1,1-Dichloro-2-ethyl-3-propylcyclopropane was prepared from (*E*)-3-heptene (62% yield): bp 70–80 °C (10–15 Torr) (lit.[30] bp 76–77 °C (20 Torr)); ^{1}H NMR δ 0.7–1.24 (8 H, m), 1.24–1.76 (6 H, m); MS (CI, NH_3) *m/e* (relative intensity) 184, 182, 180 (2, 5, 8; isotopic cluster for Cl_2), 109 (100, C_7H_{13}). Anal. Calcd for $C_8H_{14}Cl_2$: C, 53.06; H, 7.79. Found: C, 52.78; H, 7.60.

1,1-Dichloro-2-methyl-2-*tert*-butylcyclopropane was prepared from 2,3,3-trimethyl-1-butene (62.2% yield): bp 70–75 °C (15 Torr); ^{1}H NMR δ 1.08 (1 H, d, *J* = 7), 1.10 (9 H, s), 1.32 (3 H, s), 1.60 (1 H, d, *J* = 7). The compound has been reported, but without characterization data.[31] Anal. Calcd for $C_8H_{14}Cl_2$: C,53.06; H, 7.79. Found: C, 53.14; H, 7.92.

Methylcyclohexadienes. A mixture of methylenecyclohexane (50%), 2-methyl-1,3-cyclohexadiene (36%), 1-methylcyclohexadiene, and 5-methylcyclohexadiene (14% for the latter two isomers) was prepared in 85% yield (distilled) by heating 1-methyl-2-cyclohexen-1-ol in DMSO at 160–170 °C for 2.75 h according to the general method of Traynelis, Hergenrother, Hanson, and Valicenti.[32] The mixture was analyzed by GC and NMR procedures.

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Registry No. **7** (R_1 = R_2 = H; R_3 = *n*-Am), 3722-09-6; **7** (R_1 = Et; R_2 = H; R_3 = *n*-Pr), 40347-50-0; **7** (R_1 = H; R_2 = Me; R_3 = *t*-Bu), 85653-76-5.

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An Improved Synthesis of (−)-(2*R*,5*R*)-2,5-Dimethylpyrrolidine

Robert P. Short, Robert M. Kennedy, and Satoru Masamune*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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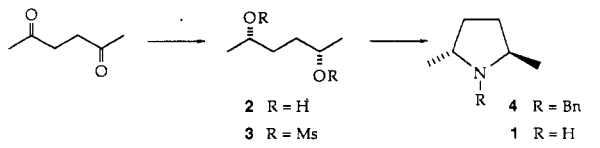
Reagents of C_2 symmetry have demonstrated utility in asymmetric synthesis.[1] With the notable exception of those derived from tartaric acid,[2] most C_2 symmetrical reagents are of synthetic origin, and thus, the preparation of these substances in optically pure form is subject to continual refinement.

As part of the strategy of reagent-controlled asymmetric synthesis,[3] we were interested in developing new reagents of C_2 symmetry and noted with particular interest the isostructural relationship between the titled compound (**1**)[4] and *trans*-2,5-dimethylborolane.[5a] The latter reagent,

Scheme I



developed in our laboratories, effects near-complete asymmetric induction in the hydroboration[5b] and aldol reactions[5c] and also in the reduction of aryl and aliphatic ketones.[5d,e]

Continuing interest in *trans*-2,5-dimethylpyrrolidine has been evidenced by recent reports on the application[6] and synthesis[7] of this versatile base, and we therefore wish to report a reaction sequence (Scheme I) which, by emphasizing brevity and minimal purification of intermediates, provides for the rapid synthesis of multigram quantities of **1** in optically pure form.

Experimental Section

Boiling points and melting points are uncorrected. Reactions were run in oven-dried glassware under Ar. Methanesulfonyl chloride was distilled before use. Triethylamine, benzylamine, and dichloromethane were distilled from CaH_2 in an atmosphere of dry N_2. Enzymatic reductions employed Fleishmann's "active dry yeast", distributed through local retail grocers. ^{1}H NMR spectra were recorded at 250 MHz on a Bruker WM 250 spectrometer, and ^{13}C NMR spectra were recorded on a Bruker WM 270 (67.9 MHz) or Varian XL-400 (100.6 MHz) spectrometer as indicated. Optical rotations were recorded on an Autopol III polarimeter. HPLC analysis was performed on a Waters 6000A instrument equipped with a Chemcosorb 3 Si column (4.6 × 250 mm) and UV detection (254 nm). Analytical gas chromatography was performed on a Hewlett-Packard 5880A instrument using a 12-m cross-linked methyl silicone column. Mass spectra were obtained with a Finnigan MAT 8200 spectrometer. Commercial (*S*)-(−)-MTPA (Aldrich) was upgraded to >99.5% ee by recrystallization of the (−)-phenylethylamine salt, and MTPA derivatives were prepared by the method of Mosher.[8]

(+)-(2*S*,5*S*)-2,5-Hexanediol (2). Reduction of 2,5-hexanedione with baker's yeast was carried out as described by Lieser[9] (0.125-mol scale) to give diol **2** (7–8 g, 50% yield) after chromatography over silica gel (EtOAc) and distillation, bp 122–125 °C (20 mm). The product solidified on standing, mp 48–53 °C, $[\alpha]^{24}_D$ +33.1° (*c* 9.87, $CHCl_3$) [lit.[10] mp 53.0–53.3 °C, $[\alpha]^{25}_D$ +35.1° (*c* 9.49, $CHCl_3$)]. HPLC analysis of the corresponding bis-MTPA esters (7% ether/hexane, 2 mL/min) indicated the presence of *S,S*, *R,S*, and *R,R* diols in the ratio 49.8:1.04:1.00 (96% ee, 2% meso). This could be upgraded to >98% ee, <1% meso by recrystallization from Et_2O [80% recovery, mp 52–53 °C, $[\alpha]^{24}_D$ +34.9° (*c* 9.48, $CHCl_3$)]. The combined product from six runs was used in the following reaction.

(−)-*N*-Benzyl-(2*R*,5*R*)-2,5-dimethylpyrrolidine (4). To a solution of (+)-(2*S*,5*S*)-2,5-hexanediol (**2**) (46.5 g, 0.39 mol) in 800 mL of CH_2Cl_2 was added triethylamine (137 mL, 0.98 mol). The solution was cooled to −15 °C, and methanesulfonyl chloride (67 mL, 0.87 mol) was added dropwise with vigorous stirring over 90 min while the temperature was maintained between −20 and −15

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°C. After addition was complete, the mixture was allowed to warm to 0 °C and then poured into 500 mL of cold 1 N HCl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were washed with 500 mL of saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The resulting oil (110 g) was homogeneous by silica gel TLC (R_f 0.55, EtOAc) and was used directly.

Bis(methanesulfonate) **3**[11] was dissolved in benzylamine (250 mL) and allowed to stand at ambient temperature for 96 h. The mixture (from which benzylammonium methanesulfonate had crystallized) was transferred to 1 L of cold 2 N NaOH, and the resulting solution was extracted with pentane (4 × 400 mL). The combined organic layers were concentrated and distilled to afford 64.9 g of **4** as a clear oil, bp 83–84 °C (2 mm).

A forerun containing benzylamine was filtered through alumina (activity I), eluting with 10% Et_2O/hexane. Concentration of the eluate afforded an additional 1.3 g of **4** for a total yield of 66.2 g (89%): $[\alpha]^{24}_D$ −109.7° (*c* 1.97, MeOH); ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (d, 6 H, *J* = 6.1 Hz), 1.25–1.45 (m, 2 H), 1.85–2.05 (m, 2 H), 2.90–3.04 (m, 2 H), 3.46 and 3.79 (AB q, 2 H, J_{AB} = 13.8 Hz), 7.12–7.37 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 16.9, 30.9, 51.6, 54.9, 126.3, 128.0, 128.3, 140.8; mass spectrum (70 eV) *m/z* (relative intensity) 190 (M + H, <1), 189 (M^+, 4), 174 (58), 91 (100).

(−)-(2*R*,5*R*)-2,5-Dimethylpyrrolidine (1). *N*-Benzylpyrrolidine **4** (39.3 g, 0.21 mol) was dissolved in glacial acetic acid (75 mL). The solution was transferred to a 500-mL Parr bottle, and 10% $Pd(OH)_2$ on carbon (2 g) was added. The mixture was shaken under H_2 (30–40 psig) for 36 h and filtered, and the catalyst was washed with methanol (2 × 10 mL). The filtrate was concentrated at 0 °C under vacuum (ca. 1 mm), and the resulting viscous oil was diluted with water (50 mL) and Et_2O (100 mL). At 0 °C, 50% NaOH (50 mL) was added dropwise over 30 min. The aqueous solution was extracted with ether (4 × 100 mL), and the combined organic layers were dried over KOH pellets. Ether was removed by careful fractional distillation, and the product was collected at 102–103 °C as a clear liquid (18.6 g). A small forerun was acidified with ethereal HCl, and 0.91 g of the amine was collected as the hydrochloride salt. The total yield was 19.5 g (94%) of **1**: ^1H NMR (250 MHz, $CDCl_3$) δ 1.12 (d, 6 H, *J* = 6.2 Hz), 1.20–1.40 (m, 3 H), 1.85–2.10 (m, 2 H), 3.20–3.40 (m, 2 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.2, 34.7, 53.2.

1·HCl: mp 200–203 °C; $[\alpha]^{24}_D$ + 5.57° (*c* 1.18, CH_2Cl_2) [lit.[7] mp 197–200 °C, $[\alpha]_D$ +5.47° (*c* 3.0, CH_2Cl_2)]; ^1H NMR (300 MHz, $CDCl_3$)[12] δ 1.52 (d, 6 H, *J* = 7.2 Hz), 1.55–1.80 (m, 2 H), 2.10–2.30 (m, 2 H), 3.75–3.90 (m, 2 H), 9.50–9.80 (br s, 2 H).

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Registry No. 1, 62617-70-3; 1·HCl, 70144-18-2; (*S*,*S*)-**2**, 34338-96-0; (*R*,*S*)-**2**, 38484-55-8; **3**, 119008-52-5; **4**, 119008-53-6; 2,5-hexanedione, 110-13-4; benzylamine, 100-46-9.

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An Improved Preparation of the Avermectin Disaccharide Unit

Timothy A. Blizzard,* Gaye Marino, Helmut Mrozik, and Michael H. Fisher

Merck Sharp and Dohme Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

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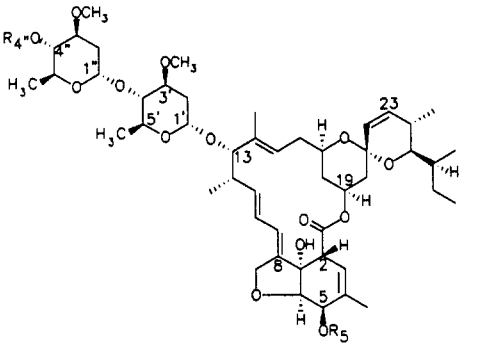
The avermectins and milbemycins are naturally occurring macrocyclic lactones with important anthelmintic and pesticidal activity.[1] The avermectins differ from the milbemycins primarily in the incorporation of a disaccharide (oleandrosyloleandrose) unit attached through an oxygen atom at position 13 of the macrocyclic ring. The extremely high antiparasitic activity of the avermectins has generated considerable interest in the synthesis of these compounds.[2] These synthetic efforts have been highlighted by the recent total synthesis of avermectin A_1 (**1a**) by Danishefsky et al.[2a,b] and the synthesis of avermectin B_1 (**1b**) by Hanessian et al.[2c,d] An important



1a $R_{4''}$ = H , R_5 = CH_3
1b $R_{4''}$ = R_5 = H
1c $R_{4''}$ = R_5 = TBDMS

consideration in the planning of an avermectin synthesis is the source of the requisite disaccharide unit (**2**). Danishefsky and co-workers solved this problem by devising a total synthesis of **2** (10 steps from acetaldehyde to the glycal analogue of 2-4″-acetate).[2b] Other total syntheses of derivatives of **2** have been developed by Nicolaou,[3a] by Wuts,[3b] and by Barrett.[3c] An alternative method is to prepare **2** by chemical degradation of a naturally occurring avermectin. This was the approach used by Hanessian and co-workers to prepare **2** (five steps from avermectin B_1)[3d] required for their synthesis of avermectin B_1.[2c,d] This method appears to be more convenient when large amounts of material are required for synthesis of avermectin analogues from aglycone derivatives, provided one has access to a large supply of natural avermectin B_1. We therefore focused on this approach when we required material for a program of avermectin analogue synthesis.

The method used by Hanessian et al.[3d] to prepare **2** involved five steps and was apparently designed primarily

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