A Three Component Coupling Approach to a Chiral 1β-Methylcarbapenem Key Intermediate

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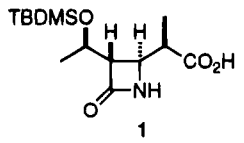
Received September 23, 1994®

Conjugate addition of *N*-benzyl-*N*-((*R*)-1-phenylethyl)amine (*R*)-**5** to (*R*)-(*E*)-*tert*-butyl 5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-2-pentenoate (**10a**) produced the (3*S*,4*R*)-syn-adduct **14** with essentially 100% de in 84% yield, whereas the addition of (*S*)-**5** to **10a** afforded the (3*R*,4*R*)-anti-adduct **15** with essentially 100% de in 95% yield. The syn adduct **14** was converted upon sequential treatment with lithium diisopropylamide–methylaluminum dichloride–acetaldehyde to the key intermediate **21**; the diastereoisomer ratio of **21** to other diasteroisomers was 80:20. Conversion of **21** to a 1β-methylcarbapenem key intermediate **26** was carried out readily according to the known procedures.

Since the presence of a 1β-methyl substituent has been found to enhance the chemical and metabolic stability of synthetic carbapenem antibiotics,[1] a number of stereoselective syntheses of the key 1β-methyl intermediate **1** have been reported.[2] Many of these syntheses proceed



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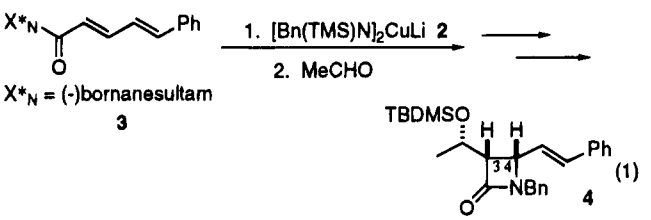
from 4-acetoxy-2-azetidinones. Other methods for introduction of the β-methyl group include catalytic hydrogenetion[2m,z] and L-Selectride[2d] or borane reduction[3a] of olefinic precursors of **1**, reduction of a hexacarbonyldicobalt-stabilized propargyl cation,[2k] β-lactam formation from components derived from either (*S*)- or (*R*)-methyl 3-hydroxy-2-methylpropionate,[2g,n,3b,c] and use of lactone intermediates.[2p,3d–f]

We previously reported an entirely new approach to the synthesis of the β-lactam framework via a three-component coupling (TCC) process using higher order amide cuprates;[4] the regioselective conjugate addition of the amide cuprate reagent **2** to the α,β,γ,δ-unsaturated ester **3** having a sultam chiral auxiliary, followed by aldol condensation with acetaldehyde and subsequent manipulation, gave the β-lactam **4** with high diastereoisomeric and enantiomeric excess (all in one pot) (eq 1). The



absolute stereochemistry at C-3 corresponds to that of natural β-lactams. The stereochemistry at C-4 and the hydroxyethyl unit, though opposite to that in the natural framework, can be converted to the correct configurations via the reported procedure.[5]

More recently, we have reported that the reaction of the chiral lithium amide (*R*)-**5** with the dienoate **6** provides regio- and diastereoselectively the β-amino ester **7** in essentially quantitative yield with >99% diastereoisomeric excess, which can be converted upon sequential treatment with $LiN(iPr)_2$–$B(OMe)_3$–CH_3CHO to the key intermediate **8** for the β-lactam **9** having the correct absolute configuration (a modified TCC process) (eq 2).[6] On the basis of these previous observations, it occurred

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® Abstract published in *Advance ACS Abstracts,* December 15, 1994.

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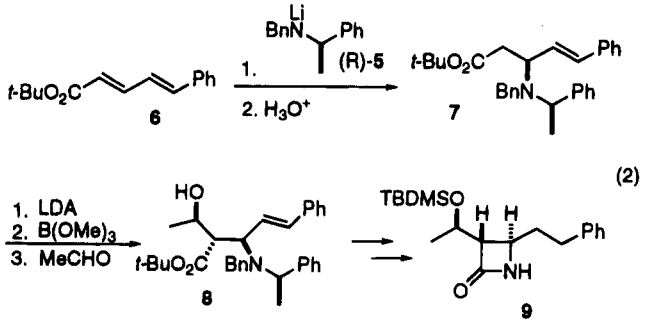


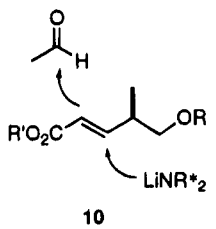
(2)

to us that the application of the modified TCC method to an optically active γ-methyl-substituted α,β-enoate **10** might enable us to stereoselectively produce a key 1β-methylcarbapenem intermediate. In fact, this is the case, and a concise synthesis of a chiral 1β-methylcarbapenem key intermediate has been accomplished using the cheap chiral source (*R*)-**5**.

Results and Discussion

Conjugate Addition of the Chiral Lithium Amides 5 to γ-Methyl-Substituted α,β-Enoates. Hawkins and Lewis have reported the highly diastereoselective 1,4-addition of the chiral lithium amide of 3,5-dihydro-4*H*-dinaphth[2,1-c:1′,2′-*e*]azepine to α,β-unsaturated esters.[7] Davies and Ichihara have shown that the conjugate addition of homochiral lithium (*R*)-(α-methylbenzyl)-benzylamide (*R*)-**5** to certain enoates proceeds with very high diastereoisomeric excess.[8a] Asymmetric conjugate addition of amines to α,β-unsaturated esters and nitriles has been reported.[9] We have previously reported the asymmetric synthesis of the β-lactam framework via a modified TCC method,[6] and this success is primarily due to the high asymmetric induction via the Davies' chiral lithium amide reagents **5**.[10]

We examined the conjugate addition of several lithium amides to (4*R*)-γ-methyl-substituted α,β-unsaturated ester **10a**. The addition of LSA (Bn(TMS)NLi)[11] gave a



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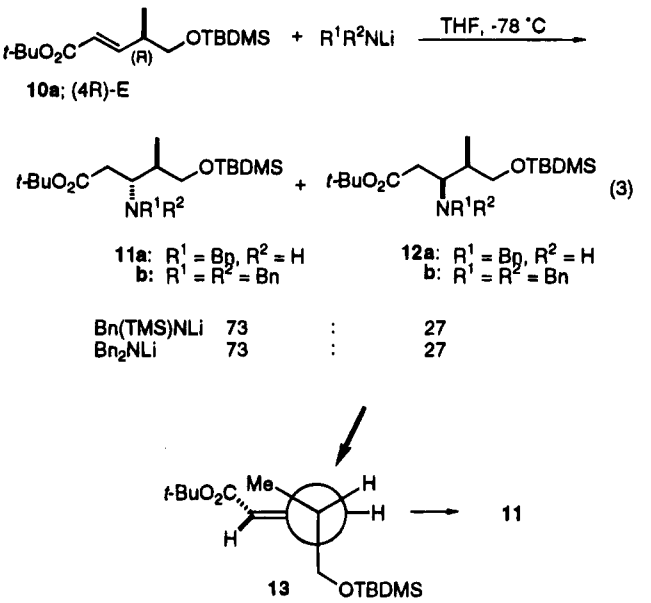
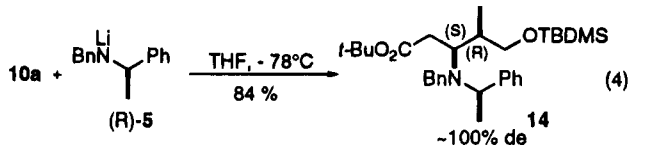
73:27 mixture of **11a** and **12a** in 93% yield (eq 3). The



(3)

conjugate addition of lithium dibenzylamide afforded a 73:27 mixture of **11b** and **12b** in 84% yield. The predominant formation of the anti-isomer **11** can be explained by a modified Felkin–Anh model **13** in which the largest siloxymethyl group is in the anti position and the medium methyl group is in the inside and the lithium amide reagents attack the β-carbon of **10a** from the less hindered outside.

The conjugate addition of (*R*)-**5** to **10a** produced the syn diastereoisomer **14** with essentially 100% de in 84% yield (eq 4). On the other hand, the addition of (*S*)-**5** to



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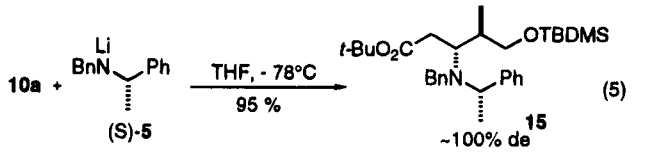

(5)

10a gave the anti diastereoisomer **15** with essentially 100% de in 95% yield (eq 5). Accordingly, the asymmetric induction at the β position of **10a** is controlled completely by the chirality of the lithium amide reagent, and the effect of the chirality of the γ-carbon upon the asymmetric induction is very small. The higher chemical yield in eq 5, in comparison with the yield in eq 4, suggests that the combination between (*R*)-**10a** and (*S*)-**5** is a matched pair; this is supported by the predominant formation of the anti-isomer **11** in eq 3.

We next examined the conjugate addition to the (*Z*)-enoate **10b**, since it was known that the diastereoselectivity of the conjugate addition of organocopper reagents to γ-chiral α,β-unsaturated esters was dependent upon

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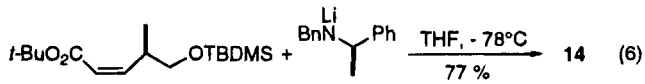
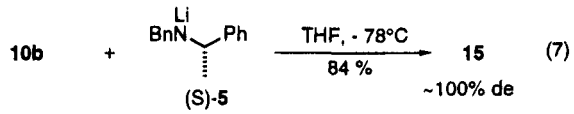
the geometry of the double bond.[12] The addition of (*R*)-**5** to **10b** gave the syn-isomer **14** with essentially 100% de in 77% yield, whereas the addition of (*S*)-**5** to **10b** afforded the anti-isomer **15** with essentially 100% de in 84% yield (eqs 6 and 7). Therefore, the double bond



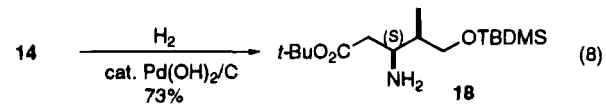


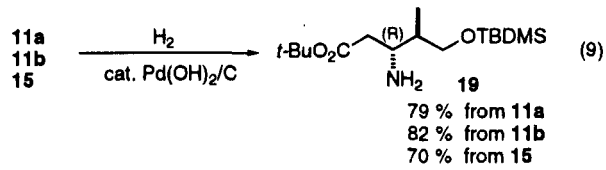
geometry of **10** did not exert any influence upon the sense and extent of asymmetric induction. This observation is not in agreement with the previous result[12] obtained from the conjugate addition of organocopper reagents to γ-methyl-substituted enoates. We carefully investigated the addition to **10a** and **10b** in order to clarify this difference.

The reactions shown in eqs 4−7 were completed within 2 h at −78 °C. When the reaction of **10b** with (*R*)-**5** was stopped at an early stage, the formation of **10a** was observed along with the production of **14**. However, the formation of **10b** was not detected on the way of the reaction of **10a** with (*R*)-**5**. The time dependences of the yields of **10a**, **10b**, and **14** are shown in Figure 1. The progress of the reaction was followed by ^{1}H NMR spectra of the product mixture (see Experimental Section). It is now clear that the isomerization from **10b** to **10a** takes place in the reaction of **10b** (eq 6) whereas no isomerization occurs in the reaction of **10a** (eq 4). The *Z*/*E* isomerization might occur via a hydrogen abstraction at the γ-position by the lithium amide base.[13] If this is the case, racemization at the γ-chiral carbon should be observed. Careful investigation indicated that only the β-amino ester isolable from the reaction mixture was **14** in which the absolute configuration at C-4 was *R*. Accordingly, no racemization takes place, indicating that a hydrogen abstraction at the γ-position does not occur.

A mechanistic rationale for the isomerization is shown in Scheme 1. The conjugate addition of (*R*)-**5** to **10b** presumably produces a mixture of the (*Z*)- and (*E*)-enolates **16** and **17**. The retroconjugate addition from **16** would take place under the reaction conditions, giving a mixture of **10b** and **10a**. The addition of (*R*)-**5** to **10a** would afford stereoselectively the (*E*)-enolate **17**,[14] which does not undergo the retro-Michael addition due to the lithium chelation between a nitrogen and oxygen atom. The (*E*)-enolate **17** affords **14** upon hydrolysis. However, a possibility that the addition of (*R*)-**5** to **10b** produces **14** directly cannot be rigorously excluded.

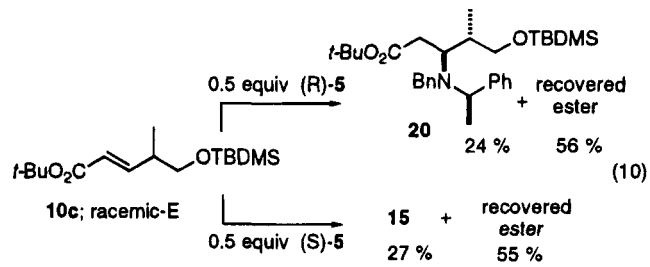
Determination of Absolute Configurations at the β-Position. The absolute configuration of **14** (3*S*,4*R*) was determined unambiguously by converting it into the known 1β-methylcarbapenem derivative **28**, as mentioned later. Hydrogenation of **14** in the presence of catalytic amounts of $Pd(OH)_2$/C gave the syn β-amino ester **18** (3*S*,4*R*) in 73% yield (eq 8). The anti β-amino





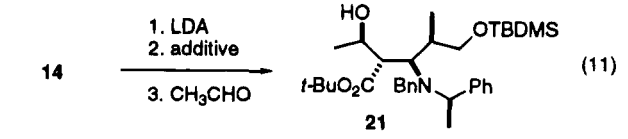
esters, **11** and **15**, were converted to **19** upon hydrogenation with $Pd(OH)_2$/C (eq 9). Comparison of the spectroscopic data of **19** with those of **18** clearly indicated that the absolute configuration of the β-carbon of **19** was R.

Kinetic Resolution. Since the asymmetric induction at the β-position of **10** was controlled completely by the chirality of the Davies reagent, it occurred to us that the kinetic resolution of racemic **10** would take place and the desired diastereoisomer **14** might be obtained from the racemic substrate. The addition of 0.5 equiv of (*R*)-**5** to **10c** (racemic) gave 24% of the anti diastereomer **20** and 56% of the recovered ester, whereas the addition of 0.5 equiv of (*S*)-**5** to **10c** afforded 27% of another anti-isomer **15** and 55% of the recovered ester (eq 10). The optical



activity of the recovered ester was not determined. Here again, the asymmetric induction at the β-position of **10c** was dictated completely by the chirality of the chiral lithium amide. The anti-diastereoisomers **20** and **15** were stereoselectively obtained, and no syn-isomers were formed. This is reasonable because the attack of the reagents to **10c** proceeds primarily via the modified Felkin−Anh geometry **13** which produces the anti isomers **20** and **15**. Accordingly, the use of **10a** is essential to obtain the desired diastereoisomer **14** in which the absolute configurations at C-3 and C-4 (3*S*,4*R*) are in agreement with those of the 1β-methyl carbapenem key intermediate **1**.

Aldol Reaction of 14 with Acetaldehyde. Treatment of **14** with LDA in THF at 0 °C for 2 h, followed by addition of acetaldehyde at −78 °C either in the absence or presence of additives, gave the desired diastereoisomer **21** along with other diastereoisomers (eq 11). The results



are summarized in Table 1. The ratio of **21** to other diastereoisomers was 59:41 in the absence of additives

(12) (a) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 464. (b) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1572. (c) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Am. Chem. Soc.* **1988**, *110*, 617. (d) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652 and references cited therein.

(13) Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 3139 and references cited therein.

(14) It is known that the conjugate addition of LSA to methyl crotonate produces the corresponding lithium (*E*)-enolate with very high stereoselectivity (ref 11b,d).

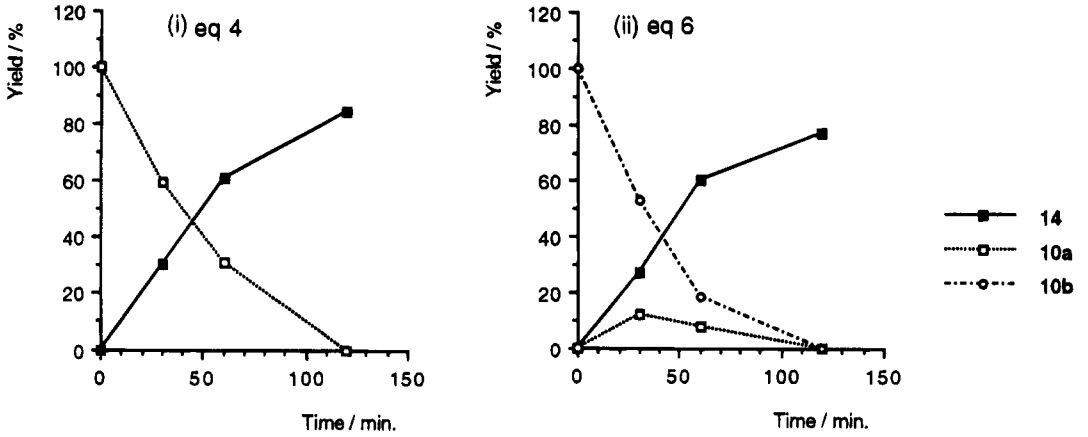
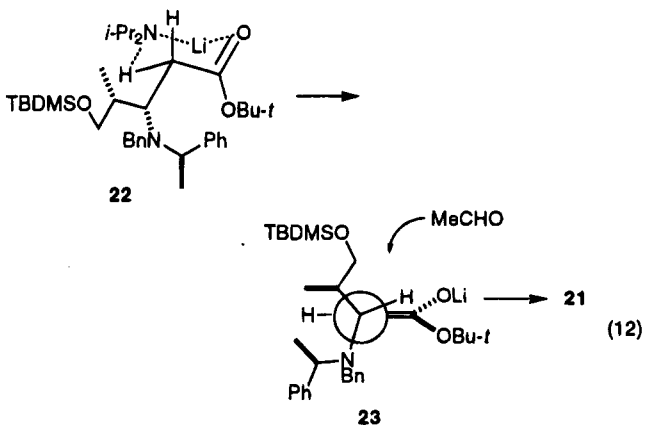


Figure 1. Time dependences of the yields of **10a**, **10b**, and **14** in eqs 4 and 6.

(entry 1). The isomer ratio was not improved even using triethylborane and trimethyl borate as an additive (entries 2 and 3); the use of trimethyl borate gave the highest diastereoisomeric ratio (91:9) in the condensation of acetaldehyde with the β-amino ester bearing no γ-methyl substituent.[6] Instead of the boron additive, the use of aluminum compounds increased the diastereoisomer ratio (entries 4 and 5). Among aluminum additives, methylaluminum dichloride gave the best result. The desired diastereoisomer **21** was separated easily from other diastereoisomers through silica gel column chromatography.

The hydrogen abstraction at the α-position of **14** by LDA presumably proceeds through a six-membered cyclic transition state **22**, as proposed by Ireland.[15] Actually, it is confirmed that treatment of a β-amino ester with LDA under the similar conditions produces the (*Z*)-enolate with high stereoselectivity.[11b,d] The resulting (*Z*)-enolate possesses a sterically demanding *tert*-butyloxy group at the cis position of the double bond, adopting conformation **23** as a stable conformer in order to avoid a severe 1,3-allylic strain. Acetaldehyde attacks from the less hindered side of the double bond, as shown in **23**, leading to the predominant formation of **21** (eq 12). It



(12)

may be argued that **23** and **16** are the same (*Z*)-enolates and **23** undergoes the aldol condensation without the retro-Michael addition which was observed in the case of **16**. Perhaps this difference is due to the difference of aggregation states of the lithium enolates and/or to the presence of iPr_2NH in the reaction medium via **23**.

(15) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

Scheme 1

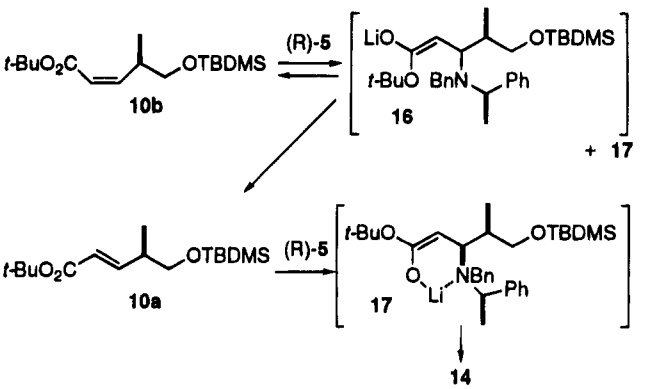


Table 1. Reaction of 14 with Acetaldehyde

entry	additive	product ratio **21**:other diastereoisomers	isolated yield (%)
1		59:41	87
2	BEt_3	53:47	74
3	$B(OMe)_3$	64:36	93
4	$EtAlCl_2$	77:23	78
5	$MeAlCl_2$	80:20	79

Protection of a hydroxy group of **21** with TBDMSCl gave **24** in 99% yield (Scheme 2). Deprotection of a benzyl and α-phenylethyl group with hydrogenation in the presence of catalytic amounts of $Pd(OH)_2/C$ afforded **25** in 66% yield. The cyclization of the β-amino ester **25** using EtMgBr[16] produced the 1β-methyl carbapenem intermediate **26** in essentially quantitative yield. Selective deprotection of a primary −OTBDMS group using NBS/aqueous DMSO[17] afforded **27** in 73% yield. Treatment of **27** with $Me_2C(OMe)_2/BF_3{\cdot}OEt_2$ gave **28** in essentially quantitative yield. The stereostructure of **28** was confirmed unambiguously by comparing its ^1H NMR data with those of the authentic sample.[18] Now it is clear that the modified TCC method provides efficiently a 1β-methyl carbapenem key intermediate **26**: (1) the conjugate addition of (*R*)-**5** to **10a** produces **14** with essentially 100% de (84% yield); (2) the conversion of **14** to **21** proceeds in 63% yield; (3) **26** is obtained from **21** in 65% overall yield.

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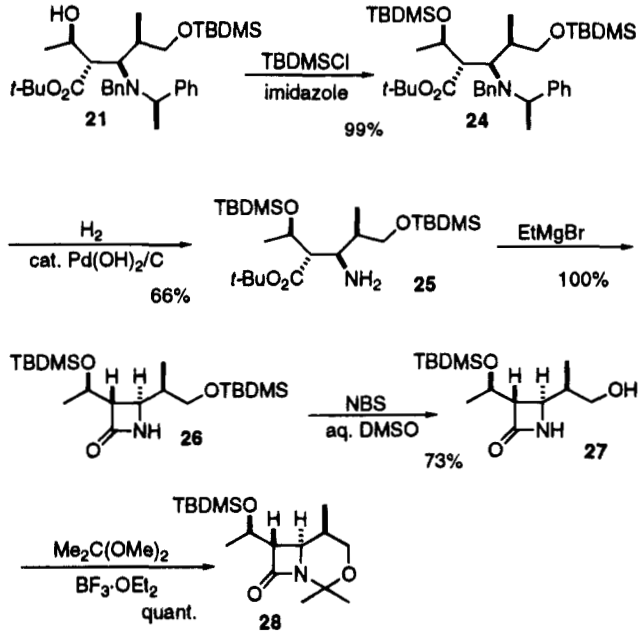
Scheme 2



Experimental Section

General. ^{1}H NMR spectra were measured at 270 MHz on a JEOL JMM-GSX-270 in $CDCl_3$ using TMS as the standard. Mass spectra were recorded on a JEOL JMS-HX-110. IR spectra were recorded on a Hitachi Model 215. Optical rotation was measured by a JASCO DIP-370 spectrometer. Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen. All other solvents were dried and stored over 3 Å molecular sieves. Butyllithium in hexane solution was purchased and titrated prior to use. Most commercially supplied chemicals were distilled and stored over molecular sieves under nitrogen.

(*R*)-(*E*)-*tert*-Butyl 5-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-2-pentenoate (10a). To a CH_2Cl_2 (50 mL) solution of (*R*)-3-hydroxy-2-methylpropionic acid methyl ester (5.54 mL, 50 mmol) at 0 °C were added imidazole (4.08 g, 60 mmol) and TBDMSCl (9.04 g, 60 mmol), and the mixture was stirred overnight at room temperature. Addition of 50 mL of H_2O, extraction with CH_2Cl_2, washing with brine, drying with anhydrous Na_2SO_4, condensation under reduced pressure, and purification with silica gel column chromatography using *n*-hexane/ethyl acetate (20/1) as an eluent gave the ester in which a hydroxy group was protected by TBDMS (11.31 g, 97%). To a CH_2Cl_2 (50 mL) solution of the TBDMS-protected ester (3.02 g, 13 mmol) at −78 °C under N_2 atmosphere was added dropwide a 1.0 M hexane solution of DIBALH (iBu_2AlH, 16.0 mL, 16.0 mmol); it took 30 min for the addition. The mixture was stirred for 1 h, and water (8.6 mL, 480 mmol) was added slowly. The mixture was stirred overnight at room temperature. Extraction with CH_2Cl_2, drying with anhydrous $MgSO_4$, and condensation under reduced pressure gave an oil, which was used for further manipulation without purification. To a THF (30 mL) solution of diisopropylamine (1.82 mL, 13.0 mmol) at 0 °C under Ar atmosphere was added slowly a 1.63 M hexane solution of n-BuLi (7.98 mL, 13.0 mmol). The mixture was stirred for 30 min at 0 °C and cooled to −78 °C. To this solution was added α-(trimethylsilyl)acetic acid *tert*-butyl ester (2.45 mL, 13.0 mmol). The mixture was stirred for 30 min at −78 °C, and the oil obtained above was added slowly. The mixture was allowed to warm, with stirring, to room temperature for 3 h. Addition of 3 N aqueous HCl (20 mL), extraction with ether, washing with brine, drying with anhydrous Na_2SO_4, condensation under reduced pressure, and purification with silica gel column chromatography using *n*-hexane/CH_2Cl_2 (3/1) as an eluent gave a mixture of **10a** (1.59 g, 43%) and **10b** (934 mg, 25%): ^{1}H NMR ($CDCl_3$) δ 6.82 (dd, *J* = 15.7 Hz, 7.2 Hz, 1 H), 5.75 (dd, *J* = 15.7, 1.5 Hz, 1 H), 3.54 (dd, *J* = 9.5, 6.5 Hz, 1 H), 3.49 (dd, *J* = 9.5, 6.5 Hz, 1 H), 2.47 (m, 1 H), 1.48 (s, 9 H), 1.04 (d, *J* = 6.5 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H); IR (neat) 3050−2800, 1725, 1660, 1370, 1260, 1150, 1100, 845, 785 cm^{-1}; $[\alpha]^{26}_D$ +17.003° (*c* 1.02, $CHCl_3$). Anal. Calcd for $C_{16}H_{32}O_3Si$ (300.51): C, 63.94; H, 10.74. Found: C, 63.758; H, 10.620.

(*R*)-(*Z*)-*tert*-Butyl 5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-2-pentenoate (10b): ^{1}H NMR ($CDCl_3$) δ 5.99 (dd, *J* = 11.5, 9.0 Hz, 1 H), 5.67 (dd, *J* = 11.5, 1.0 Hz, 1 H), 3.64−3.49 (m, 3 H), 1.48 (s, 9 H), 1.02 (d, *J* = 6.5 Hz, 3 H), 0.88 (s, 9 H), 0.04, 0.03 (2 s, each 3 H); IR (neat) 3050, 1730, 1645, 1420, 1375, 1260, 1220, 1160, 1100, 840, 785 cm^{-1}; $[\alpha]^{25}_D$ −44.388° (*c* 1.02, $CHCl_3$). Anal. Calcd for $C_{16}H_{32}O_3Si$ (300.51): C, 63.94; H, 10.74. Found: C, 64.142; H, 10.770.

***N*-Benzyl-*N*-((*R*)-1-phenylethyl)amine.** To a MeOH (200 mL) solution of (*R*)-1-phenylethylamine (10.2 mL, 100 mmol) and benzaldehyde (6.44 mL, 50 mmol) was added sodium cyanoborohydride (3.14 g, 50 mmol) at room temperature. The mixture was cooled to 0 °C, and the pH of the solution was adjusted to 6.0 by adding an appropriate amount of acetic acid. The mixture was stirred overnight. Addition of a 40% aqueous solution of K_2CO_3 (200 mL), extraction with ether, washing with brine, and condensation under reduced pressure gave an oil. Aqueous concd HCl and ether were added, and an aqueous layer was separated. By adding aqueous 10% NaOH, the aqueous layer changed to an alkaline solution. Extraction with ether, washing with brine, drying with anhydrous $MgSO_4$, condensation, and distillation gave the desired amine (7.1 g) in 67% yield: bp 124−127 °C/0.7 mmHg; ^{1}H NMR ($CDCl_3$) δ 7.42−7.19 (m, 10 H), 3.81 (q, *J* = 6.5 Hz, 1 H), 3.61, 3.66 (2 d, *J* = 13.0 Hz, each 1 H), 1.59 (br s, 1 H), 1.37 (d, *J* = 6.5 Hz, 3 H); IR (neat) 3325, 3100−2750, 1950, 1880, 1810, 1600, 1490, 1450, 1120, 1030 cm^{-1}; $[\alpha]^{27}_D$ +46.358° (*c* 0.965, $CHCl_3$). Anal. Calcd for $C_{15}H_{17}N$ (211.30): C, 85.26; H, 8.11; N, 6.63. Found: C, 85.377; H, 8.173; N, 6.612.

Conjugate Addition of (*R*)-5 and (*S*)-5 to 10. To a THF (6 mL) solution of *N*-benzyl-*N*-(1-phenylethyl)amine (*R* or *S*) (0.19 mL, 1.0 mmol) at 0 °C under Ar atmosphere was added slowly a 1.64 M hexane solution of n-BuLi (0.61 mL, 1.0 mmol). The mixture was stirred for 30 min and cooled to −78 °C. A THF (2 mL) solution of **10a** or **10b** (150 mg, 0.5 mmol) was added slowly, and the mixture was stirred for 2 h at −78 °C. Aqueous ammonium chloride solution (saturated) and ether were added. The ether layer was separated, washed with brine, dried with anhydrous Na_2SO_4, and condensed under reduced pressure. Purification with silica gel column chromatography using hexane/ethyl acetate (40/1) as an eluent gave the adduct as an oil.

Isomerization of 10b to 10a. The conjugate addition was carried out as described above. The reaction was quenched at 30 min (or 1 h) with aqueous ammonium chloride solution. A similar workup as above was employed. Excess amine was removed with silica gel column chromatography using hexane/ethyl acetate (10/1) as an eluent, giving a product mixture of **10a**, **10b**, and **14**. ^{1}H-NMR spectra of the mixture clearly indicated the ratio of the products; an olefinic proton at C-2 of **10a** appeared at δ 5.75 (dd, *J* = 15.7 and 1.5 Hz, 1H), an olefinic proton at C-2 of **10b** at δ 5.67 (dd, *J* = 11.5 and 1.0 Hz, 1H), and a methylene proton at C-2 of **14** at δ 2.11 (dd, *J* = 15.5 and 9.7 Hz, 1H). These three protons were clearly distinguishable. Accordingly, the progress of the reaction could be monitored by the ^{1}H NMR analysis of the product mixture. In the case of the reaction of **10a** with (*R*)-**5**, the signal at δ 5.67 was not observed at 30 min, 1 h, and 2 h reaction periods. The limits of detection by the NMR were 99% at most.

(3*S*,4*R*)-*tert*-Butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)-amino]-5-((*tert*-butyldimethylsilyl)oxy)-4-methylpentanoate (14): ^{1}H NMR ($CDCl_3$) δ 7.48−7.21 (m, 10 H), 3.77 (d, *J* = 15.0 Hz, 1 H), 3.73 (q, *J* = 7.0 Hz, 1 H), 3.63 (dd, *J* = 9.7, 5.5 Hz, 1 H), 3.51 (d, *J* = 15.0 Hz, 1 H), 3.49 (ddd, *J* = 9.7, 7.0, 2.2 Hz, 1 H), 3.40 (dd, *J* = 9.7, 7.6 Hz, 1 H), 2.11 (dd, *J* = 15.5, 9.7 Hz, 1 H), 1.76−1.63 (m, 2 H), 1.40 (s, 9 H), 1.39 (d, *J* = 7.0 Hz, 3 H), 1.06 (d, *J* = 6.5 Hz, 3 H), 0.90 (s, 9 H), 0.04 (2 s, each 3 H); IR (neat) 3100−2800, 1740, 1615, 1385, 1270, 1160, 1110, 850, 790, 720 cm^{-1}; $[\alpha]^{27}_D$ −11.086° (*c* 0.96, $CHCl_3$). Anal. Calcd for $C_{31}H_{49}NO_3Si$ (511.79): C, 72.75; H, 9.65; N, 2.74. Found: C, 72.265; H, 9.451; N, 2.729.

**(3*R*,4*R*)-*tert*-Butyl 3-[*N*-benzyl-*N*-((*S*)-1-phenylethyl)-amino]-5-((*tert*-butyldimethylsilyl)oxy)-4-methylpen-

tanoate (15): ^{1}H NMR ($CDCl_3$) δ 7.44–7.21 (m, 10 H), 3.99 (dd, J = 9.5, 4.2 Hz, 1 H), 3.77 (d, 15.0 Hz, 1 H), 3.76 (q, 7.0 Hz, k1 H), 3.52–3.40 (m, 3 H), 2.07 (dd, 16.0, 9.5 Hz, 1 H), 1.81–1.70 (m, 2 H), 1.41 (s, 9 H), 1.38 (d, J = 7.0 Hz, 3 H), 0.91 (s, 9 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.05, 0.03 (2 s, each 3 H); IR (neat) 3100–2800, 1740, 1610, 1380, 1270, 1150, 1100, 850, 780, 755, 710 cm^{-1}; $[\alpha]^{27}_D$ +3.7538° (c 1.05, $CHCl_3$). Anal. Calcd for $C_{31}H_{49}NO_3Si$ (511.79): C, 72.75; H, 9.65; N, 2.74. Found: C, 72.449; H, 9.552; N, 2.688.

Aldol Reaction of 14 with Acetaldehyde. To a THF (8 mL) solution of diisopropylamine (0.28 mL, 2.0 mmol) at 0 °C under Ar atmosphere was added slowly a 1.61 M hexane solution of n-BuLi (1.24 mL, 2.0 mmol), and the mixture was stirred for 20 min. The mixture was cooled to −78 °C, and a THF (2 mL) solution of **14** (100 mg, 0.20 mmol) was added dropwise. The mixture was allowed to warm to 0 °C for 1 h and again cooled to −78 °C. An additive (2.0 mmol) was added. The mixture was stirred for 30 min, and a 5 M THF solution of acetaldehyde (0.80 mL, 4.0 mmol) was added at −78 °C. The mixture was stirred for 10 min. Aqueous ammonium chloride solution (saturated) and ether were added. Extraction with ether, washing with brine, drying with anhyd Na_2SO_4, condensation under reduced pressure, and purification with silica gel column chromatography using hexane/ethyl acetate (10/1) as an eluent gave **21** along with other diastereoisomers.

(2*S*,3*R*,4*R*)-*tert*-Butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-5-((*tert*-butyldimethylsilyl)oxy)-2-((*R*)-1-hydroxyethyl)-4-methylpentanoate (21): ^{1}H NMR ($CDCl_3$) δ 7.46–7.17 (m, 10 H), 4.20 (q, J = 7.0 Hz, 1 H), 4.06, 3.98 (2 d, J = 15.0 Hz, each 1 H), 3.87 (q, J = 6.0 Hz, 1 H), 3.61 (dd, J = 10.0, 8.0 Hz, 1 H), 3.42 (dd, J = 10.0, 3.5 Hz, 1 H), 3.28 (dd, J = 6.0, 5.7 Hz, 1 H), 2.58 (dd, J = 7.3, 5.7 Hz, 1 H), 1.94 (m, 1 H), 1.48 (s, 9 H), 1.26 (d, J = 7.0 Hz, 3 H), 1.13 (d, J = 6.0 Hz, 3 H), 1.06 (d, J = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.03, 0.02 (2 s, each 3 H); IR (neat) 3450, 3100–2800, 1730, 1605, 1380, 1260, 1145, 1085, 850, 780, 700 cm^{-1}; $[\alpha]^{24}_D$ −3.5118° (c 1.06, $CHCl_3$); HRMS calcd for $C_{33}H_{53}NO_4Si$ (555.3744), found 555.3742 (M^+).

(2*S*,3*R*,4*R*)-tert-Butyl 3-[*N*-Benzyl-*N*-((*R*)-1-phenylethyl)-amino]-5-((*tert*-butyldimethylsilyl)oxy)-2-[(*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl]-4-methylpentanoate (24). To a DMF (10 mL) solution of **21** (891 mg, 1.60 mmol) were added imidazole (408 mg, 3.0 mmol) and TBDMSCl (452 mg, 6.0 mmol), and the mixture was stirred for 24 h at 50 °C. Water (15 mL) was added, and the product was extracted with CH_2Cl_2. Washing with brine, drying with anhyd Na_2SO_4, condensation in vacuo, and purification with silica gel column chromatography using hexane/ethyl acetate (40/1) as an eluent gave **24** (1.06 g) in 99% yield: ^{1}H NMR ($CDCl_3$) δ 7.54–7.16 (m, 10 H), 4.17 (q, J = 7.0 Hz, 1 H), 4.18, 4.06 (2 d, J = 16.5 Hz, each 1 H), 3.89 (dq, J = 6.0, 4.5 Hz, 1 H), 3.54 (t, J = 10.0 Hz, 1 H), 3.19 (dd, J = 11.0, 2.5 Hz, 1 H), 3.11 (dd, J = 11.0, 4.5 Hz, 1 H), 2.76 (dd, J = 10.0, 4.5 Hz, 1 H), 1.59 (s, 9 H), 1.40 (m, 1 H), 1.21 (d, J = 6.0 Hz, 3 H), 1.01 (d, J = 7.0 Hz, 3 H), 0.87–0.83 (m, 12 H), 0.06, 0.03, 0.00, −0.04 (4 s, each 3 H); IR (neat) 3100–2800, 1730, 1610, 1260, 1150, 1090, 850, 790 cm^{-1}; $[\alpha]^{24}_D$ −15.969° (c 1.13, $CHCl_3$). Anal. Calcd for $C_{39}H_{67}NO_4Si_2$ (670.11): C, 69.90; H, 10.08; N, 2.09. Found: C, 69.80; H, 10.081; N, 2.116.

(2*S*,3*R*,4*R*)-*tert*-Butyl 3-Amino-5-((*tert*-butyldimethylsilyl)oxy)-2-[(*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl]-4-methylpentanoate (25). To an ethyl acetate (15 mL) solution of **24** (1.06 g, 1.58 mmol) was added Pearlman catalyst ($Pd(OH)_2$/C, 300 mg), and the mixture was stirred vigorously for 5 days under H_2 atmosphere. Filtration through Celite, condensation in vacuo, and purification with silica gel column chromatography using hexane/ethyl acetate (10/1) as an eluent gave **25** (499 mg) in 66% yield: ^{1}H NMR ($CDCl_3$) δ 4.08 (dq, J = 7.0, 6.0 Hz, 1 H), 3.60 (dd, J = 9.5, 6.0 Hz, 1 H), 3.53 (dd, J = 9.5, 5.5 Hz, 1 H), 3.15 (dd, J = 6.5, 5.0 Hz, 1 H), 2.46 (dd, J = 7.0, 6.5 Hz, 1 H), 1.61 (m, 1 H), 1.46 (s, 9 H), 1.20 (d, J = 6.0 Hz, 3 H), 0.91 (d, J = 7.0 Hz, 3 H), 0.89, 0.88 (2 s, each 9 H), 0.08, 0.07 (2 s, each 3 H), 0.04 (s, 6 H); IR (neat) 3400, 3050–2800, 1720, 1610, 1370, 1260, 1150, 1100, 1000, 840, 780 cm^{-1}; $[\alpha]^{24}_D$ +2.7612° (c 1.23, $CHCl_3$). Anal. Calcd for $C_{24}H_{53}NO_4Si_2$ (475.84): C, 60.57; H, 11.23; N, 2.94. Found: C, 60.337; H, 11.272; N, 2.954.

(3*S*,4*R*)-3-[(*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl]-4-[(*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-methylethyl]-2-azetidinone (26). To a THF (2 mL) solution of **25** (94 mg, 0.20 mmol) at 0 °C under Ar atmosphere was added a 0.90 M THF solution of ethylmagnesium bromide (0.66 mL, 0.60 mmol). The mixture was stirred for 2 h, and aqueous ammonium chloride solution (saturated) was added. Extraction with ether, washing with brine, drying with anhyd Na_2SO_4, condensation in vacuo, and purification with silica gel column chromatography using hexane/ethyl acetate (5/1) gave **26** (81 mg) in ca. 100% yield: ^{1}H NMR ($CDCl_3$) δ 5.69 (br s, 1 H), 4.18 (dq, J = 6.0, 5.0 Hz, 1 H), 3.72 (dd, J = 5.5, 2.3 Hz, 1 H), 3.59 (dd, J = 10.0, 5.0 Hz, 1 H), 3.54 (dd, J = 10.0, 5.0 Hz, 1 H), 2.89 (ddd, J = 5.0, 2.3, 1.0 Hz, 1 H), 1.80 (m, 1 H), 1.22 (d, J = 6.0 Hz, 3 H), 0.97 (d, J = 6.5 Hz, 3 H), 0.89, 0.88 (2 s, each 9 H), 0.07, 0.04 (2 s, each 6 H); IR (KBr) 3170, 3100, 3000–2800, 1770, 1720, 1260, 1140, 1100, 850, 780 cm^{-1}; $[\alpha]^{24}_D$ −7.8777° (c 1.03, $CHCl_3$). Anal. Calcd for $C_{20}H_{43}NO_3Si_2$ (401.72): C, 59.79; H, 10.79; N, 3.49. Found: C, 59.671; H, 10.673; N, 3.445.

(3*S*,4*R*)-3-[(*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl]-4-((*R*)-2-hydroxy-1-methylethyl)-2-azetidinone (27). A mixture of **26** (192 mg, 0.48 mmol), dimethyl sulfoxide (3 mL), water (0.1 mL), and N-bromosuccinimide (85 mg, 0.48 mmol) was stirred overnight at 30 °C under Ar atmosphere. Extraction with ether, washing with brine, drying with anhyd Na_2SO_4, condensation in vacuo, and purification with silica gel column chromatography using hexane/ethyl acetate (10/1) as an eluent gave **27** (101 mg) in 73% yield: ^{1}H NMR δ 6.37 (br s, 1 H), 4.13 (dq, J = 9.0, 6.0 Hz, 1 H), 3.57 (dd, J = 11.5, 4.5 Hz, 1 H), 3.47 (dd, J = 11.5, 8.5 Hz, 1 H), 3.28 (dd, J = 8.5, 2.0 Hz, 1 H), 3.17 (m, 1 H), 1.86 (m, 1 H), 1.35 (d, J = 6.0 Hz, 3 H), 0.92 (s, 9 H), 0.90 (d, J = 7.0 Hz, 3 H), 0.14, 0.13 (2 s, each 3 H); IR (KBr) 3400, 3250–3000, 3000–2850, 1753, 1709, 1256, 1140, 1097, 964, 837, 777 cm^{-1}; $[\alpha]^{26}_D$ −16.2236° (c 1.145, $CHCl_3$); HRMS calcd for $C_{14}H_{29}NO_3Si$ (287.1917), found 287.1922.

(6*R*,7*S*)-7-[(*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl]-2,2,5-trimethyl-1-aza-3-oxabicyclo[4.2.0]octen-8-one (28). To a CH_2Cl_2 (2 mL) solution of **27** (29 mg, 0.10 mmol) at room temperature under AR atmosphere were added 2,2-dimethoxypropane (15 μL, 0.12 mmol) and BF_3·OEt_2 (5 μL), and the mixture was stirred for 30 min. Triethylamine (0.1 mL) was added, and the mixture was stirred for a while. Water and CH_2Cl_2 were added. The organic layer was washed with brine, dried with anhyd Na_2SO_4, and condensed in vacuo. Purification with silica gel column chromatography using hexane/CH_2Cl_2/ether (3/3/1) as an eluent gave **28** (33 mg) in ca. 100% yield: ^{1}H NMR ($CDCl_3$) δ 4.17 (dq, J = 6.0, 4.3 Hz, 1 H), 3.95 (dd, J = 12.0, 2.5 Hz, 1 H), 3.82 (dd, J = 5.0, 2.0 Hz, 1 H), 3.58 (dd, J = 12.0, 3.0 Hz, 1 H), 2.98 (dd, J = 4.3, 2.0 Hz, 1 H), 1.89 (m, 1 H), 1.72, 1.40 (2 s, each 3 H), 1.18 (d, J = 6.0 Hz, 3 H), 1.11 (d, J = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.08, 0.07 (2 s, each 3 H); IR (CCl_4) 3480, 3000–2800, 1750, 1390, 1370, 1140, 1090 cm^{-1}; $[\alpha]^{27}_D$ +4.5005° (c 1.13, $CHCl_3$). Anal. Calcd for $C_{17}H_{33}NO_3Si$ (327.52): C, 62.34; H, 10.16; N, 4.28. Found: C, 62.281; H, 9.684; N, 4.066.

Acknowledgment. We thank Dr. I. Shinkai of Merck Sharp & Dohme Research Laboratories for providing us with ^{1}H NMR spectra of **28**.

Supplementary Material Available: Copies of ^{1}H NMR spectra of **10a**, **10b**, N-benzyl-N-(R)-1-phenylethylamine, **14**, **15**, **21**, and **24–28** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO941628T