A Simple Synthesis of *dl*-Chalcose

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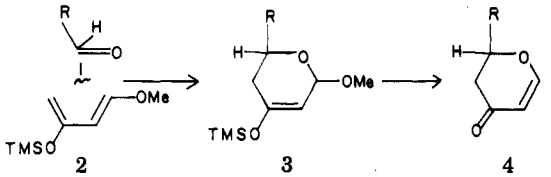
Recently we described the zinc chloride catalyzed cyclocondensation reaction of silyloxy dienes with aldehydes at room temperature to afford dihydropyrones of the type **4**, presumably via adducts such as **3**.[1] The reaction was



quite successful with a broad range of aldehydes. However, with very simple aldehydes such as acetaldehyde the yields were poor. Some improvement (from 17% to 36%) was realized in the acetaldehyde case by conducting the reaction at higher temperatures in the absence of catalyst.

In this paper we describe a major improvement in the reaction of **2** with acetaldehyde which was achieved through the use of BF_3·OEt_2 as the Lewis Acid catalyst. We demonstrate the efficacy of this methodology in the context of a very simple and efficient synthesis of the 4,6-dideoxyhexose chalcose (**8**). Chalcose[2] is one of the two pyranose units found in the antibiotic chalcomycin. It is also encountered in glycosylated form in another antibiotic, lankamycin.[3] Several previous synthesis of chalcose[4] have served to confirm its originally formulated structure and stereochemistry.

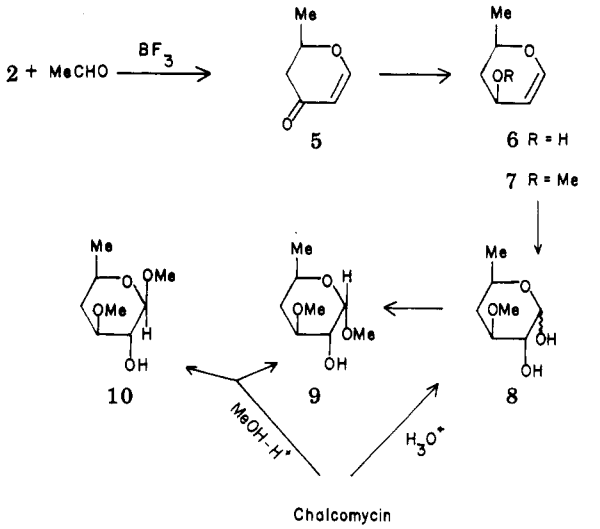
Reaction of **2** with acetaldehyde in the presence of boron trifluoride etherate in diethyl ether at −78 °C afforded **5** in 89% yield (Scheme I). Reduction of **5** with DIBAH in ether afforded stereospecifically the 4,6-dideoxyglucal (**6**) which, upon methylation, provided **7**.

Stereospecific hydroxylation anti to the methoxyl group was achieved through the action of catalytic osmium tetraoxide in tetrahydrofuran. The mixture of *dl*-chalcose (**8**) anomers thus obtained was found to be identical by NMR comparison with authentic material derived from the hydrolysis of chalcomycin.

Methanolysis of the synthetic chalcose afforded, after HPLC purification, the homogeneous methyl chalcosides **9** and **10**. These were identical, by high-field NMR analysis, with the authentic methyl chalcosides obtained by the methanolysis of chalcose.[5]

Further applications of the reaction of siloxydienes with aldehydes will be described in due course.

Scheme I



Experimental Section[6]

Synthesis of 2-Methyl-2,3-dihydropyran-4-one (5). To a solution of 4.00 mL of diene **2** (of 87% purity by NMR analysis; 17.9 mM) in 60 mL of dry diethyl ether under nitrogen at −78 °C was added 2.00 mL (34.6 mM) of acetaldehyde followed by dropwise addition of 2.25 mL (18.3 mM) of boron trifluoride etherate. After 2 h the reaction was quenched by addition of 25 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous phase was extracted with two more portions of diethyl ether. The ether extracts were combined and dried over magnesium sulfate. Evaporation of the volatiles and chromatography of the residue with 30% diethyl ether in petroleum ether for elution gave 1.79 (89%) of **5**: IR 1680, 1595, cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.33 (d, 1 H, J = 6 Hz), 5.34 (d, 1 H, J = 6 Hz), 4.52 (m, 1 H), 2.2–2.7 (m, 2 H), 1.3 (d, 3 H, J = 6 Hz); C^{13} MR δ 192.6, 163.4, 106.8, 76.1, 43.5, 20.4; mass spectrum, m/e 112 (M^+), 97.

***cis*-2,3-Dihydro-2-methylpyran-4-ol (6).** To a solution of 720 mg of **1** in 30 mL of diethyl ether at −78 °C under nitrogen was added 10 mL of DIBAH (1.0 M in hexane). After 2–3 h the reaction was quenched by addition of 3 mL of methanol followed by warming to room temperature. Filtration of the reaction and concentration of the filtrate gave 510 mg (70%) of **6**: IR 3300–3500, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 6.35 (br d, 1 H, J = 6 Hz), 4.72 (m, 1 H, J = Hz), 4.45 (m, 1 H), 4.10 (m, 1 H), 2.25 (br s, OH), 1.95–2.25 (m, 1 H), 1.45–1.8 (m, 1 H), 1.25 (d, 3 H, J = 7 Hz); ^{13}C NMR 145.0, 105.8, 71.5, 63.1, 39.9, 21.2; mass spectrum, m/e 114 (M^+), 97.

***cis*-4-Methoxy-2,3-dihydro-2-methylpyran (7).** To a solution of 776 mg of sodium hydride (60% in oil) in 40 mL of diethyl ether was added 1.096 g of alcohol **2** (9.6 mM) in 10 mL of diethyl ether. To this was added 1.5 mL of methyl iodide (24 mM). After the mixture was stirred at room temperature for 16 h, the reaction was quenched by slow addition of a saturated ammonium chloride solution. The layers were separated, and the aqueous phase was extracted with two portions of ether. Drying over magnesium sulfate and evaporation of volatiles gave 1.05 g of product. Chromatography[7] of the residue with diethyl ether for elution gave 800 mg (65%) of pure methyl ether **7**: IR 1590, 1420, 1390 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 6.30 br d, 1 H, J = 6 Hz), 4.72 (m, 1 H), 3.98 (m, 2 H), 3.32 (s, 3 H), 1.95–2.20 (m, 1 H), 1.45–1.70 (m, 1 H), 1.25 (d, 3 H, J = 7 Hz); ^{13}C NMR δ 145.6, 102.3 , 71.5,

(1) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. in *J. Am. Chem. Soc.* **1982**, *104*, 358.

(2) Woo, W. K. P.; Dion, H. W.; Bartz, Q. R. *J. Am. Chem. Soc.* **1961**, *83*, 3352. Woo, W. K, P.; Dion, H. W.; Johnson, L. F. *Ibid.* **1962**, *84*, 1066.

(3) Keller-Schierlein, W.; Roncari, G. *Helv. Chim. Acta* **1962**, *45*, 138.

(4) Ridlich, H.; Roy, W. *Carbohydr. Res.* **1979**, *68*, 275. Torssel, K.; Tyagi, M. *Acta Chem. Scand. Ser. B* **1977**, *B31*, 7. Srivastova, R. M.; Brown, R. K. *Can. J. Chem.* **1979**, *48*, 830. Lawton, B. T.; Ward, D. J.; Szarek, W. A.; Jones, J. K. N. *Can. J. of Chem.* **1969**, *47*, 2899. McNally, S.; Overend, W. G. *Chem. Ind. (London)* **1964**, 2021. Foster, A. B.; Stacey, M.; Webber, J. M.; Westwood, J. H. *J. Chem. Soc.* **1965**, 2318.

(5) No mention of methyl chalcoside **9** was made as arising from methanolysis of chalcomycin. The only chalcoside previously[2] reported was **10**.[2]

(6) ^1H NMR spectra were recorded on a Varian EM-390 MHz spectrometer or a Brüker HX-270 and ^{13}C NMR on a JOEL FX-90Q in $CDCl_3$ solution. IR spectra were measured as films on a Perkin-Elmer 710B infrared spectrometer using NaCl plates. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

(7) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

0022-3263/82/1947-1597$01.25/0

71.2, 55.4, 36.1, 21.1; mass spectrum, m/e 128 (M^+), 113, 100, 87.

4,6-Dideoxy-3-*O*-methyl-*dl*-*xylo*-hexopyranose (Chalcose, 8). To a solution of 149 mg (1.16 mM) of methyl ether **3** in 10 mL of THF at room temperature were added 264 mg (2.26 mM) of *N*-methylmorpholine oxide and 0.200 mL of OsO_4 (0.39 M in THF). After the mixture was stirred 15 h, the volatiles were evaporated, and the residue was filtered through silica (~3.0 g) with 20% MeOH/ethyl acetate. The first two column volumes were combined and the solvents removed to give 180 mg (95%) of *dl*-chalcose: IR 3300–3500, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 5.27 (br m, 0.5 H), 4.55 (br m, 0.5 H), 4.05–4.40 (m, 1 H), 3.1–3.7 (m, 5 H including a singlet at 3.44), 1.8–2.2 (m, 2 H), 1.15–1.40 (m, 5 H, including an apparent triplet); ^{13}C NMR δ 97.3, 93.4, 80.5, 73.3, 68.8, 64.6, 57.4, 37.5, 21.5; mass spectrum, m/e 145 ($M^+ - 17$), 127.

α- and β-Methylchalcosides (9 and 10). To a solution of 180 mg of **8** (1.11 mM) in 10 mL of methanol was added 1 drop of concentrated H_2SO_4. The reaction was stirred at room temperature and monitored for disappearance of starting material. After 2 days, an excess of solid potassium carbonate was added, the mixture filtered, and the residue chromatographed[7] with 3% methanol in ethyl acetate to give 137 mg (70%) of a mixture of **9** and **10** and 5% of recovered starting material. The 1:1 mixture of **9** and **10** was separated on a 3.9 mm i.d. × 30 cm μ-Bondapak CN column with 5% ethyl acetate in hexane. For **9**: IR 3300–3500 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.77 (d, 1 H, J = 3 Hz) 3.87 (m, 1 H), 3.45–3.51 (m, 2 H) 3.43 (s, 3 H), 3.42 (s, 3 H), 2.35 (br d, 1 H), 2.10 (m, 1 H), 1.26 (br m, 1 H), 1.20 (d, 3 H, J = 6.5 Hz); ^{13}C NMR 100.45, 78.2, 73.5, 64.4, 55.6, 37.7, 21.5. For **10**: IR 3300–3500 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.13 (d, 1 H, J = 7 Hz), 3.25–3.59 (m, 9 H, including singlets at 3.56 and 3.44), 2.63 (br s, 1 H), 2.10 (m, 1 H), 1.28 (d, 3 H, J = 6.5 Hz), 1.20–1.30 (m, 1 H); ^{13}C NMR δ 104.3, 80.5, 75.1, 68.53, 57.4, 37.6, 21.5; mp 69–70 °C.

Registry No. 1 (R = Me), 75-07-0; **2**, 59414-23-2; **3** (R = Me), 80754-64-9; (±)-**5**, 80754-65-0; (±)-**6**, 80754-66-1; (±)-**7**, 80754-67-2; (*dl*)-**8**, 62222-48-4; (DL)-**9**, 28072-66-4; (*dl*)-**10**, 28072-67-5.

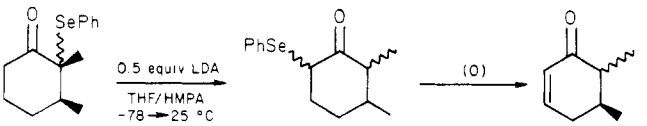
Communications

Based-Induced Rearrangements of α-Phenylselenenyl Ketones

Summary: The formal 1,3 sigmatropic rearrangement of the phenylseleno group of various α-phenylselenenyl ketones proceeds in high yield and thereby permits easy access to α′,β′-unsaturated ketones.

Sir: α-Phenylselenenyl ketones are versatile synthetic intermediates which can be selectively converted into a number of different ketones and enones in high overall yields.[1] In part, the versatility of these species hinges on the ability of an arylseleno group to stabilize an adjacent negative charge,[2] thereby effectively surpressing enolate exchange processes and permitting regiospecific alkylation. Moreover, after alkylation one possesses the option of removing the arylseleno group either oxidatively to produce an enone or reductively to produce to ketone. In this communication we report that under the proper experimental conditions one can effect formal 1,3 sigmatropic rearrangements of the phenylseleno group of an α-phenylselenenyl ketone and, as a consequence, further extend the versatility of these species. An illustration of this process is given below. Specific results are listed in Table I.

When an epimeric mixture of 1^{1a} is treated with 0.5 equiv of lithium diisopropylamide (LDA) in THF containing 2.0 equiv of hexamethylphosphoramide (HMPA) at −78 °C



2 3

and the resulting solution is allowed to slowly warm to room temperature, one isolates after workup an epimeric mixture of **2** in quantitative yield. Confirmation of the structure of **2** is achieved inter alia by its conversion to **3** via the now standard oxidative elimination procedure.[3] Mechanistically we believe the conversion of **1** to **2** occurs via a series of *intermolecular* phenylseleno and proton exchange processes whose driving force is the production of increasingly more stable enolate ions (vide infra).[4] The intermolecular nature of these exchange processes is readily established by varying the concentration of LDA used and qualitatively noting the rate of the reaction.[5] Consistent with a bimolecular process, the fastest "rates" are obtained with 0.5 equiv of LDA.[6] More convincingly, *if a full equivalent of LDA is used, no reaction occurs.*

From a synthetic point of view, these rearrangements proceed in excellent yields with a variety of structurally diverse α-phenylselenenyl ketones (see Table I). In all cases the products consist of mixtures which are epimeric at one or both α-carbon atoms. Since in subsequent synthetic manipulations these mixtures are subjected to

(1) (a) Zima, G.; Barnum, C.; Liotta, D. *J. Org. Chem.* **1980**, *45*, 2737. (b) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. (c) Grieco, P. A.; Nishizawa, M.; Oguiri, T.; Burke, S.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773.

(2) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; Daucher, G. E.; Gerhold, J.; McCollum, G. J.; Van Der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 326.

(3) (a) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697.

(4) For simplicity, these processes are illustrated as if they occur intramolecularly. A similar rearrangement with 2-(carbomethoxy)-2-(phenylseleno)cyclohexanone has been previously reported. See: Falcone, S. J.; Munk, M. E. *Synth. Commun.* **1979**, *9*, 719.

(5) This is done by varying the amounts of LDA used and then determining the amount of product formed under a standard set of conditions.

(6) It should be noted that although these processes involve only 0.5 equiv of LDA, at any given time there are also a variety of weaker bases present which also may participate in the overall process. These include **4–6**, as well as diisopropylamine.

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