nylsulfonyl)ethylene[9] (**11b**) (191 mg, 0.6 mmol) in xylene (5 mL) was heated under reflux for 30 min. The cooled solution was diluted with ether, and the white adduct **12b–15b** (277 mg, 92.5%) was collected by filtration: ^{1}H NMR ($CDCl_3$) δ 2.27 (m, 2 H), 3.68–4.05 (m, 2 H), 4.10 (m, 2 H), 4.90 (m, 2 H), 6.65 (m, 2 H), 7.00–8.05 (m, 18 H).

Sodium Amalgam Reduction of Adducts 12b–15b. A mixture of adducts **12b–15b** (272 mg, 0.45 mmol) was taken up in dry tetrahydrofuran (5 mL) and methanol (10 mL), containing sodium dihydrogen phosphate (1.2 g), and purged with nitrogen. With efficient stirring, 3% sodium amalgam (ca. 2.5 g) was added in small portions. After 16 h, the mixture was filtered through a Celite pad and poured onto brine (20 mL). The solvent was evaporated off on the rotary evaporator, and the aqueous residues were extracted with dichloromethane (4 × 20 mL). The combined organic layer was washed with water (2 × 20 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated to give **16–19** as a light yellow solid (140 mg, 97.8%). GC–MS analysis of this mixture showed it to be an isomeric mixture of four components, in the approximate ratio of 2:1:2:7 (column used: 12 m × 0.32 mm (i.d.), packed with fused silica–BP_1 type, column temperature 250 °C, isothermal conditions), all with the m/e (M^+) of 318: IR (film, NaCl plate) 3054, 3000, 2960, 2930, 1460, 1448, 1322, 1305, 1283, 1264, 1225, 1181, 1145, 1133, 1098, 1082, 903, 879, 838, 817, 746, 738, 704, 681 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.20 (m, 2 H), 3.50–3.95 (m, 2 H), 5.02 (m, 2 H), 6.57 (m, 2 H), 6.70–7.75 (m, 10 H); MS, m/e (M^+) calcd 318.1404, obsd 318.1396.

Acknowledgment. I wish to thank J. Keegan for running the mass spectra and L. Ambrose for some technical assistance. I also wish to thank L. Green for the drawings.

Registry No. **3**, 117202-21-8; **4**, 15098-01-8; **5**, 117202-22-9; **6**, 117202-23-0; **8**, 13209-15-9; **9**, 716-39-2; **10**, 18071-92-6; **11b**, 963-16-6; **12a**, 117202-24-1; **12b**, 117202-26-3; **13a**, 117305-58-5; **13b**, 117305-60-9; **14a**, 117202-25-2; **14b**, 117202-27-4; **15a**, 117305-59-6; **15b**, 117305-61-0; **16**, 117202-28-5; **17**, 117305-62-1; **18**, 117202-29-6; **19**, 117305-63-2; maleic anhydride, 108-31-6; 1,4-hydroquinone, 123-31-9; cyclopentadiene, 542-92-7.

A Convenient Stereoselective Synthesis of 1,2,3-Aminodiols from α-Amino Acids

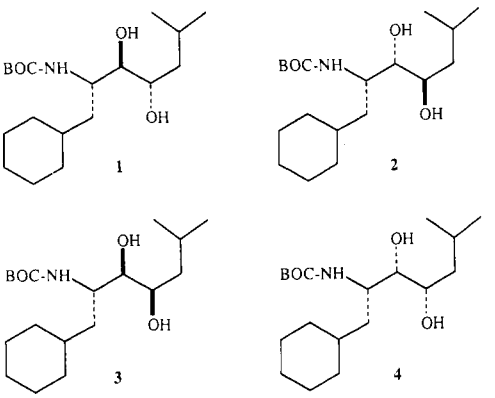
Jay R. Luly,* Chi-Nung Hsiao, Nwe BaMaung, and Jacob J. Plattner

Abbott Laboratories, Pharmaceutical Products Division, Abbott Park, Illinois 60064

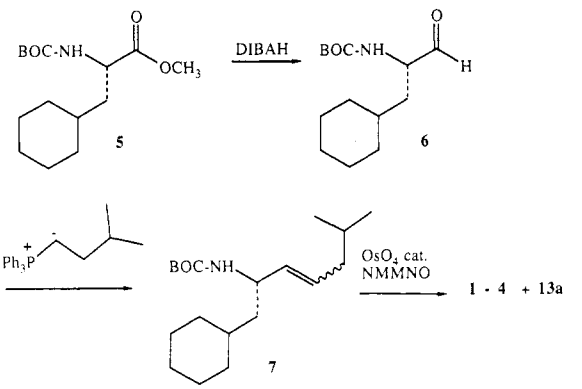
Received May 23, 1988

Recently, we reported that dipeptides attached to appropriately substituted amino diols **1–4** (Chart I) are potent inhibitors of the aspartic proteinase renin.[1] If the diol were mimicking the transition state for hydrolysis of the Leu[10]–Val[11] amide bond of the enzyme substrate, angiotensinogen, then one might expect a stereochemical bias for the diol geometry in the active site. Therefore, we initially sought a synthesis which, from naturally occurring L-amino acids, would provide a synthesis of all four diastereomeric diols, realizing that after definition of the most active isomer, a highly diastereoselective route would be necessary.

Chart I



Scheme I



In this paper, we describe routes that proceed with low and high diastereoselectivity. Using an extension of our methylide olefination procedure of Boc-protected α-amino aldehydes,[2] we were able to olefinate Boc-(cyclohexyl)-alaninal **6**, derived from ester **5**[3], to give a cis/trans mixture of olefins **7**[1a,c] (Scheme I). This one-flask manipulation provided **7** in 50–60% yield (from **5**) and in 99% ee as was determined by conversion to the (+)- and (−)-MTPA amides.[1c] Diols **1–4**, as well as trace and variable amounts of hydroxy ketone **13a**, were then obtained by catalytic osmylation with little olefin facial selectivity. Although all four diol isomers were readily separable by silica gel chromatography, anti isomers **1** and **2** were obtained in higher yield due to slight preferential formation of *cis*-**7** over *trans*-**7** in the olefination step.[4]

Simultaneously, we explored an epoxidation route that would be expected to favor the formation of syn isomers **3** and **4**. Allylic alcohol **8** (*R*:*S*, 1:1), prepared by Swern oxidation of alcohol **10a** followed by vinyl Grignard addition, was chosen for initial study. Treatment of **8** with MCPBA for 14 h in dichloromethane provided a mixture of epoxides **9**. Since attempted purification of the isomers of **9** by silica gel chromatography led to severely reduced yields, crude **9** was used in the copper-catalyzed reaction[5] with isopropylmagnesium chloride. Assuming preferential

(1) (a) Luly, J. R.; Fung, A. K. L.; Plattner, J. J.; Marcotte, P.; BaMaung, N.; Soderquist, J. L.; Stein, H. In *Peptides: Chemistry and Biology*; Marshall, G. R., Ed.; ESCOM Science Publishers B.V.: Leiden, The Netherlands, 1988; p 487. (b) Kleinert, H. D.; Luly, J. R.; Marcotte, P. A.; Perun, T. J.; Plattner, J. J.; Stein, H. *FEBS Lett.* **1988**, *230*, 38. (c) Luly, J. R.; BaMaung, N.; Soderquist, J.; Fung, A. K. L.; Stein, H.; Kleinert, H. D.; Marcotte, P. A.; Egan, D. A.; Bopp, B.; Merits, I.; Bolis, G.; Greer, J.; Perun, T.; Plattner, J. J. *J. Med. Chem.*, in press.

(2) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487.

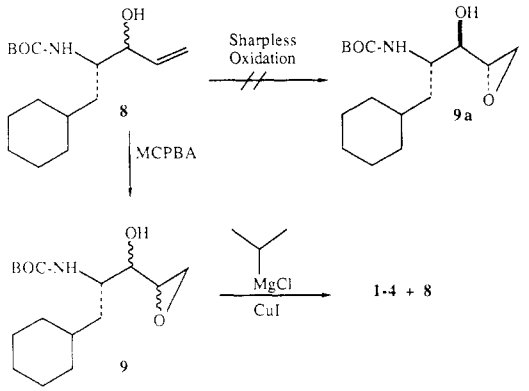
(3) Boger, J.; Payne, L. S.; Perlow, D. S.; Lohr, N. S.; Poe, M.; Blaine, E. H.; Ulm, E. H.; Schorn, T. W.; LaMont, B. I.; Lin, T.-Y.; Kawai, M.; Rich, D. H.; Veber, D. F. *J. Med. Chem.* **1985**, *28*, 1779.

(4) Syn diols **3** and **4** are formed by osmylation of *trans*-**7** while anti diols **1** and **2** are derived from *cis*-**7**. The relative stereochemistry of the adjacent carbons bearing the amino and hydroxyl groups was established by cyclization to the oxazolidinones and measurement of the chemical shifts of the ring hydrogens.[1c]

(5) (a) Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, 1503. (b) Brockway, C.; Kocienski, P.; Pant, C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 875.

0022-3263/88/1953-6109$01.50/0

Scheme II

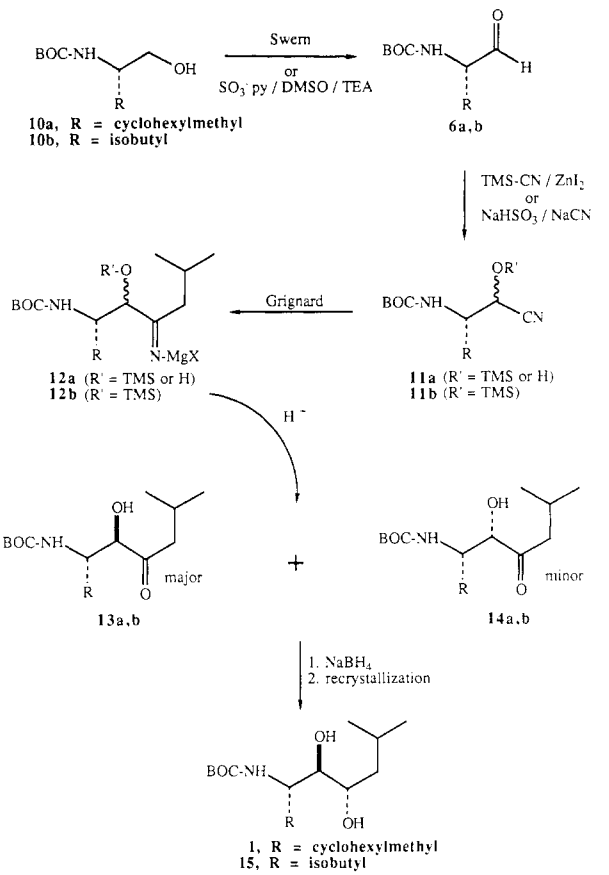


threo epoxidation,[6] one would expect isomers **3** and **4** to be formed in larger quantities than **1** and **2**. In practice, only a trace of **2** could be detected by TLC. The quantitation of **1** was complicated in that it cochromatographed with the unexpected deoxygenation product *S*-**8**, but the combined chromatographed yield of **1** and *S*-**8** was 21% and was shown by ^{1}H NMR to be a 1:4 mixture. The chromatographed yields of **3** and **4** were 23% and 11%, respectively. The above two routes provided sufficient quantities of pure isomers **1**–**4** for further elaboration, and subsequent enzymatic evaluation in a renin inhibition assay[1b] revealed isomer **1** to have the preferred orientation of the three contiguous chiral centers for binding at the enzyme active site.

The lack of cis/trans selectivity in olefination and lack of facial selectivity in the olefin osmylation make the route shown in Scheme I unattractive for large-scale preparation of **1**. The route in Scheme II would be potentially attractive if one could prepare *S*-**8** and effect erythro epoxidation to **9a**. Preparation of enriched *S*-**8** (82:18, *S*:*R*) could be effected by a one-flask DIBAH reduction/vinyl Grignard reaction on ester **5**.[7] This is to be contrasted with the lack of selectivity obtained when aldehyde **6**, isolated from Swern oxidation of alcohol **10**, is treated with the Grignard reagent. With enriched *S*-**8** in hand, we were attracted to the Sharpless epoxidation method since erythro epoxidation of simple allylic alcohols has been demonstrated.[8] Unfortunately, all attempts using *tert*-butyl hydroperoxide/Ti(O-i-Pr)$_4$/(−)-diisopropyl tartrate failed to give significant (>10%) conversion to **9a** at low temperature (−25 °C) and caused either no reaction or extensive decomposition of starting material at warmer temperatures. Presumably the nitrogen is interacting with the catalyst in a way that prevents the normally facile oxidation.

Another route to diol **1** involves stereoselective reduction of hydroxy ketone **13a**, first obtained as a trace side product in the oxidation of olefin **7**. When **13a** was treated with $NaBH_4$ in methanol, stereoselective reduction proceeded (1:3, >10:1). Encouraged by this preliminary test, we sought an expedient synthesis of **13**. Recently, Gill et al.[9] reported the synthesis of simple hydroxy ketones by Grignard addition to TMS cyanohydrins followed by hydrolysis. We therefore explored the extension of this method to TMS cyanohydrins of aldehydes derived from α-amino acids. Swern oxidation of alcohol **10** provided crude aldehyde **6**, which was converted to a mixture of major and minor TMS cyanohydrins **11a** (R′ = TMS). This reaction fixes the stereochemistry of the first hydroxyl group and introduces the latent ketone functionality in the form of a nitrile. Addition of isobutyl Grignard and then quenching the mixture under acidic conditions produced an 8:1 mixture of hydroxy ketones **13a** and **14a**, respectively, in a one-flask operation and in 99% yield. It should be noted that the one-pot synthesis of **13** and **14** using a DIBAH reduction of ester **5** as the source of **6** proceeds less cleanly, perhaps due to the reaction of excess DIBAH with TMS–CN and/or **11a** (R′ = TMS). We next reexamined the ketone reduction on the mixture. The reaction proceeded smoothly, and recrystallization of the final product gave isomerically pure diol **1** in 60% overall yield from alcohol **10**.

Scheme III



To make the synthesis more amenable to large-scale preparation, we sought a process that would proceed at room temperature with less expensive reagents. Thus, Doering/Parikh oxidation[10] (SO_3·py/DMSO/TEA) converted **10a** to **6a**, which was then treated in situ with sodium bisulfite and sodium cyanide to produce cyanohydrin (**11a**, R′ = H, 63%, *R*:*S*, ca. 8:1)[11] as a stable solid. Reaction of **11a** (R′ = H) with excess isobutylmagnesium chloride in diethyl ether followed by acidic hydrolysis delivered a mixture of **13a** and **14a** similar to that above. Without purification, the mixture was reduced with sodium

(6) Narula, A. S. *Tetrahedron Lett.* **1983**, *24*, 5421 and references cited therein.
(7) Bolis, G.; Fung, A. K. L.; Greer, J.; Kleinert, H. D.; Marcotte, P. A.; Perun, T. J.; Plattner, J. J.; Stein, H. *J. Med. Chem.* **1987**, *30*, 1729.
(8) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. (c) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922. (d) Bessodes, M.; Abushanab, E.; Antonakis, K. *Tetrahedron Lett.* **1984**, *25*, 5899.
(9) Gill, M.; Kiefel, M. J.; Lally, D. A. *Tetrahedron Lett.* **1986**, *27*, 1933.
(10) (a) Doering, W. V. E.; Parikh, J. R. *J. Am. Chem. Soc.* **1967**, *89*, 5505. (b) Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 1921.
(11) Diastereomeric ratio was determined by comparing integrations of singlet peaks (Boc) at δ 1.95 and 1.98 in the 500-MHz ^{1}H NMR spectrum.

borohydride to 1 as described above. After extractive workup, again, pure 1 (56% yield first crop from **11a**, R′ = H) crystallized directly out of the mixture as colorless needles. We next extended the sequence shown in Scheme III to the compounds with R = isobutyl (starting with Boc-L-leucinol) with similar yields and feel that this procedure for the generation of amino diols will have utility in stereoselective synthesis.

Experimental Section

All amino acids and protected amino acids were obtained from Sigma Chemical Co. (St. Louis, MO) or Bachem (Torrance, CA), and isobutylmagnesium chloride was obtained from Aldrich Chemical Co. Anhydrous solvents used were dried and freshly distilled. All reactions were run in oven-dried glassware under an atmosphere of dry nitrogen or argon. Proton magnetic resonance spectra were measured on a Nicolet QE-300 (300 MHz) or a General Electric GN-500 (500 MHz) instrument. Chemical shifts are reported as δ values (parts per million) relative to Me_4Si as in internal standard. Mass spectra were obtained with Hewlett-Packard HP5985 (CI, EI) and Varian CH7 (EI) spectrometers. Optical rotations were measured with a Perkin-Elmer automatic polarimeter. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses and the above determinations were performed by the Analytical Research Department, Abbott Laboratories. Thin-layer chromatography (TLC) was carried out by using E. Merck precoated silica gel F-254 plates (thickness 0.25 mm). Flash column chromatography was carried out using Baker silica gel (40 μm).

(2*S*,3*R*,4*S*)-2-[(*tert*-Butyloxycarbonyl)amino]-1-cyclohexyl-3,4-dihydroxy-6-methylheptane (1). Method A. 1. (2*S*,3*R*)-2-[(*tert*-Butyloxycarbonyl)amino]-1-cyclohexyl-3-hydroxy-6-methylheptan-4-one (13a) and (2*S*,3*S*)-2-[(*tert*-Butyloxycarbonyl)amino]-1-cyclohexyl-3-hydroxy-6-methylheptan-4-one (14a). To a stirred −63 °C solution of oxalyl chloride (784 mg, 6.18 mmol) in dry dichloromethane (15 mL) was added dry dimethyl sulfoxide (708 mg, 9.06 mmol) dropwise over 5 min. After another 5 min, Boc-cyclohexylalaninol (1.06 g, 4.12 mmol) in dichloromethane (5 mL) was added dropwise over 5 min, and 5 min later, triethylamine (1.67 g, 16.48 mmol) was added similarly. ZnI_2 (300 mg, 0.94 mmol) was added after 5 min. After the mixture was stirred for 2 min, trimethylsilyl cyanide (1.43 g, 14.42 mmol) was added, and the mixture was warmed to room temperature for 1 h. The mixture was then cooled to 0 °C, and isobutylmagnesium chloride (22.0 mL of a 2 M solution in ether) was added. After being warmed to room temperature for 4 h, the mixture was poured into 1 M H_3PO_4 (40 mL)/ice (50 mL) and extracted with ethyl acetate. The combined organic phase was washed sequentially with 1 M H_3PO_4, water, saturated $NaHCO_3$, and brine. Drying ($MgSO_4$), filtering, and evaporating provided 1.75 g of an oil, which was dissolved in THF (75 mL) and treated with 1 M H_3PO_4 (25 mL) for 18 h at 5 °C. The solution was partitioned between ethyl acetate/brine, and the resulting organic phase was washed sequentially with brine, saturated $NaHCO_3$, and brine. Drying ($MgSO_4$), filtering, and evaporating provided the desired product (1.39 g, 99%), which was used directly in the next step. The following chemical shifts for **13a** were derived from a spectrum of the crude mixture, which showed 1:8 **14a** (NH, 4.85 ppm): **13a** (NH, 4.52 ppm): ^1H NMR ($CDCl_3$) δ 0.93, 0.94 (2 d, 3 H each, J = 7, 7 Hz), 1.39 (s, 9 H), 0.85–1.95 (several m), 2.18 (m, 1 H), 2.41 (dd, 1 H, J = 7, 17 Hz), 2.66 (dd, 1 H, J = 7, 17 Hz), 3.8 (br, 1 H), 4.04 (br s, 1 H), 4.30 (m, 1 H), 4.52 (br d, 1 H, J = 10 Hz).

2. Reduction of 13a to 1. To a stirred solution of the above hydroxy ketone (200 mg, 0.586 mmol) in THF (10 mL) was added $NaBH_4$ (22 mg, 0.586 mmol). After 2 h, the solvent was evaporated, and the residue was partitioned between ethyl acetate and brine. The organic phase was washed (brine), dried (Na_2SO_4), filtered, and evaporated. The residue was recrystallized from methylcyclohexane to give 76 mg (38%) of the desired product, mp 130–131 °C. The mother liquor was chromatographed (silica gel, ether/hexane) to give 43 mg (21%) more. The material was identical in all respects with material prepared previously:[1c] mass spectrum $(M + 1)^+$ 344; $[\alpha]_D$ −64.91° (c 2.20, $CHCl_3$); IR ($CHCl_3$) 3430, 2940, 1680, 1500, and 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–1.85 (m, 15 H), 0.88 (d, 3 H, J = 7 Hz), 0.94 (d, 3 H, J = 7 Hz), 1.46 (s, 9 H), 1.93 (m, 1 H), 3.2 (br d, 1 H, J = 8 Hz), 3.33 (m, 1 H), 4.04 (m, 1 H), 4.25 (br, 1 H), 4.58 (br d, 1 H, J = 9 Hz). The below data were obtained in CD_3CN: 0.8–1.95 (m, 16 H), 0.84 (d, 3 H, J = 7 Hz), 0.92 (d, 3 H, J = 7 Hz), 1.42 (s, 9 H), 2.84 (d, 1 H, J = 7 Hz), 3.02 (m, 1 H), 3.22 (m, 1 H), 3.89 (m, 1 H), 4.04 (d, 1 H, J = 4 Hz), 5.23 (d, 1 H, J = 10 Hz), when D_2O was added, the 2.84, 4.04, and 5.23 ppm resonances exchanged out. The 3.02 resonance shifted to 3.06 and simplified to a dd, J = 1.5, 9 Hz. The 3.22 resonance shifted to 3.28 and simplified to a ddd, J = 2.5, 9, 9 Hz. The 3.89 resonance shifted to 3.88 and simplified to a ddd, J = 1.5, 5, 10 Hz. Anal. Calcd for $C_{19}H_{37}NO_4$: C, 66.4; H, 10.9; N, 4.1. Found: C, 66.4; H, 10.8; N, 3.9.

Method B. 1. (2*R*,3*S*)-3-[(*tert*-Butyloxycarbonyl)amino]-4-cyclohexyl-2-hydroxybutyronitrile (11a, R′ = H, 2*R*) and (2*S*,3*S*)-3-[(*tert*-Butyloxycarbonyl)amino]-4-cyclohexyl-2-hydroxybutyronitrile (11a, R′ = H, 2*S*). To a stirred solution of **10a** (14.3 g, 55.4 mmol) and triethylamine (23 mL, 165.7 mmol) in dichloromethane (200 mL) at 0–5 °C (ice bath) was added in one portion a solution of sulfur trioxide pyridine complex (26.5 g, 166.5 mmol) in dimethyl sulfoxide (90 mL). After 25 min, a solution of sodium bisulfite (35 g, 336.5 mmol) in water (120 mL) was added, and the resulting mixture was vigorously stirred for 1 h followed by addition of sodium cyanide (15 g, 306.0 mmol). After being stirred for another hour, the mixture was diluted with hexane and ethyl acetate (400 mL each), washed with water (600 mL × 6), dried ($MgSO_4$), and filtered. Evaporation of solvent under reduced pressure yielded a colorless oily residue, which was dissolved in methanol (15–20 mL) and then added dropwise to a rapidly stirred aqueous solution (500 mL) of sodium chloride (40 g). After being stirred overnight, **11a** (R′ = H, 2*R*/2*S* = ∼8/1, 9.77 g, 63%) was collected by filtration as a white solid: mp 110–113 °C; ^1H NMR (500 MHz, $CDCl_3$) for **11a** (R′ = H, 2R): δ 0.85–0.92 (m, 1 H), 0.97–1.05 (m, 1 H) 1.10–1.30 (m, 3 H), 1.32–1.43 (m, 2 H), 1.60–1.80 (m, 6 H), 1.95 (s, 9 H), 3.82 (br s, 1 H), 4.57 (br s,1 H), 4.64 (br s, 1 H) and 4.73 (d, J = 7.5 Hz, 1 H); for **11a** (R′ = H, 2*S*): δ 0.85–0.92 (m, 1 H), 0.97–1.05 (m, 1 H), 1.10–1.30 (m, 3 H), 1.32–1.43 (m, 2 H), 1.60–1.80 (m, 6 H), 1.98 (s, 9 H), 4.10 (m, 1 H), 4.35 (br s, 1 H), 4.46 (d, J = 5 Hz, 1 H), and 5.05 (br s, 1 H); IR ($CHCl_3$) 3450, 1690, 1500, and 1160 cm^{-1}; mass spectrum, m/e (M + 1) 283. Anal. Calcd for $C_{15}H_{26}N_2O_3$: C, 63.74; H, 9.21; N, 9.91. Found: C, 64.09; H, 9.41; N, 9.98.

2. (2*S*,3*R*,4*S*)-2-[(*tert*-Butyloxycarbonyl)amino]-1-cyclohexyl-3,4-dihydroxy-6-methylheptane (1). To a stirred solution of isobutylmagnesium chloride (2.0 M in ethyl ether, 20 mL, 40.0 mmol) at room temperature under nitrogen was slowly added a solution of **11a** (R′ = H, 2*R*/2*S* = ∼8/1, 2.0 g, 7.08 mmol) in ethyl ether (25 mL) so that the reaction mixture was under gentle reflux throughout the addition. After 20 min, the mixture was carefully poured into well-stirred ice water (200 mL), followed by portionwise addition of citric acid until the pH of the aqueous solution reached 4. After another 1.5 h, the mixture was extracted with ethyl ether. The organic layer was washed with saturated aqueous solution of sodium bicarbonate, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield a light yellow oil, which was directly dissolved in tetrahydrofuran (35 mL) and treated with excess sodium borohydride (0.5 g, 13.22 mmol). After the mixture was stirred at room temperature overnight, ice (∼20 g) was added followed by careful addition of citric acid to destroy the excess reducing agent. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous solution of sodium bicarbonate, dried ($MgSO_4$), plug filtered (SiO_2), and evaporated under reduced pressure to yield a colorless oil. Crystallization from hexane/ethyl acetate (20:1) gave pure 1 (1.36 g, 56%) as colorless fine needles with all physical and spectral characteristics identical with those of the sample prepared by method A.

(4*S*,5*R*,6*S*)-6-[(*tert*-Butyloxycarbonyl)amino]-4,5-dihydroxy-2,8-dimethylnonane (15). Boc-L-leucinol, **10b** (2.00 g, 9.20 mmol), was-reacted according to method A to give 2.77 g (100%) of crude **13b** and **14b**, which was directly reacted with $NaBH_4$ according to the above procedure. Chromatography of the crude product (2.8 g) provided **15** (1.35 g, 49% from **10b**): ^1H NMR ($CDCl_3$) δ 0.88 (d, 3 H, J = 7 Hz), 0.92 (d, 3 H, J = 7 Hz), 0.94 (d, 3 H, J = 7 Hz), 0.96 (d, 3 H, J = 7 Hz), 1.46 (s, 9 H),

1.2-1.75 (several m), 1.93 (m, 1 H), 3.20 (dd, 1 H, J = 1, 9 Hz), 3.34 (m, 1 H), 4.02 (m, 1 H), 4.55 (br d, 1 H, J = 9 Hz); mass spectrum, $(M + 1)^+$ 304. Anal. Calcd for $C_{16}H_{33}NO_4$: C, 63.33; H, 10.96; N, 4.62. Found: C, 63.47; H, 11.04; N, 4.72.

Registry No. **1**, 104882-10-2; **6a**, 98105-42-1; **6b**, 58521-45-2; **10a**, 103322-56-1; **10b**, 82010-31-9; (2*R*,3*S*)-**11a** (R′ = TMS), 117499-02-2; (2*S*,3*S*)-**11a** (R′ = TMS), 117499-03-3; (2*R*,3*S*)-**11a** (R′ = H), 117499-04-4; (2*S*,3*S*)-**11a** (R′ = H), 117499-05-5; (2*R*,3*S*)-**11b** (R′ = TMS), 117499-06-6; (2*S*,3*S*)-**11b** (R′ = TMS), 117499-07-7; **13a**, 114457-87-3; **13b**, 117499-08-8; **14a**, 117499-09-9; **14b**, 117678-48-5; **15**, 117161-46-3.

Reactivity of Azaannulenones

Francisco Gaviña,* Ana M. Costero, M. Rosario Andreu, and Santiago V. Luis

Departamento de Química Orgánica, Colegio Universitario de Castellón, Universidad de Valencia, Castellón de la Plana, Spain

Received May 12, 1988

We recently demonstrated the free existence in solution of 2-aza-2,4-cyclopentadienone, **1**.[1] Compound **1** was able to act either as a diene or as a dienophile in Diels-Alder reactions. It was of interest to study how the presence of another nitrogen in the ring might affect the reactivity and the stability of these reactive intermediates. We now describe the generation of 2,3-diaza-2,4-cyclopentadienone, **2** (Chart I).

Several 4,5-substituted 2,3-diaza-2,4-cyclopentadienones have been proposed as intermediates in a number of reactions.[2,3] However, the parent compound **2** has received less attention although its existence has been proposed in the oxidation of 3-pyrazolin-5-one with lead tetraacetate.[4] In order to study the free existence, reactivity, and stability of this intermediate we used the three-phase test as we did with **1**.[1] In such a test, a reagent solution liberates the suspected intermediate from a polymeric precursor, and a second solid phase suspended in the same solution is used to trap the intermediate. As polymeric precursor for **2** we prepared the 2-polymeric sulfamide of the 3-pyrazolin-5-one, **3**.

Results and Discussion

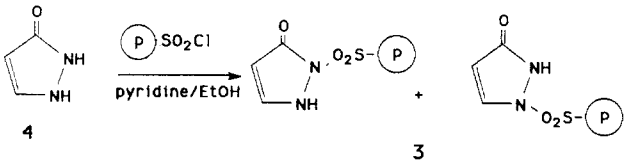
Synthesis of Precursor 3. The polymeric precursor **3** was synthesized as shown in Scheme I. Reaction of **4**[4] with chlorosulfonated macroreticular resin[5] gave **3** (IR: 3010, 2410, 1617, 1478, 1440, 1151, 1017 cm^{-1}). This resin acts as the nonpolymeric postulated precursors of **2**. Thus, when **3** reacted with 2,3-dimethyl-1,3-butadiene in the presence of a base, the product isolated, **7**, was the one previously described[4] (Scheme III).

Free Existence of 2 and Dienophilic Character. Polymeric 2-(carboxymethyl)-3-methyl-1,3-butadiene **5** was used as the trapping dienic polymer for **2**. Compound **5** was prepared in the way indicated in Scheme II. Treatment of 2,3-dimethyl-1,3-butadiene with NBS gave 2-(bromomethyl)-3-methyl-1,3-butadiene, **6**. This bromo compound was stirred with the silver salt of the polymeric carboxylic acid[6] to give **5**. A suspension of **3** and **5** in HMPT was stirred at 30 °C in the presence of $LiNH_2$ (Scheme III). The resins were separated in the usual way, and the Diels-Alder adduct, **7**, was obtained from polymer **8** via dealkylation[7] with trimethylsilyl chloride and sodium iodide followed by reduction with $NaBH_4$.[8] The formation of this adduct supports the free existence of 2,3-diaza-2,4-cyclopentadienone since direct reaction between solid phases **3** and **5** is physically precluded.

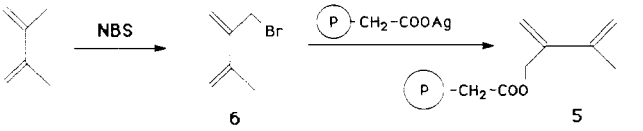
2,3-Diaza-2,4-cyclopentadienone as a Diene. Trapping of the intermediate **2** as a diene was attempted by some polymers functionalized with dienophilic groups such as the polymeric monoester of acetylenedicarboxylic acid[9] and the polymeric benzylmaleimide.[10] Under more drastic experimental conditions for which the trapping of **2** by **5** was done, both dienophilic polymers were recovered unchanged. The polymer precursor was converted into polymeric sulfonic acid, and CO release was observed.

Chart I

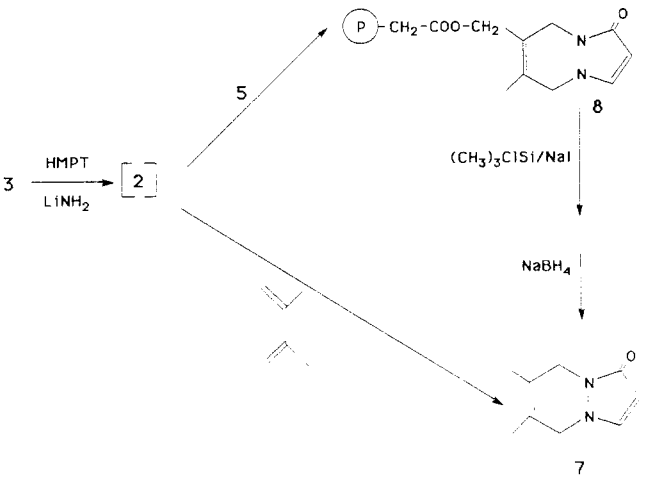
Scheme I



Scheme II



Scheme III



(1) Gaviña, F.; Costero, A. M.; Andreu, M. R.; Carda, M.; Luis, S. V. *J. Am. Chem. Soc.* **1988**, *110*, 4017-4018.
(2) Gillis, B. T.; Weinkam, R. *J. Org. Chem.* **1967**, *32*, 3321-3325.
(3) Carpino, L. A.; Terry, P. H.; Thatte, S. D. *J. Org. Chem.* **1966**, *31*, 2867-2873.
(4) Braña, M. F.; Castellanos, J. M.; González, E.; Lora-Tamayo, M.; Soto, J. L. *An. Quim.* **1979**, *75*, 927-930.
(5) Roush, W. R.; Feitler, D.; Rebek, J. *Tetrahedron Lett.* **1974**, 1391-1392.
(6) Gaviña, F.; Gil, P.; Palazón, B. *Tetrahedron Lett.* **1979**, 1333-1336.
(7) Olah, G.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247-1251.
(8) Hutchins, R. O.; Kandasamy, D.; Dux, F., III; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259-2267.
(9) Gaviña, F.; Costero, A. M.; Gil, P.; Palazón, B.; Luis, S. V. *J. Am. Chem. Soc.* **1981**, *103*, 1797-1798.
(10) Rebek, J.; Gaviña, F. *J. Am. Chem. Soc.* **1975**, *97*, 3453-3456.

0022-3263/88/1953-6112$01.50/0