A plot of the θ_N vs. ϕ_{i+1} values is shown in the Figure 2.[7] There seems to be no discernible pattern in this case.

Since the amide nitrogen $2p_\pi$ orbital is a poor electron donor in the allylic interaction as compared to the C′ $2p_\pi$ orbital,[4] the observed difference in the θ_N and $\theta_{C'}$ behavior suggests that such a donation is an important interaction in staggering of allylic moieties on the sp^2–sp^3 bonds. This explanation is supported by the fact that a rotational variance of θ_N is found in the case of *N*-glycosides[8] and by the fact that $\theta_{C'}$ increases when the electron affinity of the bond overlapping the $2p\pi$ system increases.

Examination of the points for the bonds from group III in the table, in the region 150 ± 10° of Figure 1 (the corresponding conformation is shown in Scheme II), indicates that the average $\theta_{C'}$ value equals 2.7° if the antiperiplanar bond is CH, 3.3° if it is C–CH_3 and 3.8° if it is C–CHRR′ (for 12 Gly, 9 L-Ala, and 8 additional L-amino acid, excluding L-Pro, entries, respectively), whereas the average $\theta_{C'}$ values for all the remaining points are 2.2°, 2.8°, and 1.8° (26 Gly, 12 L-Ala, and 19 additional L-amino acid, excluding L-Pro, entries).[9]

The second important aspect of conformational equilibria of the planar conjugated systems is relative stability of the syn- and anti-pyramidalized sp^2–sp^2 bonds. This question has been addressed in computational studies of olefins, which indicate a greater stability of the anti form.[10] The pertinent experimental data are collected in the table. It can be seen that the substitution of the amide bond which increases the degree of its polarization, as indicated by lowering of the C=O stretching frequency,[11] also increases stability of the syn-pyramidalized form. Furthermore, if the bonds that are more polarized toward $>C^+—N^- \leftrightarrow >C=N^+<$ mezomeric structures do tend to pyramidalize in the same direction on the C′ and N atoms, the average C′N bond length of the syn-pyramidalized amides is expected to be smaller. A trend in this direction is indeed observed.[12]

As previously mentioned, the occurrence of out-of-plane distortions attracted a good deal of attention in the structural studies of amides,[2,3] and such distortions were invoked to explain chirooptical properties of amides,[13] chiral folding of polypeptide chains in proteins,[14] in particular systematic right-handed twist of β-sheet structures,[15] reactivity of β-lactam antibiotics,[16] and the mechanism of enzymic cleavage of peptide bonds.[17] Nonetheless, there has been no attempt at explanation of the direction and magnitude of these seemingly incidental features, except for the proposition that they might be determined by hydrogen bonding in the crystal lattice,[18] polypeptide chain,[19] or the active site.[17] The energy of the $2p_\pi,\sigma^*$ two-electron stabilizing interactions, which we believe largely determine the direction and extent of staggering on the sp^2–sp^3 bonds, might be significantly higher than the energy of hydrogen bonding.[20] It seems then that the data reported here are relevant for a number of problems in structural chemistry of peptides and proteins.

On the other hand, however, these data may well reflect generally valid principles of behavior of the delocalized $2p_\pi$ systems on chiral perturbation, and we have attempted to extend these observations, using our incipient bond model of 1,2-asymmetric induction,[21] into a rule of selection for 1,N-π^n-diastereoface-differentiating reactions, i.e., the reactions where the incipient and the inducing chiral centers are separated by one, two, or more atoms of a planar $2p_\pi$ skeleton.[22]

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(7) The ϕ_{i+1} angle is defined according to the IUPAC–IUB Commission rules.[6]

(8) Cieplak, A. S., submitted for publication. The *N*-glycoside nitrogen is, presumably, less electron deficient than the amide nitrogen.

(9) The esd values for the $\theta_{C'}$ angles are about 0.3–0.5°.

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Enantioselective Synthesis of Quaternary Carbon Centers through Michael-Type Alkylation of Chiral Imines[1]

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Although quaternary carbon centers are challenging structural components of many complex natural compounds,[2] only a few methods for generating this moiety in an efficient enantioselective manner exist to date.[3]

We now report a novel and general process for the synthesis of chiral 2,2-disubstituted cycloalkanones **2**, in high enantiomeric purity. The reaction involves a new type of "*deracemizing alkylation*" of 2-monosubstituted cycloalkanones **1**, as chiral imine derivatives, by means of electron-deficient alkenes (Scheme I).

Thus imine **3**, bp 110 °C (0.1 torr) (prepared in 89% yield from *rac*-2-methylcyclohexanone and (*S*)-(−)-1-phenylethylamine[4] **7** by azeotropic removal of water, toluene, *p*-TsOH, 1 h) with 1 equiv of methyl vinyl ketone (THF, 20 °C, 3 days) led to adduct **5** (Scheme II). Hydrolysis (AcOH 10%, 20 °C, 1 h) of crude compound **5** afforded (*R*)-(+)-diketone[5] **6**, bp 130 °C (9 torr),

(1) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J., paper presented in part at the EUCHEM Conference on Asymmetric Formation of C–C Bonds, Port-Camargue, France, April 25–27, 1984.

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(4) Commercial amine **7**, $[\alpha]^{20}_D$ −39.4° (neat), was used.

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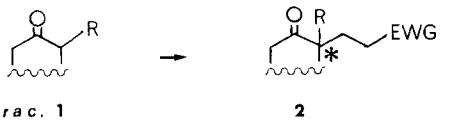
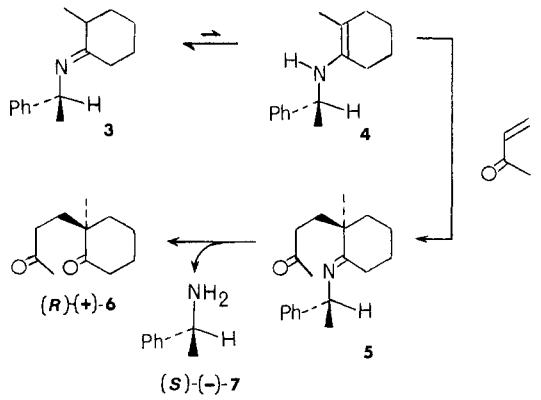
Scheme I



EWG = electron withdrawing group

Scheme II



88% yield, $[\alpha]^{20}_D$ +34.3° (*c* 1.36, EtOH), 91% ee, and the starting amine **7**, which was recovered, in an almost quantitative yield, without any loss of optical purity, merely by neutralization (NaOH) of the aqueous layers.

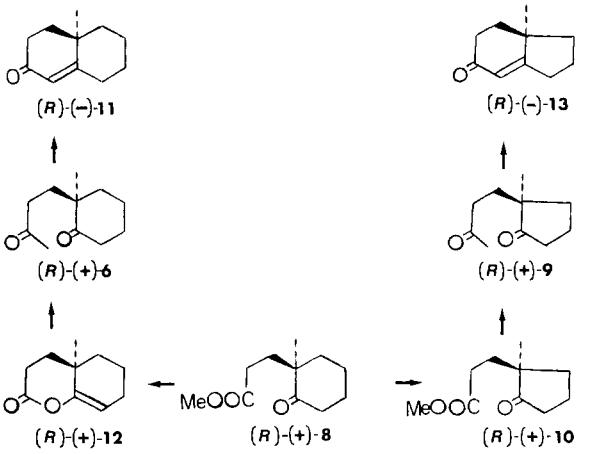
Clearly, as previously reported for alkylations of this type,[6] the reactive nucleophilic species in this reaction is the secondary enamine **4**, in tautomeric equilibrium[6a,b] with the imine **3**, which reacts with methyl vinyl ketone regiospecifically[7] and stereoselectively.

Similar results were observed under the same conditions using other cycloalkanone imines derived from amine **7** and various electron-deficient alkenes. In this manner (*R*)-(+)-keto ester **8** (from imine **3** and methyl acrylate), (*R*)-(+)-diketone **9**, and (*R*)-(+)-keto ester **10** (from 2-methylcyclopentanone imine derivative by reaction with methyl vinyl ketone and methyl acrylate, respectively) were obtained.[5,8]

The enantiomeric excesses of the new chiral compounds were established by ^{1}H NMR spectroscopy using a chiral LISR (for keto esters **8** and **10**). Furthermore the configurational assignments and the enantiomeric excesses were both determined by the chemical correlations (for all new chiral compounds) depicted in Scheme III.

Base-induced cyclization[9] of diketone **6** led to the known[10] (*R*)-(-)-octalone[5] **11**. Keto ester **8** was correlated with the same octalone through the (*R*)-(+)-enol lactone[5,11] **12**, according to the well-known Belleau-Fujimoto sequence.[12] The same six-membered ring keto ester **8** was transformed[13] into the five-membered

Scheme III



ring keto ester **10**. Finally compound **10** was converted[14] to diketone **9**, which was cyclized[15] into (*R*)-(-)-hydrindenone[16] **13**.

This new process involves the following important features: Use of an inexpensive auxiliary chiral amine (both enantiomers are commercially available), which is easily and quantitatively recycled. Very mild reaction conditions and very simple procedure allowing large-scale preparations. Exclusive alkylation at the more substituted carbon atom. Creation of quaternary carbon centers bearing functionalized side chains. Excellent chemical yields and high enantiomeric excesses.

With suitable substituents, the synthetic chiral compounds are well adapted for further diastereoselective reactions that can lead to the syntheses of important chiral biologically active compounds.

(5) Purified by "flash" chromatography on silica, homogeneous by TLC and giving satisfactory IR and ^{1}H NMR spectra.

(6) (a) Pfau, M.; Ribière, C. *J. Chem. Soc., Chem. Commun.* **1970**, 66-67. (b) Pfau, M.; Ribière, C. *Bull. Soc. Chim. Fr.* **1971**, 2584-2590. (c) Pfau, M.; Ribière, C. *Bull. Soc. Chim. Fr.* **1976**, 776-780. (d) Pfau, M.; Ughetto-Monfrin, J. *Tetrahedron* **1979**, *35*, 1899-1904. (e) Pfau, M.; Ughetto-Monfrin, J.; Joulain, D. *Bull. Soc. Chim. Fr.* **1979**, 627-632.

(7) As previously reported, the alkylation takes place exclusively at the *more* substituted carbon atom, see ref 6d and p 3411 of: Hickmott, P. W. *Tetrahedron* **1982**, *38*, 3363-3446.

(8) **8**: 81% yield, $[\alpha]^{20}_D$ +33.8° (*c* 2.95, EtOH), 90% ee. **9**: 83% yield, $[\alpha]^{20}_D$ +26.7° (*c* 1.50, EtOH), 89% ee. **10**: 79% yield, $[\alpha]^{20}_D$ +35.7° (*c* 1.68, EtOH), 90% ee.

(9) MeONa 5% in MeOH, 35 °C, 1 h, 94% yield.

(10) Following specific rotation was reported for pure (*R*)-(-)-octalone **11**: $[\alpha]^{24}_D$ -207° (*c* 1, EtOH). Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021-4023.

(11) Compound **12**, mp 33°C, $[\alpha]^{20}_D$ +157° (*c* 2.46, EtOH), 90% ee, was obtained from keto ester **8** through the corresponding keto acid, $[\alpha]^{20}_D$ +30.0° (*c* 4.77, EtOH), 90% ee.

(12) Weill-Raynal, J. *Synthesis* **1969**, 49-56.

(13) (1) Ring oxidation into diacid: CrO_3, AcOH, 75 °C, 15 h. (2) seven-membered ring anhydride formation: Ac_2O, reflux, 4 h. (3) ring contraction: 220 °C, 25 torr, neat, 15 min.

(14) (1) NaOH, then H_3O^+; (2) 3 equiv LDA and then excess LiMe.

(15) NaOH 5%, MeOH, reflux, 16 h, 80% yield.

(16) The hydrindenone **13**, $[\alpha]^{20}_D$ -108° (*c* 3.50, EtOH), 90% ee, has not been reported previously in the literature in its optically active form.

Synthesis, Structure, and Antitumor Properties of Platinum Complexes of Vitamin C

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The widespread success of cisplatin, *cis*-$[Pt(NH_3)_2Cl_2]$, in the clinical treatment of testicular and ovarian cancers has stimulated research in the area of metal-based anticancer drugs and spurred the search for compounds with improved therapeutic properties.[1] One new group of promising antitumor agents, which has shown good activity in a variety of preclinical antitumor screens, are the *cis*-diamineplatinum complexes of vitamin C. These complexes represent the first transition-metal ascorbates to yield to complete structural characterization.

A series of stable complexes of the form *cis*-$[Pt(RNH_2)_2$(ascorbate)] has been isolated and structurally characterized. The ascorbate ligand in these compounds is bound to platinum in a

(1) (a) Lippard, S. J., Ed. "Platinum, Gold and Other Metal Chemotherapeutic Agents"; American Chemical Society: Washington, DC, 1983; ACS Symp. Ser. No. 209. (b) Hacker, M. P., Doyle, E. B., Krakoff, I. H., Eds. "Platinum Coordination Complexes in Cancer Chemotherapy"; Martinus-Nijhoff: Boston, 1984.

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