Eur. J. Org. Chem. **2006** · © WILEY-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, 2006 · ISSN 1434–193X

SUPPORTING INFORMATION

Title: Stereochemistry of the Tetrabutylammonium Cyanide-Catalyzed Cyanosylilation of Cyclic α,β-Epoxyketones – Dependence of the Diastereoselectivity on the Ring Size

Author(s): Ana Aljarilla, Rubén Córdoba, Aurelio G. Csaky, Israel Fernández, Fernando López Ortiz, Joaquín Plumet,* Gloria Ruiz Gómez

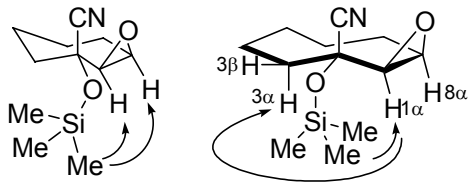
Ref. No.: O200600239

1. Configurational Assignment.

NMR spectra were recorded on a spectrometer working at a field of 11.7 T, using a 5 mm direct triple probe $^{1}H/^{31}P$, BB ($^{31}P–^{109}Ag$). Samples were prepared in $CDCl_3$ as solvent. Chemical shifts for ^{1}H (500.13 MHz) are referred to internal tetramethylsilane. 1D gCOSY, gTOCSY and gNOESY NMR spectra were acquired using standard software and processing routines implemented in the spectrometer.

In the following we discuss the assignment of cyanohydrins **9b** and **10b** as representative examples of the new compounds synthetized.

The assignment of the major isomers **9b** and **10b** formed in the cyanosilylation of epoxyketones **4** and **5**, respectively, was straightforward. Selective inversion of the methine protons of **9b** produced NOE on the TMS signal and *vice versa* (Chart S1, Figure S1). Polarization transfer effects dominated over NOE enhancements for the methine protons upon selective inversion of each CH signal. The relative configuration of **10b** was established from the NOEs observed for the protons of the TMS group with the methine proton $H^{1\alpha}$. Selective inversion of the later also produced NOE on H3α (Chart S1, Figure S2). Protons $H^{3\alpha,\beta}$ were identified through their multiplicity. They showed only one geminal and two vicinal couplings. The 1D gCOSY obtained upon selective irradiation of the double doublet of doublets at δ 2.29 ppm $H^{3\alpha}$ allowed to identify $H^{3\beta}$ and the neighbouring protons H^4 (Figure S2). Furthermore, the 1D gTOCSY resulting from the selective excitation of $H^{1\alpha}$ revealed that the signals of the methylene protons adjacent to the oxetane ring, H^7, appear as two multiplets at δ 1.92 and 2.0 ppm (Figure S2).



9b **10b**

Chart S1. Selected NOES observed in the 1D gNOESY spectra of **9b** and **10b**.

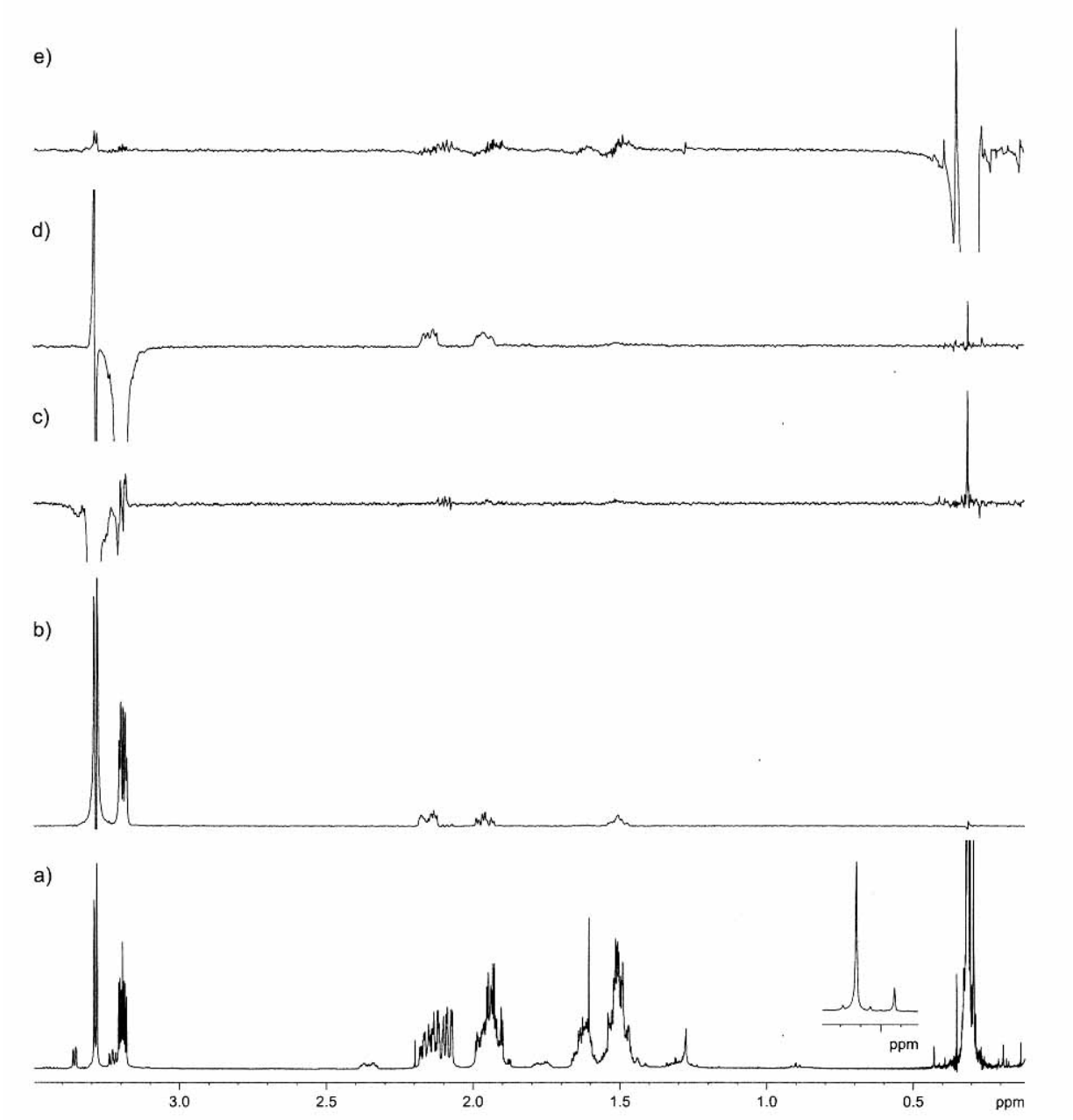


Figure S1. ^{1}H NMR spectra (500.13 MHz) of the mixture of cyanohydrins **9a** and **9b**. (a) Reference spectrum. (b) 1D gTOCSY spectrum with selective excitation of the double doublet at δ 3.29 ppm with a spin-lock duration of 60 ms. (c)- (e) 1D gNOESY spectra: (c) selective inversion of the double doublet at δ 3.29 ppm, mixing time of 0.5 s; (d) selective inversion of the double doublet of doublets at δ 3.19 ppm, mixing time of 1.5 s; (e) selective inversion of the TMS signal, mixing time of 1.5 s.

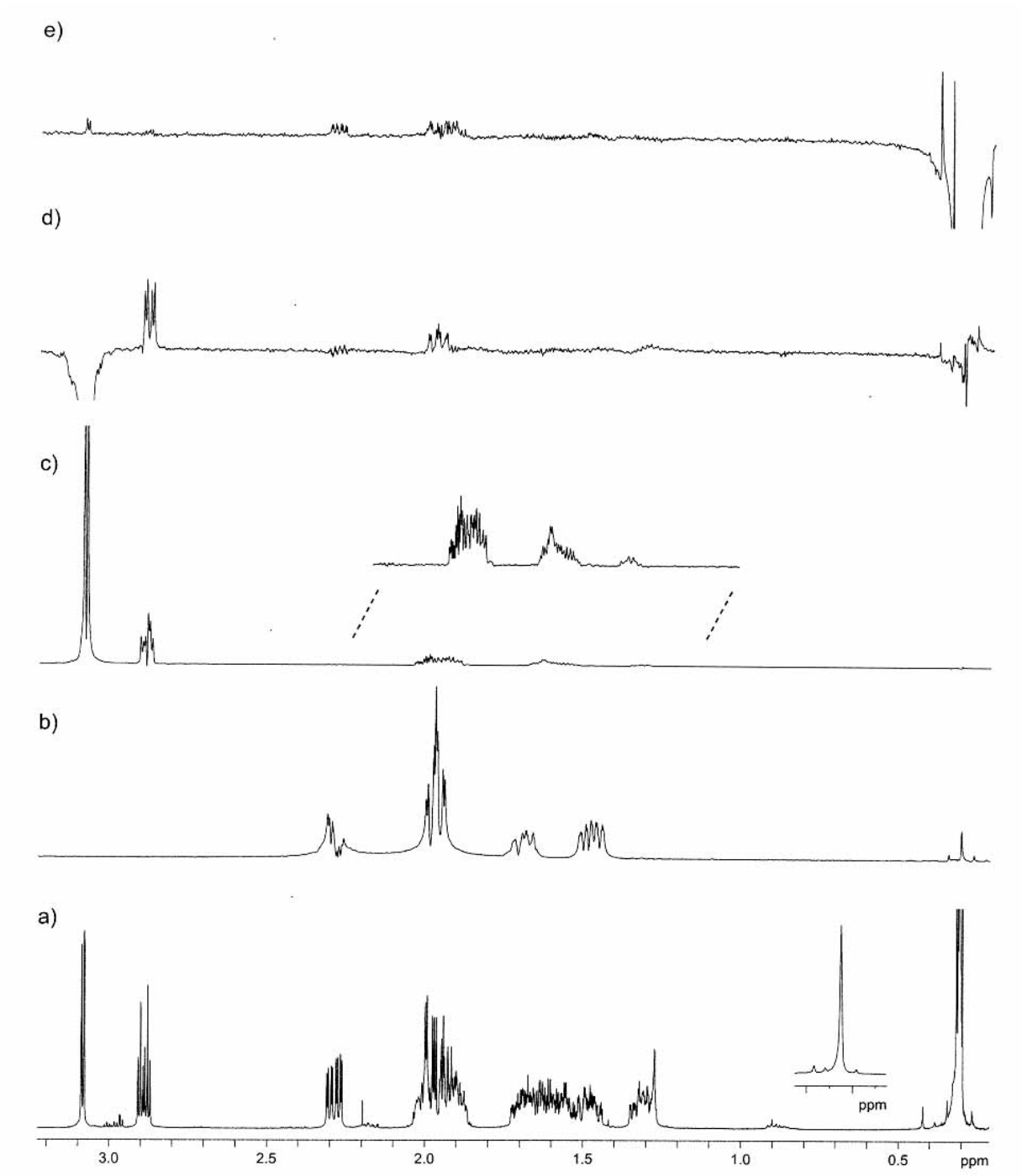


Figure S2. ^{1}H NMR spectra (500.13 MHz) of the mixture of cyanohydrins **10a** and **10b**. (a) Reference spectrum. (b) 1D gCOSY spectrum with selective excitation of the double doublet of doublets at δ 2.29 ppm. (c) 1D gTOCSY spectrum with selective excitation of the double doublet at δ 3.08 ppm with a spin-lock duration of 60 ms. (d)- (e) 1D gNOESY spectra: (d) selective inversion of the double doublet at δ 3.08 ppm, mixing time of 1.5 s; (e) selective inversion of the TMS signal, mixing time of 1.5 s.

2. Synthesis of the starting α,β-unsaturated ketones 1a-e.

Cyclopent-2-enone **1a**, cyclohex-2-enone **1b** and cyclohept-2-enone **1c** were obtained from standard commercial sources and used without further purification. Cyclooct-2-enone **1d** and inden-1-one **1e** were prepared, from their corresponding saturated ketones, according to the two steps methodology reported by T. Kumamoto *et al*.[1]

Synthesis of cyclooct-2-enone 1d and inden-1-one 1e. General procedure. Cyclooctanone or 1-indanone (7.58 mmol) was dissolved in DMF (10 mL). Et_3N (2.4 mL, 17.36 mmol) and TMSCl (1.4 mL, 11.37 mmol) were added to the solution, which was then allowed to react for 16 hours at 60 ºC. The reaction was quenched by addition of saturated $NaHCO_3$ aqueous solution and extracted with hexane (3 x 12 mL). The combined organic layer was successively washed with cold HCl 5% (1 x 10 mL), saturated $NaHCO_3$ aq. (1 x 10 mL) , H_2O (1 x 10 mL) and brine (1 x 10 mL). Drying of the organic phase with $MgSO_4$ was followed by evaporation of the solvent under vacuum to afford the corresponding enoxytrimethylsilane, which was used for the next step without further purification. A solution of the crude trimethylsilyloxysilane (3.53 mmol) in CH_3CN (2.8 mL) was added to a solution of $Pd(OAc)_2$ (387 mg, 1.73 mmol) and *p*-benzoquinone (187 mg, 1.73 mmol) in CH_3CN (8.5 mL). After 1 hour of reaction at room temperature, $Pd(OAc)_2$ (194 mg, 0.85 mmol) was added. The mixture was then stirred for 1 h. AcOEt was added and the precipitates were filtered off through a celite pad. The solvent was evaporated under vacuum. The product was purified by column chromatography on silica gel (hexane/ethyl acetate, 10/1).

(Cyclooct-1-enyloxy)trimethylsilane. Yellow oil (1.13 g, 5.69 mmol), 75%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.19 (s, 9H), 1.44-1.89 (m, 8H), 2.12 (m, 2H), 2.19 (m, 2H), 4.75 (t, *J*=8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 0.83, 26.71, 26.76, 28.19, 31.32, 31.41, 105.86, 153.42.

(*3H*-Inden-1-yloxy)trimethylsilane. Orange oil (1.09 g, 5.31 mmol), 70%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.33 (s, 9H), 3.29 (d, *J*=2.3 Hz, 2H), 5.46 (t, *J*=2.3 Hz, 1H), 7.24 (td, *J*=7.3, 1.2 Hz, 1H), 7.32 (t, *J*=7.2 Hz, 1H), 7.40 (dd, *J*=7.2, 1.2 Hz, 1H), 7.42 (d, *J*=7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 0.44, 34.37, 106.62, 118.53, 124.15, 125.50, 126.41, 142.21, 143.13, 153.90.

Cyclooct-2-enone 1d. Yellow oil (459 mg, 3.70 mmol), 65%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.42-1.94 (m, 6H), 2.51 (m, 2H), 2.65 (t, *J*=6.9 Hz, 2H), 6.00 (d, *J*=12.5 Hz, 1H), 6.35 (dt, *J*=12.5, 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.96, 23.47, 25.49, 28.96, 43.11, 132.79, 142.10, 206.52.

Inden-1-one 1e. Yellow oil (415 mg, 3.19 mmol), 60%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.91 (d, *J*=5.9 Hz, 1H), 7.08 (d, *J*=7.0 Hz, 1H), 7.24 (t, *J*=7.0 Hz, 1H), 7.36 (d, *J*=7.0 Hz, 1H), 7.43 (d, *J*=7.0 Hz, 1H), 7.58 (d, *J*=5.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 122.67, 123.08, 127.60, 129.58, 130.78, 134.10, 145.03, 150.26, 198.91.

[1] Kunamoto, T.; Tabe, N.; Yamaguchi, K.; Yagishita, H.; Iwasa, H.; Ishikawa, T., *Tetrahedron* **2001**, *57*, 2717.

3. Synthesis of the α,β-epoxyketones 2-6.

α,β-epoxy ketones **2** and **3**, were synthesized from the corresponding α,β-unsaturated ketones using the method described by T. Honma *et al.*[2] Compounds **4, 5** and **6** were obtained by an adaptation of the referred procedure.

Synthesis of 4, 5, and 6. **General procedure.** To a solution of the corresponding α,β-unsaturated ketone (5.17 mmol) in heptane (12.9 mL), were successively added hydrotalcite (388 mg), Bu_4NBr (251 mg, 0.78 mmol), H_2O (12.9 mL) and an aqueous solution of H_2O_2 30% (0.88 mL, 7.76 mmol). The mixture was allowed to react at 45 ºC for 16 hours except in the case of compound **6**, which was formed at rt in 2 h time. The catalyst was separated by filtration. The filtrate was treated with aqueous Na_2SO_3 and extracted with AcOEt. Drying of the organic phase with $MgSO_4$ was followed by evaporation of the solvent under vacuum. The product was purified by column chromatography on silica gel (hexane/ethyl acetate, 5/1).

8-oxabicyclo[5.1.0]octan-2-one, 4. Colorless oil (359 mg, 2.85 mmol), 55%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.03 (m,1H), 1.60- 2.00 (m, 4H), 2.34 (m, 1H), 2.48 (dt, *J*=13.3, 3.7 Hz, 1H), 2.67 (ddd, *J*=13.3, 11.2, 3.7 Hz, 1H), 3.40 (t, *J*=5.0 Hz, 1H), 3.43 (dd, *J*=5.0, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.33, 23.90, 27.78, 40.91, 55.48, 59.79, 210.91.

9-Oxabicyclo[6.1.0]nonan-2-one, 5. White solid (580 mg, 4.14 mmol), 80%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.04 (m,1H), 1.35- 1.83 (m, 5H), 1.91 (m, 1H), 2.22 (m, 1H), 2.38 (ddd, *J*=13.9, 10.0, 3.5 Hz, 1H), 2.68 (m, 1H), 3.27 (ddd, *J*=9.8, 5.1, 3.7 Hz, 1H), 3.75 (d, *J*=5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.97 , 25.16, 27.46, 43.26, 56.36, 59.29, 208.03.

1a,6a-Dihydro-1-oxacyclopropa[a]inden-6-one (227 mg, 1.55 mmol)**, 6**. Yellow solid, 30 %. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.97 (d, *J*=2.4 Hz, 1H), 4.48 (d, *J*=2.4 Hz, 1H), 7.39-7.68 (m, 3H), 7.73 (d, *J*=7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 53.65, 54.82, 125.42, 125.85, 129.88, 134.33, 137.78, 147.07, 195.91.

[2] Honma, T.; Nakajo, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K., *Tetrahedron Lett*., **2002**, *43*, 6229.

Cartesian coordinates (in Å) and free energies (in a. u.) of all transition states discussed in the text. All calculations have been performed at the B3LYP/6-31++G(d,p).

2-*syn*: E=-437.36172

C	0.231531000	-0.019436000	1.412911000
C	0.993843000	-1.229836000	0.831516000
C	1.340230000	-0.807863000	-0.590019000
C	0.537753000	0.349002000	-0.977612000
C	-0.370770000	0.763552000	0.195518000
O	-0.797381000	1.938961000	0.328873000
O	1.958236000	0.498126000	-0.675681000
C	-1.790265000	-0.438489000	-0.278080000
N	-2.788370000	-1.001945000	-0.529229000
H	0.919863000	0.676512000	1.904322000
H	-0.547141000	-0.295439000	2.126538000
H	0.349641000	-2.116344000	0.781304000
H	1.889771000	-1.496121000	1.409247000
H	1.713242000	-1.538908000	-1.307972000
H	0.252435000	0.585637000	-1.999781000

2-*anti*: E=-437.35605

C	-0.449885000	0.802127000	1.097271000
C	-1.883945000	0.228643000	0.904879000
C	-1.758143000	-0.706429000	-0.292800000
C	-0.478265000	-0.454451000	-0.996216000
C	0.120279000	0.772409000	-0.335240000
C	2.258744000	-0.287559000	0.195283000
N	3.360162000	-0.630464000	0.439347000
O	-0.657985000	-1.617161000	-0.172513000
O	0.374669000	1.778474000	-0.995503000
H	0.142838000	0.159432000	1.746778000
H	-0.437785000	1.825046000	1.480228000
H	-2.597684000	1.027112000	0.658742000
H	-2.257934000	-0.295422000	1.793399000
H	-2.645074000	-1.097055000	-0.793287000
H	-0.311684000	-0.624802000	-2.056222000

3-*syn*: E=-476.65092

C	0.078310000	1.452848000	0.175263000
C	-1.456800000	1.414206000	0.104884000
C	-1.923692000	0.406663000	-0.958455000
C	-1.326215000	-0.966747000	-0.725154000
C	-0.078736000	-1.126021000	0.044823000
C	0.683409000	0.084662000	0.626694000
O	-1.373617000	-1.426933000	0.635976000
O	1.074670000	-0.019313000	1.824444000
C	2.150420000	-0.043521000	-0.595515000
N	3.166800000	-0.081055000	-1.180740000
H	0.422620000	2.192053000	0.905914000
H	0.466076000	1.742064000	-0.808849000
H	-1.851193000	2.411005000	-0.138308000
H	-1.870250000	1.129951000	1.079102000
H	-1.621161000	0.749791000	-1.959543000
H	-3.021086000	0.326040000	-0.966056000
H	-1.591090000	-1.729512000	-1.463823000
H	0.529879000	-2.016586000	-0.101864000

3-*anti*: E=-476.65114

C	-0.088853000	-1.161607000	-0.733827000
C	-1.618304000	-1.277688000	-0.555302000
C	-2.304888000	0.100337000	-0.404667000
C	-1.488637000	1.136982000	0.359717000
C	-0.077708000	0.890739000	0.757015000
C	0.458075000	-0.510392000	0.538214000
O	-0.396909000	1.720643000	-0.368813000
C	2.430069000	0.151303000	-0.344370000
N	3.534592000	0.340097000	-0.705819000
O	0.680324000	-1.187653000	1.556889000
H	0.157465000	-0.559687000	-1.611478000
H	0.369424000	-2.148621000	-0.837440000
H	-1.813856000	-1.879309000	0.341080000
H	-2.064582000	-1.815653000	-1.402705000
H	-3.276201000	-0.021891000	0.094422000
H	-2.515489000	0.527495000	-1.395588000
H	-2.069937000	1.866802000	0.930597000
H	0.345184000	1.408223000	1.616558000

4-*syn*: E=-515.93070

C	0.278116000	0.917262000	1.135354000
C	-0.420268000	1.836898000	0.115883000
C	-1.906985000	1.513841000	-0.160145000
C	-2.252750000	0.019708000	-0.041981000
C	-1.356941000	-0.926487000	-0.823320000
C	0.073591000	-1.145794000	-0.514622000
C	0.904033000	-0.401399000	0.572763000
O	-0.936451000	-2.092707000	-0.092161000
O	1.504931000	-1.140755000	1.405543000
C	2.125216000	0.371761000	-0.629183000
N	3.069636000	0.742861000	-1.217297000
H	-0.404742000	0.621094000	1.943353000
H	1.107714000	1.442063000	1.618011000
H	0.146171000	1.784548000	-0.820727000
H	-0.348128000	2.882234000	0.445458000
H	-2.180665000	1.888417000	-1.157163000
H	-2.547399000	2.055418000	0.551610000
H	-3.297136000	-0.143569000	-0.344507000
H	-2.185354000	-0.282981000	1.007501000
H	-1.684256000	-1.140294000	-1.846478000
H	0.694432000	-1.554008000	-1.311531000

4-*anti*: E=-515.93621

C	0.148819000	-1.135257000	-0.769092000
C	-1.274982000	-1.693992000	-0.552619000
C	-2.259866000	-0.751712000	0.168005000
C	-2.225257000	0.715329000	-0.304164000
C	-1.086395000	1.559814000	0.270226000
C	0.274777000	1.065646000	0.588745000
C	0.670036000	-0.407962000	0.478329000
O	0.031055000	1.864129000	-0.583754000
C	2.578860000	-0.027930000	-0.255732000
N	3.723220000	0.036363000	-0.515603000

O	0.736803000	-1.020984000	1.571669000
H	0.176550000	-0.448042000	-1.620712000
H	0.829598000	-1.960711000	-0.990796000
H	-1.209893000	-2.620128000	0.030810000
H	-1.689984000	-1.966095000	-1.535101000
H	-2.048016000	-0.775008000	1.243542000
H	-3.279164000	-1.144046000	0.038828000
H	-3.168791000	1.199395000	-0.017682000
H	-2.174032000	0.763787000	-1.400475000
H	-1.426445000	2.431238000	0.838805000
H	0.828817000	1.576291000	1.376500000

5-*syn*: E=-589.77350

C	-2.540893000	-1.220238000	-0.402702000
C	-2.987860000	-0.141468000	0.371180000
C	-2.094131000	0.865997000	0.764678000
C	-0.758447000	0.760140000	0.385282000
C	-0.306222000	-0.338659000	-0.360767000
C	-1.194135000	-1.320042000	-0.780491000
C	0.377447000	1.707999000	0.601323000
C	1.570121000	1.136303000	-0.036077000
C	1.204515000	-0.245866000	-0.637455000
O	0.880530000	2.251101000	-0.655837000
O	1.715051000	-0.697218000	-1.688344000
C	1.826816000	-1.222442000	0.932108000
N	2.316343000	-1.934777000	1.725522000
H	-3.246882000	-1.990533000	-0.705794000
H	-4.034771000	-0.079057000	0.659059000
H	-2.443957000	1.716431000	1.346997000
H	-0.830578000	-2.152931000	-1.376211000
H	0.404613000	2.391307000	1.447642000
H	2.589253000	1.336811000	0.280629000

5-*anti*: E=-589.76503

C	1.907800000	1.766069000	0.493421000
C	2.757193000	0.895099000	-0.204926000
C	2.333669000	-0.394015000	-0.553805000
C	1.052447000	-0.792083000	-0.180403000
C	0.210966000	0.079366000	0.531183000
C	0.622194000	1.365305000	0.867426000
C	0.327800000	-2.074475000	-0.461394000
C	-1.026175000	-1.956768000	0.126705000
C	-1.046078000	-0.641561000	0.906788000
O	-0.830777000	-1.878065000	-1.294049000
C	-2.222124000	1.683704000	-0.919178000
N	-2.401783000	2.813060000	-1.219875000
O	-1.774751000	-0.426835000	1.856608000
H	2.247648000	2.771019000	0.728037000
H	3.750722000	1.230374000	-0.492183000
H	2.988959000	-1.061315000	-1.108769000
H	-0.063305000	2.036401000	1.372425000
H	0.848678000	-3.022009000	-0.584986000
H	-1.622158000	-2.790534000	0.489229000

6-*syn*: E=-589.77350

C	-2.540893000	-1.220238000	-0.402702000
C	-2.987860000	-0.141468000	0.371180000
C	-2.094131000	0.865997000	0.764678000
C	-0.758447000	0.760140000	0.385282000
C	-0.306222000	-0.338659000	-0.360767000
C	-1.194135000	-1.320042000	-0.780491000
C	0.377447000	1.707999000	0.601323000
C	1.570121000	1.136303000	-0.036077000
C	1.204515000	-0.245866000	-0.637455000
O	0.880530000	2.251101000	-0.655837000
O	1.715051000	-0.697218000	-1.688344000
C	1.826816000	-1.222442000	0.932108000
N	2.316343000	-1.934777000	1.725522000
H	-3.246882000	-1.990533000	-0.705794000
H	-4.034771000	-0.079057000	0.659059000
H	-2.443957000	1.716431000	1.346997000
H	-0.830578000	-2.152931000	-1.376211000
H	0.404613000	2.391307000	1.447642000
H	2.589253000	1.336811000	0.280629000

6-*anti*: E=-589.76503

C	1.907800000	1.766069000	0.493421000
C	2.757193000	0.895099000	-0.204926000
C	2.333669000	-0.394015000	-0.553805000
C	1.052447000	-0.792083000	-0.180403000
C	0.210966000	0.079366000	0.531183000
C	0.622194000	1.365305000	0.867426000
C	0.327800000	-2.074475000	-0.461394000
C	-1.026175000	-1.956768000	0.126705000
C	-1.046078000	-0.641561000	0.906788000
O	-0.830777000	-1.878065000	-1.294049000
C	-2.222124000	1.683704000	-0.919178000
N	-2.401783000	2.813060000	-1.219875000
O	-1.774751000	-0.426835000	1.856608000
H	2.247648000	2.771019000	0.728037000
H	3.750722000	1.230374000	-0.492183000
H	2.988959000	-1.061315000	-1.108769000
H	-0.063305000	2.036401000	1.372425000
H	0.848678000	-3.022009000	-0.584986000
H	-1.622158000	-2.790534000	0.489229000