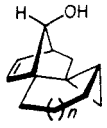
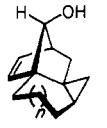
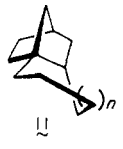
Table I. Calculated Gas-Phase Heats of Formation[a]

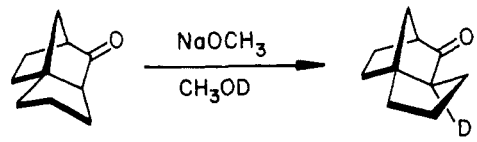
compd	$\Delta H_f°$ (25 °C) $n = 0$	$n = 1$
 **3b**, **5b**	7.36	-3.44
 **9**	13.44	-0.51
 **10**	-15.40	-26.64
 **11**	-8.84	-24.83

[a] MMP2 (OCPE 395).

figuration of the three-membered ring in these products by X-ray crystallographic analysis of 3,5-dinitrobenzoate **5c**,[5] **2** was treated with CF_3COOD in $CHCl_3$ solution. In keeping with the trend, **5e** was produced exclusively within the limits of our spectral analysis. Thus, *full retention of configuration is operational within both series.*

The above results are best reconciled with a mechanism in which only the *central* and not the flanking bicyclobutane subunit experiences initial electrophile-induced cleavage to generate carbocation **6** (Scheme I). As detailed elsewhere,[10,11] two indistinguishable pathways can deliver the requisite stereospecificity. Although the direct[12a] and indirect[12b] routes also cannot be differentiated here, the evidence requires that product formation be triggered via **6**.

At this crucial point, the systems respond by migrating bond a-b of the second bicyclobutane ring to the exclusion of bond b-c. Models of **6** suggest that this distinction is not stereoelectronically driven since both bonds appear to bisect the carbocationic center to a comparable degree. We note, however, that whereas the first option delivers **3** and **5**, the second would lead instead to **9**. MM2 calculations (Table I) of both isomeric systems denote the latter isomers to be significantly less thermodynamically stable. This ordering is comparable to that estimated for the less ornate hydrocarbons **10** and **11**[13,14] and in full agreement with the facile epimerization of ketone **12** to **13**.[15] It is, of course, this migratory event that determines the geometric orientation of the 7-norbornenyl cation in **8** relative to the cyclopropane ring. The presumption is that this facet of the rearrangement is thermodynamic in origin.



12 **13**

The means with which **1** and **2** adapt to capture by uniparticulate electrophiles[16] has several implications[16,17] which await assessment at the experimental level.

Acknowledgment. Appreciation is expressed to the National Science Foundation for financial support and to Dr. M.-A. Poupart for his assistance with the MM2 calculations.

(10) Wiberg, K. B.; Szeimies, G. *J. Am. Chem. Soc.* **1976**, *92*, 571.
(11) (a) Zon, G.; Paquette, L. A. *J. Am. Chem. Soc.* **1974**, *96*, 215. (b) Paquette, L. A.; Zon, G. *Ibid.* **1974**, *96*, 224 and pertinent references cited in these papers.
(12) (a) Regiospecific edge bond cleavage. (b) Unidirectional SE2-like cleavage of the central bond followed by Wagner-Meerwein shift within the newly generated cyclobutyl cation. Protonolysis of the C-Ag bond is assumed to occur with retention where applicable.
(13) Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005.
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(17) (a) Browne, A. R.; Paquette, L. A. *J. Org. Chem.* **1978**, *43*, 4522. (b) Christl, M.; Lang, R.; Herzog, C.; Stangl, R.; Peters, K.; Peters, E.-M; von Schnering, H. G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 611.

Enantioselective Synthesis of β-Amino Esters through High-Pressure-Induced Addition of Amines to α,β-Ethylenic Esters

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β-Amino esters **3** are important intermediates in organic synthesis since they are direct precursors of β-lactam derivatives.[1]

Conceptionally, one of the simplest method for the construction of such compounds is through the conjugated addition of amines **2** to α,β-ethylenic esters **1**[2] (Scheme I). A major advantage of this route is the possibility of controlling the stereochemistry at the created asymmetric center (starred in formula **3**) by using an appropriate chiral starting material.

Such an approach was independently investigated by two groups in 1977;[3,4] however, the reported thermally activated addition gave only modest chemical yields and the corresponding diastereoisomeric excesses (de) were low (less than 20%).

In this paper we wish to report two significant modifications that confer an enhanced synthetic value to this reaction: viz., the use of high pressure as an activating agent to produce excellent chemical yields and the use of new chiral inductors (R^2 in **1**) to allow very high stereocontrol at the newly created asymmetric center.

While sluggish under thermal conditions,[3,4] the addition of primary amines[5] to alkyl crotonates is very efficient at room temperature under 5-15 kbar pressures[6] in methanol (Table I).

Our investigations were primarily made with crotonates derived from chiral alcohols since our initial work established that the addition of asymmetric amines to methyl crotonate provides low de (entries 1, 2).[7] As previously reported,[4] *l*-menthyl crotonate was found to give poor de (entry 3). We next examined 8-phenylmenthol (8-PhM) as the chiral inductor since this auxiliary,

(1) See, for example: Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161-6163.
(2) Pfau, M. *Bull. Soc. Chim. Fr.* **1967**, 1117-1125 and references cited therein.
(3) Kinas, R.; Pankiewicz, K.; Stec, W. J.; Farmer, P. B.; Foster, A. B.; Jarman, M. *J. Org. Chem.* **1977**, *42*, 1650-1652.
(4) Furukawa, M.; Okawara, T.; Terawaki, Y. *Chem. Pharm. Bull. (Tokyo)* **1977**, *25*, 1319-1325.
(5) Because of their facile hydrogenolysis, α-substituted benzylamines were used as ammonia equivalents in this addition. Secondary amines (e.g., dibenzylamine) do not add to alkyl crotonates under high-pressure activation conditions.
(6) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1-26.
(7) This in agreement with previously reported observations.[3,4]

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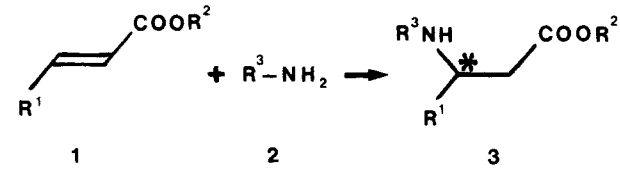
Table I

entry	R^1	R^2	R^3	operating conditions	chem. yield, %	de, %
1	Me	Me	(*R,S*)-PhMeCH–	CH_2Cl_2, 14 kbar, 20 °C, 120 h	60	5
2	Me	Me	(*R,S*)-MesMeCH–	MeOH, 5 kbar, 20 °C, 48 h	90	25
3	Me	*l*-menthyl	Ph_2CH–	MeOH, 5 kbar, 20 °C, 72 h	35	10
4	Me	8-PhM	(*R*)-PhMeCH–	CH_2Cl_2, 14 kbar, 50 °C, 24 h	60	50
5	Me	8-PhM	(*S*)-PhMeCH–	CH_2Cl_2, 14 kbar, 50 °C, 24 h	60	60
6	$(MeO)_2CHCH_2$–	8-PhM	Ph_2CH–	MeOH, 13 kbar, 20 °C, 24 h	85	60
7	Me	8-PhM	Ph_2CH–	MeOH, 15 kbar, 50 °C, 96 h	90	60
8[a]	Me	8-*p*-*t*-BuPhM	Ph_2CH–	MeOH, 15 kbar, 25 °C, 24 h	65	75
9[a]	Me	8-*p*-PhOPhM	Ph_2CH–	MeOH, 15 kbar, 25 °C, 24 h	90	95
10[a]	Me	8-βNaphtM	Ph_2CH–	MeOH, 15 kbar, 25 °C, 24 h	50	≥99

[a] Small amount of methyl ester—the result of a transesterification process—was formed in these cases. This byproduct was easily removed by flash chromatography on silica gel.

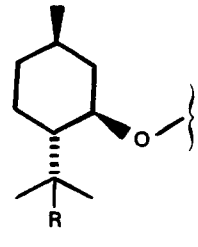
Scheme I



1 2 3

originally prepared by Corey and Ensley,[8] is known to be remarkably efficient, giving excellent asymmetric induction in several types of reactions.[9]

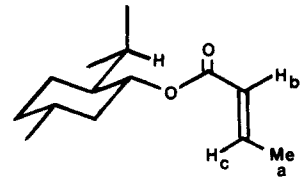
Although a significant improvement in the level of induction was, in fact, obtained with 8-phenylmenthyl crotonate (entries 4, 5, 7) and a 8-phenylmenthyl crotonate derivative (entry 6), the de's were still moderate [it should be noted that the "double-diastereodifferentation" phenomenon was not observed with chiral (α-methylbenzyl)amines and 8-phenylmenthyl crotonate (entries 4, 5)]. We therefore sought to design more effective chiral inductors derived from 8-PhM and we were nicely rewarded. *We thus observed a dramatic increase in the induction level by using analogues of 8-PhM*[10] *in which the phenyl ring is substituted in the para position by bulky groups.* The de obtained are good



l-menthyl, R = H
8-PhM : 8-phenylmenthyl, R = phenyl
8-ptBuPhM : 8-(*p*-*t*-butylphenyl)-menthyl, R = *p*-*t*-butylphenyl
8-pPhOPhM : 8-(*p*-phenoxyphenyl)-menthyl, R = *p*-phenoxyphenyl
8-βNaphtM : 8-(β-naphthyl)-menthyl, R = β-naphthyl

to excellent (entries 8–10), with essentially complete diastereofacial control being achieved in the case of 8-(β-naphthyl)menthyl crotonate (entry 10) [The de's were established from the ^1H and ^{13}C NMR spectra (entries 1–9) or from the ^1H NMR spectrum (^{13}C satellite comparison method; entry 10)].

This stereochemical outcome agrees with the "π-stacking" model previously proposed by W. Oppolzer,[11] in which the aryl group of the inductor shields a face of the crotonate unit, thereby directing the amine addition to the other face. This interpretation is strongly supported by a comparative ^1H NMR study[12] that



	H_a	H_b	H_c
	1.87	5.83	6.96
	1.72	5.32	6.44
	1.23	4.92	6.07

indicates that both olefinic protons of 8-phenylmenthyl crotonate are shifted upfield similarly (each by ca. 0.5 ppm) relative to those of menthyl crotonate and that the same phenomenon (with a similar shift magnitude) is observed between 8-phenylmethyl and 8-(β-naphthyl)menthyl crotonates. In contrast, the signal of the vinyl Me of 8-phenylmenthyl crotonate is only slightly shifted (by 0.15 ppm) compared with that of menthyl crotonate, while the corresponding Me signal of 8-(β-naphthyl)menthyl crotonate is again notably shifted upfield (by 0.49 ppm) compared with that of 8-phenylmenthyl crotonate.

All these observations are in good agreement with the "π-stacking" models depicted in Scheme III. Indeed, according to such models, only the vinylic protons of the crotonate unit should be significantly shielded by the phenyl group in 8-phenylmenthyl crotonate; in contrast all protons of the crotonate moiety (*including those of the methyl group*) should be similarly shielded by the

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(9) Whitesell, J. K.; Liu, C. L.; Buchanan, C. M.; Chen, H. H.; Minton, M. A. *J. Org. Chem.* **1986**, *51*, 551–553 and references cited therein. Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, *26*, 5025–5028.
(10) All 8-arylmenthols were prepared from commercial (+)-pulegone in close analogy with Corey's procedure,[8] except for the reduction of 8-(β-naphthyl)menthone, which was achieved with lithium aluminum hydride [the resultant equimolar epimeric mixture of 8-(β-naphthyl)menthol and 8-(β-naphthyl)neomenthol could be readily separated by flash chromatography on silica gel].
(11) Oppolzer, W.; Robbiani, C.; Bättig, K. *Helv. Chim. Acta* **1980**, *63*, 2015–2018.
(12) 200 MHz, $CDCl_3$, δ (ppm) relative to Me_4Si used as internal standard.

naphthyl substituent in 8-(β-naphthyl)menthyl crotonate.

The sense of the induction of the adducts in Table I (entries 8-10) could be established by correlation[13] with (*R*)-3-aminobutan-1-ol.[3,14] The results confirm that amine addition does, in fact, take place preferentially on the *re* face of the crotonate unit, in agreement with related work.[11,15]

This new enantioselective route to β-amino esters is incontestably one of the most efficient asymmetric carbon-nitrogen bond-forming reactions known to date; furthermore the new 8-arylmenthols that we have developed during the course of this work will undoubtedly prove to be powerful and general chiral auxiliaries in other enantioselective processes.

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Supplementary Material Available: Preparative methods and spectral data for all new compounds **1** and corresponding amino derivatives **3** (7 pages). Ordering information is given on any current masthead page.

(13) (i) LAH, Et_2O, 20 °C, quantitative; (ii) H_2 3 bar, $Pd(OH)_2$, MeOH, quantitative. The chiral auxiliary alcohols were recovered in 95% yield.

(14) This configuration—obtained by using chiral auxiliaries derived from natural, inexpensive (+)-pulegone—is precisely that required for the synthesis of the biologically active β-lactam derivatives; see, for example: Pfaendler, H. R.; Gosteli, J.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6303-6310.

(15) Oppolzer, W.; Kurth, M.; Reichlin, D.; Chapuis, C.; Mohnhaupt, M.; Moffatt, F. *Helv. Chim. Acta* **1981**, *64*, 2802-2807. Oppolzer, W.; Löher, H. G. *Ibid.* **1981**, *64*, 2808-2811. Oppolzer, W.; Moretti, R.; Godel, T.; Meunier, A.; Löher, H. *Tetrahedron Lett.* **1983**, *24*, 4971-4974.

Oxygenated Cytochrome P-450-CAM and Chloroperoxidase: Direct Evidence for Sulfur Donor Ligation Trans to Dioxygen and Structural Characterization Using EXAFS Spectroscopy

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Cytochrome P-450 and chloroperoxidase are heme iron enzymes that possess unique spectroscopic and catalytic properties.[2,3] The P-450 enzymes activate dioxygen for incorporation into organic molecules while chloroperoxidase couples the reduction of peroxides to the oxidation and incorporation into organic substrates of chloride ions. Despite catalyzing such disparate reactions, extensive spectroscopic studies have consistently shown both enzymes to contain essentially identical heme iron coordination structures.[3]

The P-450 reaction cycle consists of four known intermediates culminating in a ferrous-O_2 adduct (oxy-P-450).[4] One-electron reduction of oxy-P-450 yields the hydroxylated product and water. Through spectral comparison of heme protein and synthetic porphyrin complexes of known structure with isolated P-450 intermediates, cysteinate sulfur has been established as the axial ligand for ferric, deoxyferrous, and ferrous-CO P-450.[2] Recently, the presence of the cysteine ligand in ferric P-450 has been verified by X-ray crystallography.[5] Oxy-P-450 is the last identified intermediate in the reaction cycle and the state about which the least is known. Although replacement of the cysteinate ligand by histidine upon dioxygen binding has been proposed,[6] spectral studies of oxy-P-450 appear to rule out histidine ligation.[7] A thiolate/O_2-ligated ferrous porphyrin complex with Mössbauer properties similar to those of oxy-P-450 has been structurally characterized by Weiss and co-workers.[8]

In contrast to P-450, chloroperoxidase functions without reduction to the ferrous state. Instead, peroxide addition to the ferric enzyme produces an iron-oxo species that reacts with chloride to effect chlorination.[9] Recently, an oxygenated derivative of ferrous chloroperoxidase has been reported[10,11] which, unexpectedly, is spectrally distinct from oxy-P-450-CAM.[10,12] In order to more fully elucidate the structural properties of these enzymes and to further probe the structure/function relationship between P-450 and chloroperoxidase,[3] especially in light of earlier chemical evidence against cysteine ligation in the latter,[13] extended X-ray absorption fine structure (EXAFS) spectroscopy has been used. EXAFS is a particularly useful technique for determining the number, identity, and distance of donor atoms surrounding the central metal in metalloenzymes.[14] In favorable cases, metal-ligand bond distances can be determined in the first coordination shell to an accuracy of ±0.02 Å and coordination number to ±25-35% (±1 atom in 3-4). Here we report the structural characterization of oxygenated P-450-CAM and chloroperoxidase with EXAFS spectroscopy. Evidence is presented that both the enzyme states contain a thiolate sulfur donor axial ligand trans to dioxygen.

The oxygenated derivatives of P-450-CAM (1.4 mM, pH 7.4, in the presence of 4 mM *d*-camphor) and chloroperoxidase (3.5 mM, pH 6.0) were prepared at -40 °C in potassium phosphate buffer containing 65% (v/v) ethylene glycol as described previously.[10] The homogeneity and integrity of the samples before *and* after EXAFS experiments were verified by UV-visible absorption spectroscopy; less than 15% autooxidation occurred during sample manipulation. The spectra were obtained at -80 °C and the

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