pad was washed twice with 10 mL of CH_2Cl_2, and the combined filtrate was concentrated in vacuo to obtain a red oil. Chromatographic separation of the title compound was achieved by using a short silica gel flash column [CH_2Cl_2 followed by CH_2Cl_2/EtOAc (9:1)] to obtain 0.17 g (94% from **3**) of **6** as an oil: NMR ($CDCl_3$) δ 1.3 (two d, J = 7 Hz, CH_3CH), 1.6 (br, THP methylenes), 3.5 (dd, J = 3 and 6 Hz, H3), 3.9 and 4.4 (two d, J = 18 Hz, N-CH_2), 4.55 (m, $COOCH_2$), 5.2 (m, $=CH_2$), 5.8 (m, CH=), 6.05 (d, J = 2 Hz, H4), 7.2-8 (m, aromatic); MS (FAB, thioglycerol) m/e 516 $(M + H)^+$.

Allyl (5*R*,6*S*)-2-[[2-(Carbamoyloxy)ethyl]thio]-6-[(*R*)-1-(tetrahydropyranyloxy)ethyl]penem-3-carboxylate (8). Steps f-h. (A) From 6. Step g. To a vigorously stirred solution of 0.89 g (1.72 mmol) of **6** in 40 mL of dry THF at -78 °C was added 2.5 mL (2.5 mmol) of 1 M $LiN(SiMe_3)_2$ in hexane. The reaction mixture was stirred for 10 min, and then 1.27 mL of glacial CH_3COOH followed by 85 mL of EtOAc was added. This cold (0 °C) solution was quickly washed with 25 mL of 2% aqueous tartaric acid solution followed by 30 mL of cold (5 °C) distilled H_2O. The cold aqueous phases were back-extracted with cold (0 °C) EtOAc; the EtOAc extract was treated as above and combined with EtOAc/THF extract. The combined, cold (0 °C) organic phase was dried over $MgSO_4$ and then concentrated in vacuo at $\leq$0 °C to obtain 0.93 g of an orange oil containing **7** and β-naphthol. Compound **7** was not isolated from this oil but was directly converted to **8** as given below.

Step h. To a stirred solution of the above oil in 11 mL of THF was added 0.41 g (2.06 mmol) of iodoethyl carbamate, followed by 0.17 g (2.06 mmol) of $NaHCO_3$ in 2 mL of H_2O. Approximately 1 mL of CH_3CN was added after 5 min to avoid the formation of two phases. The reaction mixture was stirred at room temperature for 18 h, diluted with 120 mL of CH_2Cl_2, and washed thoroughly with 25 mL of brine containing traces of Na_2SO_3, followed by 25 mL of distilled H_2O. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to obtain 1.05 g (quantitative from **6**) of oil consisting of the title compound and β-naphthol.

For the purpose of characterization, the above oil was column chromatographed [silica gel, CH_2Cl_2 followed by CH_2Cl_2/MeOH (96:4)] to obtain 0.58 g (73.4% from **6**) of **8** as a viscous oil and 0.03 g (4.7% from **6**) of **9** (resulting from tetrahydropyranyl ether cleavage during the workup and column chromatography). **8**: NMR ($CDCl_3$) δ 1.3 (two d, J = 7 Hz, CH_3CH), 1.6 (br, THP methylenes), 3.15 (m, SCH_2), 3.75 (dd, J = 1.5 and 6 Hz, H6), 4.3 (m, CH_2OCO), 4.6 (m, CO_2CH_2), 5.3 (m, $=CH_2$), 5.6 (d, J = 1.5 Hz, H7), 5.8 (m, CH=), 7.2 (br, 2 H, $CONH_2$); MS (FAB, thioglycerol) m/e 458 $(M)^+$.

(B) From 5. Step f. A solution of 0.09 g (0.20 mmol) of **5** in 15 mL of dry THF was converted to **7** as described above under step g with one difference. After the reaction mixture was quenched with 0.15 mL of glacial CH_3COOH, the EtOAc solution was washed thoroughly with 30 mL of 2% aqueous tartaric acid to remove imidazole. This reaction gave 0.07 g of **7** as an orange oil. [TLC [silica gel, EtOAc/CH_2Cl_2 (2:8)] of this oil indicated slight desilylation and slight decomposition. See text for details.]

Step h. Compound **7** was converted to compound **8** as described above in 85% (from **5**) yield.

Allyl (5*R*,6*S*)-2-[[2-(Carbamoyloxy)ethyl]thio]-6-[(*R*)-1-hydroxyethyl]penem-3-carboxylate (9). Step i. To a stirred solution of 0.35 g (0.76 mmol) of **8** in 10 mL of 80% aqueous EtOH under N_2 was added 0.04 g (0.15 mmol) of pyridinium p-toluenesulfonate. The reaction mixture was stirred at 45° C for 8 h, and then 0.03 g (0.15 mmol) of p-toluenesulfonic acid was added. The reaction mixture was stirred for 1 h more, and the solvent was removed in vacuo. The resultant oil was taken in 120 mL of EtOAc and washed with distilled H_2O, distilled H_2O containing a small amount of $NaHCO_3$, and finally distilled H_2O. The organic phase was dried over Na_2SO_4 and then concentrated in vacuo to obtain a yellow solid. Silica gel column chromatography [MeOH/CH_2Cl_2 (5:95)] of this solid gave 0.27 g (96%) of the title compound as a white solid.

The analytical sample was crystallized from CH_3CN: mp 152-152.5 °C; NMR (Me_2SO-D_6/$CDCl_3$) δ 1.17 (d, 3 H, J = 7 Hz, CH_3CH), 3.15 (m, 2 H, SCH_2), 3.65 (dd, 1 H, J = 1.5 and 6 Hz, H6), 3.8-4.3 (m, 3 H, CH_3CH and CH_2OCO), 4.6 (m, 2 H, $COOCH_2$), 5.1-5.4 (m, 2 H, $=CH_2$), 5.65 (d, 1 H, J = 1.5 Hz, H5), 5.75 (m, 1 H, CH=), 6.45 (br, 2 H, $CONH_2$); IR (Nujol) 3420, 3305, 1780, 1690, 1610 cm^{-1}; MS (FAB, thioglycerol) m/e 375 $(M + H)^+$; $[\alpha]_D$ +188.9 (c 0.46, Me_2SO). Anal. Calcd for $C_{14}H_{18}N_2O_6S_2$: C, 44.93; H, 4.81; N, 7.48; S, 17.13. Found: C, 44.88; H, 4.84; N, 7.44; S, 16.85.

(5*R*,6*S*)-2-[[2-(Carbamoyloxy)ethyl]thio]-6-[(*R*)-1-hydroxyethyl]penem-3-carboxylic Acid (10). Step j. The allyl ester deblocking on penems was accomplished as reported before:[7,8] NMR (Me_2SO-d_6) δ 1.15 (d, 3 H, J = 7 Hz, CH_3CH), 3.13 (m, 2, SCH_2), 3.76 (dd, 1 H, J = 1.52 Hz, H_6), 3.98 (br, H, $CHCH_3$), 4.12 (m, 2, CH_2OCO), 5.68 (d, 1 H, J = 1.5 Hz, H_5), 6.55 (br, 2 H, NH_2); IR (CH_2Cl_2) 3400, 1790, 1710, 1690 cm^{-1}; MS (FAB, thioglycerol) m/e 335 (M + H); $[\alpha]_D$ +208.7 (c 0.3, DMF).

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Synthesis of β-Benzyl *N*-(*tert*-Butoxycarbonyl)-L-*erythro*-β-(benzyloxy)aspartate from (*R*,*R*)-(+)-Tartaric Acid

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Various diastereomers of β-hydroxyaspartic acid occur in microorganisms and in fungi as free amino acids[1] and as constituents of peptides.[2] The free amino acid has also been found in urine from several mammals, including man.[3] Recently, L-*erythro*-β-hydroxyaspartic acid was found in several of the vitamin K dependent plasma proteins involved in the blood clotting cascade.[4] The role of this amino acid in these proteins is unknown. To facilitate further investigations of the biological role of β-hydroxyaspartic acid, we have developed a synthesis of β-benzyl-*N*-(*tert*-butoxycarbonyl)-L-*erythro*-β-(benzyloxy)aspartate (**8**), a derivative suitable for "solid-phase" peptide synthesis.

One of the main synthetic approaches to *erythro*-β-hydroxyaspartic acid has relied on the ammonolysis of *trans*-epoxysuccinic acid. Previously, resolution of the product obtained from racemic *trans*-epoxysuccinic acid was required.[5] Preparations of the chiral *trans*-epoxysuccinic acid esters have recently been reported.[6] Starting from (*R*,*R*)-(+)-tartaric acid and proceeding via diethyl (-)-*trans*-epoxysuccinate, L-*erythro*-β-hydroxyaspartic acid is thus obtained[7] in a procedure involving three consecutive inversions of one of the stereocenters in (*R*,*R*)-(+)-tartaric acid. We now report a synthesis of β-benzyl *N*-(*tert*-butoxycarbonyl)-L-*erythro*-β-(benzyloxy)aspartate (**8**)

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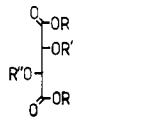
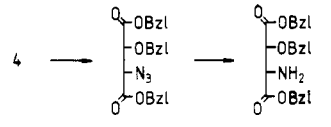
starting from (*R*,*R*)-(+)-tartaric acid with only one inversion of a stereocenter.

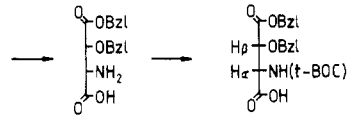
(*R*,*R*)-Tartaric acid (**1**) was converted[8] to dibenzyl (*R*,*R*)-(+)-tartrate (**2**) (89%), which, since the hydroxy groups are symmetry equivalent, yielded only one monobenzyl ether (**3**) on treatment with benzyl trichloroacetimidate.[9] Reaction of the alcohol **3** with trifluoromethanesulfonic anhydride[10] gave the triflate **4** (87%), which underwent nucleophilic substitution with tetrabutylammonium azide in dichloromethane to give the azide **5** in 90% yield.



1 R=R'=R''=H
2 R=Bzl R'=R''=H
3 R=R'=Bzl R''=H
4 R=R'=Bzl R''=CF_3SO_2



5 6



7 8

Attempted formation of the azide **5** from the alcohol **3** using diethyl azodicarboxylate (DEAD), triphenylphosphine, and hydrazoic acid resulted in elimination, in accord with other reports on similar systems.[11] Reduction of the azide **5** to the amine **6** was accomplished (80%) with hydrogen sulfide,[12] whereas catalytic hydrogenation[13] and reduction with sodium borohydride[14] were unsuccessful. Several methods[15] aiming at selective hydrolysis of the α-benzyl ester of **6** were found to be rather unselective. A procedure involving the addition of aqueous potassium hydroxide to a solution of the amine **6** in acetone–water was then adopted, providing the α-amino acid **7** in 46% yield. Reaction of **7** with di-*tert*-butyl dicarbonate gave β-benzyl *N*-(*tert*-butoxycarbonyl)-L-*erythro*-β-(benzyloxy)aspartate (**8**) in 71% yield.

The structural assignment of **8** as a β-benzyl ester of L-*erythro*-β-hydroxyaspartic acid was established by the addition of triethylamine to an NMR sample of **8** in Me_2SO-d_6. This resulted in downfield ^{13}C shifts of 0.63 and 0.15 ppm for C(α) and C(β), respectively, and in an upfield ^1H shift of 0.14 ppm for H(α) (no shift of the H(β) resonance). This is in accord with previous reports[16] on NMR shifts for titrations of amino acids. The optical purity of **8** was demonstrated by deprotection using HF, which gave L-*erythro*-β-hydroxyaspartic acid containing less than 1% of the *threo* isomer as determined by HPLC[4a] and with $[\alpha]^{20}_D$ +54° (*c* 0.88, 1 M HCl) [lit.[5] $[\alpha]^{20}_D$ +54.6° (*c* 1.9, 1 M HCl)].

Experimental Section

^1H NMR spectra were recorded on a Nicolet WB360 and a Varian XL-300 NMR spectrometer with Me_4Si as an internal standard. Melting points are uncorrected. Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254}. Organic solutions were dried over Na_2SO_4. Dibenzyl (*R*,*R*)-(+)-tartrate (**2**) was prepared by a modification of a known procedure,[8] from benzyl alcohol and (*R*,*R*)-(+)-tartaric acid with toluene-*p*-sulfonic acid as catalyst. Compound **2** had a melting point and optical rotation in agreement with the literature data[8] and gave a satisfactory elemental analysis.

Dibenzyl (2*R*,3*R*)-2-*O*-Benzyltartrate (3). Trifluoromethanesulfonic acid (0.80 mL) was added to a solution of **2** (8.00 g, 24.2 mmol) and benzyl trichloroacetimidate[9] (10.8 g, 48.2 mmol) in cyclohexane–CH_2Cl_2 (2:1, 240 mL). The solution was stirred at room temperature for 12 h, then washed with saturated aqueous hydrogen carbonate (3 × 75 mL), dried, and concentrated. Column chromatography (SiO_2, 1:4 EtOAc–hexane) of the residue followed by treatment with charcoal gave **3** (6.50 g, 64%); mp 50–52 °C; $[\alpha]^{20}_D$ +64.0° (*c* 1.0, EtOAc); IR (KBr) 3520 (OH), 1760 (ester C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.16 (1 H, d, J = 9.0 Hz, OH), 4.33 (1 H, d, J = 11.5 Hz, $COCH_2Ph$), 4.38 (1 H, d, J = 2.2 Hz, HC2), 4.66 (1 H, dd, J = 9.0 and 2.2 Hz, HC3), 4.78 (1 H, d, J = 11.5 Hz, $COCH_2Ph$), 5.02 (1 H, d, J = 11.9 Hz, CO_2CH_2Ph), 5.19 (1 H, d, J = 11.9 Hz, CO_2CH_2Ph), 5.24 and 5.26 (2 H, AB q, J_{AB} = 11.9 Hz, CO_2CH_2Ph). Anal. Calcd for $C_{25}H_{24}O_6$: C, 71.4; H, 5.75. Found: C, 71.5; H, 5.74.

Dibenzyl (2*R*,3*R*)-2-*O*-Benzyl-3-*O*-[(trifluoromethyl)-sulfonyl]tartrate (4). A solution of trifluoromethanesulfonic anhydride (2.55 g, 9.04 mmol) in dry CH_2Cl_2 (10 mL) was slowly added to a solution of pyridine (0.76 g, 9.48 mmol) in dry CH_2Cl_2 (10 mL) at −20 °C.[10] After the mixture was stirred for 5 min, a solution of **3** (3.04 g, 7.23 mmol) in CH_2Cl_2 (40 mL) was added during 20 min. The solution was stirred for 1.5 h at −20 °C and then concentrated. Flash chromatography (SiO_2, 1:4 EtOAc–hexane) of the residue gave **4** (3.46 g, 87%) as a syrup with $[\alpha]^{20}_D$ +46.1° (*c* 1.0, EtOAc): IR (neat) 1770 (ester C=O), 1420 (triflate) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.41 (1 H, d, J = 11.5 Hz, $COCH_2Ph$), 4.57 (1 H, d, J = 3.1 Hz, HC2), 4.76 (1 H, d, J = 11.5 Hz, $COCH_2Ph$), 5.09 (1 H, d, J = 11.5 Hz, CO_2CH_2Ph), 5.10 (1 H, d, J = 12.2 Hz, CO_2CH_2Ph), 5.22 (1 H, d, J = 12.2 Hz, CO_2CH_2Ph), 5.28 (1 H, d, J = 11.5 Hz, CO_2CH_2Ph), 5.54 (1 H, d, J = 3.1 Hz, HC3). Anal. Calcd for $C_{26}H_{23}O_8F_3S$: H, 4.20; S, 5.80. Found: H, 4.12; S, 5.80. (Interference from fluorine hinders the analysis of carbon.)

Dibenzyl (2*S*, 3*R*)-2-Azido-3-(benzyloxy)succinate (5). A solution of **4** (2.36 g, 4.27 mmol) in dry CH_2Cl_2 (50 mL) was added during 20 min to a solution of tetrabutylammonium azide[17] [*caution*[18]] (6.07 g, 21.3 mmol) in dry CH_2Cl_2 (50 mL) at −70 °C. After 2.5 h at −70 °C, the solution was allowed to attain room temperature and was then concentrated to 15 mL. The mixture was extracted with ethyl ether (5 × 25 mL), the combined ethereal extracts were concentrated, and the residue was subjected to flash chromatography (SiO_2, 1:4 EtOAc–hexane) to give **5** (1.72 g, 90%) as a syrup with $[\alpha]^{20}_D$ +50.3° (*c* 1.0, EtOAc): IR (neat) 2120 (azide), 1760 (ester C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.28 (1 H, d, J = 3.4 Hz, HC2), 4.41 (1 H, d, J = 3.4 Hz, HC3), 4.58 (1 H,

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d, J = 11.3 Hz, $COCH_2Ph$), 4.85 (1 H, d, J = 11.3 Hz, $COCH_2Ph$), 5.05 and 5.08 (2 H, AB q, J_{AB} = 12.2 Hz, CO_2CH_2Ph), 5.11 and 5.13 (2 H, AB q, J_{AB} = 12.4 Hz, CO_2CH_2Ph). Anal. Calcd for $C_{25}H_{23}O_5N_3$: C, 67.4; H, 5.20. Found: C, 67.4; H, 5.12.

Dibenzyl L-*erythro*-β-(Benzyloxy)aspartate (6). Hydrogen sulfide was led into a solution of **5** (400 mg, 0.90 mmol) and triethylamine (0.2 mL) in CH_2Cl_2 (20 mL) at room temperature.[12] After 4 h the solution was washed with water (10 mL), brine (10 mL), and aqueous sodium hydrogen carbonate (10 mL), then dried, and concentrated. Column chromatography (SiO_2, 1:3 EtOAc–hexane and then EtOAc) gave **6** (0.303 g, 80%) as a syrup with $[\alpha]^{20}_D$ +35.6° (*c* 1.0, EtOAc); IR (neat) 3400 (NH_2), 1750 (ester C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.01 (1 H, d, J = 3.8 Hz, HC(α)), 4.31 (1 H, d, J = 3.8 Hz, HC(β)), 4.48 (1 H, d, J = 11.5 Hz, $COCH_2Ph$), 4.84 (1 H, d, J = 11.5 Hz, $COCH_2Ph$), 5.01 and 5.08 (2 H, AB q, J_{AB} = 12.2 Hz, CO_2CH_2Ph), 5.06 (2 H, s, CO_2CH_2Ph). Anal. Calcd for $C_{25}H_{25}O_5N$: C, 71.6; H, 6.01; N, 3.34. Found: C, 72.3; H, 6.10; N, 3.38.

β-Benzyl L-*erythro*-β-(Benzyloxy)aspartate (7). Aqueous potassium hydroxide (0.25 M, 3.6 mL, 0.90 mmol) was added over a period of 3 h to a solution of **6** (380 mg, 0.91 mmol) and potassium iodide (150 mg, 0.90 mmol) in acetone–water (25:2, 54 mL) at −20 °C. After an additional 30 min, the solution was allowed to attain room temperature and the acetone was evaporated. The resulting aqueous phase was extracted with EtOAc (3 × 30 mL), from which **6** (202 mg) was recovered. Addition of aqueous acetic acid (0.125 M, 7.2 mL) to the aqueous phase gave a precipitate of **7** (76 mg). Two further cycles of hydrolysis were applied to recovered **6**, yielding 37 mg of **7**. Column chromatography (SiO_2, 15:2:1 EtOAc–HOAc–water) of the combined filtrates gave 24 mg of **7**, providing a total of 137 mg (46%) of crystalline **7** with mp 182–184 °C:$[\alpha]^{20}_D$ +49.1° (*c* 0.8, Me_2SO); IR (KBr) 3700–2100 (CO_2H, NH_2), 1760 (ester C=O) cm^{-1}; ^1H NMR (CD_3OD) δ 4.05 (1 H, d, J = 3.6 Hz, HC (α/β)), 4.54 (1 H, d, J = 3.6 Hz, HC (α/β)), 4.62 (1 H, d, J = 11.2 Hz, $COCH_2Ph$), 4.82 (1 H, d, J = 11.2 Hz, $COCH_2Ph$), 5.18 and 5.26 (2 H, AB q, J_{AB} = 12.2 Hz, CO_2CH_2Ph). Anal. Calcd for $C_{18}H_{19}O_5N$: C, 65.6; H, 5.81; N, 4.25. Found: C, 65.8; H, 5.82; N, 4.19.

β-Benzyl *N*-(*tert*-Butoxycarbonyl)-L-*erythro*-β-(benzyloxy)aspartate (8). Triethylamine (81 mg, 0.80 mmol) and di-*tert*-butyl dicarbonate (175 mg, 0.80 mmol) were added to a suspension of **7** (246 mg, 0.80 mmol) in DMF (9 mL). After 1 h, EtOAc (9 mL) and water (16 mL, acidified to pH 1–2 with aqueous 1 M $KHSO_4$) were added. The aqueous phase was extracted with EtOAc (9 mL), and the combined organic phases were dried and concentrated. Column chromatography (SiO_2, 1:1 EtOAc–hexane) of the residue gave **8** (246 mg, 71%) as a syrup with $[\alpha]^{20}_D$ +74.7° (*c* 1.0, EtOAc): IR (KBr) 3700–2400 (CO_2H, NH); ^1H NMR (acetone-d_6) δ 1.39 (9 H, s, Me_3C), 4.46 (1 H, d, J = 3.2 Hz, HC(β)), 4.60 (1 H, d, J = 11.5 Hz, $COCH_2Ph$), 4.84 (1 H, d, J = 11.5 Hz, $COCH_2Ph$), 4.86 (1 H, m, HC (α)), 5.24 (2 H, s, CO_2CH_2Ph), 6.00 (1 H, br d, NH). Anal. Calcd for $C_{23}H_{27}O_6N$: C, 64.3; H, 6.34; N, 3.26. Found: C, 64.2; H, 6.49; N, 3.14.

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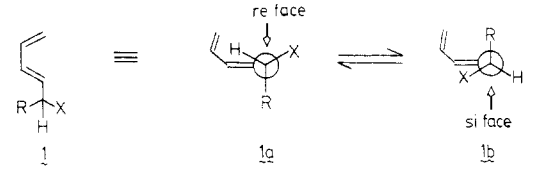
Registry No. 1, 87-69-4; 2, 622-00-4; 3, 103710-70-9; 4, 103710-71-0; 5, 103694-08-2; 6, 103694-09-3; 7, 103694-10-6; 8, 103694-11-7; benzyl trichloroacetimidate, 81927-55-1; trifluoromethanesulfonic anhydride, 358-23-6; di-*tert*-butyl dicarbonate, 24424-99-5.

Communications

Direct β-Lithiation of 2-Alkoxy Dienes: Use in an Asymmetric Diels–Alder Reaction

Summary: Aldehydes react with β-lithiated 2-alkoxy dienes, obtained via direct deprotonation, to produce a class of asymmetric dienes which exhibit complete face selectivity in the intermolecular Diels–Alder reaction.

Sir: Asymmetric Diels–Alder reactions involving chiral dienes have begun to attract attention.[1,2] More specifically chemists have been interested in determining the effect an adjacent chiral center has on the diastereoselectivity of the Diels–Alder reaction.[2,3] As illustrated in structure **1**, the adjacent chiral center is most often substituted with an alkyl group (R), a heteroatom (X), and a hydrogen. In accord with recently proposed perpendicular models[4] for electrophilic attack on chiral allyl or dienyl systems, the reactive conformers can be depicted as either **1a** or **1b**, both of which place the alkyl group (R) in the plane of the π-system. While intuitively one would then prefer to place the bulkier heteroatom away from the dienyl system (i.e., **1a**), recent calculations have shown that electronic factors tend to favor the conformer **1b** with the "inside" heteroatom.[4b,5] Experimental results for the Diels–Alder reaction are conflicting as products arising from both conformer **1a** (X = OR)[2a,b] and **1b** (X = NR^1R^2)[2c] have been reported. Furthermore no dienyl system related to structure **1** has yet to exhibit complete π-face selectivity in the intermolecular Diels–Alder reaction.[3,18] In this paper we wish to report on the synthesis of some novel diene structures (see **7–10**) that react with complete π-face selectivity apparently via conformer **1a**.



1 **1a** **1b**

We have recently described the direct β-lithiation of an enol ether (**2a** → **2b**).[6] In an effort to extent this methodology to synthetically more interesting examples we have

(1) For a review that contains the earlier examples, see: Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, Chapter 8, pp 474–477.

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