the racemic compound (0.15 g, 39%), $[\alpha]_D$ +21° (c 4, $CHCl_3$). The (S)-(-)-MTPA ester of racemic **2d**, prepared as described in ref 9, showed, with decoupling of the C-2 methyl signals (double doublet at 0.945 ppm) by irradiation of the resonance at 2.04 ppm due to the corresponding hydrogen at the tertiary carbon, the resonances of the C-2 methyl groups for (R)- and (S)-**2d** at 0.925 and 0.936 ppm. In the spectrum of the corresponding derivative from (R)-(+)-**2d**, the resonance of the methyl group at 0.936 ppm was absent. In a control, this signal could be detected when 2% of racemate was added to (R)-**2d**, corresponding to 1% of the S isomer, and 98% ee was therefore established for the enzymatically produced (R)-(+)-**2d**.

(R)-(+)-4-(Phenylsulfonyl)-2-methyl-1-butanol (3b). A solution of the racemic alcohol **3b** (0.25 g, 1.1 mmol), vinyl acetate (0.42 mL, 4.55 mmol), and PFL (12.3 mg, 517 units) in chloroform (2.5 mL) was stirred for 16 h. After workup and purification, fractions eluted with hexane/ethyl acetate(6/4) contained the acetate **3c** (0.125 g, 42%), $[\alpha]_D$ -5° (c 4, $CHCl_3$). Fractions eluted with hexane/ethyl acetate (4/6) contained the alcohol **3b**, with chemicophysical characteristics in complete agreement with those of the racemic compound (0.140 g, 56%), $[\alpha]_D$ +10° (c 4, $CHCl_3$). The (S)-(-)-MTPA ester of racemic **3b** showed the resonances of the C-2 methyl groups for (R)- and (S)-**3b** as two overlapped doublets (J = 6.93 Hz) centered at 0.900 and 0.912 ppm. In the spectrum of the corresponding derivative from (R)-(+)-**3b**, the resonance of the methyl group at 0.912 ppm was absent. In a control, this signal could be detected when 2% of racemate was added to (R)-**3b**, corresponding to 1% of the S isomer, and 98% ee could be established for (R)-(+)-**3d**.

(S)-(-)-Acetate 2e. In order to prepare enantiomerically pure (S)-(-)-**2e**, the hydrolysis was repeated as described for the preparation of (R)-(+)-**2d**, with the same amounts of substrate and enzyme, the reaction being stopped at 40% conversion. Pure acetate **2e** was obtained by column chromatography (0.177 g, 38%): bp 240 °C (16 mm Hg); $[\alpha]_D$ -15° (c 4, $CHCl_3$); ^1H NMR δ 1.0 (d, 3 H, J = 7 Hz, CH_3), 1.5-1.9 (m, 3 H, CH_2 and CH), 2.0 (s, 3 H, CH_3CO), 2.95 (t, 2 H, J = 8 Hz, CH_2S), 4.0 (d, 2 H, J = 6 Hz, CH_2O), 7.35 (m, 5 H, Ar). Anal. Calcd for $C_{13}H_{18}O_2S$: 65.55; H, 7.56. Found: C, 65.7; H, 7.65.

(S)-(-)-Acetate 3c. The hydrolysis was repeated as described for the preparation of (R)-(+)-**3b**, with the same amounts of substrate and enzyme, the reaction being stopped at 40% conversion. Pure acetate **3c** was obtained by column chromatography (0.104 g, 36%): bp 205 °C (0.3 mm Hg); $[\alpha]_D$ -10.5° (c 4, $CHCl_3$); ^1H NMR δ 0.95 (d, 3 H, J = 7 Hz, CH_3), 1.2-2.0 (m, 3 H, CH_2 and CH), 2.0 (s, 3 H, CH_3CO), 3.2 (t, 2 H, J = 8 Hz, CH_2SO_2), 3.95 (d, 2 H, J = 6 Hz, CH_2O), 7.65-7.9 (m, 3 H, Ar), 7.9-8.2 (m, 2 H, Ar). Anal. Calcd for $C_{13}H_{18}O_4S$: C, 57.75; H, 6.66. Found: C, 57.88; H, 6.75.

(R)-(+)-1-(Ethoxymethoxy)-2-methyl-4-(phenylthio)butane (2a). This compound was synthesized from enzymatically prepared (R)-(+)-**2d** as described in ref 3. The purified compound had characteristics in agreement with those of a standard sample. Starting from alcohol **2d** of $[\alpha]_D$ +21°, the derivative **2a** presented $[\alpha]_D$ +11.5° (c 2, $CHCl_3$).

(R)-(+)-1-(Ethoxymethoxy)-2-methyl-4-(phenylsulfonyl)butane (3d). This compound was synthesized from enzymatically prepared (R)-(+)-**3b** as described in ref 3. The purified compound had characteristics in agreement with those of a standard sample. Starting from alcohol **3b** of $[\alpha]_D$ +10.5°, the derivative **3d** presented $[\alpha]_D$ +5.2° (c 2, $CHCl_3$).

Acknowledgment. We thank Ministero della Pubblica Istruzione for financial help, Dr. Maurizio Anastasio for his participation at the latest stages of the work, and Mr. Carlo Cavarretta and Miss Elisa Verza for technical assistance.

Registry No. (R)-(+)-**2a**, 129423-06-9; (±)-**2b**, 129518-64-5; (±)-**2c**, 129518-65-6; (R)-**2e**, 129423-10-5; (±)-**2d**, 129423-00-3; (R)-(+)-**2d**, 129518-67-8; (R)-**2d** ((S)-(-)-MTPA ester), 129423-04-7; (S)-**2d** ((S)-(-)-MTPA ester), 129423-08-1; (S)-(-)-**2e**, 129423-01-4; (±)-**3b**, 129518-66-7; (R)-(+)-**3b**, 129423-03-6; (R)-**3b** ((S)-(-)-MTPA ester), 129423-05-8; (S)-**3b** ((S)-(-)-MTPA ester), 129423-09-2; (S)-(-)-**3c**, 129423-02-5; (R)-(+)-**3d**, 129423-07-0; PFL, 9001-62-1; PhSH, 108-98-5; α-methyl-γ-butyrolactone, 69010-09-9.

Addition of Activated Grignard Reagents to 2-Phenyloxazolines

Giovanni Fronza, Andrea Mele, Giuseppe Pedrocchi-Fantoni, Domenica Pizzi, and Stefano Servi*

CNR, Centro di Studio per le Sostanze Organiche Naturali, Dipartimento di Chimica, Politecnico di Milano, Piazza, L. da Vinci 32, 20133, Milano, Italy

Received February 9, 1990

Introduction

The role of amino sugars and amino deoxy sugars as parts of biologically active molecules is well recognized, and numerous efforts have been devoted to their synthesis in enantiomerically pure form.[1] Recently[2] we have been using an approach to isomeric 2,4,6-trideoxy-4-C-methyl-4-amino-L-hexose derivatives starting from L-threonine (1) (Scheme I).

Thus oxazoline **2** obtained as described from L-threonine[3] was methylated to give the aldehyde **3**. Treatment of **3** with allylmagnesium bromide gave the isomeric alcohols **4**. Ozonization of the terminal double bond and deprotection of the β-amino alcohol gave 4-C-methyl amino deoxy sugars of type **5** in enantiomerically pure form. Under the conditions used, even with an excess of nucleophile, addition to the C=N double bond was never observed, as expected from the known stability of 2-oxazolines to Grignard reagents.[4]

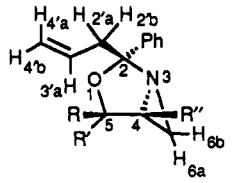
In order to prepare differently substituted 2,3,4,6-tetradeoxy-4-aminohexoses of the L series, we considered an approach similar to the one described in Scheme I, namely, the preparation of the tosylates **6a-d**, chain elongation with allyl Grignard reagent, double-bond oxidation, and final deprotection. This procedure should eventually lead to isomeric compounds of type **8** through acyclic precursors like **7** (Scheme II).

Results and Discussion

In contrast to our expectations, reaction of tosylates **6** with allyl Grignard reagents under various conditions,[5] did not affect chain elongation[6] but gave bicyclic compounds **9a-d** as the only products. Structural assignement was made on the basis of high resolution ^1H NMR spectroscopy (Table I) combined with IR and MS data. The formation of a three-membered ring is evident from the chemical shifts and coupling constants of the protons H-4, H-6a, and H-6b.[7] In particular, the magnitude of the geminal coupling constants ^2J(6a,6b), <0.5 Hz, is characteristic of the aziridine ring.[8] The erythro or threo stereochemistry of C-4 and C-5 in **9a,b** reflects the stereochemistry of the starting materials and can be easily recognized from the vicinal coupling constants ^3J(4,5). In the erythro compound **9b** with the protons H-4 and H-5 cis oriented in the five-membered ring, ^3J(4,5) is 3.0 Hz, while for the threo compound **9a** with H-4 and H-5 in a trans relationship, the value of ^3J(4,5) is ~0. In the latter case the two

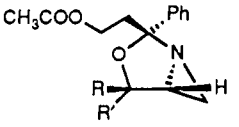
(1) Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35.
(2) Fronza, G.; Fuganti, C.; Pedrocchi-Fantoni, G. *J. Carbohydr. Chem.* **1989**, *8*, 85.
(3) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1983**, *24*, 3211.
(4) Meyers, A. I.; Mihelich, E. D. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 270.
(5) No difference was oserved by using THF or diethyl ether with commercially available Grignard solutions or fresly prepared in the presence of Li_2CuCl_4 (ref 6) or without the latter reagent.
(6) Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82.
(7) Jackman, L. A.; Sternhell, S. In *Application of NMR Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1969; p 272.
(8) Manatt, S. L.; Ellemann, D. D.; Brois, S. J. *J. Am. Chem. Soc.* **1965**, *87*, 2220.

0022-3263/90/1955-6216$02.50/0



9a: R = Me, R′ = R″ = H
9b: R = R″ = H, R′ = Me
9c: R = H, R′ = R″ = Me
9d: R = CF_3, R′ = R″ = H

protons must be in a trans pseudoequatorial orientation, with a dihedral angle of ~90°. The stereochemistry of C-2 has been elucidated on the basis of NOE observed from the irradiation of H-5 and Me-5. In the erythro series (**9b**), the selective excitation of H-5 causes NOE enhancements of the protons at C-2′ (~3%), while saturation of the Me-5 group shows the enhancements of the phenyl ring ortho protons (1.5%). On the contrary, in the threo series (**9a**), the selective perturbation of H-5 enhances the signals of H-6a (4%) and of the ortho hydrogens (2%) of the phenyl substituent, while irradiation of the Me-5 group causes variations of the H-2′ protons. Similar observations on the ^{1}H NMR spectra of compounds **10a** and **10b**, obtained from **9a** and **9b**, confirmed the assignment of the structure to these compounds.



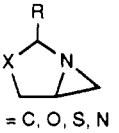
10a: R = Me, R′ = H
10b: R = H, R′ = Me

When substrates **6** were treated with methyl Grignard reagents, the products of conjugate addition were suppressed, and tosylate displacement was observed only in trace amounts. This indicates that the reaction is limited to "activated" organomagnesium reagents. Thus reaction of **6c** with methylmagnesium iodide gave **6f** as the only product. Treatment of **6f** with allyl Grignard gave **9c**.

The activated nature of allylmetals is well documented,[9] and addition reactions of these reagents to unactivated double bonds, or 1,4 addition to unsaturated carbonyl compounds, have been reported as well as the displacement of the tosylate from the iodide.[10] Addition to imines has also been reported,[11] but as already mentioned, 2-oxazolines are considered to be stable to Grignard reagents.

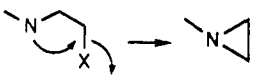
From these observations it appears that addition to the C=N double bond of substituted 2-phenyloxazolines requires the use of an activated Grignard reagent and the presence of a leaving group in the γ position. This addition cyclization is the only reaction observed and its outcome is not affected by changing solvent, temperature, and origin of the allyl Grignard.[5] Addition of the nucleophile takes place in an antiperiplanar fashion with respect to the tosylate irrespective of the configuration of C-5. The stereochemistry of the newly formed chiral center at C-2 appears to be dictated by the configuration at C-4.

This new addition–cyclization reaction allows the preparation of a bicyclic heterocyclic system not readily available by other methods. In fact, heterocyclic compounds of type **11** are well known, but while azabicyclo-



X = C, O, S, N
11

[3.1.0]hexane[12] and 1,3-diazabicyclo[3.1.0]hexane[13] are rather common and can be prepared by several methodologies, thia- and oxaazabicyclo[3.1.0]hexanes are rather rare and only a few synthetic methods are available. In particular, cis and trans **11** (X = O, R = 2-propyl) have been prepared by SiO_2-catalyzed decomposition of the corresponding triazolines.[14] At the same time, whereas intramolecular nucleophilic displacement is a common procedure for the preparation of aziridines,[15] this methodology has not previously been applied to the synthesis of azabicyclohexanes of type **11**. The possibility of ex-



tending this approach to the synthesis of other bicyclic compounds of type **11** is being considered.

Experimental Section

^{1}H NMR spectra were recorded at 300 MHz on a Bruker CXP spectrometer. Melting points are uncorrected. $[\alpha]^{20}_D$ are at *c* 1 in $CHCl_3$. Purification of products was performed by flash chromatography on silica gel (Merck 60) with mixtures of hexane and ethyl acetate. Analytical samples were prepared by bulb-to-bulb distillation under reduced pressure.

(4*R*,5*R*)-2-Phenyl-4-(hydroxymethyl)-5-methyl-4,5-dihydrooxazole *p*-Toluenesulfonate (6a). (4*R*,5*R*)-2-Phenyl-4-(hydroxymethyl)-5-methyl-4,5-dihydrooxazole[16] (14 g, 0.071 mol) was dissolved in 150 mL of anhydrous pyridine and cooled to 0 °C. To the stirred solution was added 27 g (0.14 mol) of *p*-toluenesulfonyl chloride in portions during 30 min. The mixture was stirred for 24 h at room temperature, poured into ice water, and extracted twice with methylene chloride. The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness to give an oily residue, which after purification by silica gel chromatography gave 18.1 g (0.052 mol, 73%) of **6a**: $[\alpha]^{20}_D$ = +28.8°; ^{1}H NMR ($CDCl_3$) δ 1.4 (3 H, d), 2.45, (3 H, s), 3.8–4.3 (2 H, m), 4.4–4.9 (2 H, m), 7.25–7.45 and 7.75–8 (9 H, m). Anal. Calcd for $C_{18}H_{19}O_4NS$: C, 62.59; H, 5.54. Found: C, 62.31; H, 5.83.

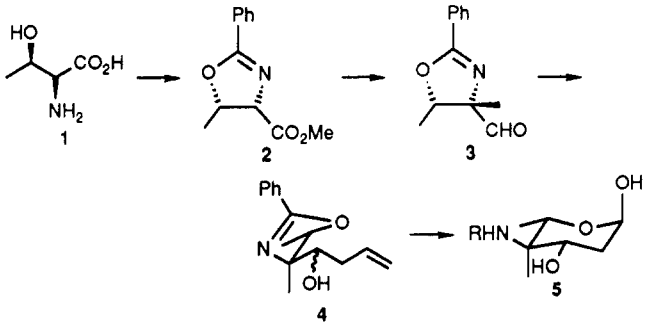
(4*R*,5*S*)-2-Phenyl-4-(hydroxymethyl)-5-methyl-4,5-dihydrooxazole *p*-Toluenesulfonate (6b). Compound **6b** was prepared as described for **6a** starting from the corresponding alcohol[17] in 70% yield: $[\alpha]^{20}_D$ = +91.9°; ^{1}H NMR ($CDCl_3$) δ 1.45 (3 H, d), 2.48 (3 H, s), 4.0–4.55 (3 H, m), 4.75–5.1 (1 H, m), 7.3–7.6 and 7.75–8.0 (9 H, m). Anal. Calcd for $C_{18}H_{19}O_4NS$: C, 62.59; H, 5.54. Found: C, 62.79; H, 5.21.

(4*R*,5*S*)-2-Phenyl-4-(hydroxymethyl)-4,5-dimethyl-4,5-dihydrooxazole *p*-Toluenesulfonate (6c). Compound **6c** was prepared as described for **6a** starting from the corresponding alcohol:[3] yield 30.6 g (77%); $[\alpha]^{20}_D$ = +51.2°; ^{1}H NMR ($CDCl_3$) δ 1.33 (3 H, s), 1.45 (3 H, d), 2.45 (3 H, s), 4.0 (2 H, s), 4.45 (1 H, q), 7.2–7.5 and 7.65–7.9 (9 H, m). Anal. Calcd for $C_{19}H_{21}O_4NS$: C, 63.49; H, 5.89. Found: C, 63.71; H, 5.93.

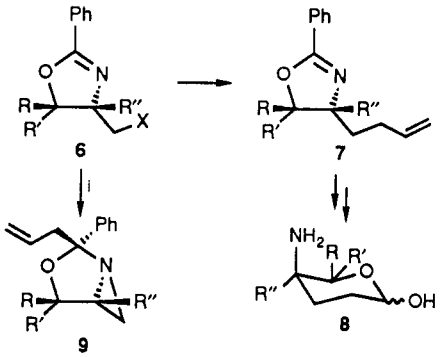
(4*RS*,5*SR*)-2-Phenyl-4-(hydroxymethyl)-5-(trifluoromethyl)-4,5-dihydrooxazole *p*-Toluenesulfonate (6d). Starting from racemic trifluorothreonine ethyl ester[18] and following

(9) Wilkinson, S. G., Ed. *Comprehensive Organometallic Chemistry*; Pergamon Press: 1982; Vol. 1 p 167, and Vol. 7, p 4.
(10) Felkin, H.; Umpleby, J. D.; Hagaman, E.; Wenkert, E. *Tetrahedron Lett.* **1972**, 2285. Vara Prasad, J. V. N.; Pillai, C. N. *J. Organomet. Chem.* **1983**, *259*, 1.
(11) Huet, J. *Bull. Soc. Chim. Fr.* **1964**, 952.
(12) Gassmann, P. G.; Fentiman, A. *J. Org. Chem.* **1967**, *32*, 2388.
(13) Padwa, A.; Glazer, E. *J. Am. Chem. Soc.* **1972**, *94*, 7788.
(14) Hassner, A.; Amarasekara, A. S.; Andisik, D. *J. Org. Chem.* **1988**, *53*, 27.
(15) Padwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Lwowski, W., Eds.; Pergamon Press: 1984; Vol 7, p 80.
(16) Moss, R. A.; Lee, T. B. K. *J. Chem. Soc., Perkin Trans. I* **1973**, 2278.
(17) Elliott, D. F. *J. Chem. Soc.* **1950**, 62.

Scheme I



Scheme II[a,b]



[a] **a**, R = Me, R′ = R″ = H, X = OTs; **b**, R = R″ = H, R′ = Me, X = OTs; **c**, R = H, R′ = R″ = Me, X = OTs; **d**, R = CF_3, R′ = R″ = H, X = OTs; **f**, R = H, R′ = R″ = Me, X = I. [b](i) Allylmagnesium bromide.

Table I. ^{1}H NMR Spectral Data for Compounds 9a–d and 10a,b[a]

	9a	9b[b]	9c[b]	9d	10a	10b
H-5	4.48	4.09	4.48	3.90	4.48	4.42
H-4	2.65	2.20	1.07 (Me)	2.99	2.64	2.69
H-6a	1.13	1.16	1.32	1.10	1.11	1.28
H-6b	1.67	1.19	1.13	1.82	1.63	1.44
H-2′a	2.72	2.72	2.70	2.75	2.30	2.26
H-2′b	2.87	2.81	2.80	2.75	2.50	2.33
H-3′a	5.59	5.89	5.90	5.48	4.08	3.88
H-3′b					3.90	4.04
H-4′a	4.93	4.93	4.90	4.82		
H-4′b	4.89	4.95	4.93	4.86		
Me-5	1.50	1.08	1.08		1.45	1.37
COMe					1.83	1.85
J(4,5)	0.0	3.1		0.0	0.0	3.0
J(4,6a)	3.5	3.5		3.4	3.5	3.5
J(4,6b)	5.0	5.0	5.0		5.0	5.5
J(6a,6b)	<0.5	0.5	<0.5	<0.5	<0.5	<0.5
J(2′a,2′b)	15.0	14.3	13.7		14.0	14.0
J(2′a,3′a)	7.0	7.0	7.0	7.0	9.0	6.1
J(2′a,3′b)					5.5	8.5
J(2′b,3′a)	7.0	7.0	7.0	7.0	6.1	8.3
J(2′b,3′b)					8.5	6.0
J(3′a,3′b)					11.0	11.0
J(3′a,4′a)	16.5	16.6	16.2	16.0		
J(3′a,4′b)	10.5	10.5	10.4	10.0		
J(4′a,4′b)	2.0	1.5	1.5	2.0		
J(5,Me)	6.3	6.0	6.0		6.5	6.0

[a] Chemical shifts in ppm from internal TMS; coupling constants in hertz. solvent $CDCl_3$ except as otherwise indicated. [b] Solvent C_6D_6.

the procedure described in the literature,[3] (4*RS*,5*RS*)-2-phenyl-4-(ethoxycarbonyl)-5-(trifluoromethyl)-4,5-dihydrooxazole was obtained in 70% yield: ^{1}H NMR ($CDCl_3$) δ 1.35 (3 H, t), 4.3 (2 H, q), 4.97 (1 H, d), 5.26 (1 H, m), 7.3–7.5 (3 H, m), 8.0–8.2 (2 H, m). The ester was reduced with $LiAlH_4$ in THF, giving in 70% crude yield 2-phenyl-4-(hydroxymethyl)-5-(trifluoromethyl)-4,5-dihydrooxazole. The crude alcohol (12.2 g, 0.049 mol) was treated with *p*-toluenesulfonyl chloride (10.1 g, 0.053 mol) in dry pyridine (90 mL) as usual. After workup, the tosylate **6d** (13.3 g, 68%) was obtained as white crystals (hexane/ethyl acetate, mp 99–101 °C): ^{1}H NMR ($CDCl_3$) δ 2.42 (3 H, s), 4.25 (2 H, m), 4.45–4.6 (1 H, m), 4.7–4.9 (1 H, m), 7.2–7.5 and 7.6–7.9 (9 H, m). Anal. Calcd, for $C_{18}H_{16}O_4F_3NS$: C, 54.13; H, 4.04. Found: C, 53.98; H, 4.08.

Compounds 9a–d. To a solution of **6a–d** (0.140 mol) in 200 mL of anhydrous THF under nitrogen with stirring was added 15.6 mL (0.154 mol) of a commercial 2 M THF solution of allylmagnesium chloride in 15 min at 0 °C. After being stirred at that temperature for 1 h, the reaction mixture was heated at reflux for 3 h and finally quenched with 5 mL of methanol at room temperature. The solid material was filtered off and the solution was diluted with ethyl acetate and washed with water. The residue obtained after evaporation of the solvent was chromatographed on SiO_2, giving ~20 g (70% yield) of a pure oily product (**9a–d**). Experiments using freshly prepared Grignard reagent in THF or diethyl ether gave the same results. Also the use of Li_2CuCl_4 under the Schlosser conditions[6] gave compounds **9** as the only isolated products in comparable yields. In all the experiments, ratios of allylmetal to substrate ranging from 1 to 5 were used without significant change in the reaction.

(2*R*,4*R*,5*R*)-2-Phenyl-2-(2-propen-1-yl)-5-methyl-1-oxa-3-aza[3.1.0]bicyclohexane (9a): $[\alpha]^{20}_D$ = −125.3°; ^{1}H NMR, see Table I. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96. Found: C, 77.98; H, 7.87.

(2*R*,4*R*,5*S*)-2-Phenyl-2-(2-propen-1-yl)-5-methyl-1-oxa-3-aza[3.1.0]bicyclohexane (9b): $[\alpha]^{20}_D$ = −32.8°; ^{1}H NMR, see Table I. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96. Found: C, 78.21; H. 7.79.

(2*R*,4*R*,5*S*)-2-Phenyl-2-(2-propen-1-yl)-4,5-dimethyl-1-oxa-3-aza[3.1.0]bicyclohexane (9c): $[\alpha]^{20}_D$ = −36.3°; ^{1}H NMR, see Table I. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35. Found C, 78.79; H, 8.38.

(2*RS*,4*RS*,5*SR*)-2-Phenyl-2-(2-propen-1-yl)-5-(trifluoromethyl)-1-oxa-3-aza[3.1.0]bicyclohexane (9d): ^{1}H NMR, see Table I. Anal. Calcd for $C^{14}H_{14}F_3NO$: C, 62.45; H, 5.24. Found: C, 62.37; H, 5.12.

Preparation of 10a and 10b. Ozonized oxygen was passed through a methanolic solution of **9a,b** (10 mmol in 30 mL of methanol) at −40 °C during 20 min. Nitrogen was then passed through the solution to eliminate the excess of ozone. The solution was then treated with excess $NaBH_4$ at 0 °C and kept at room temperature overnight. The residue obtained after removal of the solvent was dissolved in ethyl acetate, washed with water, and dried. The crude oily product was dissolved in pyridine (5 mL) and acetic anhydride (8 mL) at room temperature. Standard workup of the mixture gave the acetates in 55% yield after purification.

(2*R*,4*R*,5*R*)-2-Phenyl-2-(2-acetoxyethyl)-5-methyl-1-oxa-3-aza[3.1.0]bicyclohexane (10a): $[\alpha]^{20}_D$ = −76.14°; ^{1}H NMR, see Table I. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33. Found: C, 68.56; H, 7.23.

(2*R*,4*R*,5*S*)-2-Phenyl-2-(2-acetoxyethyl)-5-methyl-1-oxa-3-aza[3.1.0]bicyclohexane (10b): $[\alpha]^{20}_D$ = −28.8°; ^{1}H NMR, see Table I. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33. Found: C, 68.37; H, 7.31.

(4*S*,5*S*)-2-Phenyl-4-(iodomethyl)-4,5-dimethyl-4,5-dihydrooxazole (6f). Compound **2c** was treated in anhydrous ethyl ether with an excess of a freshly prepared ethereal solution of methylmagnesium iodide at −10 °C and then stirred at room temperature for 16 h. After workup and silica gel chromatography, compound **6f** was obtained as the only isolated product in 65% yield: $[\alpha]^{20}_D$ = −32.5°; MS M+ 315, 300, 188, 174; ^{1}H NMR ($CDCl_3$) δ 1.48 (3 H, d), 1.49 (3 H, s), 3.27 (2 H, d), 4.44 (1 H, q), 7.38 (3 H, m), 7.88 (2 H, m). Anal. Calcd for $C_{12}H_{14}INO$: C, 45.73; H, 4.48. Found: C, 45.69; H, 4.51. When compound **6f** was treated with a THF solution of allylmagnesium chloride, compound **6c** was obtained as the main product.

Registry No. **6a**, 88549-76-2; **6b**, 129679-96-5; **6b** alcohol derivative, 129783-77-3; **6c**, 129679-97-6; **6c** alcohol derivative,

(18) Scolastico, C.; Conca, E.; Prati, L.; Guanti, G.; Banfi, L.; Berti, A.; Farina, P.; Valcavi, U. *Synthesis* **1985**, 850.

129679-98-7; **6d**, 129679-99-8; **6f**, 129680-00-8; **9a**, 129680-01-9; **9b**, 129783-78-4; **9c**, 129680-02-0; **9d**, 129680-03-1; **10a**, 129680-04-2; **10b**, 129783-79-5; (4*R*,5*R*)-2-phenyl-4-(hydroxymethyl)-5-methyl-4,5-dihydrooxazole, 104068-55-5; trifluorothreonine ethyl ester, 102608-32-2; (4*RS*,5*RS*)-2-phenyl-4-(ethoxycarbonyl)-5-(trifluoromethyl)-4,5-dihydrooxazole, 129680-05-3; 2-phenyl-4-(hydroxymethyl)-5-(trifluoromethyl)-4,5-dihydrooxazole, 129680-06-4; allylmagnesium chloride, 2622-05-1.

Lithium/Ammonia Cleavage of the N–N Bond in *N*-(Methoxycarbonyl)- and *N*-Acetylhydrazines

Scott E. Denmark,* Olivier Nicaise, and James P. Edwards

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

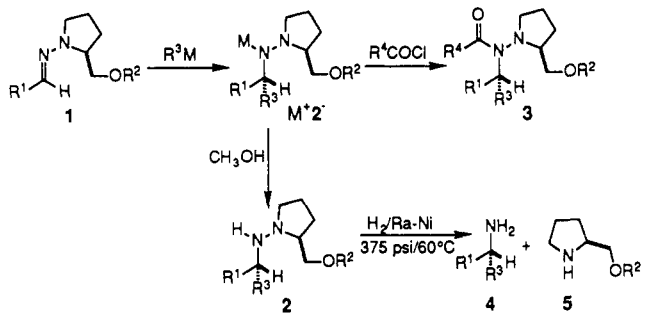
Received March 16, 1990

The diastereoselective addition of organocerium reagents to L-proline-derived hydrazones **1** has recently been reported from these laboratories[1] (Scheme I). The reaction is compatible with a wide range of substrates (R^1 = Ph, $PhCH_2$, $PhCH_2CH_2$, (*E*)-$CH_3CH{=}CH$) and accommodates a variety of unstabilized nucleophiles (R^3 = Me, *n*-Bu, *i*-Pr, *t*-Bu, Ph, *i*-$Pr_3SiCH{=}CH$) derived from either lithium or halomagnesium precursors. The additions proceed in good yield (67–81%) and with high diastereoselectivity (>93:7 ds).

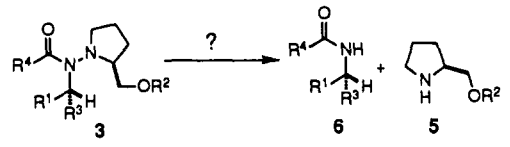
To facilitate isolation, characterization, and isomer analysis, the addition products M^+2^- were trapped as benzyl or methyl carbamates, **3**. However, to secure the scalemic amines **4**, ultimately desired as end products of this transformation, the crude, air-sensitive hydrazines were hydrogenated over W-2 Raney nickel[2] (Scheme I). Although usually successful, this N–N bond cleavage protocol[3] suffers from a number of disadvantages. Primarily, the conditions are rather harsh (375 psi/60 °C) and saturation of aromatic residues can become competitive.[4a] Further, we have found that certain chiral auxiliaries cannot be cleaved, and under still more forcing hydrogenolytic conditions, epimerization of the amine and the auxiliary occurred. Finally, the separation of the amine **4** from the auxiliary **5** requires selective Schiff-base formation and chromatography.[4a]

The development of an improved N–N bond cleavage protocol which addressed these problems focused on the protected hydrazines **3** (Scheme II). These stable derivatives offered several important advantages: (1) handling of sensitive hydrazines is avoided, (2) the products **3** can be further diastereomerically enriched by chromatography, (3) the amines **6** are produced in protected form, (4) the auxiliary **5** can be recovered by aqueous acidic extraction, and finally (5) the acyl group was expected to facilitate reductive cleavage of the hydrazine.[5]

Scheme I



Scheme II



Initial failures to cleave a methyl carbamate[4b] (**3**, R^4 = OCH_3) with H_2/Raney Ni, H_2/Pd–C, Na(Hg), Zn/AcOH, $TiCl_3$, and BH_3·THF are consistent with the resistance of doubly activated hydrazines to these reagents found by Mellor.[6] The preferred method for reductive cleavage of mono-,[7] *N,N'*-di-,[6,8] and tetraacylhydrazines[8a] is sodium in liquid ammonia.[9] In this paper, we report that lithium in ammonia is an equally effective reagent for the cleavage of scalemic, monoacylated hydrazines *with complete preservation of configuration on both sides of the hydrazine.*

Orienting experiments employed racemic *N,N*-dimethylhydrazine **7**. The results of these studies (Table I) may be summarized as follows: (1) 2 equiv (4 g-atom equiv) of the reducing agent was required to consume the substrate (entries 1, 2 and 4, 5), (2) with lithium, reaction times longer than 1 h did not improve the yield significantly (entries 5–7), (3) the isolated benzene ring was not reduced (no added proton source), (4) either THF or Et_2O are suitable cosolvents, and (5) lithium was marginally superior to sodium (entries 3, 6). Finally, an attempt to reduce the corresponding benzyl carbamate resulted only in deprotection without N–N bond cleavage.

With a workable method in hand, the optically active, acylated hydrazines **9** and **10** were next examined (Table II). In the SAMEMP[1b] series **9**, the reductions of both methyl carbamates (**9xa**) and an acetamide (**9cb**) proceeded smoothly to give the corresponding protected amines in good yield. The low recoveries of **12** and **13** in the table reflect the water solubility (**12**) and volatility (**13**) of the pyrrolidines. The auxiliary **12** was recovered by derivatization as a 1-naphthamide **15**. This derivative was directly analyzed by chiral HPLC[10a] and was enantio-

(1) (a) Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc.* **1987**, *109*, 2224. (b) Weber, T.; Edwards, J. P.; Denmark, S. E. *Synlett* **1989**, *1*, 20.

(2) Review of Ni-Al reductions: (a) Keefer, L. K.; Lunn, G. *Chem. Rev.* **1989**, *89*, 459. See also (b) Lunn, A.; Sansone, E. B.; Keefer, L. K. *Synthesis* **1985**, 1104.

(3) Reviews of N-N bond cleavage see: (a) Marshalkin, M. F.; Yakhontov, L. N. *Russ. Chem. Rev.* **1986**, *55*, 1016. (b) Rylander, P. N. *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, 1979; pp 299–306. (c) Newbold, B. T. In *The Chemistry of the Hydrazo, Azo and Azoxy Groups*; Patai, S., Ed.; Wiley: New York, 1975; Part 2, Chapter 15; pp 629–631.

(4) (a) Enders, D.; Schubert, H.; Nubling, C. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1109. (b) Piotrowski, D. W., unpublished observations from these laboratories.

(5) Horner, L.; Jordan, M. *Liebigs Ann. Chem.* **1978**, 1505.

(6) Mellor, J. M.; Smith, N. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2927.

(7) (a) Wasserman, H. H.; Robinson, R. P.; Matsuyama, H. *Tetrahedron Lett.* **1980**, *21*, 3493. (b) Wasserman, H. H.; Matsuyama, H. *J. Am. Chem. Soc.* **1981**, *103*, 461. (c) Kuo, C. H.; Wendler, N. L. *Tetrahedron Lett.* **1984**, *25*, 2291. (d) Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc.* **1984**, *106*, 5594.

(8) (a) Kemp, D. S.; Sidell, M. D.; Shortridge, T. J. *J. Org. Chem.* **1979**, *44*, 4473. (b) Forrest, A. K.; Schmidt, R. R. *Tetrahedron Lett.* **1984**, *25*, 1769. (c) Forrest, A. K.; Schmidt, R. R.; Huttner, G.; Jibril, I. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1981. (d) Gilchrist, T. L.; Hughes, D.; Wasson, R. *Tetrahedron Lett.* **1987**, *28*, 1573. (e) Meng, Q.; Hesse, M. *Synlett* **1990**, 148.

(9) Lithium/ammonia has also been used to cleave diacylhydrazines. Vedejs, E.; Meier, G. P. *Tetrahedron Lett.* **1979**, 4185.

0022-3263/90/1955-6219$02.50/0