Preparation of Amines 7a–c. Schiff's base **3a** was reacted with 2-furanyllithium and methyllithium under the conditions given above to furnish anilines **7a** and **7b**, respectively. A similar reaction of **3c** with 2-furanyllithium gave **7c**.

***N*-[α-(2-Furanyl)benzyl]aniline (7a)**: yield 96%; oil; NMR (400 MHz) δ 4.35 (br d, J = 4 Hz, 1 H), 5.58 (d, J = 4 Hz, 1 H), 6.11 (m, 1 H), 6.31 (m, 1 H), 6.60 (d, J = 8 Hz, 2 H), 6.71 (t, J = 8 Hz, 1 H), 7.14 (t, J = 8 Hz, 2 H), 7.26–7.43 (m, 6 H). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.89; H, 6.07. Found: C, 81.75; H, 6.00.

***N*-(1-Phenylethyl)aniline (7b)**: yield 91%, oil. The NMR spectrum was virtually identical with that published.[10]

***N*-(2-Furanyl-2-thienylmethyl)aniline (7c)**: yield 92%; oil; NMR δ 4.37 (br d, J = 5 Hz, 1 H), 5.88 (d, J = 5 Hz, 1 H), 6.13–6.37 (m, 2 H), 6.50–7.40 (m, 13 H). Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13. Found: C, 70.76; H, 5.20.

Preparation of Schiff's Bases 5a–h, 8a,c. Amines **4a–h** and **7a,c** were dehydrogenated by treatment with DDQ using a general procedure published by us recently[7] and purified by flash chromatography on silica gel (triethylamine/hexanes, 1:9). Solid products **5a–e,g,h** and **8a** were additionally crystallized from hexanes.

***N*-(Diphenylmethylene)aniline (5a)**: yield 99%; mp 106–110 °C (lit.[11] mp 111–112 °C).

***N*-[Bis(2-methylphenyl)methylene]aniline (5b)**: yield 99%; mp 83–85 °C (lit.[12] mp 85.5–86 °C).

***N*-[Di(2-thienyl)methylene]aniline (5c)**: yield 96%; mp 112–114 °C; NMR δ 6.60–7.50 (m); IR 1581 cm^{-1}. Anal. Calcd for $C_{15}H_{11}NS_2$: C, 66.88; H, 4.12; N, 5.20. Found: C, 66.68; H, 4.05; N, 5.10.

***N*-[Di(3-thienyl)methylene]aniline (5d)**: yield 88%; mp 93–95 °C; NMR δ 6.60–6.95 (m, 4 H), 6.98–7.43 (m, 5 H), 7.48–7.73 (m, 2 H); IR 1595 cm^{-1}. Anal. Calcd for $C_{15}H_{11}NS_2$: C, 66.88; H, 4.12; N, 5.20. Found: C, 66.75; H, 4.16; N, 5.12.

***N*-[Di(2-benzo[*b*]thienyl)methylene]aniline (5e)**: yield 99%, mp 170–172 °C; NMR δ 6.63–7.83 (m); IR 1584 cm^{-1}. Anal. Calcd for $C_{23}H_{15}NS_2$: C, 74.76; H, 4.09; N, 3.79. Found: C, 74.68; H, 4.03; N, 3.68.

***N*-[Di(2-furanyl)methylene]aniline (5f)**: yield 94%; oil, unstable on air; NMR δ 6.07 (m, 2 H), 6.45 (m, 1 H), 6.65 (m, 1 H) 6.78 (m, 1 H), 7.03 (m, 3 H), 7.25 (m, 2 H), 7.53 (m, 1 H); IR 1602 cm^{-1}. Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90. Found: C, 76.00; H, 4.71; N, 5.78.

***N*-[Di(2-thiazolyl)methylene]aniline (5g)**: yield 99%; mp 120–121 °C: NMR δ 6.60–7.25 (m, 5 H), 7.32 (d, J = 3 Hz, 1 H), 7.42 (d, J = 3 Hz, 1 H), 7.73 (d, J = 3 Hz, 1 H), 7.87 (d, J = 3 Hz, 1 H); IR 1606 cm^{-1}. Anal. Calcd for $C_{13}H_9N_3S_2$: C, 57.54; H, 3.34; N, 15.49. Found: C, 57.46; H, 3.25; N, 15.37.

***N*-[Bis(1-methylpyrrol-2-yl)methylene]aniline (5h)**: yield 87%; mp 53–55 °C; NMR δ 3.00 (s, 3 H), 3.92 (s, 3 H), 5.88–7.25 (m, 11 H); IR 1571 cm^{-1}. Anal. Calcd for $C_{17}H_{17}N_3$: C, 77.53; H, 6.51; N, 15.96. Found: C, 77.43; H, 6.43; N, 16.00.

***N*-[α-(2-Furanyl)benzylidene]aniline[13] (8a)**: yield 95%; mp 72–73 °C; NMR δ 6.10–7.90 (m). Anal. Calcd for $C_{17}H_{13}NO$: C, 82.55; H, 5.30. Found: C, 82.53; H, 5.35.

***N*-(2-Furanyl-2-thienylmethylene)aniline (8c)**: yield 96%; oil; NMR δ 6.10–6.55 (m, 2 H), 6.66–7.70 (m, 9 H). Anal. Calcd for $C_{15}H_{11}NOS$: C, 71.12; H, 4.38. Found: C, 71.20; H, 4.41.

General Procedure for the Preparation of Ketones 6a–h and 9a,c. A solution of Schiff's base **5a–h** (1.0 mmol) in methanol (15 mL) was treated with a 5% solution of HCl in aqueous methanol (1:1, 5 mL), and the mixture was stirred at 23 °C for 2 h. Then the mixture was diluted with water (10 mL) and extracted with ether. The ether was washed with an aqueous solution of $NaHCO_3$, dried over Na_2SO_4, and concentrated. Crude ketones **6** were purified by flash chromatography on silica gel (triethylamine/hexanes, 1:1), and the purified samples were crystallized from dry hexanes. **6a**: yield 99%; mp 49–51 °C. **6b**: yield 95%; mp 69–71 °C (lit.[6b] mp 72 °C). **6c**: yield 99%; mp 86–88 °C (lit.[6f] mp 87–88.5 °C). **6d**: yield 95%; mp 75–78 °C (lit.[6h] mp 78–80 °C); NMR δ 7.90 (dd, J = 3 Hz, J = 2 Hz, 2 H), 7.52 (dd, J = 5 Hz, J = 2 Hz, 2H), 7.27 (dd, J = 5 Hz, J = 3 Hz). **6e**: yield 95%; mp 167–169 °C (lit.[6i] mp 167.5 °C); NMR δ 8.07 (s, 2 H), 7.13–7.97 (m, 8 H). **6f**: yield 92%; mp 30–32 °C (lit.[6j] mp 33 °C). **6g**: yield 92%; mp 138–140 °C (lit.[6k] mp 140–141 °C). **6h**: yield 84%; mp 24–26 °C (lit.[6o] mp 25–26 °C). Schiff's bases **8a,c** were hydrolyzed using the same procedure. **9a**: yield 93%; mp 42–44 °C (lit.[6v] mp 43.5–44 °C). **9c**: yield 92%; oil [lit.[6w] bp 140–141 °C (5 mm)]. Ketones **6** and **9** gave NMR spectra virtually identical with those published: **6b**,[6d,e] **6c**,[6x] **6f**,[6y] **6g**,[6k,m] **6h**,[6n–p] **9a**,[6z] **9c**.[6x]

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Registry No. 1, 6780-49-0; **3a**, 538-51-2; **3c**, 5918-68-3; **4a**, 1865-12-9; **4b**, 123209-08-5; **4c**, 123209-09-6; **4d**, 123209-10-9; **4e**, 123239-43-0; **4f**, 123209-11-0; **4g**, 123209-12-1; **4h**, 123209-13-2; **4i**, 29647-68-5; **5a**, 574-45-8; **5b**, 62093-69-0; **5c**, 123209-15-4; **5d**, 123209-16-5; **5e**, 123209-17-6; **5f**, 123209-18-7; **5g**, 123209-19-8; **5h**, 123209-20-1; **6a**, 119-61-9; **6b**, 1018-97-9; **6c**, 704-38-1; **6d**, 26453-81-6; **6e**, 97978-07-9; **6f**, 17920-86-4; **6g**, 55707-55-6; **6h**, 80838-84-2; **7a**, 36749-19-6; **7b**, 779-54-4; **7c**, 123209-14-3; **8a**, 123209-21-2; **8c**, 123209-22-3; **9a**, 2689-59-0; **9c**, 20409-51-2; PhMgBr, 100-58-3; PhLi, 591-51-5; *o*-MeC_6H_4Li, 6699-93-0; BuLi, 109-72-8; 2-thienylmagnesium bromide, 5713-61-1; 2-thienyllithium, 2786-07-4; 3-thienyllithium, 1192-06-9; 2-benzo[*b*]thienyllithium, 50779-55-0; 2-furyllithium, 2786-02-9; 2-thiazolyllithium, 40610-14-8; (*N*-methyl-2-pyrrolyl)lithium, 31785-72-5.

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A Practical, Efficient Large-Scale Synthesis of 1,6-Anhydrohexopyranoses[1]

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1,6-Anhydrohexopyranoses have proven to be valuable synthons for the preparation of biologically important and structurally diverse natural products (e.g. rifamycin S,[3a] indanomycin,[3b] thromboxane B2,[3c] (+)-biotin,[3d] tetrodotoxin,[3e] quinone,[3f] and macrolide[3g] antibiotics, etc.) as well as for modified sugars.[4,5] Their [3.2.1]bicyclic framework elicits high stereo- and regioselectivities, and the fact that the pyranose ring is locked in the $^1C_4$ conformation generates stereocenters which are opposite to those encoun-

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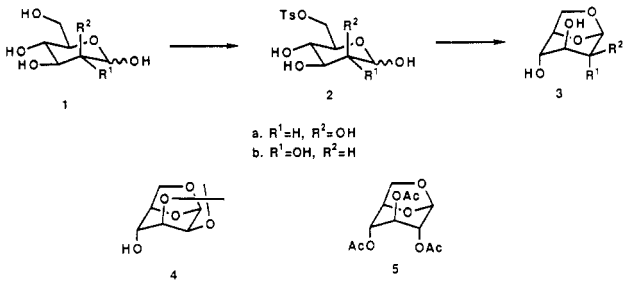
Scheme I



tered with the conventional $^4C_1$ counterparts. In addition to these topological properties,[6] the internal acetal reduces the number of protecting groups that are needed. In spite of these advantages the use of these substances has been limited by a lack of procedures to generate large quantities of these compounds in a rapid and reproducible manner.[7]

Our interest in the subject goes back several years ago, when we needed reasonable quantities of 1,6-anhydro-β-D-mannopyranose (**3a**) for a synthesis of sibirosamine.[4] We then developed a very simple, 1-g scale procedure from D-mannose,[8] which was modeled after an earlier method by Angyal.[9] Subsequently our procedure was adapted for small scale synthesis of levoglucosan (1,6-anhydro-β-D-glucopyranose) from D-glucose by Van Boom and coworkers.[10]

Larger quantities of these anhydro sugars could be obtained by the pyrolytic procedures.[11] However, the idiosyncrasies of that process (including, for example, the commercial source of the glycan to be pyrolyzed) have prompted us to re-evaluate our earlier route.[8]

Here we report a practical and efficient procedure that allows us to obtain 32 g of 2,3-isopropylidene-1,6-anhydro-β-D-mannopyranose (**4**) from 100-g batches of D-mannose **1a** (29% yield). This result provides a very consistent route for the large-scale preparation of the 1,6-anhydromannopyranose derivatives. Similarly, application of this procedure for preparation of 1,6-anhydro-β-D-glucopyranose provided 39 g of the 2,3,4-triacetate derivatve **5** (24% from D-glucose **1b**). Although higher yields of the latter compound by alternatives routes have been reported,[7] our method has the following advantages: (a) the starting materials are the free, unprotected sugars, (b) the reagents required (pyridine, tosyl chloride, and sodium hydroxide) are cheap and readily available, (c) the techniques involved are standard laboratory manipulations, (d) the formation of the anhydro sugar is a one-pot procedure, and (e) the isolation of the anhydro derivatives **4** and **5** is done by direct crystallization.

The method is based on the selective tosylation of the primary hydroxyl group of the free sugar under carefully controlled conditions, followed by the intramolecular displacement of the C-6 tosylate by the anomeric hydroxyl group on treatment of the reaction mixture with aqueous sodium hydroxide (Scheme I).

Thus from D-mannose or D-glucose the major products present in the reaction mixture after this two-step, one-pot procedure are the desired 1,6-anhydro-β-D-manno or -gluco derivatives **3a** or **3b**, respectively. However, workup procedures on this scale proved to be exceedingly difficult, causing the yields of isolated products to be very low. This was mainly due to the large amount of salts that hampered removal of the solvents (water and pyridine) prior to the derivatization to the more easily isolable forms **4** and **5**, respectively.

Initial attempts to isolate **3a** or **3b** from the reaction mixture by liquid–liquid continuous extraction were only marginally successful. An alternative method consisted of the addition of Celite to the crude reaction mixture (around 70 g for the 100-g scale reaction) followed by the rotary evaporation of the solvents and drying overnight under high vacuum. The solid residue so obtained was suitable for soxhlet extraction using ethyl acetate or acetonitrile. Treatment of the crude anhydro sugar **3a** with 2,2-dimethoxypropane in acetone, followed by crystallization afforded the 2,3-isopropylidene-1,6-anhydro-β-D-mannopyranose **4**.

However, a much simpler procedure resulted from the treatment of the rotary-evaporated crude reaction mixture with ethanol followed by filtration through florisil. In this way most of the salts were removed and the crude 1,6-anhydro sugar obtained after evaporation could be easily derivatized to the 2,3-isopropylidene **4** or the 2,3,4-triacetate **5**, and isolated by crystallization.

In summary, large quantities of the 1,6-anhydro sugars **4** and **5** are now quickly and efficiently available via the process reported herein, and the only limitation to further scale up should be the size of available glassware. This should enhance their proven synthetic utility and broaden their application for the preparation of optically active compounds.

Experimental Section

D-Mannose and D-glucose were used as obtained from chemical supply houses. Commercial freshly opened pyridine was allowed to sit over potassium hydroxide overnight before use. *p*-Toluenesulfonyl chloride was purified by extracting a diethyl ether solution with 3 N sodium hydroxide until the aqueous extracts were colorless. After drying (Na_2SO_4) and rotary evaporation, the white solid so obtained was stored overnight under high vacuum. The glassware was oven-dried and allowed to cool under an argon atmosphere just prior to use. The reactions were monitored by TLC using precoated silica gel aluminum plates containing a fluorescent indicator (5539 Merck). Detection was by charring with a solution of ammonium molybdate(VI) tetrahydrate (12.5 g) and cerium(IV) sulfate tetrahydrate (5 g) in 10% aqueous sulfuric acid (500 mL).

General Procedure. A 2-L round-bottom flask, equipped with a Claisen tube to which a thermometer and a 250-mL pressure-equalizing dropping funnel were attached, was charged with D-mannose[12a] or D-glucose (100 g, 0.56 mol) and pyridine (400 mL or 1 L, respectively). To this magnetically stirred suspension, a solution of *p*-toluenesulfonyl chloride (158.7 g, 0.83 mol, 1.5 equiv) in pyridine (300 mL) was added, keeping the internal temperature of the reaction between 20 and 25 °C (18 and 22 °C for D-glucose) with the aid of an ice–water bath.[12b] After stirring for 30 additional min (90 min for D-glucose),[13] the reaction mixture

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(12) (a) On scales of 300 g or larger, the use of 1.1 equiv of tosyl chloride is recommended. This suppresses the formation of side products that inerfere with the isolation of the final compound **4**. (b) This addition process requires about 30 min. The reaction mixture becomes homogeneous after approximately one-third of the *p*-toluenesulfonyl chloride has been added.

(13) At this point the main product by TLC is the 6-*O*-tosyl derivative **2a** or **2b**: R_f (**2a**, 20% MeOH/CH_2Cl_2) = 0.53; R_f (**2b**, 25% MeOH/CH_2Cl_2) = 0.53.

was brought to pH 9 and carefully maintained at this value by addition of 3 N aqueous sodium hydroxide.[14] After 90 min (60 min for D-glucose),[15] the pH was carefully raised to 7 by addition of 3 N HCl (typically only 2–4 mL were necessary), and the solvents were eliminated under reduced pressure. Azeotropic removal of pyridine with toluene (3 × 200 mL) gave a semisolid that was triturated with absolute ethanol and filtered through florisil (200-mesh size from Aldrich Chemical Co.), typically a pad ~14 cm wide and 5 cm deep. Impurities, which show up as a brown residue, were not allowed to penetrate through the pad. Washing with ethanol was continued until the filtrate was free of sugar derivatives (TLC, ~2 L EtOH). Rotary evaporation of the solvent afforded the desired crude 1,6-anhydro sugars **3a** and **3b**, which were dried under high vacuum and derivatized to the crystalline derivatives **4** and **5**, respectively.

1,6-Anhydro-2,3-isopropylidene-β-D-mannopyranose (4). 1,6-Anhydro-β-D-mannopyranose (**3a**), obtained as described above, was treated with acetone (reagent grade, 800 mL) and stirred with heating until only a free-flowing solid remained (~30 min). Dimethoxypropane (300 mL) and *p*-toluenesulfonic acid (5 g) were added, and the mixture was stirred until no mannosan **3a** was detected by TLC. After basification with triethylamine (pH 8) and filtration to remove the white solid, the solvents were rotary evaporated, and the residue was taken in ethyl acetate and filtered through florisil. Removal of the solvents under reduced pressure afforded the crude acetonide **4**, which was recrystallized from ethyl acetate as clear needles (32 g, 29% from **1a**, R_f (80% EtOAc/hexane) = 0.48); mp 157 °C (lit.[11b] mp 161–162 °C). Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.59; H, 7.16.

2,3,4-Tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (5). To the crude 1,6-anhydro-β-D-glucopyranose (**3b**), obtained as described above, were added acetic anhydride (314 mL, 3.3 mol, 2 equiv), (*N*,*N*-dimethylamino)pyridine (6.80 g, 56 mmol, 0.1 equiv), and ethyl acetate (300 mL), and the mixture was stirred until no **3b** was detected by TLC. The reaction mixture was quenched with ethanol (125 mL) and treated with solid sodium bicarbonate until CO_2 evolution ceased (additional ethyl acetate (~1 L) was added to facilitate stirring). Filtration through florisil and evaporation of the solvents under reduced pressure gave crude triacetate **5**, which was crystallized from methyl *tert*-butyl ether (24 g, 15%, R_f (40% acetone/hexane) = 0.37). Concentration of the mother liquors and column chromatography on silica gel (eluent: 60% diethyl ether–hexanes), followed by recrystallization, afforded another 15 g of **5**, raising the yield to 24%: mp 106 °C (lit.[10] mp 108–109 °C).

Registry No. **3a**, 14168-65-1; **3b**, 498-07-7; **4**, 14440-51-8; **5**, 13242-55-2; D-mannose, 3458-28-4; D-glucose, 50-99-7.

(14) During this process the reaction color changes from pale yellow to deep yellow, at which stage a white precipitate begins to form. Further addition of sodium hydroxide causes the precipitate to redissolve, with development of a deep red color. This color formation was found to be indicative of a pH of 9.

(15) At this point the main product by TLC is the 1,6-anhydro sugar **3a** or **3b**: R_f (**3a**, 20% MeOH/CH_2Cl_2) = 0.38; R_f (**3b**, 20% MeOH/CH_2Cl_2) = 0.43.

Novel Synthesis of Cyclohexa-2,4-dien-1-ones. Its Use in a Partial Synthesis of the Chromophore Portion of Phomenoic Acid

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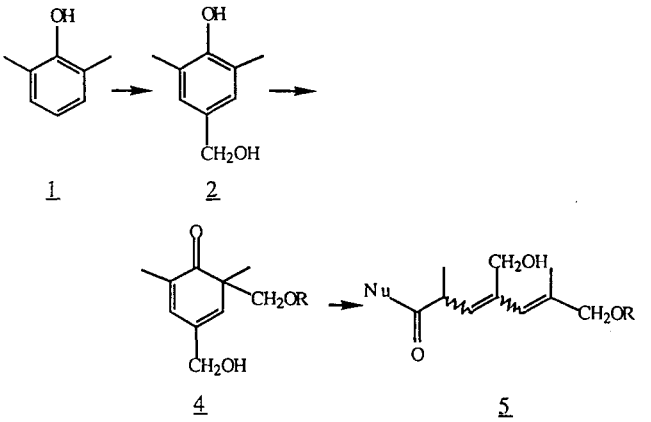
The interesting structural feature of phomenoic acid[1] and phomenolactone[2] isolated from the mycelium of the fungus *Phoma lingum* Tode lies in the diene system. Hence the partial synthesis of this unit containing the diene system was undertaken, hoping to establish a general method for such diene fragments.

Scheme I



The photochemical cleavage of cyclohexa-2,4-dien-1-ones is well established.[3] Based on the same principle Scheme I was considered.

Hydroxymethylation of 2,6-dimethylphenol **1** to give phenol **2** can be easily accomplished by formaldehyde and base.[4] However further hydroxymethylation leading to the cyclohexadienone **4** is not known. Our efforts in using *tert*-butyl alcohol–potassium *tert*-butylate as the medium, chloromethyl methyl ether as a hydroxymethyl equivalent, and phenol **3** as a substrate led to the formation of cyclohexadienone **6** in trace quantities. However, when this method was applied to phenol **2**, formation of cyclohexadienone **4** was not observed.

Alkali metal phenolates are known to give ethers when treated with chloromethyl methyl ether.[5] In aryl metalation studies the methoxymethyl group allows regiospecific aryl metalation and subsequent reaction with a variety of electrophiles in good yields.[6] Coordinative and inductive effects are operative in ortho-lithiation of alkylaryl ethers.[7] This indicates the methoxymethyl group's ability to bind alkali metals and its pronounced binding capability toward lithium. Taking into consideration of these facts, when lithium phenolate **3** was treated with chloromethyl methyl ether, cyclohexadienone **6** was obtained in 65% yield. Similarly when the same phenolate **3** was treated with chloromethyl benzyl ether, the cyclohexadienone **7** was obtained in 75% yield. When the above method was applied to the lithium salt of phenol **2** using chloromethyl benzyl ether, cyclohexadienone **8** was obtained in 66% yield (see Table I).

Furthermore, the advantage of lithium as an efficient phenolate counter cation and its enhanced ability to complex with the methoxymethyl group as well as the (ben-

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