Pergamon

*Tetrahedron*, Vol. 53, No. 26, pp. 8795-8806, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00203-2

# Chiral Bicyclic Lactams as Homoenolate Equivalents: An Asymmetric Route to 5-Substituted Cyclohexenones†

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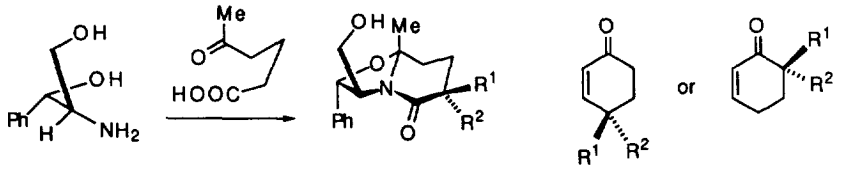
***Abstract:*** *Bicyclic Lactam **2** was transformed into α-cyanoenamine **8** in a four-step, high-yielding process. γ-Metalation of **8** was achieved using LiTMP in THF/HMPA, and the resultant homoenolate equivalent underwent stereoselective alkylation and subsequent hydrolysis to provide lactams of type **10** as a single diastereomer. Partial reduction and hydrolysis of lactams **10** furnished enantiopure 5-substituted cyclohexenones **13** in good overall yield.* © 1997 Elsevier Science Ltd.

Bicyclic lactams **2**, derived from the commercially available aminodiol **1**, have previously been shown to alkylate, via their enolate, to the α,α-dialkyl derivatives **3**. The latter, which were formed or purified to a single diastereomer gave, upon reduction or alkyllithium addition and subsequent hydrolysis, either the 4,4-disubstituted or the 6,6-disubstituted cyclohexenones **4** or **5** in high enantiomeric purity.[1] This novel approach to chiral cyclohexenones has also led to



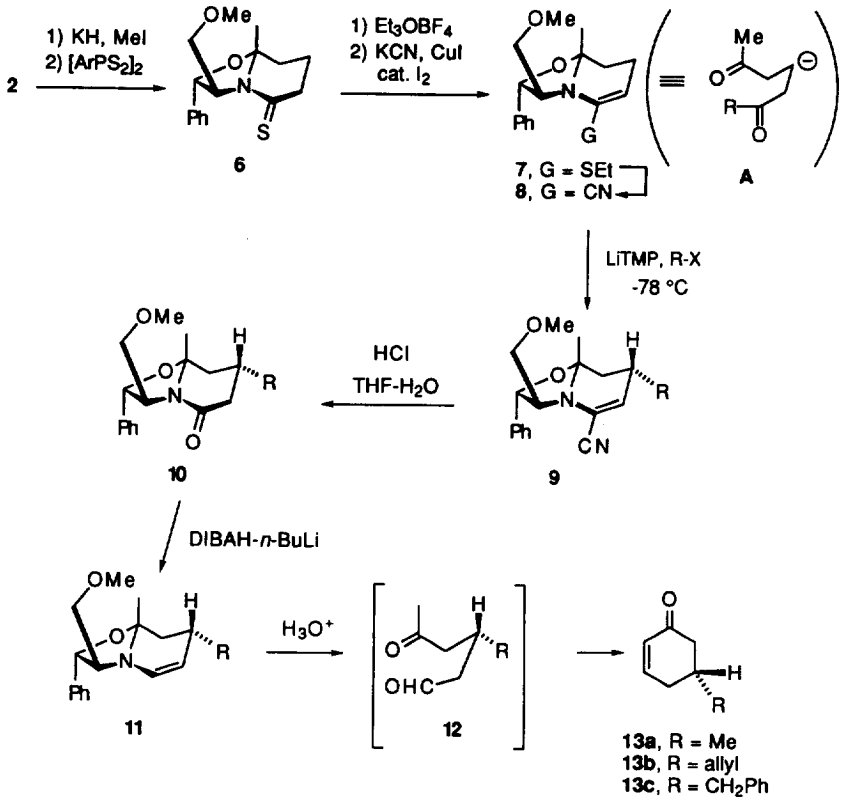

(*S*,*S*)-**1** — **2**, $R^1 = R^2 = H$; **3**, $R^1 \neq R^2$ = alkyl — **4** — **5**

asymmetric syntheses of (+)-mesembrine[2] and (+)-aspidospermine.[3] More recently, chiral cyclohexenones containing vicinal quaternary and tertiary stereocenters,[4] obtained via a thio-Claisen rearrangement, were accessed from the corresponding chiral thiolactams **6**. We now describe further behavior of the thiolactam, **6**, as an efficient homoenolate equivalent (Scheme 1).

Transformation of the lactam **2** to its methyl ether was followed by treatment with the Belleau reagent[5] to afford the thiolactam **6** in 89% yield. Formation of the ene thiolate derivative **7** proceeded smoothly with triethyloxonium tetrafluoroborate and subsequent aqueous bicarbonate

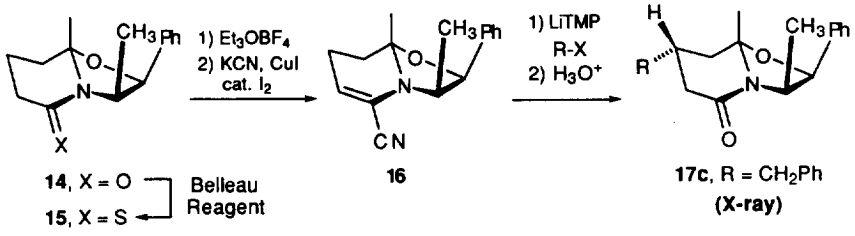
† This paper is dedicated to Professor Samuel Danishefsky on the occasion of the awarding of the Tetrahedron Prize.

**Scheme 1**




workup. Addition of potassium cyanide containing cuprous iodide and catalytic iodine gave the α-cyanoenamine **8** in 90% overall yield from the thiolactam **6**.[6] When the iodine was omitted from the reaction, no displacement of the ethyl thiolate group by cyanide had occurred. Presumably, the role of iodine in the process was to activate the N,S-ketene acetal toward displacement by cyanide ion. The mechanism of the process is not entirely clear and is currently under investigation. The cyanoenamine **8** may now be considered as a precursor to a homoenolate species (e.g., **A**)- a group of synthetic intermediates that have attracted much attention by virtue of their useful properties.[7] It is noteworthy that **A** contains not one, but two distinct homoenolate equivalents. It has been shown[8] that α-cyanoenamines may be deprotonated at the γ-carbon and although an allylic anion is generated, alkylation dominates at the γ-carbon, particularly when bulky substituents are present on the enamine nitrogen. Therefore, it was not entirely unexpected when the cyanoenamine **8** was first treated with 1.6 equiv LiTMP and then several electrophiles, only the γ-substituted products **9** were obtained. More importantly, however, the stereoselectivity of the alkylation was such that the product obtained was exclusively the α-isomer. Only a single diastereomer could be detected in the NMR spectrum of the crude product.[9]

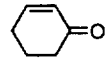
Furthermore, the chiral lactam **14**, derived from (+)-(1*S*, 2*R*)-norephedrine was prepared and transformed into the cyanoenamine **16** via the thiolactam **15**. Metalation (LiTMP, -78 °C) and alkylation with benzyl bromide gave the γ-benzyl derivative, **17c** as a single diastereomer, indicating that the stereochemistry of the alkylation of the cyanoenamines **8** and **16** appear to




be independent of the nature of the chiral amino alcohol. Thus, replacement of the methoxy group in **8** by methyl in **16** had no visible effect on the extent or direction of the stereoselectivity. An x-ray crystal structure of **17c** confirmed that the alkyl group entered the cyanoallyl anion from **16** from the α-face. A series of electrophiles were introduced into the cyanoenamines derived from **8** and **16** and all gave exclusively one diastereomer from alkylation at the α-face (Table 1).

To demonstrate the versatility of the alkylated lactams **10** toward more generally useful chiral products, they were shown to reduce cleanly with the "ate" complex generated from DIBAH and *n*-BuLi[10] to afford the intermediate carbinolamines which spontaneously dehydrated to the

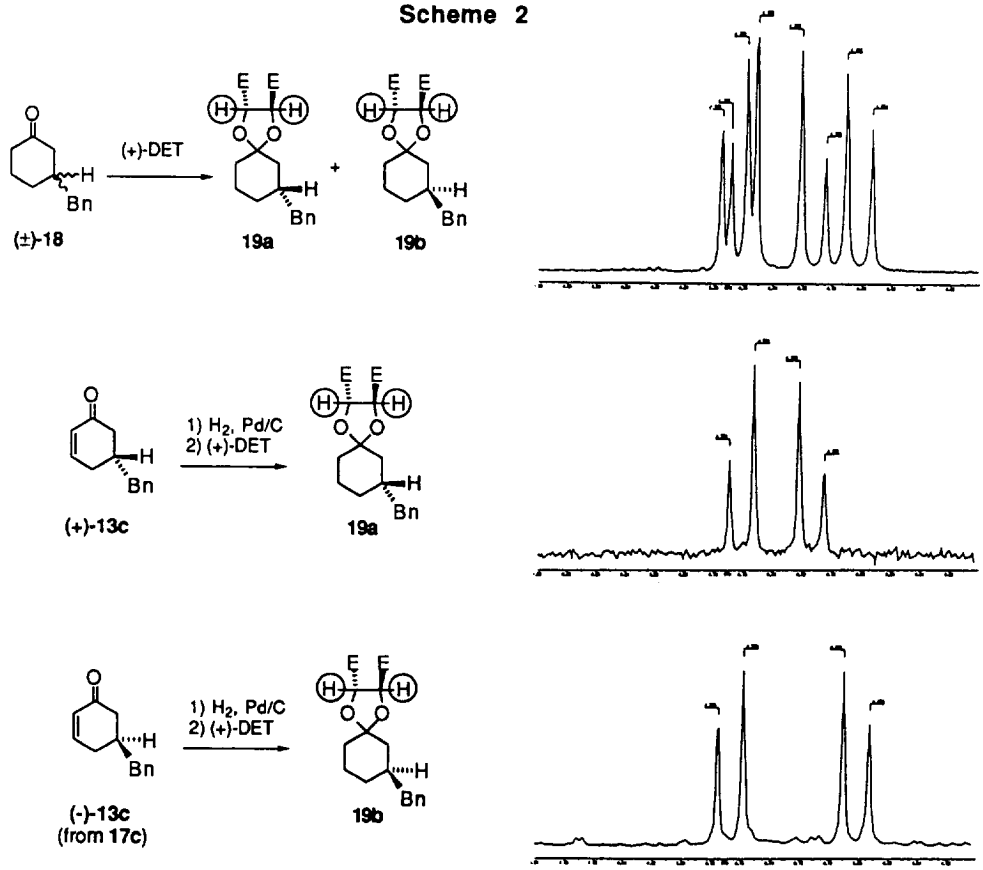
**Table 1. Metalation/Alkylation[a]/Hydrolysis of Cyanoenamines 8 and 16.**

| Entry | Cyanoenamine | Electrophile | Lactams 10 | Yield[b] (%) |
|---|---|---|---|---|
| 1 | **8** | MeI | **10a** | 38 |
| 2 | **8** | $^n$PrI | **10b** | 79 |
| 3 | **8** |  | **10c** | 65 |
| 4 | **8** | $PhCH_2Br$ | **10d** | 83 |
| 5 | **8** | TMSCl | **10e** | 79 |
| 6 | **8** | PhCHO | **10f** | 81[c] |
| 7 | **8** |  | **10g** | 60[d] |
| 8 | **16** | MeI | **17a** | 62 |
| 9 | **16** |  | **17b** | 69 |
| 10 | **16** | $PhCH_2Br$ | **17c** | 76 |

a) Alkylation Conditions: 1.6 equiv LiTMP, 1.6 equiv HMPA, 2.0 equiv R-X, 0.2 M **8** or **16** in THF, -78 °C, see experimental. b) Isolated yield of pure diastereomer ($^1$H NMR) after flash chromatography. c) Total yield of a 3:1 mixture of hydroxyl epimers. d) 3:2 mixture of diastereomers at the cyclohexanone carbon, products of 1,4-addition.

unstable enamines **11**, and were subsequently hydrolyzed (*p*-TsOH, THF-$H_2O$) to the 5-substituted cyclohexenones, **13**.[11] The intermediate keto-aldehyde **12**, was not detected, presumably proceeding spontaneously to the cyclohexenones **13** under the hydrolytic conditions employed. The 5-substituted cyclohexenones **13a-c** were obtained in overall yields of 57-65% from **10**. Comparison of the optical rotation of synthetic **13a** ($[\alpha]_D$ -77.3, c = 1.2, $CHCl_3$) with the literature value ($[\alpha]_D$ -90.2, c = 2.55, $CHCl_3$, c = 0.76, $CHCl_3$)[12] demonstrated that the expected absolute configuration (levoratory) had been obtained by this route. Proof of optical purity was obtained by subjecting synthetic **13a**, **13b**, and **13c** to hydrogenation to saturate the double bond, followed by treatment with (-)-diethyl tartrate to generate the ketal, and examination of the $^1H$ NMR spectrum (Scheme 2). The corresponding racemic cyclohexanones **18** were also ketalized to provide a 1:1 mixture of inseparable diastereomers, and the protons on the ketal α- to the ester groups in each diastereomer displayed discernible chemical shifts. Comparison with the tartrate diastereomer obtained from both **13a** and **13c** further demonstrated that no epimerization of the stereocenter present in the lactams **10a** and **10d** occurred during the reduction/hydrolysis sequence.

**Scheme 2**



## Experimental

**General Methods:** All $^1H$ NMR spectra were recorded on a Bruker AC 300 MHz spectrometer. $^{13}C$ NMR spectra were recorded at 75 MHz and were also obtained on a Bruker AC 300 MHz instrument. Fourier transform infrared absorption spectra were recorded on a Perkin-Elmer model PE 1600 spectrophotometer. Optical rotations were determined with a Rudolph Research Autopol III instrument and are referenced to the D-line of sodium. Melting points were measured in open pyrex capillary tubes on a MEL-TEMP melting point apparatus. Melting points are uncorrected. Elemental analyses were obtained from Atlantic Microlabs of Norcross, Ga. Thin layer chromatography and flash chromatography were performed with E. Merck or Amicon Matrix silica gel (230-400 mesh). All non-aqueous reactions were conducted under an argon atmosphere in a flame dried apparatus. Dichloromethane and toluene were dried via distillation from calcium hydride prior to use. HMPA was dried via distillation from calcium hydride under reduced pressure. Tetrahydrofuran was dried via distillation from sodium-benzophenone ketyl. Concentrations were performed under reduced pressure with a Buchi rotary evaporator.

***O*-Methylated Lactam 2a:** To a stirred suspension of potassium hydride (0.46 g, 11.5 mmol) in 80 mL THF at 0 °C was added lactam **2**[13] (2.00 g, 7.65 mmol) in one portion. The mixture was stirred 1 h at 0 °C, and methyl iodide (0.57 mL, 9.18 mmol) was added in one portion, resulting in a colorless precipitate. The mixture was stirred 1 h at 0 °C, quenched with saturated $NH_4Cl$ (aq) (10 mL), and concentrated. The residue was partitioned between ether (50 mL) and water (50 mL). The phases were separated and the organic phase washed with saturated $Na_2S_2O_3$ (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated to yield 2.04 g (97%) of lactam **2a** as a pale yellow oil which crystallized upon standing, mp 82-83 °C; $[\alpha]_D^{23}$ +10.0 (c 1.87, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.56 (s, 3H), 1.68-1.99 (m, 3H), 217-2.54 (m, 3H), 3.34 (s, 3H), 3.59 (dd, $J$ = 3.0 Hz, $J$ = 10.2 Hz, 1H), 3.79 (dd, $J$ = 5.1 Hz, $J$ = 10.2 Hz, 1H), 4.05 (m, 1H), 5.21 (d, $J$ = 7.9 Hz, 1H), 7.31 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 17.1, 23.8, 30.6, 35.5, 59.2, 63.2, 70.4, 78.0, 93.6, 126.6, 128.2, 128.5, 139.1, 169.1; IR (neat): 3061, 3032, 2934, 2896, 2828, 1646, 1398 $cm^{-1}$.

**Thiolactam 6:** To a stirred solution of lactam **2a** (2.04 g, 7.41 mmol) in 37 mL dry toluene was added Belleau's reagent[5] (2.06 g, 4.45 mmol). The mixture was heated to reflux 90 min, cooled, and concentrated onto silica gel. Flash chromatography of the residue (4:1, hexanes:ethyl acetate) provided 1.98 g (92%) of thiolactam **6** as a white crystalline solid, mp 110-111 °C; $[\alpha]_D^{23}$ -41.8 (c 0.97, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.60 (s, 3H), 1.77-1.97 (m, 3H), 2.27 (m, 1H), 3.09 (m, 2H), 3.37 (s, 3H), 3.70 (dd, $J$ = 2.7 Hz, $J$ = 10.5 Hz, 1H), 4.30 (dd, $J$ = 4.6 Hz, $J$ = 10.5 Hz, 1H), 4.50 (m, 1H), 5.37 (d, $J$ = 7.8 Hz, 1H), 7.32 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 17.3, 22.5, 35.1, 40.2, 59.2, 68.3, 68.3, 77.4, 95.4, 126.7, 128.6, 128.7, 138.6, 197.5; IR (neat): 3032, 2925, 1466, 1125 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.94; H, 7.26. Found: C, 66.06; H, 7.17.

**Cyanoenamine 8:** To thiolactam **6** (1.01 g, 3.47 mmol) in 17 mL dry $CH_2Cl_2$ was added triethyloxonium tetrafluoroborate (1.4 M solution in $CH_2Cl_2$, 3.22 mL, 4.51 mmol), and the solution heated to reflux 1 h. The solution was cooled to ambient temperature, poured into saturated $NaHCO_3$ (aq) (20 mL), and shaken. The phases were separated, and the aqueous phase extracted with $CH_2Cl_2$ (2 X 10 mL). The combined organic phases were dried ($K_2CO_3$), and

concentrated to yield 1.10 g (99%) of N,S-ketene acetal **7** as a cloudy, colorless oil. To a stirred solution of the crude N,S-ketene acetal **7** in 30 mL THF was added potassium cyanide (0.34 g, 5.20 mmol), copper (I) iodide (0.99 g, 5.20 mmol), and iodine (44 mg, 0.17 mmol). The mixture was heated to reflux 12 h, then cooled to ambient temperature. The mixture was concentrated to ca. 3 mL total volume, then diluted with hexanes:ethyl acetate (8:1) (3 mL) and loaded onto a 4 X 4 cm plug of basic alumina. Elution with 8:1 hexanes:ethyl acetate yielded 0.96 g (97% from thiolactam **6**) of cyanoenamine **8** as a pale yellow oil. Analytically pure material was obtained by flash chromatography on silica gel (8:1, hexanes:ethyl acetate) to provide cyanoenamine **8** as a colorless oil: $[\alpha]_D^{23}$ +228 (c 1.89, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.60 (m, 1H), 2.03-2.34 (m, 3H), 3.41 (s, 3H), 3.42 (m, 1H), 3.60 (dd, $J$ = 3.1 Hz, $J$ = 10.7 Hz, 1H), 3.83 (dd, $J$ = 5.0 Hz, $J$ = 10.7 Hz, 1 H), 5.17 (d, $J$ = 7.5 Hz, 1H), 5.63 (m, 1H), 7.32 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 21.3, 25.1, 31.6, 59.3, 68.1, 70.9, 79.6, 93.4, 116.3, 117.8, 118.2, 126.7, 128.3, 128.5, 138.9; IR (neat): 3066, 3038, 2981, 2924, 2895, 2838, 2221, 1607, 1100 $cm^{-1}$. HRMS (FAB, M + H) Calcd for $C_{17}H_{20}N_2O_2$: 285.1604. Found: 285.1597.

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09. Found: C, 71.56; H, 7.16.

**General Procedure for Alkylation of Cyanoenamine 8. β-*n*-Propyl Lactam 10b:** To a stirred solution of 2,2,6,6-tetramethylpiperidine (69 μL, 0.41 mmol) in 1.0 mL THF at -78 °C was added *n*-butyllithium (2.30 M solution in hexanes, 0.18 mL, 0.41 mmol) followed by HMPA (72 μL, 0.41 mmol). The solution was stirred for 5 min at -78 °C, warmed to 0 °C and stirred 1.5 min, then cooled to -78 °C at which time cyanoenamine **8** (73 mg, 0.26 mmol) in 0.5 mL THF was added dropwise over 1 min. The solution was stirred at -78 °C for 20 min and 1-iodopropane (50 μL, 0.51 mmol) was added dropwise. The mixture was stirred for 4 h at -78 °C and quenched with saturated $NaHCO_3$ (3 mL). The mixture was diluted with ether (10 mL), water was added to dissolve the solids (2 mL), and the phases separated. The aqueous phase was extracted with ether (10 mL), and the combined organic phases concentrated. To the crude cyanoenamine **9b** was added THF (10 mL) and 1 N HCl (aq) (10 mL), and the mixture stirred at ambient temperature for 4 h. The mixture was concentrated, the residue extracted with ether (3 X 10 mL), and the combined organic phases dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (1:1, hexanes:ethyl acetate) provided 65 mg (79%) of β-propyl lactam **10b** as a colorless oil. $[\alpha]_D^{23}$ +20.2 (c 1.37, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 0.92 (m, 3H), 1.34 (m, 4H), 1.47 (app t, $J$ = 12.2 Hz, 1H), 1.58 (s, 3H), 1.98 (m, 2H), 2.19 (m, 1H), 2.64 (app q, $J$ = 10.9 Hz, 1H), 3.35 (s, 3H), 3.59 (dd, $J$ = 3.0 Hz, $J$ = 10.2 Hz, 1H), 3.78 (dd, $J$ = 5.2 Hz, $J$ = 10.2 Hz, 1H), 4.04 (m, 1H), 5.22 (d, $J$ = 7.9 Hz, 1H), 7.31 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 14.0, 19.7, 24.5, 29.3, 38.0, 38.6, 42.2, 59.2, 63.2, 70.5, 78.2, 93.6, 126.6, 128.3, 128.5, 139.2, 169.4; IR (neat): 3067, 3030, 2956, 2918, 2872, 1649, 1398 $cm^{-1}$.

Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.58. Found: C, 71.70; H, 8.60.

**γ-Methyl Cyanoenamine 9a:** Obtained in 13% yield using 2 equiv methyl iodide following silica gel chromatography (8:1, hexanes:ethyl acetate): $[\alpha]_D^{23}$ +18.7 (c 1.98, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.11 (d, $J$ = 7.0 Hz, 3H), 1.30 (app t, $J$ = 12.6 Hz, 1H), 1.40 (s, 3H), 2.08 (qd, $J$ = 1.4 Hz, $J$ = 5.4 Hz, 1H), 2.37 (m, 1H), 3.40 (s, 3H), 3.42 (m, 1H), 3.57 (dd, $J$ = 2.9 Hz, $J$ = 10.8 Hz, 1H), 3.84 (dd, $J$ = 4.8 Hz, $J$ = 10.8 Hz, 1H), 5.19 (d, $J$ = 7.8 Hz, 1H), 5.40 (m, 1H), 7.33 (m, 5H); $^{13}C$ NMR

($CDCl_3$) δ 19.6, 25.7, 27.7, 40.7, 59.3, 67.8, 70.6, 79.9, 93.8, 116.1, 116.9, 123.1, 126.8, 128.3, 128.5, 138.7; IR (neat): 3068, 3039, 2963, 2924, 2877, 2226, 1607, 1458 $cm^{-1}$.

**β-Methyl Lactam 10a:** The reaction was complete in 20 min instead of 4 h, and **10a** was obtained from methyl iodide in 38% yield as a pale yellow oil: $[\alpha]_D^{23}$ +18.7 (c 1.98, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.06 (d, *J* = 6.3 Hz, 3H), 1.51 (app t, *J* = 12.9 Hz, 1H), 1.58 (s, 3H), 1.91-2.17 (m, 3H), 2.62 (m, 1H), 3.34 (s, 3H), 3.59 (dd, *J* = 3.1 Hz, *J* = 10.2 Hz, 1H), 3.78 (dd, *J* = 5.2 Hz, *J* = 10.2 Hz, 1H), 4.03 (m, 1H), 5.22 (d, *J* = 7.9 Hz, 1H), 7.31 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 21.7, 24.5, 24.6, 39.6, 44.1, 59.2, 63.1, 70.6, 78.2, 93.5, 126.6, 128.2, 128.5, 139.2, 169.3; IR (neat): 3064, 3034, 2954, 2933, 1648, 1397 $cm^{-1}$.

Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01. Found: C, 70.31; H, 7.91.

**β-Allyl Lactam 10c:** Obtained from allyl bromide in 65% yield as a pale yellow oil: $[\alpha]_D^{23}$ +21.6 (c 2.07, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.49 (app t, *J* = 12.1 Hz, 1H), 1.57 (s, 3H), 1.97-2.24 (m, 5H), 2.61 (m, 1H), 3.34 (s, 3H), 3.59 (dd, *J* = 3.0 Hz, *J* = 10.3 Hz, 1H), 3.78 (dd, *J* = 5.1 Hz, *J* = 10.3 Hz, 1H), 4.04 (m, 1H), 5.05 (br s, 1H), 5.09 (m, 1H), 5.22 (d, *J* = 7.9 Hz, 1H), 5.75 (m, 1H), 7.31 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 24.4, 29.4, 37.5, 40.4, 41.7, 59.2, 63.1, 70.5, 78.2, 93.5, 117.5, 126.6, 128.3, 128.5, 134.9, 139.1, 169.1; IR (neat): 3065, 3037, 2979, 2921, 2835, 1649, 1394 $cm^{-1}$.

**β-Benzyl Lactam 10d:** Obtained from benzyl bromide in 83% yield as colorless crystals, mp 114-115 °C: $[\alpha]_D^{23}$ +39.4 (c 1.73, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.55 (m, 4H), 2.04-2.36 (m, 3H), 2.57 (m, 1H), 2.67 (d, *J* = 7.2 Hz, 2H), 3.34 (s, 3H), 3.58 (dd, *J* = 3.0 Hz, *J* = 10.2 Hz, 1H), 3.77 (dd, *J* = 5.1 Hz, *J* = 10.2 Hz, 1H), 4.04 (m, 1H), 5.22 (d, *J* = 7.9 Hz), 7.26 (m, 10H); $^{13}C$ NMR ($CDCl_3$) δ 24.5, 31.7, 37.8, 41.8, 42.6, 59.2, 63.1, 70.5, 78.2, 93.5, 126.5, 126.6, 128.3, 128.5, 128.5, 129.0, 138.7, 139.1, 169.0; IR (neat): 3058, 3030, 2984, 2928, 2900, 1649, 1398 $cm^{-1}$.

Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.58; H, 7.45. Found: C, 75.43; H, 7.38.

**β-Trimethylsilyl Lactam 10e:** Obtained from TMSCl in 79% yield as a colorless oil: $[\alpha]_D^{23}$ +24.5 (c 2.22, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 0.02 (s, 9H), 1.20 (m, 1H), 1.54 (app t, *J* = 13.3 Hz, 1H), 1.59 (s, 3H), 2.07-2.23 (m, 2H), 2.49 (m, 1H), 3.35 (s, 3H), 3.60 (dd, *J* = 2.7 Hz, *J* = 10.2 Hz, 1H), 3.78 (dd, *J* = 5.0 Hz, *J* = 10.2 Hz, 1H), 4.05 (m, 1H), 5.21 (d, *J* = 7.9 Hz, 1H), 7.32 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ -4.0, 16.3, 23.7, 32.0, 36.7, 59.2, 63.2, 70.1, 78.0, 94.2, 126.7, 128.2, 128.5, 139.1, 169.7; IR (neat): 3037, 2950, 2896, 1647, 1391 $cm^{-1}$.

Anal. Calcd for $C_{19}H_{29}NO_3Si$: C, 65.66; H, 8.41. Found: C, 65.38; H, 8.51.

**β-Hydroxybenzyl Lactam 10f (high $R_f$):** Obtained from benzaldehyde in 45% yield as a white foam: $[\alpha]_D^{23}$ +45.3 (c 1.58, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.57 (s, 3H), 1.61 (app t, *J* = 12.6 Hz, 1H), 2.22 (m, 4H), 2.54 (dd, *J* = 1.8 Hz, *J* = 12.9 Hz, 1H), 3.33 (s, 3H), 3.55 (dd, *J* = 3.0 Hz, *J* = 10.2 Hz, 1H), 3.75 (dd, *J* = 5.4 Hz, *J* = 10.5 Hz, 1H), 4.01 (m, 1H), 4.46 (d, *J* = 6.9 Hz, 1H), 5.22 (d, *J* = 8.1 Hz, 1H), 7.32 ( m, 10H); $^{13}C$ NMR ($CDCl_3$) δ 24.4, 34.3, 37.3, 38.1, 59.2, 63.2, 70.4, 77.3, 78.3, 93.7, 126.4, 126.6, 128.2, 128.3, 128.5, 128.7, 139.1, 141.9, 168.8; IR (neat): 3382, 3066, 2985, 2923, 1625, 1452, 1431, 1401 $cm^{-1}$.

**β-Hydroxybenzyl Lactam 10f (low $R_f$):** Obtained from benzaldehyde in 26% yield as a white crystalline solid, mp 182-183 °C: $[\alpha]_D^{23}$ +30.8 (c 1.22, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.53 (s, 3H), 1.61 (app t, *J* = 12.6 Hz, 1H), 1.99 (m, 1H), 2.38 (m, 3H), 2.64 (m, 1H), 3.35 (s, 3H), 3.57 (dd, *J*

= 2.7 Hz, *J* = 10.2 Hz, 1H), 3.78 (dd, *J* = 4.8 Hz, *J* = 10.5 Hz, 1H), 4.03 (m, 1H), 4.57 (d, *J* = 5.7 Hz, 1H), 5.22 (d, *J* = 7.8 Hz, 1H), 7.33 (m, 10H); $^{13}$C NMR ($CDCl_3$) δ 24.3, 33.6, 37.3, 38.8, 59.2, 63.1, 70.3, 77.6, 78.2, 93.5, 126.3, 126.6, 128.1, 128.3, 128.5, 128.6, 139.0, 142.1, 169.2; IR (neat): 3382, 3029, 2990, 2921, 1627, 1456, 1431, 1397 cm$^{-1}$.

**β-3-Cyclohexanone Lactams 10g:** Obtained from cyclohexenone as a 3:2 inseparable mixture of epimers at the cyclohexanone carbon in 60% yield as a white foam. $^1$H NMR ($CDCl_3$) δ 1.57 (s, 3H), 1.38-2.65 (m, 14H), 3.33 (s, 3H), 3.56 (dd, *J* = 3.3 Hz, *J* = 10.5 Hz, 1H), 3.77 (dd, *J* = 4.8 Hz, *J* = 9.9 Hz, 1H), 4.03 (m, 1H), 5.22 (d, *J* = 8.1 Hz, 1H), 7.31 (m, 5H); $^{13}$C NMR ($CDCl_3$) δ (24.3, 24.3), 24.9, (27.9, 28.2), (34.3, 34.5), (35.0, 35.2), (39.3, 39.4), (41.2, 41.3), (43.1, 43.3), (44.7, 45.3), 59.2, 63.2, (70.2, 70.3), 78.1, 93.4, 126.5, 128.3, 128.5, 138.9, 168.6, (210.3, 210.4) (carbons in parentheses appear to be diastereomeric); IR (neat): 3060, 3034, 2937, 2893, 1710, 1648, 1455, 1425, 1398 cm$^{-1}$.

**Norephedrine-Derived Lactam 14:** To a solution of 4-acetylbutyric acid (Aldrich) (0.13 g, 0.99 mol) in 5.0 mL toluene was added (*1S,2R*)-(+)-norephedrine (0.15 g, 0.99 mmol). The mixture was heated to reflux under azeotropic removal of water for 12 h, cooled, and concentrated. Flash chromatography of the residue (ethyl acetate) provided 194 mg (80%) of lactam **14** as a colorless oil. $[\alpha]_D^{23}$ +57.7 (c 1.25, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ 0.85 (d, *J* = 7.0 Hz, 3H), 1.62 (s, 3H), 1.88 (m, 4H), 2.41 (m, 2H), 4.71 (quint, *J* = 6.9 Hz, 1H), 5.07 (d, *J* = 5.7 Hz, 1H), 7.29 (m, 5H); $^{13}$C NMR ($CDCl_3$) δ 15.6, 15.8, 27.2, 28.6, 34.0, 54.7, 79.3, 92.8, 126.1, 127.7, 128.2, 136.5, 168.6; IR (neat): 3067, 3027, 2976, 2875, 1648, 1400 cm$^{-1}$.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81. Found: C, 73.17; H, 7.77.

**Thiolactam 15:** To a stirred solution of lactam **14** (194 mg, 0.79 mmol) in 4.0 mL dry toluene was added Belleau's reagent[5] (220 mg, 0.47 mmol). The mixture was heated to reflux 1 h, cooled, and concentrated onto silica gel. Flash chromatography of the residue (4:1, hexanes:ethyl acetate) provided 149 mg (72%) of thiolactam **14** as a colorless crystalline solid, mp 114-115 °C: $[\alpha]_D^{23}$ -87.6 (c 1.68, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ 0.98 (d, *J* = 6.5 Hz, 3H), 1.65 (s, 3H), 1.86 (m, 3H), 2.06 (m, 1H), 2.83 (m, 1H), 3.20 (m, 1H), 5.21 (m, 2H), 7.32 (m, 5H); $^{13}$C NMR ($CDCl_3$) δ 13.4, 15.4, 26.2, 32.6, 37.9, 61.3, 78.1, 94.2, 126.1, 128.0, 128.4, 135.5, 196.9; IR (neat): 3062, 3032, 2983, 2943, 2873, 1474, 1449 cm$^{-1}$.

Anal. Calcd for $C_{15}H_{19}NOS$: C, 68.93; H, 7.33. Found: C, 68.83; H, 7.29.

**Cyanoenamine 16:** To thiolactam **15** (0.29 g, 1.10 mmol) in 6 mL dry $CH_2Cl_2$ was added triethyloxonium tetrafluoroborate (1.4 M solution in $CH_2Cl_2$, 1.02 mL, 1.43 mmol), and the solution was heated to reflux 1 h. The solution was cooled to ambient temperature, poured into saturated $NaHCO_3$ (aq) (15 mL), and shaken. The phases were separated, and the aqueous phase extracted with $CH_2Cl_2$ (2 X 10 mL). The combined organic phases were dried ($K_2CO_3$), and concentrated to yield 0.32 g (100%) of the N,S-ketene acetal as a cloudy, colorless oil. To a stirred solution of the crude N,S-ketene acetal in 15 mL THF was added potassium cyanide (0.11 g, 1.65 mmol), copper (I) iodide (0.31 g, 1.65 mmol), and iodine (14 mg, 0.06 mmol). The mixture was heated to reflux 12 h, then cooled to ambient temperature. The mixture was concentrated to ca. 2 mL, diluted with 3 mL hexanes:ethyl acetate (8:1), and loaded onto a 3 X 4 cm plug of basic

alumina. Elution with hexanes:ethyl acetate (8:1) provided 0.28 g (98% from thiolactam **15**) of cyanoenamine **16** as a pale yellow oil. Analytically pure material was obtained by flash chromatography on silica gel (16:1, hexanes:ethyl acetate) to provide cyanoenamine **16** as a colorless crystalline solid: mp 124-126 °C: $[\alpha]_D^{23}$ -62.1 (c 1.36, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 0.87 (d, *J* = 6.7 Hz, 3H), 1.44 (s, 3H), 1.63 (dt, *J* = 6.0 Hz, *J* = 12.6 Hz, 1H), 1.84 (dd, *J* = 6.2 Hz, *J* = 12.6 Hz, 1H), 2.15 (m, 1H), 2.32 (m, 1H), 3.86 (quint, *J* = 6.5 Hz, 1H), 5.21 (d, *J* = 5.9 Hz, 1H), 5.46 (dd, *J* = 2.4 Hz, *J* = 5.7 Hz, 1H), 7.31 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 18.4, 22.1, 26.4, 28.5, 60.7, 79.0, 92.2, 114.1, 116.3, 118.6, 126.3, 127.7, 128.3, 136.6; IR (neat): 3069, 3032, 2978, 2932, 2869, 2222, 1615, 1378 $cm^{-1}$.

**General Procedure for Alkylation of Norephedrine-Derived Cyanoenamine 16: β-Methyl Lactam 17a:** To a stirred solution of 2,2,6,6-tetramethylpiperidine (0.21 mL, 1.21 mmol) in 3.0 mL THF at -78 °C was added *n*-butyllithium (2.30 M solution in hexanes, 0.53 mL, 1.21 mmol) followed by HMPA (0.21 mL, 1.21 mmol). The solution was stirred for 5 min at -78 °C, warmed to 0 °C and stirred for 1.5 min, then cooled to -78 °C at which time cyanoenamine **16** (0.19 g, 0.76 mmol) in 0.8 mL THF was added dropwise over 2 min. The solution was stirred at -78 °C for 20 min and methyl iodide (95 μL, 1.52 mmol) was added dropwise. The mixture was stirred for 1 h at -78 °C and quenched with saturated $NaHCO_3$ (5 mL). The mixture was extracted with ether (2 X 15 mL), and the combined organic phases concentrated. To the crude cyanoenamine was added THF (10 mL) and 1 N HCl (aq) (10 mL), and the mixture stirred at ambient temperature 6 h. The mixture was concentrated and the residue extracted with ether (3 X 10 mL) and the combined organic phases dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (1:1, hexanes:ethyl acetate) provided 0.12 g (62%) of β-methyl lactam **17a** as a colorless oil which crystallized upon standing, mp 67-68 °C: $[\alpha]_D^{23}$ +64.3 (c 1.89, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 0.87 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 5.8 Hz, 3H), 1.43 (app t, *J* = 12.1 Hz, 1H), 1.64 (s, 3H), 1.98-2.15 (m, 3H), 2.67 (m, 1H), 4.73 (quint, *J* = 6.6 Hz, 1H), 5.07 (d, *J* = 5.9 Hz, 1H), 7.31 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 15.9, 22.4, 23.6, 28.1, 38.1, 43.3, 54.8, 79.5, 92.8, 126.0, 127.6, 128.2, 136.6, 168.6; IR (neat): 3064, 3035, 2955, 2866, 1651, 1394 $cm^{-1}$.

**β-Allyl Lactam 17b:** Obtained in 69% yield as a pale yellow oil: $[\alpha]_D^{23}$ +62.0 (c 1.03, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 0.87 (d, *J* = 7.3 Hz, 3H), 1.43 (app t, *J* = 11.1 Hz, 1H), 1.66 (s, 3H), 2.11 (m, 5H), 2.64 ( m, 1H), 4.73 (quint, *J* = 6.9 Hz, 1H), 5.07 (m, 3H), 5.74 (m, 1H), 7.31 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 16.0, 28.1, 28.5, 35.9, 41.1, 41.2, 54.9, 79.6, 92.9, 117.5, 126.1, 127.7, 128.3, 135.0, 136.7, 168.5; IR (neat): 3075, 2982, 2927, 2863, 1648, 1422, 1395 $cm^{-1}$.

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42. Found: C, 75.94; H, 8.44.

**β-Benzyl Lactam 17c:** Obtained in 76% yield as colorless crystals, mp 125-126 °C: $[\alpha]_D^{23}$ +24.5 (c 1.88, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 0.86 (d, *J* = 7.0 Hz, 3H), 1.48 (app t, *J* = 12.4 Hz, 1H), 1.61 (s, 3H), 2.07 (dd, *J* = 4.1 Hz, *J* = 12.5 Hz, 1H), 2.12-2.33 (m, 2H), 2.55-2.67 (m, 3H), 4.73 (quint, *J* = 6.8 Hz, 1H), 5.08 (d, *J* = 5.8 Hz, 1H), 7.13-7.36 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 15.9, 28.1, 30.7, 36.1, 41.2, 43.2, 54.9, 79.6, 92.8, 126.0, 126.4, 127.7, 128.3, 128.5, 129.0, 136.6, 138.8, 168.5; IR (neat): 3061, 3024, 2978, 2931, 2857, 1649, 1394 $cm^{-1}$.

Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51. Found: C, 78.64; H, 7.60.

**(*R*)-5-Benzylcyclohexenone 13c:** To diisobutylaluminum hydride (1.0 M solution in hexanes, 5.9 mL, 5.86 mmol) was added 5.9 mL THF. The solution was cooled to 0 °C at which time *n*-butyllithium (2.30 M solution in hexanes, 2.54 mL, 5.86 mmol) was added dropwise. The solution was stirred for 30 min and transferred dropwise via cannula to a stirred solution of lactam **10d** (107 mg, 0.29 mmol) in 3.0 mL THF at 0 °C. The resultant mixture was allowed to warm slowly to room temperature over 12 h. The excess hydride was quenched by dropwise addition of 2 mL MeOH, and concentrated. The residue was dissolved in 50 mL 1:1 hexanes:ether and washed with 10% NaOH (50 mL), water (50 mL), brine (50 mL), dried ($K_2CO_3$), and concentrated. The crude enamine **11c** was dissolved in 1:1 THF:water (20 mL), *p*-toluenesulfonic acid monohydrate (0.56 g, 2.93 mmol) was added, and the mixture was heated to reflux 24 h. The mixture was cooled to ambient temperature and partitioned between ether (15 mL) and water (10 mL). The aqueous phase was extracted with ether (2 X 15 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (2:1, hexanes:ether) yielded 35 mg (65%) of (*R*)-5-benzylcyclohexenone **13c** as a colorless oil: $[\alpha]_D^{23}$ +8.4 (c 1.36, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 2.03-2.21 (m, 2H), 2.31-2.54 (m, 3H), 2.66 (d, $J$ = 7.1 Hz, 2H), 6.00 (m, 1H), 6.92 (m, 1H), 7.23 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 31.8, 37.0, 42.0, 44.1, 126.4, 128.5, 129.0, 129.9, 138.9, 149.6, 199.6; IR (neat): 3061, 3032, 2925, 2857, 1680, 1495, 1456, 1388, 1247 $cm^{-1}$. HRMS (FAB, M + H) Calcd for $C_{13}H_{14}O$: 187.1124. Found: 187.1127.

**(*R*)-5-Methylcyclohexenone 13a:** Obtained in 60% yield using 10 equiv DiBAH-*n*-BuLi after chromatography (4:1, pentane:ether) as a colorless oil: $[\alpha]_D^{23}$ -77.3 (c 0.30, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.05 (d, $J$ = 6.4 Hz, 3H), 1.96-2.29 (m, 3H), 2.35-2.50 (m, 2H), 5.99 (m, 1H), 6.94 (m, 1H); $^{13}C$ NMR ($CDCl_3$) δ 21.2, 30.3, 34.0, 46.3, 129.6, 149.8, 200.1. Spectral characteristics and sign of optical rotation are in accordance with the cyclohexenone **13a** obtained from (+)-pulegone.[12] They obtained $[\alpha]_D^{25}$ -90.2 (c 2.55, $CHCl_3$).

**(*R*)-5-Allylcyclohexenone 13b**: Obtained in 57% yield using 5 equiv DiBAH-*n*-BuLi as a colorless oil after chromatography (4:1, pentane:ether): $[\alpha]_D^{23}$ -43.7 (c 1.23, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.99-2.17 (m, 5H), 2.37-2.52 (m, 2H), 5.01 (m, 1H), 5.05 (br s, 1H), 5.72 (m, 1H), 5.99 (m, 1H), 6.93 (m, 1H); $^{13}C$ NMR ($CDCl_3$) δ 31.7, 34.8, 39.9, 44.0, 117.2, 129.8, 135.2, 149.7, 199.7; IR (neat): 3075, 3034, 2922, 1681 $cm^{-1}$. HRMS (FAB, M + H) Calcd for $C_9H_{12}O$: 137.0967. Found: 137.0966.

**General procedure for formation of tartrate ketals from racemic cyclohexanones 18:**[14] To a solution of 3-benzylcyclohexanone[15] **(±)-18** (44 mg, 0.23 mmol) in 10 mL toluene was added (+)-tartaric acid diethyl ester (0.08 mL, 0.47 mmol), *p*-toluenesulfonic acid monohydrate (5 mg, 0.03 mmol), and the mixture heated to reflux with azeotropic removal of water for 24 h. The mixture was cooled and concentrated. The residue was purified by flash chromatography (hexanes:ethyl acetate, 4:1) to yield 65 mg (74%) of the inseparable ketals **19a** and **19b** as a colorless oil. $^1H$NMR analysis of the protons α- to the tartrate esters (4.5-5.0 ppm) showed distinct signals for each diastereomer (two diastereomers X two doublets for each α-proton = eight total signals).

**General procedure for formation of tartrate ketals from chiral cyclohexenones (+)-13c:** To a solution of (+)-5-benzyl-2-cyclohexenone **(+)-13c** (73 mg, 0.39 mmol) in 2 mL ethyl acetate was added 10% palladium on carbon (10 mg). The reaction vessel was evacuated and purged three times with hydrogen, then placed under 1 atm hydrogen for 1 h. The mixture was gravity filtered and concentrated to yield 72 mg (98%) of (*S*)-3-benzylcyclohexanone **(+)-18** as a colorless oil. Physical and spectral properties were identical to those described previously.[15] The crude cyclohexanone **(+)-18** was ketalized with (+)-diethyl tartrate to provide **19a** as described above and the diastereomeric purity assayed by $^1$HNMR. The region between 4.5 and 5.0 ppm showed two doublets, one for each proton α- to the tartrate ester (four total signals). None of the tartrate ketal diastereomer α-protons were detected by 300 or 500 MHz NMR, indicating that the starting cyclohexenone **(+)-13c** was no less than 95% optically pure.

**Acknowledgements:** The authors are grateful to the National Institutes of Health for support of this study, and to Boehringer Ingelheim for a graduate fellowship (JBS).

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(*Received* 6 *January* 1997; *revised* 22 *February* 1997; *accepted* 24 *February* 1997)