Naturally Occurring Spirocyclic Ketals from Lactones. 3†

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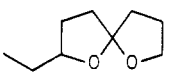
Our earlier methodology for the synthesis of 1,6-dioxaspiro[4.4]nonane and 1,6-dioxaspiro[4.5]decane derivatives has been applied to the synthesis of substances found in the mandibular gland secretions of *Andrena* bees. Use of optically active propylene oxide as a precursor gave 7-methyl-1,6-dioxaspiro[4.5]decane, reported from *Andrena* and *Vespula* species, in 80% optical purity as shown by ^{13}C NMR spectroscopy with a chiral shift reagent. Adaptations of the method allowed synthesis of a tetramethyl-1,6-dioxaspiro[4.4]nonene found in Japanese hop oil and of exogonic acid, a resin constituent of the Brazilian tree *Ipomoae operculata* (Martin). We have also simplified our synthesis of chalcogran, 2-ethyl-1,6-dioxaspiro[4.4]nonane, by using γ-caprolactone and the lithium reagent prepared from 3-bromo-1-propyl 1-ethoxyethyl ether.

Recent years have brought increasing attention to a class of low-molecular-weight natural products containing 1,6-dioxaspiro[4.4]nonane and -[4.5]decane units. The discovery of chalcogran, 2-ethyl-1,6-dioxaspiro[4.4]nonane (1), a "Kupferstecher" beetle aggregation substance, by Francke et al. in 1977[3] was followed by implication of related compounds in odors of wasps[4] and bees[5] by groups in Germany, Sweden, and the United States. These discoveries have, in turn, given impetus to a variety of synthetic studies. Chalcogran, for example, has been prepared by some half-dozen routes to date,[3,6,7] including several that result in optically active material.[7] A recent article by Seebach and co-workers[7d] describes methodology for preparing several optically active dioxaspirocycles from a common precursor and summarizes developments in the area.

We report some extensions in our studies[8,9] on the preparation of spirocyclic ketals from lactones and lithium alkynides. This approach provides a straightforward route to the recently reported[5] *Andrena* bee mandibular gland substances **2** and **3**, in 56% and 52% yields, respectively.



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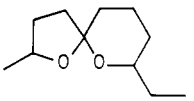

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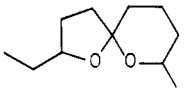
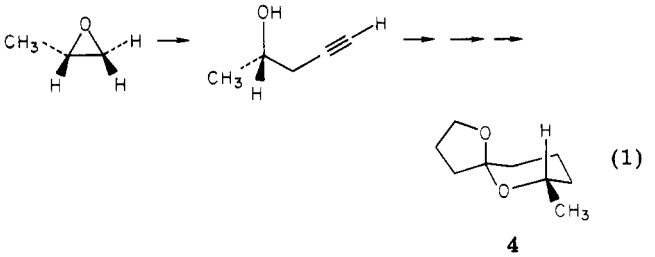


3

In both cases a tetrahydropyranyl (THP)-protected alkynol was converted into its lithium salt by methyllithium and then allowed to react with the appropriate lactone. Hydrogenation over rhodium on alumina was followed by acid treatment and fractional distillation to give the product. Details appear in the experimental section.

Use of optically active propylene oxide, preparable as the pure *S* isomer from (*S*)-ethyl lactate by the procedure of Golding et al.,[10] provided 7-methyl-1,6-dioxaspiro-[4.5]decane (**4**), reported both from wasps[4] and *Andrena* bees,[5] in optically active form. Reaction of (*S*)-propylene oxide with lithium acetylide–ethylenediamine complex in liquid ammonia[11] gave (*S*)-4-pentyn-2-ol (eq 1), which was converted to the THP ether. Generation of the lithium anion, followed by reaction with γ-butyrolactone and the usual hydrogenation–deprotection sequence, gave (7*S*)-**4**, $[\alpha]^{22}_D$ − 78.3° (in pentane).

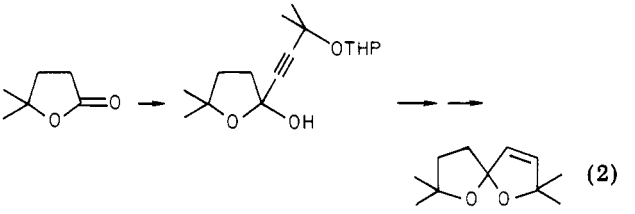


(1)

4

The chiral shift reagent Eu(hfc)$_3$ was used to determine the optical purity of this product. Since the proton NMR is extremely complicated, carbon spectra were used as in our chalcogran studies.[7a] With racemic **4**, 2 equiv of Eu(hfc)$_3$ in $CDCl_3$ gave rise to signals at δ 108.2 and 107.1 for the ketal carbon and signals at δ 66.6 and 66.8 for carbon 3. Addition of approximately the same amount of reagent to the optically active compound gave a sharp single peak at δ 67.3 for carbon 3, but peaks at δ 108.2 and 109.7 indicated that the isomer of lesser shift had undergone 10% isomeric conversion during the synthetic process.

In addition to the synthesis of these insect substances, we are exploring the synthesis of structurally related plant metabolites. For example, we have synthesized 2,2,7,7-tetramethyl-1,6-dioxaspiro[4.4]non-3-ene (**5**, eq 2) a com-



(2)

5 (42%)

† Approved as TA 17094 by the Director of the Texas Agricultural Experiment Station.

(1) Oberlin College. Current address for L.R.S.: Academic Press, Inc., 1001 Polk St., San Francisco, CA 94109.

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(3) (a) Francke, W.; Heemann, V.; Gerken, B.; Renwick, J. A. A.; Vité, J. P. *Naturwissenschaften* **1977**, *64*, 590. (b) Francke, W.; Reith, W. *Justus Liebigs Ann. Chem.* **1979**, 1.

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(9) (a) Phillips, C.; Smith, L. R. Presented at the 31st Southeast Regional Meeting of the American Chemical Society, Roanoke, VA, Oct 1979. (b) Jacobson, R.; Kemp, E. B.; Adolph, E.; Smith, L. R. Presented at 1981 Central/Great Lakes Regional Meeting of the American Chemical Society, Dayton, OH, May 1981.

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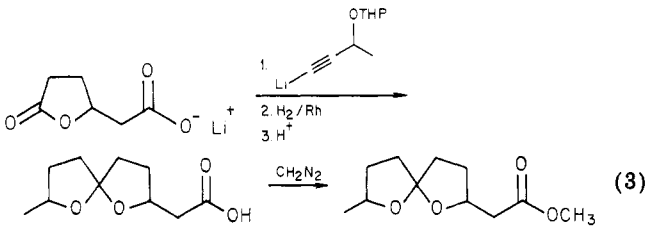
pound isolated from Japanese hop oil by Naya and Kotake in 1967.[12] Use of Lindlar catalyst instead of rhodium in the hydrogenation of the alkyne was the only procedural modification required.

Another plant metabolite accessible by variation of our method is exogonic acid, identified as a resin constituent of *Ipomoea operculata* (Martin), a Brazilian tree, by Graf and Dahlke in 1964.[13] For this synthesis, we started with the lithium salt of γ-(carboxymethyl)-γ-butyrolactone (eq 3). The anion's charge protected the carboxyl function

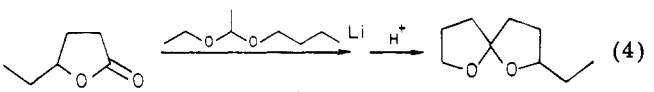


(3)

6 (28%)

during reaction with 3-lithio-3-butyn-2-yl tetrahydropyranyl ether. For isolation and characterization, we converted exogonic acid to its methyl ester using diazomethane.[13] An appreciable amount of dimethyl adipate also forms in this sequence, presumably originating from base-promoted ring opening of the lactone in the first step.

The use of readily obtainable alkynyl alcohols as starting materials makes these dioxaspirocycle syntheses very convenient. Suitable halo alcohols, also potential precursors, are generally less available but would shorten the procedure by removing the hydrogenation step. With this in mind, we tried the hydroxypropylation method of Eaton et al.[14] for the direct preparation of chalcogran (1, eq 4).



(4)

1 (63%)

Distilled yields of up to 63% of 1 have been obtained by this route. Such an approach could substitute for the alknylation method in other cases as well.

Experimental Section

THP ethers were prepared by standard methods.[15] Proton NMR spectra were run by using a Perkin-Elmer Model R12B, JEOL FX 90Q FT NMR, or Varian XL 200 FT NMR spectrometer. Carbon NMR spectra were run on a JEOL FX 90Q. IR spectra were obtained by using a Perkin-Elmer 727 instrument, and mass spectra were run on a Perkin-Elmer RMS-4 instrument. Analytical and preparative GLC analyses were carried out by using a 1.8 m × 0.64 cm o.d. 8% SE-30 or 8% Carbowax 20M column in a Carle Model 111 gas chromatograph. Optical rotations were measured on a Perkin-Elmer 241 polarimeter by using a 1-mL thermostated microcell. Microanalyses were performed by Atlantic Microlab, Inc.

2,2,7,7-Tetramethyl-1,6-dioxaspiro[4.4]non-3-ene (5). A 100-mL, N_2-filled three-necked (septum, stopper, nitrogen inlet) flask containing a magnetic stirring bar was charged with 50 mL of anhydrous Et_2O and 4.2 g (25 mmol) of 2-methyl-3-butyn-2-yl tetrahydropyranyl ether. The flask was chilled in an ice bath, and, with stirring, 14 mL of 1.8 M methyllithium in ether (Aldrich) was injected (ca. 5 min). After 5 min of stirring, the solution was added (transfer needle) to a magnetically stirred solution of 3.0 g (26 mmol) of γ,γ-dimethyl-γ-butyrolactone[16] in 50 mL of anhydrous Et_2O in a 250-mL N_2-filled flask closed with a septum. The clear golden solution was stirred at room temperature for 4 h, and then 20 mL of 20% aqueous NH_4Cl was rapidly added. Stirring continued until all the precipitate dissolved. The layers were separated, and the aqueous layer was extracted with an additional small portion of Et_2O. After being dried (anhydrous K_2CO_3) the organic phase was concentrated. The resulting oil was hydrogenated in 1 atm of H_2 in 40 mL of reagent hexane over 0.40 g of 5% Pd on $CaCO_3$ (Aldrich, poisoned with lead) with 1.0 mL of added quinoline. Hydrogen uptake almost ceased after 1 equiv of hydrogen had been absorbed; the mix was then filtered and stirred well with 10 mL of 3 M aqueous HCl. After the mixture was allowed to stand overnight, the aqueous layer was separated and the organic layer was stirred over 10 mL of 20% aqueous NaOH for 1 h. Fractional distillation at 740 torr through a 20-cm Vigreaux column gave 1.92 g (42%) of product: bp 174–176 °C; NMR and IR spectra were in accord with data reported by Naya and Kotake;[12] MS, *m/e* (relative intensity) 182 (M^+, 0.3), 168 (2), 167 (20), 149 (3), 139 (1), 124 (9), 113 (23), 109 (85), 99 (4), 97 (6), 95 (15), 81 (14), 69 (20), 67 (21), 55 (27), 53 (21), 43 (100), 41 (50). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.13; H, 9.85.

2-Ethyl-7-methyl-1,6-dioxaspiro[4.5]decane (3). Generation of the lithium alkynide and addition to the lactone were carried out as described for **5** by using 4.2 g (25 mmol) of 4-pentyn-2-yl tetrahydropyranyl ether, 18 mL of 1.4 M ethereal methyllithium, and 3.0 g of γ-caprolactone. Hydrogenation was carried out at 1 atm of H_2 in 80 mL MeOH over 0.30 g of 5% rhodium on alumina. After hydrogenation, the mixture was filtered, concentrated (rotary evaporator), taken up in 40 mL of 3:1 pentane–ether, and treated with 5 mL of 3 M aqueous HCl. After 48 h, the aqueous layer was discarded, and the organic layer was stirred 3 h over 10 mL of 10% aqueous NaOH. Separation and drying (K_2CO_3) of the organic layer were followed by fractional distillation, giving (after removal of the solvent and some methyl tetrahydropyranyl ether) 2.4 g (52%) of product, bp 194–200 °C (740 torr). GLC analysis (SE-30 column at 120 °C) indicated a mixture of epimers. The mass spectrum was in accord with that reported by Francke et al.[17] IR and NMR spectra also appeared to be satisfactory. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.73, H, 10.95. Found: C, 71.69; H, 11.34.

7-Ethyl-2-methyl-1,6-dioxaspiro[4.5]decane (2). The synthesis was carried out as with compound **5** by using 4.55 g (25 mmol) of 5-hexyn-2-yl tetrahydropyranyl ether, 18 mL of 1.4 M ethereal methyllithium, and 3.0 g (30 mmol) of γ-valerolactone: yield of pure product 2.8 g (56%); bp 201–203 °C (740 torr). The mass spectrum was in accord with literature data,[17] and the IR and NMR spectra were satisfactory. GLC analysis indicated a roughly 1:1 mixture of epimers. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.73; H, 10.95. Found: C, 71.66; H, 10.94.

Methyl Exogonate (6). A 50-mL three-necked flask (septum, stopper, nitrogen inlet) was fitted with a magnetic stirring bar and then charged with 25 mL of anhydrous Et_2O and 2.2 g (14 mmol) of 3-butyn-2-yl tetrahydropyranyl ether. With cooling (ice bath), the stirred solution was treated with 10 mL of 1.4 M ethereal methyllithium. A second flask (100 mL) was flushed with nitrogen, fitted with a magnetic stirring bar and a reflex condenser topped by a septum/nitrogen inlet, and charged with 2.0 g (14.5 mmol of γ-(carboxymethyl)-γ-butyrolactone and 20 mL of anhydrous THF. With cooling (ice bath) the stirred solution was treated with 10 mL of 1.4 M methyllithim in Et_2O. The resulting suspension was then treated (transfer needle) with the lithium alkynide solution in the first flask. The mixture was stirred at room temperature for 3 h and then was quenched by addition of 10 mL of 3 M aqueous HCl. Separation of the layers was followed by addition of 5 mL more of 3 M HCl to the aqueous layer and extraction with two 20-mL portions of Et_2O. The combined organic phase was dried (Na_2SO_4), concentrated (rotary

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(15) Robertson, D. N. *J. Org. Chem.* **1960**, *25*, 931.
(16) Prepared from the THP ether of 2-methyl-3-butyn-2-ol by treatment with methyllithium, followed by reaction with carbon dioxide, followed in turn by hydrogenation and acid treatment: Vigneron, J. P.; Bloy, V. *Tetrahedron Lett.* **1980**, *21*, 1735.
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evaporator), and taken up in 50 mL of MeOH. Hydrogenation was carried out at 1 atm of H_2 over 0.30 g of 5% Rh on alumina. Filtration and evaporation were followed by addition of 50 mL of Et_2O and 5 mL of 3 M aqueous HCl. After 24 h, the aqueous layer was removed, and methyl exogonate formed on treatment with excess ethereal diazomethane. GLC analysis with dimethyl phthalate as an internal standard showed a 28% yield of methyl exogonate, accompanied by an almost equal amount of dimethyl adipate. Pure product was isolable by preparative GLC first with the SE-30 column and then with the Carbowax 20M column. The NMR (CCl_4) matched that illustrated by Graf and Dahlke,[13] and the IR was also satisfactory: MS *m/e* (relative intensity) 214 (M^+, 3), 199 (12), 183 (15), 170 (21), 167 (5), 160 (3), 159 (34), 158 (3), 157 (4), 156 (2), 149 (7), 142 (7), 141 (74), 138 (5), 137 (4), 127 (18), 125 (8), 123 (7), 115 (8), 114 (44), 113 (11), 112 (33), 111 (9), 101 (29), 99 (29), 98 (54), 97 (30), 96 (21), 95 (17), 85 (100), 83 (32), 82 (20), 81 (32), 74 (17), 72 (10), 71 (22), 70 (24), 69 (11), 68 (8), 67 (8), 59 (53), 57 (39), 56 (70), 55 (98), 54 (23), 53 (22), 45 (18), 43 (99), 42 (37), 41 (67), 40 (8).

2-Ethyl-1,6-dioxaspiro[4.4]nonane (Chalcogran, 1). A 100-mL three-necked flask was fitted with a magnetic stirrer, septum, stopper, and argon inlet. The flask was charged with 2.0 g of lithium shot (Lithcoa, containing ca. 0.7% sodium) and 100 mL of anhydrous Et_2O. The flask was chilled in an ice bath, and 12.7 g (60 mmol) of 3-bromopropyl 1-ethoxyethyl ether was injected. When shiny spots appeared on the lithium, salt was added to the ice bath, and the mixture was stirred at ca. −10 to −15 °C until the metal tarnished (ca. 3 h). The mixture was then added (transfer needle, leaving excess lithium behind) to a magnetically stirred solution of 8.0 g of γ-caprolactone in 100 mL of anhydrous Et_2O in a N_2-filled 500-mL flask fitted with a condenser topped by a N_2 inlet/septum adapter. After the addition, the mixture was gently refluxed 16 h. The reaction was then quenched by cautious addition of 50 mL of 6 M aqueous HCl. After the mixture was stirred 7 h at room temperature, the layers were separated (the aqueous layer was extracted with two small portions of pentane), and the organic phase was stirred over 25 mL of 20% aqueous NaOH overnight. After separation, the organic phase was dried (K_2CO_3) and then fractionated to give 5.88 g (63%) of chalcogran. Analysis by GLC (SE-30 column), NMR, and IR[3a,7a] showed no impurities.

(*S*)-4-Pentyn-2-ol. A 250-mL three-necked flask was fitted with a septum, an ammonia inlet, a magnetic stirring bar, and a dry-ice-filled cold-finger condenser topped by a nitrogen bubbler connection. A dry ice bath was placed around the flask. The flask was charged with 17.5 g (190 mmol) of lithium acetylide–ethylenediamine complex (Aldrich), and then ca. 100 mL of liquid NH_3 was condensed into the flask. (*S*)-Propylene oxide (5.3 g, 92 mmol, prepared as in ref 10, $[\alpha]^{10}_D$ −12.0° (neat) was injected with stirring with ca. 10 mL of anhydrous Et_2O to flush the syringe. After the mixture was stirred for 6 h, the dry ice bath was removed, and the flask was allowed to warm for 2 h. Anhydrous Et_2O (120 mL) was then added, followed by cautious addition of 150 mL of 20% aqueous NH_4Cl. After stirring overnight, the layers were separated, the aqueous phase was extracted with ether (3 × 150 mL), and the combined organic phase was dried over anhydrous K_2CO_3. Evaporation of the solvent gave 6.7 g of product whose IR spectrum was superimposable on that of racemic 4-pentyn-2-ol purchased from CPL, Inc. The product was distilled at ca. 20 torr (distilled yield ca. 50%) before optical rotation measurement and THP protection; $[\alpha]^{22}_D$ −20.0° (*c* 0.265 g/mL, ether).

(*S*)-4-Pentyn-2-yl Tetrahydropyranyl Ether. This was prepared by the procedure of ref 15. The IR spectrum of distilled material was identical with that of material prepared previously from the commercially available racemic alcohol; $[\alpha]^{22}_D$ −12.6° (*c* 0.295 g/mL, ether).

(7*S*)-7-Methyl-1,6-dioxaspiro[4.5]decane (4). A 100-mL three-necked (septum, stopper, nitrogen inlet) flask was fitted with a magnetic stirrer, flushed with N_2, and charged with 4.0 g (24 mmol) of (*S*)-4-pentyn-2-yl tetrahydropyranyl ether and 50 mL of anhydrous ether. With stirring and cooling (ice bath), 18.3 mL of 1.3 M (Aldrich) ethereal methyllithium (24 mmol) was injected (5 min). After 10 min, the solution was added (transfer needle) to a briskly mechanically stirred solution of 3.0 g (34 mmol) of γ-butyrolactone in 50 mL of anhydrous Et_2O in a three-necked (septum, stirrer, stopper) 250-mL flask. Stirring was continued at room temperature for 45 min, and then the reaction was quenched by rapid addition of 20 mL of 20% aqueous NH_4Cl. The mixture was stirred until all the precipitate dissolved, the ether layer was dried (K_2CO_3) and concentrated (rotary evaporator), and the resulting oil was taken up in 50 mL of MeOH. Hydrogenation at 1 atm over 0.3 g of 5% Rh/alumina was followed by filtration, concentration, and addition of 40 mL of 3:1 pentane–ether and 2 mL of 6 M aqueous HCl. After the mixture was stirred 5.5 h, the aqueous layer was removed and the organic phase stirred with 10 mL of 20% aqueous NaOH overnight. Separation and drying were followed by distillation to give, after solvent removal and a forerun (bp 125–135 °C) of MeOTHP, 1.02 g (27%) of product, bp 166–184 °C (740 Torr). IR and NMR spectra were identical with those of pure material prepared previously.[8] GLC analysis (SE-30, 120 °C) indicated only traces of contaminants; $[\alpha]^{22}_D$ −78.3° (*c* 0.0859 g/mL, pentane).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Research Corp. for grants made to L.R.S. in support of this work.

Registry No. 1, 38401-84-2; 2 (isomer 1), 73788-49-5; 2 (isomer 2), 72713-27-0; 3 (isomer 1), 72748-31-3; 3 (isomer 2), 72713-26-9; 4, 77715-03-8; 5, 15031-05-7; 6, 20969-25-9; 2-methyl-3-butyn-2-yl tetrahydropyranyl ether, 27943-46-0; γ,γ-dimethyl-γ-butyrolactone, 3123-97-5; 4-pentyn-2-yl tetrahydropyranyl ether, 58654-09-4; γ-caprolactone, 695-06-7; 5-hexyn-2-yl tetrahydropyranyl ether, 66216-74-8; γ-valerolactone, 108-29-2; γ-(carboxymethyl)-γ-butyrolactone, 60551-20-4; 3-butyn-2-yl tetrahydropyranyl ether, 57188-99-5; 3-bromopropyl 1-ethoxyethyl ether, 34399-67-2; (*S*)-4-pentyn-2-ol, 81939-73-3; (*S*)-propylene oxide, 16088-62-3; (*S*)-4-pentyn-2-yl tetrahydropyranyl ether, 81969-74-6; γ-butyrolactone, 96-48-0.

Supplementary Material Available: ^{13}C NMR spectral data for compounds 2–6 (1 page). Ordering information is given on any current masthead page.