In our case, we have shown that this model is valid by varying the surfactant concentration, incident laser power intensity,  $H_2O/D_2O$  ratio, and ionic strength.

We also have synthesized a hydrophobic  $ReO_2^+$  derivative,  $\text{ReO}_2(3-\text{Ph-py})_4^+$ , whose electronic properties are virtually identical with those of the unsubstituted complex. With this hydrophobic derivative, we have been able to probe other environments (e.g., nonionic micelles) by means of the  $SDS/ReO_2^+$  model.

#### **Experimental Section**

Materials. Solvents used for syntheses were reagent grade. Photochemical measurements were made in spectrograde solvents that were freshly distilled from appropriate drying agents under an inert atmosphere. Triton X-100 was used as received. Sodium dodecyl sulfate (Aldrich) and Brij 35 (Aldrich) were recrystallized from acetone/water. Water was purified by a nanopure water system. KReO<sub>4</sub> (Aersar) was used as received. Deuterium oxide (Aldrich, 99.8 atom %) was placed under vacuum immediately after opening and was distilled just before use

**Dioxo Complexes.** The chloride salt of  $\text{ReO}_2(\text{py})_4^+$  was prepared by the method of Beard et al.<sup>23</sup> The PF<sub>6</sub> salt was precipitated by addition of saturated aqueous NH<sub>4</sub>PF<sub>6</sub> to a water solution of the chloride and recrystallized from 5:1 acetone/pyridine. The 3-phenylpyridine (3-Phpy) complex was prepared by an analogous method where 3-Ph-py (Aldrich) was substituted for pyridine.

Physical Measurements. Electrochemistry was performed as described elsewhere.<sup>4</sup> Time-resolved emission measurements were performed with use of an OMA system that has been described previously.<sup>24</sup> The spectra were averaged for 15-25 shots and smoothed by two-point smoothing. Electronic absorption spectra were obtained with use of a Shimadzu

UV-260 recording spectrophotometer. Steady-state emission spectra<sup>25</sup> and emission decay curves<sup>26</sup> were obtained as described previously. Four parameter biexponential fits were performed with use of a program written by M. Albin. This program is based on the techniques of Marquadt as described by Bevington.<sup>27</sup> In all cases described here, the ratio of integrated intensities  $\tau_1/\tau_2$  was ~2:1.

Sample Preparation. Solutions for emission lifetime measurements were prepared in a two-compartment cell fitted with a 10-mL Pyrex bulb and a 1 cm pathlength cuvette.<sup>28</sup> Solvent was transferred on a highvacuum line and degassed by 5 freeze-pump-thaw cycles. For surfactant solutions, the metal complex was added to the bulb and the surfactant was placed in the cuvette. Nanopure water was added directly and D<sub>2</sub>O was vacuum transferred into the bulb. Thus, the metal complex was dissolved before mixing with the surfactant. In "Stern-Volmer" experiments, the "quencher" (H2O, D2O, NaCl, SDS) was added to the cuvette while the solution was kept in the bulb under vacuum. Liquids were degassed by 3 freeze-pump-thaw cycles before mixing with the solution. Repeating the emission lifetime measurements with use of less rigorous degassing methods did not quantitatively affect the decay curve. Extreme care was taken to ensure that the surfactant, metal complex, and NaCl were completely dissolved. Concentrations of ReO<sub>2</sub><sup>+</sup> were approximately 1 mM in all experiments.

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# Stereoselective Syntheses of *ervthro-* and *threo-\beta-Amino* Alcohol Derivatives via Hetero-Diels-Alder Reactions

### M. Mark Midland\* and Maria M. Afonso

Contribution from the Department of Chemistry, University of California, Riverside, Riverside, California 92521. Received August 22, 1988. Revised Manuscript Received January 9, 1989

Abstract: The reaction of 1,3-dimethoxy-1-[(trimethylsilyl)oxy] but a variety of N-protected  $\alpha$ -amino aldehydes under the influence of Lewis acid has been studied. The reaction provides an  $\alpha,\beta$ -unsaturated lactone that is useful in further transformations. When N-tert-butoxycarbonyl-protected amino aldehydes are used with diethylaluminum chloride or tris-[3-[(heptafluoropropyl)hydroxymethylene]camphorato]europium(III) as a catalyst, the reaction provides a diastereomer consistant with a chelation-controlled process. Diastereomeric ratios range from 80:20 (alaninal) to 95:5 (valinal). This stereochemistry is dramatically reversed when N,N-dibenzyl-protected amine aldehydes are used. Diastereomeric ratios are consistantly 99:1 in favor of the Cram-type product.

The presence of  $\beta$ -amino alcohols in biological active molecules such as amino sugars, antibiotics, and peptides has raised the interest in the preparation of these type of compounds.<sup>1</sup> In 1982, Danishefsky<sup>2</sup> reported the stereoselective (9:1) syntheses of a statine derivative, using a cycloaddition reaction of a substituted diene with N-(tert-butoxycarbonyl)leucinal. The stereochemical results could be interpreted as arising from a "chelation-control" process in which the Lewis acid complexes both the aldehyde oxygen and the protected nitrogen. This favors approach of the diene in an "anti-Cram" fashion affording the threo product. Garner and co-workers<sup>3</sup> have studied the cycloaddition of a N-Boc-serine-derived aldehyde with Danishefsky's diene. Their results also seem to indicate the participation of the Lewis acid

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Scheme I



**Table I.** Hetero-Diels-Alder Reactions of Various  $\alpha$ -Amino Aldehydes

aldehyde	Lewis acid <sup>a</sup>	products ratio <sup>b</sup> threo-erythro	% yield <sup>c</sup>
$(2)^d$	Eu(hfc) <sub>3</sub> <sup>e</sup>	80:20	83
$(2)^d$	ZnCl <sub>2</sub>	70:30	30⁄
$(2)^d$	Et <sub>2</sub> AlCl	70:30	48 <sup>g</sup>
$(2)^d$	MgBr <sub>2</sub> ·Et <sub>2</sub> O	50:50	30⁄
3	Eu(hfc) <sub>3</sub>	95:5	80
3	Et <sub>2</sub> AlCl	92:8	82 <sup>g</sup>
4	$Eu(hfc)_3$ or $Et_2AlCl$	90:10	65 (66 <sup>g</sup> )
5 <sup>d</sup>	Et <sub>2</sub> AlCl	<1:>99	67
5 <sup>d</sup>	Eu(hfc) <sub>3</sub>	4:96	72
6	Et <sub>2</sub> AlCl	<1:>99	79
6	Eu(hfc) <sub>3</sub>	24:76	51 <sup>f</sup>
7	Eu(hfc) <sub>3</sub>	<1:>99	87

<sup>a</sup>1.1 equiv of Lewis acid was used, except for Eu(hfc)<sub>3</sub> (0.05 equiv) in dichloromethane as solvent (0.1 M). <sup>b</sup>Ratio determinated by GC. <sup>c</sup>Isolated yield. <sup>d</sup>Used in racemic form. <sup>e</sup>Chloroform was used as solvent. <sup>f</sup>Starting material was recovered. <sup>g</sup>Overall yield (lactone + open-chain compounds).

in a "chelation process." The preparation of the erythro diastereomers from the same starting materials<sup>3</sup> has been possible only by means of alternative methods, such as addition of an enolate to the carbonyl carbon in the presence of HMPA in order to minimize chelation.

In previous studies<sup>4</sup> we have found that 1,3-dimethoxy-1-(silyloxy)butadiene (8, Brassard's diene<sup>5</sup>) under Lewis acid catalysis reacts with heterodienophiles (aldehydes, ketones, and imines) to give Diels-Alder adducts, often with high stereoselectivity. The  $\alpha,\beta$ -unsaturated lactone or lactam derivative, obtained after workup, is useful in further transformations.<sup>4</sup> We have therefore investigated the use of Brassard's diene in the Diels-Alder reaction of N-protected  $\alpha$ -amino aldehydes in the presence of several Lewis acid. This process provides a simple means for making either diastereomeric  $\beta$ -amino alcohol isomer from a common starting material. The results obtained are summarized in Table I.

The cycloaddition of Brassard's diene<sup>5</sup> 8 with N-(carbobenzyloxy)- (Cbz,  $1^6$ ) or N-(*tert*-butoxycarbonyl)- (*t*-Boc,  $2^7$ )







Scheme III



protected alaninal, in the presence of (+)-Eu(hfc)<sub>3</sub><sup>8</sup> at room temperature, gave an 80:20 ratio of lactones **9a(10a)/9b(10b)** (threo/erythro)<sup>9</sup> (see Scheme I). When dichloromethane or toluene was used as solvent, a slight decrease in the diastereoselectivity was observed. No improvement was observed when other Lewis acids, such as zinc chloride or diethylaluminum chloride, were used. In the later case, open-chain compounds **16a(17a)/16b(17b)** were also obtained, in the same 80:20 ratio as the lactones. These open-chain products can be converted to the lactones, in quantitative yield, by treatment with sodium methoxide in methanol (3.0 equiv, room temperature, 12 h).

Even higher selectivity (95:5) was observed with the valinal derivative  $3^7$  with (+)-Eu(hfc)<sub>3</sub> as a catalyst. The use of diethylaluminum chloride led to slightly lower selectivity (92:8). The cycloaddition of *N*-*t*-Boc-leucinal<sup>10</sup> **4** with **8**, in dichloromethane, with either Eu(hfc)<sub>3</sub> or Et<sub>2</sub>AlCl afforded a 90:10 ratio of lactones **12a**/**12b**.

These results are consistant with a chelation-control process, which affords the major threo compound. The higher diastereoselectivity obtained with **3**, in comparison with alanine moeity,

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<sup>(5)</sup> Brassard, P.; Savard, J. Tetrahedron Lett. 1979, 4911.

<sup>(6)</sup> The aldehyde was prepared by Swern oxidation of N-Cbz-alaninol and used without purification. Schlessinger, R. H.; Iwanowicz, E. J. Tetrahedron Lett. 1987, 28, 2083.

<sup>(7)</sup> Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Nwe, Y. J. Org. Chem. 1987, 52, 1487. The aldehydes were prepared by Swern oxidation. For N-Boc-valinal no racemization was observed by NMR shifts studies with racemic sample. The optical rotation agrees with literature value (Fehrentz, J-A.; Castro, B. Synthesis 1983, 676).

<sup>(8)</sup> Danishefsky, S.; Harvey, D. F.; Quallich, G.; Vang, B. J. Org. Chem. 1984, 49, 393.

<sup>(9)</sup> We have demonstrated that optically active Eu(hfc)<sub>3</sub> gives essentially no asymmetric induction in other hetero-Diels-Alder reactions. (See ref 4a.)

<sup>(10)</sup> Rittle, K. E.; Homnick, C. F.; Ponticello, G. S.; Evans, B. E. J. Org. Chem. 1982, 47, 3016. The N-Boc-leucinal racemizes very easily during Swern oxidation.

may be explained by the steric difference between the methyl and isopropyl groups. No racemization occurred during the cycloaddition reaction, as judged by <sup>1</sup>H NMR shift studies with (+)-Eu(hfc)<sub>3</sub> for comparison of racemic and optically active lactones.

We felt that the protecting group on nitrogen may not be a suitable group for  $\alpha$ -chelation control since the nitrogen lone pair may be substantially delocalized. We therefore investigated an alkyl protecting group. However, the cycloaddition of  $5-7^{11}$  with 8, in dichloromethane, with diethylaluminum chloride as Lewis acid yielded a (1:>99 ratio of lactones 13a-15a/13b-15b. With use of (+)-Eu(hfc)<sub>3</sub>, ZnCl<sub>2</sub>, or MgBr<sub>2</sub>-Et<sub>2</sub>O, the selectivity decreased slightly to 4:96 (threo/erythro) for the alanine case or even more for the valine derivative. The stereochemistry was confirmed by conversion to the *N*-*t*-Boc series of lactones. The dramatic reversal in stereoselectivity is consistent with a nonchelation-control mechanism, where the large group is the dibenzyl-protected amine.

The stereochemistry of the lactones, in the case of R = methyl or isopropyl, was assigned on the basis of NOE studies carried out on the  $\gamma$ -lactams formed as shown in Scheme II. For R =isobutyl, ozonolysis<sup>12</sup> of lactones **12a** and **12b** afforded statine derivative **25a** and the diastereomer **25b**, respectively (Scheme III). The stereochemistry of these compounds was assigned by comparison to the spectroscopic data in the literature.<sup>1a,13</sup> The absolute configuration of **25a** was confirmed by comparison of its optical rotation to the literature value.

In conclusion, with the appropiated N-protected  $\alpha$ -amino aldehydes it is possible to prepare highly funcionalizated lactones with excellent diastereoselectivity. The transformation of these lactones, by means of an ozonolysis, provides an entrance to the wide variety of natural products containing the  $\beta$ -amino alcohol moiety in either diastereomeric form.

#### **Experimental Section**

General Procedure for Cycloaddition Reactions of N-Protected  $\alpha$ -Amino Aldehydes with Brassard's Diene with Eu(hfc)<sub>3</sub>, ZnCl<sub>2</sub>, or MgBr<sub>2</sub>·Et<sub>2</sub>O as Lewis Acid Catalyst. To a solution (0.1 M) of N-protected  $\alpha$ -aminoaldehydes, in anhydrous methylene chloride at 0 °C, and under N<sub>2</sub>, was added Lewis acid [Eu(hfc)<sub>3</sub>, ZnCl<sub>2</sub>, or MgBr<sub>2</sub>·Et<sub>2</sub>O] (0.05, 1.1, or 1.1 equiv, respectively). Brassard's diene (1.1 equiv) was then added dropwise and the reaction mixture was allowed to warm to room temperature. The reaction was followed by TLC (12-20 h). For the leucinal case, the reaction was kept at 0 °C. The reaction was quenched by addition of water and extracted with methylene chloride and/or ethyl ether. The combined organic layers were washed with brine, dried, and concentrated. The resulting oil was purified by flash column chromatography (40-60% ethyl acetate/hexane). Diastereomeric ratios were determined by capillary gas chromatography and confirmed by <sup>1</sup>H NMR.

General Procedure for Cycloaddition Reaction of N-Protected  $\alpha$ -Amino Aldehydes with Brassard's Diene with Et<sub>2</sub>AlCl as Lewis Acid Catalyst. To a solution (0.1 M) of N-protected  $\alpha$ -aminoaldehyde in anhydrous methylene chloride under N<sub>2</sub> was added Brassard's diene (1.1 equiv). The solution was cooled to -78 °C and stirred for 10 min. Diethylaluminum chloride (1.1 equiv in hexane, 1 M) was added dropwise. The solution was stirred at -78 °C for 1 h and then was allowed to warm to room temperature for 3 h. The reaction was cooled to 0 °C, quenched by cautious addition of water, poured into a stirred solution of potassium sodium tartrate, and extracted with ethyl ether. The combined organic layers were washed with brine, dried, and concentrated. The crude was purified by flash column chromatography (40-60% ethyl acetate/hexane).

*threo* -6-[1-[(Benzyloxycarbonyl)amino]ethyl]-5,6-dihydro-4-methoxypyran-2-one (9a): mp 111-112 °C; IR (CHCl<sub>3</sub>) 3440, 3010, 1710, 1625, 1510, 1460, 1445, 1400, 1350, 1240 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.35 (s, 5 H), 5.11 (s, 3 H), 5.02 (m, 1 H), 4.38 (m, 1 H), 3.98 (m, 1 H), 3.74 (s, 3 H), 2.70 (dd, 1 H, J = 12.9, 17.3 Hz), 2.25 (dd, 1 H, J = 3.4, 17 Hz), 1.35 (d, 3 H, J = 6.8 Hz); <sup>13</sup>C NMR  $\delta$  172.98, 166.41, 155.91, 136.16, 128.32, 127.93, 127.79, 89.69, 77.77, 66.68, 55.93, 48.44, 29.95, 17.74; MS *m/e* 305, 198, 178, 134, 127, 91; exact mass calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>5</sub> 305.1277, found 305.1263. threo-Methyl 4-[(Benzyloxycarbonyl)amino]-3-hydroxypentanoate (20a). A solution of the alkene 16a (590 mg, 1.75 mmol) in dichloromethane (25 mL) and pyridine (2.5 mL) was cooled to -78 °C and ozone was bubbled through the solution until the blue color persisted. The reaction was purged with nitrogen to remove the excess ozone, and dimethyl sulfide (1.18 mL) was added at -78 °C. The reaction was warmed to room temperature and stirred for 6 h. The solvent was evaporated, and the residue was chromatographed (50% ethyl acetate/ hexane) to give 420 mg (85%) of 20a: IR (CHCl<sub>3</sub>) 3680, 3520, 3450, 3020, 1715, 1510, 1440, 1340, 1220 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.36 (s, 5 H), 5.10 (s, 3 H), 4.01 (m, 1 H), 3.76 (m, 1 H), 3.71 (s, 3 H), 3.27 (s, 1 H), 2.53 (m, 2 H), 1.25 (d, 3 H, J = 6.8 Hz); <sup>13</sup>C NMR  $\delta$  173.26, 156.23, 136.35, 128.38, 127.95, 70.24, 66.66, 51.76, 50.30, 38.50, 18.25; MS m/e 178, 134, 108, 91; exact mass calcd for C<sub>14</sub>H<sub>19</sub>NO<sub>5</sub> 281.1259 found 281.1259.

erythro-Methyl 4-[(Benzyloxycarbonyl)amino]-3-hydroxypentanoate (20b). A mixture of 16a and 16b (ratio 70/30 by GC) was subjected to the reaction conditions described above. A mixture of two compounds, 20a and 20b (ratio 70/30 by GC), was obtained. A sample of 20b could be separated by HPLC (Whatman Partisil M9 10/50, 60% ethyl acetate/hexane, recyclation): <sup>1</sup>H NMR  $\delta$  7.36 (s, 5 H), 5.10 (s, 2 H), 5.04 (m, 1 H), 4.06 (m, 1 H), 3.78 (m, 1 H), 3.71 (s, 3 H), 3.26 (s, 1 H), 2.49 (s, 1 H), 2.46 (d, 1 H, J = 2.4 Hz), 2.32 (d, 3 H, J = 6.8 Hz); <sup>13</sup>C NMR  $\delta$  173.02, 155.99, 136.35, 128.50, 128.08, 70.43, 66.78, 51.88, 50.42, 37.89, 14.91.

threo-Methyl 4-[(Benzyloxycarbonyl)amino]-3-[(tert-butyldimethylsilyl)oxy]pentanoate (21a). To a solution of 20a (126 mg, 0.448 mmol) in 5 mL of DMF was added 91.50 mg (1.34 mmol) of imidazole, followed by 101.29 mg (0.672 mmol) of tert-butyldimethylsilyl chloride. The solution was stirred at room temperature until no starting material was present by TLC (20 h). The mixture was poured into a saturated sodium chloride solution and extracted with ethyl ether. The organic layers were combined, dried, and concentrated. After purification by flash column chromatography (20% ethyl acetate/hexane), 167 mg (94%) of 21a were obtained: IR (CHCl<sub>3</sub>) 3440, 2900, 1720, 1630, 1500, 1450, 1440, 1410, 1370, 1320, 1250, 1220 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.37 (s, 5 H), 5.11 (s, 2 H), 4.87 (m, 1 H), 4.16 (m, 1 H), 3.82 (m, 1 H), 3.67 (s, 3 H), 2.50 (AB part of ABX, 2 H, J = 6.35, 15.8 Hz), 1.17 (d, 3 H, J = 6.8 Hz), 0.88 (s, 9 H), 0.11 (s, 3 H), 0.06 (s, 3 H); <sup>13</sup>C NMR δ 171.62, 155.93, 136.47, 128.44, 128.08, 71.28, 66.66, 51.58, 50.48, 39.23, 25.79, 17.96, 17.95, -4.72, -4.84; MS m/e 338, 217, 134, 91; exact mass calcd for C<sub>16</sub>H<sub>24</sub>-NO<sub>5</sub>Si (M<sup>+</sup> - C<sub>4</sub>H<sub>9</sub>) 338.1431, found 338.1423.

threo -4-[(tert -Butyldimethylsilyl)oxy]-5-methyl-2-oxopyrrolidine (22a). To 90 mg (0.228 mmol) of 21a in methanol (2 mL) was added 35 mg of 10% palladium-carbon, followed by 0.21 mL of cyclohexene. The reaction was refluxed for 2 h. The mixture was filtered, washed with methanol, and concentrated. The crude product was dissolved in methanol (5 mL) and 3.7 mg (0.3 equiv) of sodium methoxide was added. The solution was stirred at 25 °C for 16 h. After evaporation, the crude product was purified by flash column chromatography (30% acetone/ hexane), which yielded 36 mg (69%) of 22a, as a crystalline compound (hexane/ethyl acetate): mp 71-72 °C; IR (CHCl<sub>3</sub>) 3420, 3200, 2950, 1700, 1520, 1470, 1410, 1260, 1210 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  4.40 (q, 1 H, J = 5.2 Hz), 3.76 (dt, 1 H, J = 6.3, 6.3 Hz), 2.52 (dd, 1 H, J = 6.3, 16.7 Hz), 2.27 (dd, 1 H, J = 4.2, 16.7 Hz), 1.17 (d, 3 H, J = 6.5 Hz), 0.90 (s, 9 H), 0.08 (s, 6 H); <sup>13</sup>C NMR δ 175.81, 69.58, 54.92, 40.45, 25.61, 18.01, 15.03, -4.78, -5.09; MS m/e 172, 130; exact mass calcd for  $C_{10}H_{20}NO_2Si (M^+ - CH_3) 214.1268$ , found 214.1263.

erythro 4-[(tert - Butyldimethylsilyl)oxy]-5-methyl-2-oxopyrrolidine (22b). The synthesis of 22b was carried out with the same sequence as described above for 22a starting with 20a and 20b (ratio 70/30 by GC). The diastereomeric 2-oxopyrrolidines could be separated by HPLC (Dynamax Macro Column, 50% acetone/hexane): <sup>1</sup>H NMR  $\delta$  4.01 (m, 1 H), 3.52 (m, 1 H), 2.60 (dd, 1 H, J = 6.9, 16.7 Hz), 2.28 (dd, 1 H, J = 5.7, 16.7 Hz), 1.22 (d, 3 H, J = 6.5 Hz), 0.90 (s, 9 H), 0.08 (s, 6 H); <sup>13</sup>C NMR  $\delta$  175.08, 74.93, 58.69, 40.39, 25.67, 19.35, 17.95, -4.66, -4.84.

(3S, 4S)-Methyl 4-[(tert-butoxycarbonyl)amino]-3-hydroxy-5methylhexanoate (23a). A mixture of 11a and 11b (ratio 80/20 by GC) (986 mg, 3.29 mmol) in dichloromethane (125 mL) and methanol (12.5 mL) was cooled to -78 °C and ozone was bubbled through the solution until the blue color persisted. The reaction was purged with nitrogen to remove the excess ozone, and sodium borohydride (125 mg, 3.29 mmol) was added at -78 °C. The reaction was warmed to room temperature and stirred for 6 h. The solution was concentrated to one-third of its volume, diluted with brine, and extracted with dichloromethane. The combined organic layers were concentrated. Separation by HPLC (Dynamax Macro Column, 40% ethyl acetate/hexane) gave 269 mg of 23a, 80 mg of 23b, and 274 mg of a mixture of compounds which under treatment with sodium methoxide in methanol (3.0 equiv, room temperature, 12 h) afforded in almost quantitative yield 23a and 23b, as a

<sup>(11)</sup> For the preparation of these aldehydes, see ref 1e. They do not racemize at room temperature.

<sup>(12)</sup> Ozonolysis of the N,N-dibenzyl derivatives gave poor results.
(13) Rich, D. H.; Sun, E. T.; Boparai, A. S. J. Org. Chem. 1978, 43, 3624.

(23a): mp 102-103 °C;  $[\alpha]^{25}_{D}$ -28.28° (*c* 2.075, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 3420, 2940, 1700, 1470, 1420, 1370, 1350, 1150 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  4.57 (br d, 1 H, *J* = 9.9 Hz), 4.25 (br d, 1 H, *J* = 9.1 Hz), 3.70 (s, 3 H), 3.30 (s, 1 H), 3.14 (t, 1 H, *J* = 9.1 Hz), 2.51 (m, 2 H), 1.85 (m, 1 H), 1.43 (s, 9 H), 0.98 (d, 3 H, *J* = 6.8 Hz), 0.95 (d, 3 H, *J* = 6.8 Hz); <sup>13</sup>C NMR  $\delta$  173.26, 156.29, 78.76, 66.84, 59.54, 51.45, 39.05, 29.99, 28.17, 19.53, 19.29; MS *m/e* 232, 202, 172, 132, 116, 100, 72, 57; exact mass calcd for C<sub>13</sub>H<sub>25</sub>NO<sub>5</sub> 275.173, found 275.173. (23b): <sup>1</sup>H NMR  $\delta$  4.42 (br d, 1 H, *J* = 9.5 Hz), 3.93 (m, 1 H), 3.72

(23b): <sup>1</sup>H NMR  $\delta$  4.42 (br d, 1 H, J = 9.5 Hz), 3.93 (m, 1 H), 3.72 (s, 3 H), 3.52 (m, 1 H), 3.24 (br, d, 1 H, J = 4 Hz), 2.53 (m, 2 H), 2.12 (m, 1 H), 1.44 (s, 9 H), 0.95 (d, 3 H, J = 6.9 Hz), 0.88 (d, 3 H, J = 6.9 Hz); <sup>13</sup>C NMR  $\delta$  173.50, 156.35, 79.49, 69.21, 58.87, 51.70, 38.26, 28.29, 27.50, 20.08, 16.19.

(45,55)-4-Hydroxy-5-isopropyl-2-oxopyrrolidine (24a). To 352 mg (1.28 mmol) of 23a was added 4 mL of 3 M HCl/ethyl acetate solution. The reaction was stirred at room temperature for 30 min. After neutralization with a saturated sodium bicarbonate solution, the solvents were evaporated, and the residue was washed with acetone. These layers were concentrated and purified by flash column chromatography (75%, acetone/hexane) to give 24a as a crystalline compound: mp 127–129 °C;  $[\alpha]^{25}_{D}$ –11.03° (*c* 0.825, MeOH); IR (CHCl<sub>3</sub>) 3450, 3400, 2990, 1700, 1400 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  4.38 (t, 1 H, *J* = 4.52 Hz), 3.22 (dd, 1 H, *J* = 4.3, 9.3 Hz), 2.64 (dd, 1 H, *J* = 5.6, 17.0 Hz), 2.20 (d, 1 H, *J* = 17.0 Hz), 1.96 (m, 1 H), 1.03 (d, 3 H, *J* = 6.6 Hz), 0.98 (d, 3 H, *J* = 6.6 Hz); <sup>13</sup>C NMR (CD<sub>3</sub>OD)  $\delta$  179.44, 68.94, 67.97, 42.61, 28.44, 20.35, 19.44; MS *m/e* 143, 128, 114, 100, 83, 72, 55; exact mass calcd for C7H<sub>13</sub>NO<sub>2</sub> 143.095, found 143.094.

(3S, 4S)-Methyl 4-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-6methylheptanoate (25a). A solution of 12a (50 mg, 0.16 mmol) in dichloromethane (10 mL) and methanol (1 mL) was cooled to -78 °C and ozone was bubbled through the solution until the blue color persisted. The reaction was purged with nitrogen to remove the excess ozone, and sodium borohydride (6.05 mg, 0.16 mmol) was added at -78 °C. The reaction was warmed to room temperature and stirred for 5 h. The same workup as described for 23a was followed. After HPLC (Whatman Partisil M9 10/50, 30% ethyl acetate/hexane) 24 mg (52%) of 25a (white solid) and 6 mg (10%) of 26a were obtained. Treatment of 26a with sodium methoxide in methanol (3.0 equiv, room temperature, 6 h) afforded quantitatively **25a**. **25a**:  $[\alpha]^{25}{}_{\rm D}$  -36.8° (*c* 1.0, EtOH), (lit.<sup>1a</sup>  $[\alpha]^{25}{}_{\rm D}$  -37.6°, (*c* 1.0, EtOH)]; IR (CHCl<sub>3</sub>) 3480, 3000, 1730, 1520, 1460, 1390, 1270, 1180 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  4.71 (br d, 1 H, *J* = 9.3 Hz), 4.02 (m, 1 H), 3.71 (s, 3 H), 3.61 (m, 1 H), 3.26 (br s, 1 H), 2.54 (m, 2 H), 1.70 (m, 3 H), 1.44 (s, 9 H), 0.93 (d, 6 H, *J* = 6.5 Hz); <sup>13</sup>C NMR  $\delta$  173.44, 155.99, 79.00, 69.64, 52.00, 51.64, 41.54, 38.62, 28.23, 24.64, 22.93, 22.15; MS *m/e* 216, 186, 176, 158, 142, 130, 86, 57; exact mass calcd for C<sub>14</sub>H<sub>27</sub>NO<sub>5</sub> 289.187, found 289.188.

Stereochemical Determination of 10a and 10b. To 112 mg (0.367 mmol) of 9a (or 9b) in methanol (8 mL) was added 67 mg of 10% palladium-carbon followed by 1 mL of cyclohexene. The reaction was refluxed for 2 h and then filtered, washed with methanol, and concentrated. The crude product was dissolved in chloroform (8 mL) and 81 mg (0.37 mmol) of di-*tert*-butyldicarbonate was added. The reaction was stirred at room temperature for 12 h. The solvent was evaporated and the residue diluted with ethyl ether. The organic phase was washed sequentially with 0.5 M H<sub>3</sub>PO<sub>4</sub>, 1 M NaHCO<sub>3</sub>, and brine. Concentration of solvents and purification by flash column chromatography (60% ethyl acetate/hexane) gave 10a (or 10b) as an only isomer.

Stereochemical Determination of 13b, 14a, 14b, and 15b. The same procedure as described before was followed. Deprotection of the dibenzyl group by catalytic transfer hydrogenation and protection of the amino group as t-Boc [2-[[(tert-butyloxycarbonyl)oxy]imino]-2-phenylaceto-nitrile (Aldrich, BOC-ON)] afforded 10b, 11a, 11b, and 12b, respectively.

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Supplementary Material Available: General experimental and characterization data for compounds 9b, 10a,b, 11a,b, 12a,b, 13b, 14a,b, 15b, 16a,b, 18a, 19a, 24b, 25b, and 26a (8 pages). Ordering information is given on any current masthead page.

## A New Approach to Probing Conformational Space with Molecular Mechanics: Random Incremental Pulse Search

## David M. Ferguson and Douglas J. Raber\*

Contribution from the Department of Chemistry, University of South Florida, Tampa, Florida 33620. Received September 8, 1988

Abstract: A computational method is described that permits reliable searching for different molecular conformations. A Monte Carlo type routine is employed to randomly search the potential energy surface for a given molecule, and Allinger's MM2 force field is employed for energy calculations and minimizations. The method has two modes of operation: conformational search (by torsional or energetic criterion) and global minimum location. The Monte Carlo type routine, called random incremental pulse search (RIPS), logically couples the benefits of random searching with those of analytical minimization. The method has been tested by searching conformational space for a series of cycloalkanes. All conformational families and minimum-energy structures are reliably located in each case.

During the last decade the computation of molecular structure has become a standard tool of organic chemists,<sup>1-3</sup> and molecular mechanics has proved to be an extremely powerful technique for this purpose.<sup>3-5</sup> Until recently almost all efforts in this area have

focused on minimizing the energy of a trial geometry that is supplied by the investigator, but it has become increasingly important to evaluate the molecular geometries and energies of other structures as well.<sup>6,7</sup> Two specific problems are particularly

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