N,N'-Diamino-N,N,N',N'-tetraethyl-1,2-ethanediylbis(ammonium nitrate) (5): ^{13}C NMR (DMSO-d_6) δ 59.0, 54.4, 7.7; ^{1}H NMR (DMSO-d_6) δ 5.95 (s, 4 H), 3.84 (s, 4 H), 3.46 (q, 8 H, J = 6.6 Hz), 1.26 (t, 12 H, J = 6.6 Hz); IR (KBr) 3462, 3444, 3134, 1384 cm^{-1}.

N,N'-Diamino-N,N,N',N'-tetramethyl-1,3-propanediylbis(ammonium nitrate) (6): ^{13}C NMR (DMSO-d_6) δ 64.6, 55.5, 17.3; ^{1}H NMR (DMSO-d_6) δ 6.11 (s, 4 H), 3.53 (t, 4 H, J = 7.8 Hz), 3.29 (s, 12 H), 2.34 (quint, 2 H, J = 7.8 Hz); IR (KBr) 3437, 3226, 3101, 1629, 1385, 1013 cm^{-1}.

1-Aminopyridinium nitrate[13a,b,e] **(8):** ^{13}C NMR (DMSO-d_6) δ 139.8, 138.4, 128.2; ^{1}H NMR (DMSO-d_6) δ 8.83 (d, 2 H), 8.60 (s, 2 H), 8.31 (t, 1 H), 8.06 (pseudo t, 2 H); IR (KBr) 3180, 3109, 3055, 1515, 1482, 1385 cm^{-1}.

1-Amino-4-(dimethylamino)pyridinium nitrate (9): ^{13}C NMR (DMSO-d_6) δ 156.8, 154.7, 142.2, 139.0, 107.1, 106.8, 39.6, 39.5; ^{1}H NMR (DMSO-d_6) δ 8.23–8.18 (d, 2 H), 7.15 (br s, 1 H), 7.01–6.88 (d, 2 H), 3.19–3.17 (s, 6 H); IR (KBr) 3440, 1646, 1569, 1385, 1211, 826 cm^{-1}.

1-Aminopyrazinium nitrate (10): ^{13}C NMR (DMSO-d_6) δ 150.1, 128.0; ^{1}H NMR (DMSO-d_6) δ 9.63 (br s, 2 H), 9.16 (m, 2 H), 8.76 (m, 2 H); IR (KBr) 3459, 3206, 3043, 1385, 916, 831 cm^{-1}.

1-Aminopyridazinium nitrate (11): ^{13}C NMR (DMSO-d_6) δ 154.2, 136.5, 134.5, 128.5; ^{1}H NMR (DMSO-d_6) δ 9.90 (s, 2 H), 9.28 (ddd, 6 H, J^1 = 5.3 Hz, J^2 = 2.0 Hz, J^3 = 1.0 Hz), 9.15 (ddd, 3 H, J^1 = 6.2 Hz, J^2 = 1.0 Hz, J^3 = 1.0 Hz), 8.51 (ddd, 4 H, J^1 = 8.1 Hz, J^2 = 6.2 Hz, J^3 = 2.0 Hz), 8.14 (ddd, 5 H, J^1 = 8.1 Hz, J^2 = 5.3 Hz, J^3 = 1.0 Hz); IR (KBr) 3447, 1435, 1385, 786 cm^{-1}.

N,N,N',N'-Tetramethyl-1,3-propanediamine 1,3-bis(nitroimide), B: ^{13}C NMR (DMSO-d_6) δ 63.5, 53.3, 18.9; ^{1}H NMR (DMSO-d_6) δ 3.65 (t, 4 H, J = 7.8 Hz), 3.24 (s, 12 H), 1.92 (quint, 2 H, J = 7.8 Hz); IR (KBr) 3052, 1364, 1305, 873, 775 cm^{-1}.

1,4-Diazabicyclo[2.2.2]octane 1,4-bis(nitroimide), C:[13c] ^{13}C NMR (solid) δ 52.0.

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Registry No. 1, 51470-59-8; 2, 1185-49-5; 3, 25230-43-7; 4, 51518-00-4; 5, 138385-72-5; 6, 138385-73-6; 7, 51470-64-5; 8, 28460-22-2; 9, 138407-38-2; 10, 138385-74-7; 11, 138385-75-8; B, 138385-76-9; C, 51470-74-7; NMe_3, 75-50-3; NEt_3, 121-44-8; *N*-methylpiperidine, 626-67-5; *N,N,N',N'*-tetramethylethylenediamine, 110-18-9; *N,N,N',N'*-tetraethylethylenediamine, 150-77-6; *N,N,N',N'*-tetramethyl-1,3-propanediamine, 110-95-2; 1,4-diazobicyclo[2.2.2]octane, 280-57-9; pyridine, 110-86-1; 4-(dimethylamino)pyridine, 1122-58-3; Pyrazine, 290-37-9; Pyridazine, 289-80-5; bis(dimethylamino)methane, 51-80-9; tetraazaadamantane, 100-97-0; tetraazabishomoadamantane, 51-46-7; pyrimidine, 289-95-2; 1,3,5-triazine, 290-87-9; hydroxylamine-*O*-sulfonic acid, 2950-43-8; barium nitrate, 10022-31-8; barium oxide, 1304-28-5.

Supplementary Material Available: Details of the X-ray structure determinations, including atomic coordinates, bond lengths and angles, as well as anisotropic thermal parameters and ^{1}H NMR spectra of 5, 6, 9, 10, and 11 (29 pages). Ordering information is given on any current masthead page.

Synthesis of (+)-(*E*)-(2*S*,5*R*)-5-Acetoxy-3-hexen-2-ol via Enantioselective Enzymatic Hydrolysis. An Enantiodivergent Palladium-Catalyzed Route to (+)- and (−)-*cis*-2-Methyl-5-hexanolide

Hans E. Schink and Jan-E. Bäckvall*

Department of Organic Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala, Sweden

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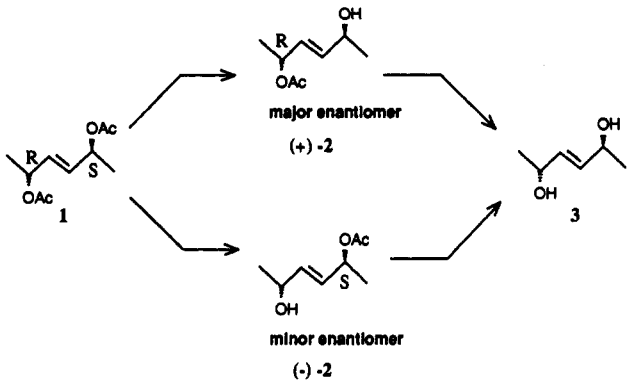
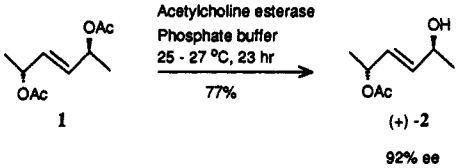
The use of enzymes as a tool in asymmetric organic synthesis has increased dramatically during the last decade.[1] A particularly attractive approach is the use of enzymes for enantioselective transformations (eg. hydrolysis[1b,d,2] reduction,[3] and oxidation[4]) of meso compounds and other compounds having enantiotopic groups. The advantage of employing such substrates in enantioselective reactions is that, theoretically, 100% of the starting material can be transformed into an enantiomerically pure product.

Scheme I



Enantioselective hydrolysis of meso diesters and diacylated meso diols is an extensively used enzyme mediated reaction. The most successfully used enzyme for this purpose is probably pig-liver esterase,[1b,d,2a] but other enzymes, such as lipases[2f] and acetylcholine esterase[2b-e] (ACE), have also proved useful. The enzyme ACE attracted our interest since it has been applied successfully to the asymmetric hydrolysis of cyclic *meso*-1,4-diacetoxy-2-cycloalkenes,[2b,d-e] a type of alkene readily available by the palladium-catalyzed diacetoxylation of 1,3-cycloalkadienes.[5] However, acyclic meso diacetates, such as *meso*-(*E*)-2,5-diacetoxy-3-hexene (1) also available via the diacetoxylation procedure,[5] have not been studied in enzymatic reactions.

In this paper we report a successful enantioselective enzymatic hydrolysis of 1 and the application of the product to the syntheses of both enantiomers of the Carpenter bee pheromone.



(1)

Results and Discussion

Enzymatic Hydrolysis of *meso*-(*E*)-2,5-diacetoxy-3-hexene (1). Performing the hydrolysis of 1, using the conditions described by Johnson,[2c] resulted in a very slow

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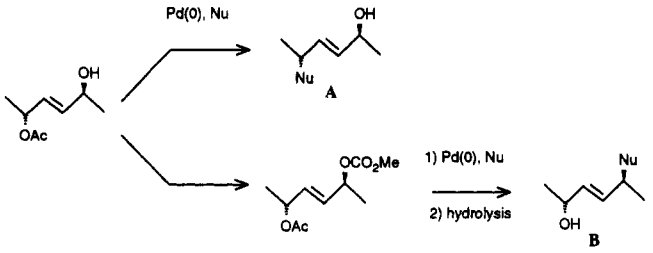
Scheme II



reaction. Being aware of the low solubility of 1 in the aqueous phosphate-buffer used, the concentration of phosphate was decreased from 0.58 to 0.14 M. This change now resulted in a synthetically useful rate of hydrolysis, and (+)-(*E*)-(2*S*,5*R*)-5-acetoxy-3-hexen-2-ol [(+)-2] could be isolated in 77% yield, in 92% ee.[6]

To assure a high enantiomeric excess it was important to run the reaction for a period of 6–8 h after all of the diacetate 1 had been consumed. If the monoacetate (+)-2 was isolated prior to, or just after, complete conversion, then the ee of the product was typically 85%. In a control experiment (+)-2 (1.25 g, 85% ee) was stirred with ACE (3 mg) for 14 h. After purification, 1.05 g of enantiomerically enriched (92% ee) monoacetate (+)-2 was isolated.

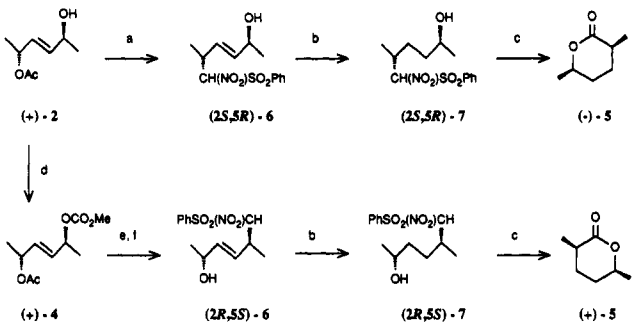
This phenomenon[7] is easily understood if one recognizes that the reaction involves two processes, assuming that the steps are irreversible (Scheme I). First, an enantioselective hydrolysis of 1, in which the enzyme preferably hydrolyzes the acetoxy group at the carbon of *S*-configuration. Secondly, an enzymatic kinetic resolution of the mixture of enantiomers, in which the minor enantiomer (−)-2 becomes the preferred substrate since it has the acetoxy group at the carbon of *S*-configuration. Thus, (−)-2 is hydrolyzed faster to diol 3 than the major enantiomer (+)-2.

Synthesis of (+)- and (−)-*cis*-2-Methyl-5-hexanolides [(+)-5 and (−)-5]. The monoacetate (+)-2 with its two allylic functional groups now offers possibilities for stereocontrolled introduction of nucleophiles via Pd(0) catalysis (Scheme II). Palladium-catalyzed nucleophilic displacement of the acetoxy group[8] in (+)-2 would yield product A, while the same type of reaction on the carbonate[9] (+)-4 would, after hydrolysis, yield the other enantiomer B.

To demonstrate this proposed scheme and to establish the absolute configuration of (+)-2, the monoacetate was converted to both enantiomers of *cis*-2-methyl-5-hexanolide [(+)-5 and (−)-5][10] (Scheme III). This lactone is the major component of the pheromone of the Carpenter bee *Xylocopa hirutissima*.[11] The synthetic approach was based on a previously reported Pd-catalyzed route to racemic 5,[12] but with significant improvements.

The Pd-catalyzed substitution of the acetate in (+)-2 with the anion of (phenylsulfonyl)nitromethane[13] afforded

Scheme III[a]

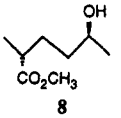


[a] (a) $LiCH(NO_2)SO_2Ph$, $Pd(OAc)_2$, PPh_3, THF, 60 °C; (b) KO_2CNNCO_2K, AcOH, DMSO; (c) (1) O_3, NaOMe, MeOH; (2) H^+, MeCN; (d) $ClCO_2Me$, pyridine, CH_2Cl_2; (e) $CH_2(NO_2)SO_2Ph$, $Pd(OAc)_2$, PPh_3, THF, 40 °C; (f) OH^-/H_2O, MeOH.

(2*S*,5*R*)-6 in 89% yield. The reaction was not completely stereoselective, yielding (2*S*,5*R*)-6 and its C-5 epimer in a ratio of 93:7.

The previously described $Rh(PPh)_3Cl$-catalyzed hydrogenation of racemic 6 was reported to give 7 in moderate yields (50%) together with side products.[12] Another method was therefore sought. Diimide reduction[14] with potassium azodicarboxylate (PADA) and acetic acid in dimethyl sulfoxide turned out to be a more useful reaction. This method did not give complete conversion, but the yield of (2*S*,5*R*)-7 was still high (≈80%).

In the previous sequence,[12] racemic 7 was converted to the lactone via an oxidation of the nitrosulfonyl group to a carboxylic acid function using potassium permanganate. This procedure requires protection of the hydroxyl function and the workup is troublesome and tedious. In search of an alternative method, we found that ozone had been used for the very same type of oxidation under mild conditions and in good yield.[15] Since methanol was used as solvent we expected that this procedure could be applied directly to compound 7 without prior protection of the hydroxy group. Indeed, treatment of (2*S*,5*R*)-7 with ozone in methanol at −78 °C afforded a crude product containing a mixture (1:2) of the corresponding methyl ester (8)[16] and the lactone (−)-5. Subsequent acidic treatment of this crude product afforded, after purification, the desired lactone (93% cis) in 58% yield. Repeated recrystallizations (hexane) afforded (−)-5 (>98% cis) with an optical rotation of $[\alpha]_D$ −92° (lit. $[\alpha]_D$ −91°).[10b]



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The preparation of the other enantiomer (+)-5 started by converting (+)-2 into its corresponding carbonate (+)-4. The Pd(0)-catalyzed reaction with the anion of (phenylsulfonyl)nitromethane as nucleophile and (+)-4 proceeded smoothly, substituting only the carbonate in a stereoselective (>95%) manner. After subsequent hydrolysis, (2*R*,5*S*)-6 was obtained in 86% overall yield from (+)-2.

The conversion of (2*R*,5*S*)-6 into lactone (+)-5 was then performed as described above in an overall yield of 55%. The lactone obtained from this sequence was 96% cis, and recrystallization (hexane) afforded the pure (>98% cis)

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cis isomer with $[\alpha]_D$ +88° (lit. $[\alpha]_D$ +93.5°).[10b]

Experimental Section

^1H and ^{13}C NMR spectra were recorded for $CDCl_3$ solutions at 300 and 75.4 MHz, respectively. Chemical shifts are reported in ppm with tetramethylsilane as internal standard. Optical rotations were measured at 22–23 °C on a Perkin-Elmer 241 polarimeter, and concentrations are expressed as g/100 mL. Mass spectra were obtained using a GC–MS with electron impact ionization (70 eV). IR spectra were recorded for neat samples on NaCl plates, and only the strongest and structurally most important peaks are listed. Melting points are uncorrected. Elemental analyses were performed by Mikrokemi AB, Uppsala, Sweden. The reactions were carried out in flame-dried glassware under N_2 atmosphere unless otherwise stated. Solvents were dried and distilled using standard procedure. For flash chromatography either Merck Kieselgel 60 (230–400 mesh) or Riedel-de Haen Kieselgel S (230–400 mesh) was used. "Collected on silica" means that silica gel was added to a solution of the crude product. The slurry obtained was stripped down to dryness in vacuo, and the dry powder was applied to a silica column and chromatographed as usual.[17]

(+)-(*E*)-(2*S*,5*R*)-5-Acetoxy-3-hexen-2-ol [(+)-2]. Solid *meso*-(*E*)-2,5-diacetoxy-3-hexene[5] (1) (4.00 g, 20.0 mmol) was added to a stirred solution of acetylcholine esterase[18] (8 mg) in aqueous sodium phosphate buffer (0.14 M, pH 6.9, 800 mL) containing NaN_3 (25 mg/L). The heterogeneous mixture was then stirred in a stoppered flask, at 25–27 °C, for 23 h. The resulting homogeneous solution was extracted with ether (6 × 200 mL), and the combination of organic extracts was then washed with brine (30 mL) and dried ($MgSO_4$). The crude oil obtained after concentration in vacuo was purified by flash chromatography (hexane/EtOAc, 70/30) to afford 2.43 g (77%) of monoacetate (+)-**2** as a colorless liquid. α_D: +7.30° (neat, 0.10 dm), $[\alpha]_D$: +70.5° (*c* 20.0, $CHCl_3$). A sample of the product was converted to its Mosher ester derivative,[6] showing that the ee was 92%. ^1H NMR: δ 5.77 (ddd, *J* = 15.5, 5.5, 1 Hz, 1 H, =C*H*CHOH), 5.67 (ddd, *J* = 15.5, 5.5, 1 Hz, 1 H, =C*H*CHOAc), 5.36 (dq, *J* = 5.5, 6.5 Hz, 1 H, C*H*OAc), 4.32 (dq, *J* = 5.5, 6.5 Hz, 1 H, C*H*OH), 2.04 (s, 3 H, OAc), 1.7 (broad s, 1 H, OH), 1.32 (d, *J* = 6.5 Hz, 3 H, CH(OAc)C*H*$_3$), 1.28 (d, *J* = 6.5 Hz, 3 H, CH(OH)C*H*$_3$). ^{13}C NMR: δ 170.3, 135.8, 129.1, 70.2, 67.9, 23.2, 21.3, 20.2. IR: 3419 (broad), 2977, 2933, 2875, 1734, 1373, 1246, 1144, 1042 cm^{-1}. MS: *m*/*z* (relative intensity) 158 (M^+, <1), 114 (5), 99 (2), 98 (12), 83 (12), 71 (8), 55 (11), 43 (100). Anal. Calcd for $C_8H_{14}O_3$: C, 60.7; H, 8.92. Found: C, 60.8; H, 8.8.

(+)-(*E*)-(2*R*,5*S*)-2-Acetoxy-3-hexen-5-yl Methyl Carbonate [(+)-4]. To a stirred solution of monoacetate (+)-**2** (791 mg, 5.00 mmol) and pyridine (1.25 mL, 15.5 mmol) in CH_2Cl_2 (20 mL) was slowly added (5 h, syringe pump) methyl chloroformate (1.16 mL, 15.0 mmol) in CH_2Cl_2 (4 mL) at ambient temperature. After completed addition the reaction mixture was stirred for another 14 h. The solution was washed with 1 M aqueous HCl (5 × 5 mL) and brine (5 mL). The aqueous phase was extracted with ether (2 × 10 mL), and to avoid emulsions the ethereal phase was washed with brine (5 mL) prior to combining the organic extracts. After drying ($MgSO_4$) and concentration of the combined organic extracts in vacuo, the crude product was purified by flash chromatography (hexane/EtOAc, 80/20). This afforded 989 mg (91%) of (+)-**4** as a colorless liquid. α_D: +0.32° (neat, 0.10 dm), α_{365} +2.00° (neat, 0.10 dm). ^1H NMR: δ 5.73 (m, 2 H, olefinic), 5.36 (dq, *J* = 5, 6.5 Hz, 1 H, C*H*OAc), 5.21 (dq, *J* = 5, 6.5 Hz, 1 H, C*H*OCO$_2$CH$_3$), 3.78 (s, 3 H, OCO$_2$C*H*$_3$), 2.04 (s, 3 H, OAc), 1.38 (d, *J* = 6.5 Hz, 3 H, CH(OCO$_2$Me)C*H*$_3$), 1.31 (d, *J* = 6.5 Hz, 3 H, CH(OAc)C*H*$_3$). ^{13}C NMR: δ 170.1 154.9, 131.9, 130.2, 74.2, 69.8, 54.6, 21.3, 20.1, 20.0. IR: 2982, 2959, 2937, 1743, 1443, 1373, 1268, 1148, 1037, 934 cm^{-1}. MS: *m*/*z* (relative intensity) 216 (M^+, <1, 157 (1), 156 (2), 141 (4), 129 (6), 113 (10), 99 (18), 98 (35), 83 (17), 71 (13), 59 (16), 55 (10), 43 (100). Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.6; H, 7.46. Found: C, 55.6; H, 7.3.

(*E*)-(2*S*,5*R*)-5-[(Phenylsulfonyl)nitromethyl]-3-hexen-2-ol [(2*S*,5*R*)-6]. Monoacetate (+)-**2** (796 mg, 5.03 mmol) dissolved in THF (10 mL) was added to a stirred solution of [(phenylsulfonyl)nitromethyl]lithium[13] (2.07 g, 10.0 mmol), $Pd(OAc)_2$ (56 mg, 0.25 mmol), and PPh_3 (787 mg, 3.0 mmol) in THF (30 mL). The resulting yellow solution was then stirred at 60 °C for 14 h. After cooling of the reaction mixture, the product was collected on silica. Flash chromatography (hexane/EtOAc, 60/40, and hexane/EtOAc/EtOH, 49/49/2) afforded 1.34 g (89%) of the desired product as a pale yellow oil. ^1H and ^{13}C NMR spectra were in accordance with the data reported earlier.[12] The ratio between (2*S*,5*R*)-**6** and its (2*S*,5*S*)-isomer was determined by ^1H NMR spectroscopy to be ≈9:1. The subsequent lactonization showed this ratio to be 93:7.

(*E*)-(2*R*,5*S*)-5-[(Phenylsulfonyl)nitromethyl]-3-hexen-2-ol [(2*R*,5*S*)-6]. To a stirred solution of (phenysulfonyl)nitromethane[13] (1.22 g, 6.06 mmol), $Pd(OAc)_2$ (34 mg, 0.15 mmol), and PPh_3 (472 mg, 1.80 mmol) in THF (20 mL) was added carbonate (+)-**4** (656 mg, 3.03 mmol) dissolved in THF (5 mL). The yellow solution obtained was then stirred at 40 °C for 9.5 h. The solution was cooled, and the product was collected on silica. Flash chromatography (hexane/EtOAc, 80/20 and 70/30) afforded 1.67 g of a crude oil containing the desired product plus nucleophile. This oil was dissolved in CH_3OH (35 mL), 15% aqueous K_2CO_3 (25 mL) was added, and the solution was stirred at 40 °C for 2 h. The reaction mixture was concentrated in vacuo (to ≈10 mL), the pH was adjusted to ≈2 (2 M HCl), and then the mixture was extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the product was collected on silica. Flash chromatography (hexane/EtOAc, 60/40 and hexane/EtOAc/EtOH, 49/49/2) yielded 864 mg (95%) of (2*R*,5*S*)-**6** as a colorless oil. ^1H and ^{13}C NMR spectra were in accordance with those reported earlier,[12] and no (2*R*,5*R*)-isomer could be detected. However, the subsequent lactonization revealed that the ratio between these isomers was 96:4.

(2*S*,5*R*)-5-[(Phenylsulfonyl)nitromethyl]hexan-2-ol [(2*S*,5*R*)-7]. To a stirred slurry of freshly prepared potassium azodicarboxylate[19] (PADA) (1.87 g, 9.63 mmol) in DMSO (5 mL) was added a solution of (2*S*,5*R*)-**6** (1.16 g, 3.87 mmol) in DMSO (10 mL) and neat glacial acetic acid (550 μL, 9.60 mmol). The reaction was stirred at 30 °C for 20 h, and then more PADA (750 mg, 3.86 mmol) and more acetic acid (550 μL) were added. After a total reaction time of 40 h the reaction was quenched by dropwise addition of aqueous 2 M HCl, which turned the color of the reaction mixture from yellow to colorless. The resulting solution was extracted with ether (50 + 3 × 25 mL), and the combined ethereal extracts were washed with aqueous 2 M HCl/brine (1/4, 10 mL). After drying ($MgSO_4$) of the combined organic extracts, the product was collected on silica. Flash chromatography (hexane/EtOAc, 60/40 and hexane/EtOAc/EtOH, 49/49/2) afforded 982 mg of a colorless oil, containing the desired product and unreduced starting material in a 10:1 ratio. The spectral data were consistent with those previously reported.[12] The remaining unreduced material does not interfere with the succeeding steps since it is lost in the next reaction.

(2*R*,5*S*)-5-[(Phenylsulfonyl)nitromethyl]hexan-2-ol [(2*R*,5*S*)-7]. In the same way as described for (2*S*,5*R*)-**7**, (2*R*,5*S*)-**6** (806 mg, 2.96 mmol) was converted into 780 mg of a 10:1 mixture of (2*R*,5*S*)-**7** and unreduced starting material. The spectral data were in accordance with those earlier reported.[12]

(2*S*,5*R*)-2-Methyl-5-hexanolide [(+)-5]. A solution of (2*R*,5*S*)-**7**[20] (435 mg, 1.14 mmol) in methanol (50 mL) was added to a solution of sodium (46 mg, 2.02 mmol) in methanol (20 mL). After stirring for 10 min at ambient temperature the solution was cooled to −78 °C. Ozone was bubbled through the solution until all of the starting material had been consumed (1.5 h, as indicated by TLC). After concentration in vacuo the residue was stirred with ether (three portions of 20 mL each). The combined ethereal extracts were dried ($MgSO_4$) and then concentrated in vacuo. The crude product, containing a mixture of the methyl ester **8** and the lactone (+)-**5**, was treated as described by Giese[16] to afford the title compound in 65% yield (120 mg, 96% cis). The product was recrystallized twice (hexane). $[\alpha]_D$: +88° (*c* 0.40, $CHCl_3$). Mp:

(17) Still, W. C.; Kahn, M.; Mitra, A. *Ibid.* **1978**, *43*, 2923.
(18) Supplied by Sigma, No. C-3389.

(19) Thiele, J. *Ann.* **1892**, *271*, 127. If PADA stored (desiccated, +4 °C) for more than 1 week was used, yields were significantly lower. This has also been observed by Hamersma and Snyder, ref 14b.
(20) Containing 10% of unreduced material.

49–50 °C (lit.[10b] $[\alpha]_D$ +93.5° (c 0.795, $CHCl_3$), mp 49–50 °C). ^1H and ^{13}C NMR spectra were in accordance with earlier reported NMR-data.[10b]

(2*R*,5*S*)-2-Methyl-5-hexanolide [(−)-5]. In the same manner as described above for compound (+)-5, (2*S*,5*R*)-7[20] (166 mg, 0.55 mmol) was converted to (−)-5 in 58% yield (93% cis). The product was recrystallized three times (hexane). $[\alpha]_D$: −92° (c 0.80, $CHCl_3$). Mp: 50 °C (lit.[10b] $[\alpha]_D$ −91° (c 0.730, $CHCl_3$), mp 49–50 °C). ^1H and ^{13}C NMR spectra were in accordance with earlier reported NMR data.[10b]

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Highly Selective Acylation of Di- and Polyhydroxyl Compounds by 3-Acylthiazolidine-2-thiones

Shinji Yamada

Department of Materials Science, Faculty of Science, Kanagawa University, Hiratsuka, Kanagawa 259-12, Japan

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It is important in organic synthesis to distinguish among hydroxyl groups of various polyhydroxyl compounds. Selective etherification of primary hydroxyl groups has been accomplished by trityl chloride, and this method has been widely used in organic synthesis.[1] However, selective acylation of hydroxyl groups has not yet been achieved despite considerable effort.[2]

I have focused on 3-acylthiazolidine-2-thiones,[3] which have moderate reactivity and can easily react with a variety of nucleophiles to yield the corresponding carboxylic acid derivatives,[4] and has studied their potential usefulness for the selective acylation of diols and polyols.[5] In this paper, a general method for the highly selective acylation of primary hydroxyl groups of diols and polyols by 3-acylthiazolidine-2-thiones in the presence of NaH is described. This method may be one of the most selective so far reported.

The selective acylation of 1,4-pentanediol (4) using known 3-acetyl- (1)[6] and 3-benzoylthiazolidine-2-thione (3)[7] and newly prepared 3-pivaloylthiazolidine-2-thione (2)[8] as acylating reagents (Figure 1) was studied. The reaction of 1,4-pentanediol and 1.1 equiv of 1 in THF in the presence of 1.1 equiv of NaH at room temperature for 4 h gave a 75:1 mixture of 1-acetoxypentan-4-ol (**5a**) and 1,4-diacetoxypentane (**7a**) in 98% yield as shown in Table I. Moreover, 4-acetoxypentan-1-ol (**6a**) was not detectable. On the other hand, acetylation by acetyl chloride gave a 3:1.2:1 mixture of the primary and secondary alkyl esters and the diester. Other bases such as DMAP, t-BuOK, KH, and LiH were not as effective as NaH. Pivaloylation of 4 with 2 afforded the primary monoester **5b** with nearly 100% selectivity, while pivaloylation with pivaloyl chloride gave a 4.7:2.3:1 mixture of the primary and secondary alkyl ester and the diester as in the case of acetylation. Benzoylation was also performed using 3. As can be seen from these results, the regioselectivity of 3-acylthiazolidine-2-thiones with 4 is in the order of 3-pivaloyl- (2) > 3-acetyl- (1) > 3-benzoylthiazolidine-2-thione (3).

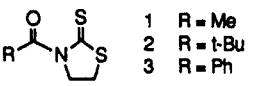
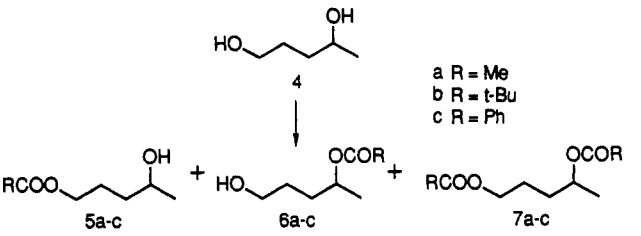


Figure 1.

Table I. Selective Acylation of 1,4-Pentanediol[a]



reagent	base	time, h	total yield,[b] %	product ratio[c] (5:6:7)
1	NaH	4	98	75:0:1
2	NaH	1	93	>100:0:1
3	NaH	2	95[d]	21:0:1
CH_3COCl	Et_3N	4	95	3:1.2:1
$(CH_3)_3CCOCl$	Py	2	92	6:2:1

[a] Conditions: see text. Acylations by 1–3 were conducted in THF and by acid chlorides were conducted in CH_2Cl_2. [b] GLC yield based on internal standard. Conversion of 4 was almost complete unless otherwise indicated. [c] Determined by GLC and/or 400 MHz ^1H NMR. [d] Isolated yield.

In order to explore the usefulness of this method, selective acylation of several diols was examined. The results are summarized in Table II. Acylation of 1,3-butanediol (**8a**), a cyclic diol **8b**, and 1,5-hexanediol (**8c**) was also achieved selectively in the same manner as with 4 to give primary alkyl esters in high yields. In general, the separation and purification of these primary and secondary alkyl esters are difficult because of the similarity of their physical properties. However, in this reaction the secondary monoesters are rarely generated and therefore the pure primary monoesters are obtained without difficulty. A limitation of this method was found in the acylation of 1,2-butanediol (**8d**). The lower selectivities are attributed to the ease of intramolecular 1,2-migration of the acyl groups under these reaction conditions. The present method was applicable not only to diols but also to polyols such as cholane-3α,7α,12α,24-tetrol (**12**)[8] (Scheme I). The monopivaloylation of the tetrol 12 by reagent 2 gave a

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(5) Plusquellec and Backzko (*Tetrahedron Lett.* **1987**, *28*, 3809) reported that methyl α-D-glucoside was acylated by 3-acylthiazolidine-2-thiones to give methyl 6-*O*-acyl-α-D-glucosides in about 60–70% yields based on the acylating reagents. However, in this reaction 3 molar equiv of substrates were used in the presence of a catalytic amount of NaH and DMAP in dry pyridine. Only the long chain alkyl esters were synthesized and the isomer ratio was not reported.

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