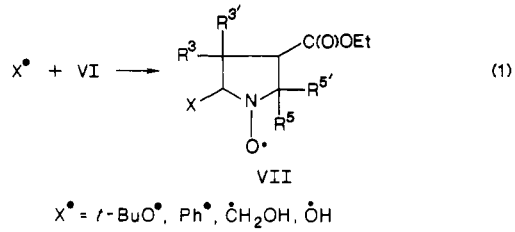
the 4-position, which can be elaborated during the synthesis as required.[13] The approach makes use of a 2 + 3 cycloaddition[14] in which the groups at the 5,5-position are derived from a ketone and those at the 3,3-position are introduced via an unsaturated ester (Scheme I). The synthesis of VIa that is described in the Experimental Section illustrates the method in detail.

A variety of nitrones VIa–d (Scheme I) were prepared by this method and all proved to be excellent spin traps (eq 1). Spin adducts VII derived in the trapping reaction



(1)

typically had half-lives of several hours at radical concentrations of ca. 10^{-4} M (Table I).

The synthesis described above achieves the flexibility of design advocated by Rosen[14] who argued in favor of structures that would allow site selective incorporation of spin traps into biological systems.

Experimental Section

The description of the synthesis of IVa that follows illustrates the synthetic method in detail. Diethyl (aminomethyl)-phosphonate[15] (I) was stirred for 48 h with acetone (10 mol excess) in the presence of molecular sieves. The solution was evaporated to give the corresponding imine IIIa. A tetrahydrofuran (THF) solution of IIIa (0.5 M) was then added under argon at −70 °C to a stirred solution of 1 equiv of butyllithium (0.5 M in THF). This was followed by the slow addition of 1 equiv of ethyl 3,3-dimethylacrylate in the same solvent at −70 °C. The mixture was then allowed to warm to 20 °C. After normal workup[14] the resulting pyrroline, IVa, was purified by distillation [bp 47 °C (0.1 mm); yield 47%].[16]

Pyrroline IVa (0.1 M, in ethanol) was reduced with a 2-fold excess of sodium borohydride at room temperature to give pyrrolidine Va. After isolation, the crude pyrrolidine (0.5 M, in methanol) was oxidized to the nitrone by using 3 equiv of hydrogen peroxide (30% in water) and sodium tungstate (4 mol %).[17] The inorganic salts were separated and the solvent was removed leaving VIa (yield 90%). The nitrone (mp 44–45 °C) was recrystallized from pentane before it was used in spin-trapping experiments. ^{1}H NMR ($CDCl_3$; standard Me_4Si) CH_3, m, δ 1.1–1.6 (15 H); H^4, s, δ 2.9 (1 H); OCH_2, q, δ 4.2 (2 H); H^2, s, δ 6.6 (1 H). ^{13}C NMR ($CDCl_3$; standard Me_4Si) CH_3, q, δ 14.2–28.5 (5 C); C^3, s, δ 41.0; C^4, d, δ 59.4; OCH_2, t, δ 60.7; C^5, s, δ 75.9; C^2, d, δ 139.0; C(O), s, δ 168.7.

In general, the compounds described in this work were new materials, with the exception of IVd, and they were characterized by elemental analysis [(calcd) found].

Pyrrolines obtained in the cycloaddition reactions were analyzed as picrates: IVa, $C_{17}H_{22}N_4O_9$, mp 138–139 °C, C (47.88), 47.60; H (5.20), 5.70; N (13.19), 13.01. IVb, $C_{22}H_{24}N_4O_9$, mp 167–168 °C, C (54.99), 54.82; H (4.95) 4.78; N (11.47), 11.37. IVc was used as a crude distillate. IVd, $C_{23}H_{30}N_4O_9$, mp 165 °C (lit.[5] mp 165 °C).

Pyrrolidines were analyzed as their hydrochloride salts or as pure crystalline materials: Va (hydrochloride), $C_{11}H_{22}NO_2Cl$, mp 115–116 °C, C (56.04), 55.83; H (9.41), 9.26; N (5.94), 5.58; Cl (15.04), 14.51. Vb, $C_{16}H_{24}NO_2$, mp 142–143 °C, C (64.50), 64.70; H (8.12), 8.30; N (4.70), 4.52. Vc used as a crude oil. Vd, $C_{17}H_{29}NO_2$, mp 51–52 °C, C (73.07), 72.70; H (10.46), 10.37; N (5.01), 4.88.

Nitrones were generally analyzed as pure solids: VIa, $C_{11}H_{19}NO_3$, mp 44–45 °C, C (61.94), 61.69; H (8.98), 9.02; N (6.57), 6.50. VIb, $C_{16}H_{21}NO_3$, mp 60–61 °C, C (69.75), 69.95; H (7.69), 7.21; N (5.09), 4.73. VIc, $C_{22}H_{41}NO_3$, oil identified by GC/MS; ion (relative abundance), 367.4 (4) p^+, 278.4 (100). VId, $C_{17}H_{29}NO_3$, mp 130 °C, C (69.59), 68.79; H (9.28), 9.07; N (4.77), 4.42.

Registry No. I, 50917-72-1; IIIa, 113086-37-6; IVa, 113086-38-7; IVb, 113086-41-2; IVc, 113086-42-3; IVd, 75373-56-7; Va, 113086-39-8; Vb, 113086-43-4; Vc, 113086-44-5; Vd, 113086-45-6; VIa, 113086-40-1; VIb, 113086-46-7; VIc, 113086-47-8; VId, 113086-48-9; VIIa (x = t-BuO), 113086-49-0; VIIa (X = Ph), 113086-52-5; VIIa (X = $HOCH_2$), 113086-55-8; VIIa (X = OH), 113086-58-1; VIIb (X = t-BuO), 113086-50-3; VIIb (X = Ph), 113086-53-6; VIIb (X = $HOCH_2$), 113086-56-9; VIIb (X = OH), 113086-59-2; VIIc (X = t-BuO), 113086-51-4; VIIc (X = Ph), 113086-54-7; VIIc (X = $HOCH_2$), 113086-57-0; VIId (X = Ph), 113108-96-6; VIId (X = $HOCH_2$), 113108-97-7; VIId (X = OH), 113108-98-8; t-BuO•, 3141-58-0; Ph•, 2396-01-2; $HOCH_2$•, 2597-43-5; HO•, 3352-57-6; acetone, 67-64-1; ethyl 3,3-dimethylacrylate, 638-10-8.

(13) For example, base hydrolysis of pyrrolidine V leads to the free acid which can be elaborated before the final oxidation step to the nitrone.

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(16) Overall yields of pyrrolines IV were much greater when condensations to form III from other ketones were carried out by azeotropic distillation of water.

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Enhanced and Reversed Enantioselectivity of Enzymatic Hydrolysis by Simple Substrate Modifications: The Case of 3-Hydroxyglutarate Diesters

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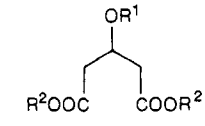
The enzymatic resolution of meso and prochiral compounds has been applied to several diesters in order to prepare chiral synthons of high enantiomeric excess (ee).[1,2] Among 3-substituted glutarate diesters, 3-hydroxyglutarates **1a** and **1b** have been used as substrates for the enzymatic hydrolysis catalyzed by pig liver esterase (PLE),[3] α-chymotrypsin (CHY),[3,4] and esterases from microorganisms.[5] From the results so far obtained, glutarates **1a**



1a: R^1 = H, R^2 = Me
b: R^1 = H, R^2 = Et
c: R^1 = Ac, R^2 = Me
d: R^1 = Ac, R^2 = Et

and **1b** appear to be poor substrates for PLE and CHY, since variable and low enantioselectivity has been found in the enzymatic hydrolyses.[2,6] On the other hand, methyl hydrogen (*R*)- and (*S*)-3-hydroxyglutarates (**2a**) could be excellent starting materials for the synthesis of several natural products such as pimaricin,[3] the lactone portion of mevinic acids,[7] L-carnitine, and (*R*)-4-amino-3-hydroxybutanoic acid (GABOB).[5]

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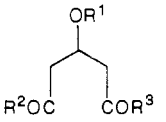
Table I. Stereoselectivity of Enzymatic Hydrolysis of Diesters 1

products	enzyme	ee, %	stereochem	chem yield, %
2a	PLE	30 ± 5[a]	*S*	76
2a	CHY	55 ± 5[a]	*R*	78
2c	PLE	90[c]	*R*	38[b]
2c	CHY	84[c]	*R*	82
2d	PLE	83[c]	*R*	41[b]
2d	CHY	95[c,d]	*R*	84

[a] As determined by HPLC analysis of the diastereomeric mixture **2b**, according to ref 8. [b] Hydrolyses were stopped at a 50% consumption of theoretical amount of 1 N NaOH. [c] Determined by 200-MHz ^{1}H NMR analysis of derivatives **2e** and **2f**: the $COCH_3$ resonances were at 1.96 ppm for *R* isomer and 1.94 ppm for the *S* isomer. [d] At 50% consumption of 1 equiv of base, ee for this compound was 98%.

We wish to report that protection of the 3-hydroxy group of diester **1a** as the acetate affects the stereochemistry of the enzymatic hydrolysis with PLE and enhances the enantioselectivity of the PLE- and CHY-catalyzed hydrolysis, so that 3-acetoxyglutarate monoesters of *R* configuration may be obtained in high enantiomeric purity. Since low and variable optical rotations have been reported for enantiomeric monoester **2a**,[8] another method was needed to establish the optical purity of the products from enzymatic hydrolyses of prochiral diester **1a**. The recently described



2a: R^1=H, R^2=OH, R^3=OMe
b: R^1=Si(Me)$_2$-*t*-Bu, R^2=(+)-NHCH(CH$_3$)Ph, R^3=OMe
c: R^1=Ac, R^2=OH, R^3=OMe
d: R^1=Ac, R^2=OH, R^3=OEt
e: R^1=Ac, R^2=(+)-NHCH(CH$_3$)Ph, R^3=OMe
f: R^1=Ac, R^2=(+)-NHCH(CH$_3$)Ph, R^3=OEt

HPLC method by Rosen et al.[8] was of great help and suggested that the ee of the reaction could be determined by this method. We had to adapt the original analytical conditions which had been set up only for the chemically prepared diastereomeric mixture. In fact, the enzymatic reaction showed a somewhat more complicated product composition, and the quantitative determination of the diastereomeric ratio was more difficult, owing to the presence of new peaks. Finally, HPLC analysis of the diastereomeric derivatives **2b**[8] from the enzymatic reaction showed that, although variable within certain ranges, PLE afforded *S* hydroxy ester **2a** with low enantioselectivity (30 ± 5% ee) and CHY worked with modest enantioselection so that *R* ester **2a** was produced in 55 ± 5% ee[9] (Table I).

When the 3-acetoxy diesters **1c** and **1d** were subjected to enzymatic hydrolysis, interesting results were obtained. In fact, hydrolysis with both enzymes showed that, under our conditions, the acetate group remained unaffected and that a considerable enhancement in the stereoselectivity was observed. This was especially appreciable for PLE, the enantiomeric excess increasing from 30 ± 5% for **2a** to 90% and 83% for **2c** and **2d**, respectively. We obtained the best chemical yields of enantiomeric monoesters **2c** and **2d** when the hydrolysis was stopped at a 50% conversion. When the reaction was continued until 1 equiv of base was consumed, no improvement in the yields of the monoesters was achieved, since hydrolysis of the acetoxy group became a competitive side reaction. In the enzymatic hydrolysis of **1c**, for instance, no starting diester was yet present, but acetoxy monoesters **2c** were accompanied by considerable amounts of deacetylated diester **1a** and monoester **2a**.

The *R* configuration could be assigned to both monoesters **2c** and **2d** obtained from the PLE-mediated hydrolysis from their consistent positive optical rotation by comparison with reported optical rotations.[10,11] For the evaluation of ee, the enzymatically prepared *R* monoesters **2c** and **2d** were converted into amides **2e** and **2f**. The 200-MHz ^{1}H NMR spectra of the above diastereomeric derivatives prepared from racemic and the chiral monoesters, easily allowed the assignment of the resonances for the $COCH_3$ signals of the *R* and *S* isomers at 1.96 and 1.94 ppm. The values of the ee were therefore established by integration of these signals (Table I).

It is clear that the PLE-catalyzed hydrolysis of **1c** and **1d** occurred with a stereoselectivity opposite to that observed with the 3-hydroxy ester **1a**. In accord with the PLE binding site presented by Tamm,[2] Jones,[12] and Bjorklin et al.[13] for PLE, the size and polarity of substituents at C-3 in 3-alkyl glutarates direct the stereochemical outcome of the hydrolysis. Our findings indicate that protection of the 3-hydroxy group as acetate may lead to a reversed steric disposition of the substituent in the transition-state conformation, so that the stereochemistry of the hydrolysis products is reversed and a considerable improvement in enantioselectivity achieved.

Hydrolysis of acetoxy esters **1c** and **1d** by CHY was also investigated. The methyl ester **1c** was hydrolyzed with a stereoselection corresponding to 84% ee, whereas the ethyl ester **1d** was converted to the monoester **2d** in 95% ee. In contrast to the PLE-catalyzed hydrolysis, consumption of 1 equiv of base in the CHY-catalyzed reaction led to a quantitative hydrolysis of the carbalkoxy moiety of the acetoxy diesters, without any loss of the acetoxy group, thus making the methods convenient also from a synthetic point of view. As for the hydrolysis of 3-hydroxyglutarate **1a**, 3-acetoxy esters **1c** and **1d** afforded the monoesters **2c** and **2d** with the *R* configuration (Table I). Also in this case, protection of the 3-hydroxy group had a beneficial effect on the stereochemical outcome, since a maximum value of ee of 95% was reached in the hydrolysis of ethyl ester **1d**. From the last compound (**1d**), *R* acetoxy ester **2d** can now be obtained with excellent ee and good chemical yield (84%), especially from the CHY-catalyzed hydrolysis. Accordingly, this useful chiral synthon is now readily available in high enantiomeric purity.

Note Added in Revision. Variously protected 3-hydroxyglutarates have been shown to be hydrolyzed by CHY to yield *R* monoesters with a very high degree of enantioselectivity (Roy, R.; Rey, A. W. *Tetrahedron Lett.* **1987**, *28*, 4935). The authors stated also that with the

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(8) Rosen, T.; Watanabe, M.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3657.
(9) Similar results, from using different diastereomeric derivatives, have been very recently reported: Mohr, P.; Rosslein, L.; Tamm, C. *Helv. Chim. Acta* **1987**, *70*, 142.
(10) R-(+)-Methyl monoester **2c**: Krogsgard Larsen, P.; Eichstedt Nielsen, B.; Lemmich, J. *Acta Chem. Scand.* **1969**, *23*, 2552.
(11) Optical rotation of −6.23° (*c* 2.36, $CHCl_3$) has been reported for >0.97 ee *S* ester **2d**; see ref 5.
(12) Lamb, L. K. F.; Hei, R. A. H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51*, 1153.
(13) Bjorkling, F.; Boutelje, J.; Gatenbeck, S.; Hult, K.; Norin, T.; Szmulik, P. *Tetrahedron* **1985**, *41*, 1347.

protecting groups chosen (Bn, Bz, MOM), *S* monoesters of very low ee were formed by PLE-catalyzed hydrolysis of 3-protected diesters.

Experimental Section

PLE was purchased from Boehringer Mannheim (West Germany) and CHY was from Fluka (Switzerland). All enzymes were used without further purifications, and activities were assayed under standard conditions as indicated in the catalogs. Infrared spectra were recorded for solutions in chloroform; 60- and 200-MHz ^{1}H NMR spectra were taken on a Varian EM 360 L and XL 200, respectively, as chloroform-*d* solutions. The mass spectra were determined on a LKB 2091 mass spectrometer by direct inlet methods or by GC, using a 1% OV 17 column and helium as carrier. The progress of all reactions was monitored by TLC on silica gel (HF_{254}) plates or by GC analyses on a 2-m silanized column of 1% SE-30 on Gas Chrom Q, operating at 70–200 °C. Distillations were performed with a Buchi 500 glass oven. High-performance liquid chromatography (HPLC) was done with a Gilson Model 302 liquid chromatograph using a Merck Li Chrosorb Si 60 column (7 μm).

Methyl and Ethyl 3-Hydroxypentanedioates (1a and 1b). The ethyl ester was commercially available (Aldrich), while methyl ester **1a** was obtained by a modification of the literature procedure.[4] To a solution of dimethyl acetonedicarboxylate[4] (Fluka) (13 g, 74 mmol) in absolute ethanol (25 mL) at −30 °C was slowly added solid $NaBH_4$ (1.4 g, 37.8 mmol). The solution was stirred and cooled at −30 °C for 10 min, after which 2 N HCl was slowly added to pH 7. The solution was concentrated at reduced pressure and, after filtration of salts, evaporated to dryness. Water was added, and the products were extracted with ethyl acetate (4 × 15 mL). Evaporation of the solvent afforded 10.4 g of a mixture, which was purified by a silica gel chromatography (100 g) eluting with hexane/ethyl acetate (8:2). Distillation at 138–140 °C (8 mmHg)[4] afforded 10.8 g (83%) of ester **1a**: ^{1}H NMR δ 2.60 (d, 4 H), 3.50 (s, 1 H, exchangeable), 3.75 (s, 6 H), 4.27–4.77 (m, 1 H). Anal. Calcd for $C_7H_{12}O_5$: C, 47.7; H, 6.8. Found: C, 47.9; H, 7.0.

Methyl and Ethyl 3-Acetoxypentanedioates (1c and 1d). The title acetates were prepared by standard acetylation procedure. Thus to a solution of diester (2.5 mmol) in anhydrous pyridine (2 mL) at room temperature was added acetic anhydride (0.7 mL), and the solution was kept overnight at the same temperature. After the solution was poured into water (10 mL), the product was extracted with dichloromethane (3 × 5 mL) and the organic solution washed with water and dried (Na_2SO_4). Evaporation of the solvent at reduced pressure afforded the title compound as oils, which were purified by silica gel column chromatography (hexane–ethyl acetate, 8:2) and distilled under vacuum.

1c: 86% yield; bp 194 °C (16 mmHg) [lit.[14] bp 134–135 °C (8 mmHg)]; IR 1720, 1740 cm^{-1}; ^{1}H NMR δ 2.00 (s, 3 H), 2.75 (d, 4 H), 3.75 (s, 6 H), 5.30–5.80 (m, 1 H). Anal. Calcd for $C_9H_{14}O_6$: C, 49.55; H, 6.4. Found: C, 49.7; H, 6.5.

1d: 88% yield; bp 230 °C (16 mmHg) [lit.[14] bp 138–140 °C (8 mmHg)]; IR 1720, 1740 cm^{-1}; ^{1}H NMR δ 1.25 (t, 6 H), 2.00 (s, 3 H), 2.70 (d, 4 H), 4.20 (q, 4 H), 5.30–5.80 (m, 1 H). Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.6; H, 7.3. Found: C, 53.8; H, 7.45.

CHY-Catalyzed Hydrolysis of 3-Acetoxyglutarate (1d). In a typical experiment 605 mg (2.46 mmol) of diester **1d** was suspended in a 0.1 M KH_2PO_4 solution (1 mL), and CHY (0.22 g, 60 U/mg) in distilled water (9 mL) was added. The suspension was stirred for 2 h while keeping the pH constant at 7.8 by addition of 1 M NaOH with a Radiometer automatic titrator. The extent of the reaction was estimated by the volume of base consumed during the reaction. The reaction was then acidified (HCl), the product was extracted with diethyl ether, and the organic phase was treated with diluted ammonia. Diethyl ether extraction of neutral products was done (3 × 5 mL), and acidification of ammonia solution (HCl) followed by extraction with ether afforded 450 mg (84%) of ester **2d**, which was essentially pure by TLC and ^{1}H NMR analyses. For analytical purposes, ester **2d** was purified by silica gel column chromatography (hexane/ethyl acetate, 6:4) and distilled at 141–143 °C at 0.2 mmHg: $[\alpha]_D$ +7.7° (*c* 1, $CHCl_3$); IR 3200, 1710 cm^{-1}; ^{1}H NMR δ 1.20 (t, 3 H), 2.00 (s, 3 H), 2.70–2.90 (dd, 4 H), 4.20 (q, 2 H), 5.20–5.80 (m, 1 H), 8.20 (s, 1 H, exchangeable). Anal. Calcd for $C_9H_{14}O_6$: C, 49.55; H, 6.4. Found: C, 49.7; H, 6.5.

PLE-Catalyzed Hydrolysis of Diester 1c. Diester **1c** (501 mg, 2.3 mmol) was suspended in a 0.1 M KH_2PO_4 solution (1 mL), and PLE (0.43 mL, 130 U/mg) was added. The suspension was stirred for 1.5 h, while the progress of the reaction was monitored by TLC (benzene/ethyl acetate, 1:1). When ca. 50% of starting diester reacted, the mixture was acidified (1 N HCl) and extracted with diethyl ether (4 × 10 mL). The solvent was removed, the residue was treated with dilute ammonia, and the neutral products were removed by extraction with diethyl ether. Acidification of ammonia solution (HCl) and extraction with ether afforded 0.169 g (36%) of monoester **2c**, which was essentially pure by TLC and ^{1}H NMR analyses. For analytical purposes, ester **2c** was purified by silica gel column chromatography (hexane/ethyl acetate, 6:4): bp 138–140 °C (0.2 mmHg) [lit.[10] bp 138–140 °C (0.2 mmHg)]; $[\alpha]_D$ +5.1° (*c* 1, $CHCl_3$); IR 3200, 1710 cm^{-1}; ^{1}H NMR δ 2.10 (s, 3 H), 2.70–2.90 (dd, 4 H), 3.70 (s, 3 H), 5.20–5.70 (m, 1 H), 8.20 (s, 1 H, exchangeable). Anal. Calcd for $C_8H_{12}O_6$: C, 47.05; H, 5.9. Found: C, 47.15; H, 6.1.

HPLC Analysis of Derivatives 2b from Monoester 2a. The procedure followed for preparation of the standard diastereomeric mixture and derivatives **2b** from enzymatic hydrolysis of diester **1a** was according to Rosen et al.[8] Products were analyzed by HPLC with the following parameters: solvent, 8:2 hexane/ethyl acetate; flow rate, 2.0 mL min^{-1}; pressure, 1500–2000 psi; detector, UV (254 nm); t_R 10.3 min (*R*)-(**2b**), t_R 16.2 min (*S*)-(**2b**).

Derivative 2e for 200-MHz ^{1}H NMR Analysis. To 3-acetoxy monoester **2d** (0.146 g, 0.67 mmol) from the enzymatic reaction dissolved in anhydrous benzene (5 mL) under nitrogen was added oxalyl chloride (0.08 mL, 0.94 mmol). The solution was stirred at room temperature (1.5 h). The solution was then cooled to 0 °C, and (*R*)-(+)-2-phenylethylamine (0.2 mL) was added. The solution was brought to ambient temperature and stirred (2 h). The product was isolated as described for silyl derivative **2b**.[8] A sample of **2e** was crystallized from diisopropyl ether: mp 81–82 °C; IR 3400, 1715 cm^{-1}, ^{1}H NMR δ 1.5 (d, 3 H), 2.00 (s, 3 H), 2.50–2.90 (m, 4 H), 3.65 (s, 3 H), 4.90–5.80 (m, 2 H), 6.65–7.10 (m, 1 H), 7.30–7.60 (m, 5 H). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.55; H, 6.85; N, 4.6. Found: C, 62.7; H, 7.0; N, 4.75.

Derivative 2f. This compound was prepared exactly as the amide **2e** for the purpose of the 200-MHz ^{1}H NMR analysis: IR 3400, 1715 cm^{-1}; ^{1}H NMR δ 1.20 (t, 3 H), 1.5 (d, 3 H), 2.00 (s, 3 H), 2.50–2.90 (m, 4 H), 4.20 (q, 2 H), 5.00–5.80 (m, 2 H), 6.10–6.40 (m, 1 H), 7.30–7.60 (m, 5 H).

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Registry No. **1a**, 7250-55-7; **1b**, 32328-03-3; **1c**, 90613-44-8; **1d**, 91967-12-3; (*S*)-**2a**, 87118-64-7; (*R*)-**2a**, 87118-53-4; (*R*)-**2c**, 26432-16-6; (*R*)-**2d**, 113036-11-6; PLE, 9013-79-0; CHY, 9004-07-3; dimethyl acetonedicarboxylate, 1830-54-2.

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Synthesis of (α-Hydroxyalkyl)silanes from Formyltrimethylsilane. A New Route to Acetylenic Acylsilanes

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There has been considerable interest in the synthesis and chemistry of acylsilanes.[1] Many procedures have been

