by chromatography (silica gel, 20% ether in dichloromethane) to give 0.69 g of **8** (74% yield): ^1H NMR ($CDCl_3$, 470 MHz) 1.04 (9 H, s, 3 CH_3), 1.58 (1 H, s, OH), 1.78 (2 H, m), 2.53 (2 H, d, J = 6.4 Hz), 3.53 (3 H, s, OCH_3), 3.54 (2 H, m), 4.37 (1 H, m, CHOSi), 7.37–7.71 (10 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 19.2 (C), 26.9 (3 CH_3), 39.0 (CH_2), 41.8 (CH_2), 51.5 (OCH_3), 59.2 (CH_2OH), 68.6 (CHOSi), 127.6 (2 CH), 127.7 (2 CH), 129.8 (CH), 129.9 (CH), 133.4 (C), 133.6 (C), 135.8 (2C), 171.6 ($COOCH_3$); MS (CI), $M^+ + H^+$ 387.

(*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-5-hydroxypentanoic Acid, Lactone (10*R*). To a solution of 0.3 g (0.75 mmol) of **8** in 1 mL of THF was added 0.5 mL of 1 M H_2SO_4, and the mixture was stirred for 16 h, after which 20 mL of H_2O was added and the mixture was extracted with ether (2 × 25 mL). The ether extract was dried over $MgSO_4$, filtered, and evaporated, and the crude product was purified by chromatography (silica gel, 2% methanol in dichloromethane) to give 0.1 g of **10R** (40% yield): ^1H NMR ($CDCl_3$, 470 MHz) 1.07 (9 H, s, 3 CH_3), 1.83 (2 H, m), 2.57 (2 H, m), 4.22 (2 H, m), 4.61 (1 H, m), 7.37–7.64 (10 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 19.1 (C), 26.9 (3 CH_3), 31.0 (CH_2), 39.7 (CH_2), 53.3 (CHOSi), 55.9 (CHOCO), 127.9 (4 CH), 130.1 (2 CH), 133.1 (C), 133.3 (C), 135.6 (4 CH), 169.9 (CO); IR (thin film) (cm^{-1}) 3050, 2950, 2850, 1740; $[\alpha]_D$ + 9.2° (c 7.69, $CHCl_3$). Anal. Calcd for $C_{21}H_{26}O_3Si$: C, 71.15; H, 7.39. Found: C, 70.88; H, 7.57.

5-(Benzyloxy)-3-((*tert*-butyldiphenylsilyl)oxy)pentanal (12). To a solution of 1 g (2.2 mmol) of 11 in 20 mL of dichloromethane containing 0.5 g of NaOAc was added 1.46 g (5 mmol) of 2,2′-bipyridinium chlorochromate. The mixture was stirred for 5 h, after which 100 mL of ether was added, the mixture was filtered through a pad of silica gel, and the solids were washed with ether (2 × 25 mL). The filtrate was evaporated to give a colorless oil of crude **12**, which was used directly in the next step.

8-(Benzyloxy)-6-((*tert*-butyldiphenylsilyl)oxy)-4-hydroxy-1-octene (13). To the crude product **12** from the previous step dissolved in 20 mL of THF was added dropwise 3 mL of 1.0 M allylmagnesium bromide in ether. The mixture was stirred for 0.5 h, after which 40 mL of aqueous saturated NH_4Cl was added followed by 100 mL of ether. The phases were separated, the organic extract was washed with 25 mL of 0.5 N HCl and 25 mL of aqueous saturated NaCl, dried over $MgSO_4$, filtered, and evaporated, and the crude product was purified by chromatography (silica gel, 20% ether in hexane) to give a separable mixture of diastereomeric alcohols **13**, 0.35 g (32% yield overall from 11). The mixture of diastereomeric alcohols **13** was used directly in the next step.

8-(Benzyloxy)-6-hydroxy-1-octene (17). To a solution of 0.24 g (0.5 mmol) of **13** in 5 mL of dichloromethane at 0 °C were added 0.15 mL of triethylamine and 0.05 mL (0.65 mmol) of methanesulfonyl chloride. The mixture was stirred for 0.5 h, after which 10 mL of 10% $NaHCO_3$ and 20 mL of dichloromethane were added. The organic phase was collected, dried over $MgSO_4$, filtered, and evaporated to provide the corresponding mesylate derivative **14**.

To a solution of **14** in 5 mL of THF was added 0.2 g of LiI, and the mixture was stirred at 55 °C for 16 h. Dichloromethane (10 mL) was added, the mixture was filtered through a small pad

of silica gel, the solids were washed with dichloromethane (2 × 10 mL), and the combined filtrate was evaporated to provide crude iodide **15**.

A solution of **15** dissolved in 10 mL of toluene was degassed and then brought under a nitrogen atmosphere, after which 0.5 mL (17 mmol) of tributyltin hydride and a catalytic amount (10 mg) of 2,2'-azobis(2-methylpropionitrile) was added as a radical initiator. The mixture was heated at 80 °C for 3 h, after which the solvent was evaporated, and the crude mixture was chromatographed (silica gel, 5% ether in hexane) to provide 0.16 g of **16** (68% yield overall from **13**).

To a solution of 0.15 g (0.32 mmol) of **16** in 3 mL of THF was added 1 mL of 1 M tetrabutylammonium fluoride in THF. The mixture was stirred, for 16 h under a nitrogen atmosphere, after which the solution was directly chromatographed (silica gel, 50% ether in hexane) to provide 0.065 g of **17** (88% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) 1.2–1.6 (4 H, m), 1.71 (2 H, q, J = 6 Hz), 2.03 (2 H, m), 2.85 (1 H, d, J = 3 Hz, OH), 3.57–3.73 (2 H, m), 3.78 (1 H, m, CHOH), 4.48, 4.50 (2 H, ABq, J = 10 Hz, $CH_2C_6H_5$), 4.89–5.00 (2 H, m, $=CH_2$), 5.77 (1 H, m, CH=), 7.20–7.35 (5 H, m, C_6H_5); ^{13}C NMR ($CDCl_3$, 75 MHz) 24.86 (CH_2), 33.70 (CH_2), 36.42 (CH_2), 36.85 (CH_2), 69.26 (CH_2O), 71.31 (CHOH), 73.33 (CH_2O), 114.48 ($=CH_2$), 127.64 (2 CH), 127.72 (CH=), 128.43 (2 CH), 137.92 (C), 138.76 (CH); MS, M^+ 234; $[\alpha]_D$ -3.2° (*c* 3, CH_3OH). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.51; H, 9.62.

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Electron-Transfer Substitution Reactions: The *p*-Nitrocumyl System[1]

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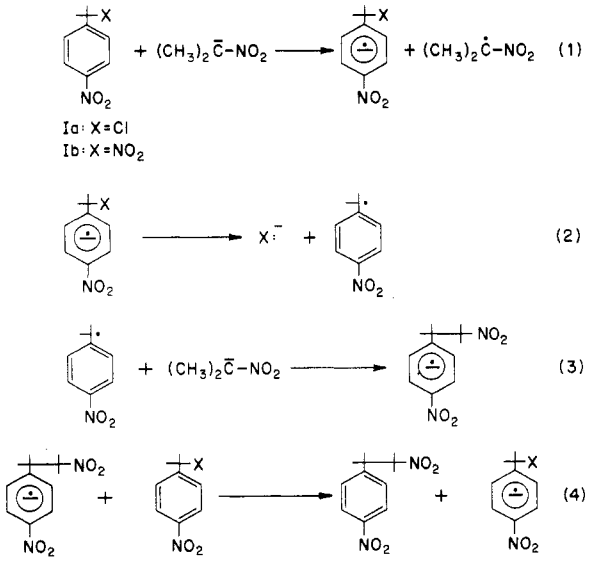
Facile substitution reactions at the tertiary carbon of *p*-nitrocumyl chloride and α,*p*-dinitrocumene are described. These reactions occur with a wide range of organic and inorganic nucleophiles and are noteworthy for providing novel and powerful means of synthesis; they occur readily under mild conditions, give excellent yields of pure products, and, in contrast to S_N2 displacements, are rather insensitive to steric hindrance. They are, therefore, especially valuable for the preparation of highly branched compounds. The view that these are electron-transfer chain processes derives from inhibition studies and, also, from the fact that these reactions are induced by one-electron-transfer agents.

The salts of nitroparaffins are capable of covalency formation at either carbon or oxygen.[2] In 1961 a detailed study of the alkylation reactions of nitroparaffin salts led to the conclusion that oxygen alkylation is a consequence of an S_N2 displacement by the nitroparaffin anion on the alkyl halide.[3] In 1964 it was shown that carbon alkylation derives from an electron-transfer process involving radical anions and free radicals as intermediates.[4a,b] Further evidence for the view that carbon alkylation is an electron-transfer process was reported in 1966, and by this time it had become clear that the carbon alkylation of nitroparaffin salts is a chain reaction. Consequently, the original nonchain mechanism was amended;[4c,d] the resulting chain sequence is illustrated by eq 1–4.

This type of substitution at a saturated carbon atom would constitute an interesting but thoroughly parochial phenomenon were it restricted to reactions of *p*-nitrobenzyl and *p*-nitrocumyl halides with nitroparaffin salts. In actuality electron-transfer chain processes prove to be much more widespread than originally envisaged[5,6] and, in this



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