The present results showed that the enzymatic cleavage patterns of the dianhydrocyclodextrins **7–10** were understandable by superimpositions of patterns of two monoanhydrocyclodextrins. Since Taka amylolysis patterns of $6^A,6^X$-di-*O*-sulfonyl-α- or -β-cyclodextrins[1c,d,f] and $2^A,3^A;2^X,3^X$-dianhydro-α- or -β-cyclodextrins[6] were also understandable by "superimposition", the Taka amylolysis method may be widely applicable to structure determination of polysustituted cyclodextrins or oligosaccharides, after an appropriate chemical conversion, if necessary. In the present study, all 6-O-disulfonylated γ-cyclodextrins and 3,6-dianhydro-γ-cyclodextrins were isolated as pure materials and structurally assigned. These disulfonated γ-cyclodextrins will serve as the starting materials for the synthesis of unique enzyme mimics with binding of two substrates in the active site. The 3,6-dianhydro-γ-cyclodextrins have unique cavity shapes which are different from one another and from that of γ-cyclodextrin itself and are expected to show unique molecular recognition. Also, the present study shows that the Taka amylolysis is an effective synthetic method for linear maltooligosaccharides containing 3,6-anhydroglucose units at specific positions.

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Acknowledgment. We are indebted to Japan Maize Products Co. Ltd. (Japan) for a generous gift of γ-cyclodextrin.

Diastereoselective Alkylation Guided by Electrophile–Nucleophile π-Interactions

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Alkylation of the enolate **1a** obtained from the (*R*)-camphor imine of *tert*-butyl glycinate with a variety of alkylating agents gives products whose trends in diastereomeric excesses appear to correlate with π electron density and steric effects in the electrophile. Secondary allylic or benzylic halides undergo efficient double chiral induction. Anion **1a** undergoes smooth Michael additions with no chiral discrimination, but aldol condensations cannot be achieved.

Enantioselective alkylation reactions are the subject of current intense investigation. A recent comprehensive review[2] summarizes much of the currently available information. An especially active area is the asymmetric alkylation of derivatized glycine using a variety of reaction types[3–6] to provide higher amino acids of known configuration and high optical purity. Recently we reported[7] the results of a study designed to examine the use of camphor as a chiral auxilliary in such alkylations. The specific reaction probed was the alkylation of the (*R*)-camphor imine of *tert*-butyl glycinate (**1**). The diastereomeric excesses (de) of the products showed several distinct trends. For primary alkylating agents that do not have an adjacent π-system, increasing steric bulk increased the de values to a maximum of ca. 50% (R = *i*-Bu or Bu) while significantly higher values were observed for halides which contained a π-system attached to the reacting center (allylic and benzylic halides). The latter observation was true even though the steric requirements of the R group in these alkylating agents were, in many examples, significantly less than the saturated cases. In all instances, attack from the *re* face (opposite side from camphor C8) was favored and the products were shown to be those of kinetic control. It is worth noting that **1a** can be classified as a type of azallyl anion[8] that has not received the study accorded the more usual type derived from enamines.

On the basis of these results, a conceptual model for the alkylation process was developed (Figure 1)[7] that included the following points. Imine **1**, which appears to be stereochemically homogeneous from its ^1H and ^{13}C NMR spectra and presumably exists in the *E* configuration, affords an enolate (**1a**) on treatment with LDA. In accord

(1) (a) Taken in part from the Ph.D. Dissertation of R. K. Leavitt, University of Windsor, 1986. (b) Taken in part from the Ph.D. Dissertation of P. Mishra, University of Windsor, 1985. (c) Holder, Natural Sciences and Engineering Research Council of Canada Predoctoral Fellowship, 1981–85. (d) Taken in part from the undergraduate research report of K. C. Cassidy, 1987.

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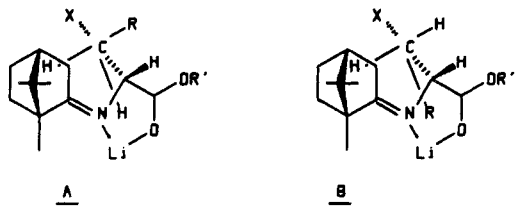
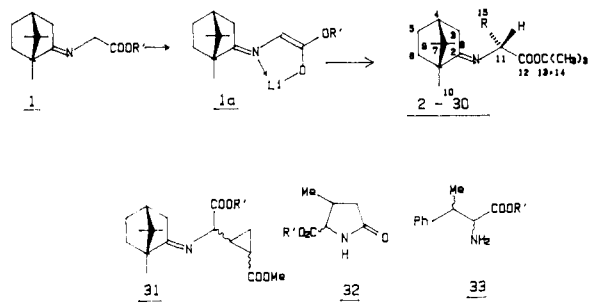


Figure 1. Conformations for *re* face attack on **1a**.

Scheme I[a]



[a] R′ = $C(CH_3)_3$.

with other work[9] on similar types of enolates, **1a** is considered to exist in an internally chelated form (**1a**). Two considerations lead to the assignment of the *E* configuration to this enolate. Models show that the *Z* form has a severe interaction with the C10 methyl group of camphor which is lacking in the *E* isomer and all products obtained showed a preference for the formation of the *R* isomer. If the configuration of **1a** was *Z*, this would require approach of the electrophile from the more hindered side, syn to the C8 methyl group of camphor. For saturated alkyl halides, orientation of the R group away from the planar enolate system (conformation A, Figure 1) provides a situation where the de values reflect the *steric* bias provided by the C8 methyl group of camphor (preferential attack from the bottom or *re* face of the enolate). Increasing the bulk of R at a point remote from the reacting center does not influence the size of this bias. For allylic or benzlic halides, the positive character induced in the π-system by the partial breaking of the C–hal bond at the transition state was suggested as the cause of an electrostatic interaction with the enolate π-system (π–π interaction). This would lead to a reacting conformation in which the oppositely charged π-systems are coplanar and eclipsed (conformation B, Figure 1). In such a situation, the steric effects of the camphor moiety are enormously magnified and the expected increased de values are observed (e.g. **15**, de = 76%; **5**, de = >98%).

In this paper, we provide more examples of the selectivity including details[10] of some examples of the reaction of secondary halides, note some deviations from the previously noted trends, and suggest a refined model that explains the results.

Results

The diastereomeric excesses were determined in several ways. In almost every case, integration of the C11 methine proton signals in the 300-MHz ^{1}H NMR spectrum could be used.[7] However, when high de values were obtained, determination by this method became unreliable. In these instances, the camphor methyl groups showed separate, easily integrated singlets for each diastereomer. In several cases (Table I) hydrolysis of the imine bond and derivatization of the *tert*-butyl amino esters with (+)-MPTA[11] afforded Mosher amides that could be examined by both ^{1}H and ^{19}F NMR. The results of the three methods are internally self-consistent (±1%). In addition the ^{19}F results support the assignment of the *R* configuration to the products. The spectra of the Mosher amides which are mixtures all show the major signal at lower field (10–20 Hz) than the minor one. Previous work has shown that the *R* isomer is associated with the lower field signal.[11] All reactions were run in the presence of 1 equiv of HMPA and at −78 °C unless otherwise indicated.

Table I. Alkylations of Enolate 1a with Primary Halides[a]

entry	alkylating agent	product	yield (%)[b]	% de[e]
1	CH_3CH_2I	**2**	38 [81]	33
2	$PhCH_2CH_2Br$	**3**[c]	58 [70]	34
3	$C_6H_{11}CH_2Br$	**4**	0	
4	$PhCH_2Br$	**5**[c]	89	>98
5	2-$CH_3C_6H_4CH_2Br$	**6**	74	>98
6	4-$CH_3C_6H_4CH_2Br$	**7**	71	>98
7	4-$FC_6H_4CH_2Br$	**8**	89	>98 (99[f])
8	4-*t*-$BuC_6H_4CH_2Br$	**9**	71	85[g] (84[f])
9	4-$CF_3C_6H_4CH_2Br$	**10**	71	79[g] (81[f])
10	4-$NCC_6H_4CH_2Br$	**11**	75	76[g] (77[f])
11	4-$MeOC_6H_4CH_2Br$	**12**	83	88 (86[f])
11a	4-$MeOC_6H_4CH_2Cl$	**12**	49[d]	73
12	4-$O_2NC_6H_4CH_2Br$	**13**	69	51
13	1-naphthylmethyl chloride	**14**	31 [98]	93
14	CH_2=$CHCH_2Br$	**15**[c]	85	76
15	CH_2=$C(CH_3)CH_2Cl$	**16**[c]	79[d]	76
16	CH_2=$C(CH_3)CH_2Br$	**16**	60	72
17	$(CH_3)_2C$=CCH_2Br	**17**	80	33
18	HC≡$CHCH_2Br$	**18**	78	67
19	CH_3CH=$CHCH_2Br$ (trans)	**19**[c]	76	60

[a] All reactions run at −78 °C unless otherwise noted. [b] Numbers in brackets are yields based on unrecovered starting material. [c] Reported in ref 7. [d] Reaction run at −20 °C. [e] Based on ^{1}H NMR of alkylated imine unless otherwise noted. [f] Based on ^{19}F NMR of MPTA derivative of amino ester. [g] Based on ^{1}H NMR of MPTA derivative of amino ester.

Two new examples of primary *saturated* alkyl halides have been obtained (Table I, entries 1 and 3). As expected, the de for ethyl iodide was intermediate between that of R = Me (de = 0%) and R = Bu (de = 50%). (Bromomethyl)cyclohexane (entry 3) was used as a steric model for benzyl bromide. The results of several new examples of primary allylic and benzylic halides are also given in Table I. Entries 5–13 were selected to provide a comparison with benzyl bromide (entry 3). These give more insight into the balance between steric and electronic effects on the reaction stereoselectivity. Reaction of propargyl bromide (entry 18) gave no observable allenic product and hydrogenation of **18** gave the propyl derivative (**18a**) quantitatively and with unchanged de.

Several examples of secondary halides have been examined[10] (Table II). The reaction between **1a** and the secondary halides used an give rise, in all but two cases (entries 1 and 3), to one enantiomer of each of four possible diastereomers since two new chiral centers are being established. Based on the results using primary halides, it was expected that one pair of these, derived from attack on the *re* face of the enolate, should predominate. In addition, a kinetic resolution of the enantiomeric forms

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Table II. Alkylations of Enolate 1a with Secondary Halides

entry		product	yield (%)[a] 1 equiv	yield (%)[a] 2 equiv	temp (°C)	% de (ratio) 1 equiv	% de (ratio) 2 equiv
1	$(CH_3)_2CHI$	**20**	20 [80]		−78	67	
1a	$(CH_3)_2CHI$	**20**	86		−20	65	
2	$CH_3CH_2(CH_3)CHI$	**21**	40		−20	(3.4/2.6/1/1)	
3	cyclohexyl-I	**22**	0		−20		
4	$PhCH(Br)CH_3$	**23**	50 [99]	60	−78	80	80
4a	$PhCH(Br)CH_3$	**23**	60		−20	(2.4/1.5/1)	
5	$PhCH(Br)CH_2CH_3$	**24**	31 [64]		−20	(4.4/3.0/1.4/1)	
6		**25**[b]	54 [70]	66	−78	63	89
7		**26**	11 [99]	66	−78	70	76
8	$HC{\equiv}CCH(Br)CH_3$	**27**	40 [82]		−78	(3.9/2.7/1.3/1)	

[a] Numbers in brackets are yields based on unrecovered starting material. [b] Reported in ref 10.

Table III. Michael Addition Products

acceptor	product	yield (%)[a]
$CH_3CH{=}CHCOOEt$ (trans)	**28**	53 [71]
$CH_3CH{=}(COOMe)_2$	**29**	97
$CH_3CH{=}C(COOEt)_2$	**30**	76 [99]
$BrCH_2CH{=}CHCOOMe$ (trans)	**31a**	26 (de = 80%)
	31b	21 (de = 0%)

[a] Numbers in brackets are yields based on unrecovered starting material. All reactions run at −78 °C for 1 h.

of the racemic electrophile seemed possible on the basis of the "double chiral induction" principle enunciated by Masamune and others.[12] As the data indicate, this was observed.

In Table III are listed the results of some reactions of **1a** with simple enones and related materials. No reaction with styrene oxide could be effected and no aldol condensations could be achieved with simple aldehydes, a result consistent with previous observations[13] on the reactions of anions of this type. It is interesting to note that when a choice between alkylation and Michael addition is available, the products (**31**) of the latter process are formed exclusively.[14] The NMR data for the products **28–30** could not be used to determine the diastereomeric composition due to overlapping signals. However, the camphor methyl groups were doubled in each case, indicating the presence of a mixture. Compound **30** was converted to **32**, which was a 1:1 mixture of syn and anti isomers. For **31**, chromatography afforded a less polar (**31a**) fraction that was a 9:1 mixture of two diastereomers and a more polar fraction (**31b**) that was a 1:1 diastereomeric mixture.

Discussion

A. Saturated Halides. The 33% de and 67% de values obtained with ethyl and isopropyl iodide are in complete agreement with the concept that steric factors control the direction of attack on this type of halide and also emphasize the unusual nature of the stereoselectivity of much less hindered primary allylic halides (e.g. allyl). Even in the case of **20** where, using the proposed model, one methyl substituent must lie over the plane of the enolate system, the stereoselectivity imparted to the reaction is moderate at best. It is perhaps surprising that increasing the temperature does not significantly alter the de value obtained. Racemic 2-iodobutane (entry 2, Table II) required a reaction temperature of −20 °C and afforded a mixture of all four possible diastereomers of **21**. In agreement with the known[15] inert nature of cyclohexyl halides, cyclohexyl iodide was recovered unchanged from the alkylation at −20 °C.

B. Allylic and Benzylic Halides. In the series of benzylic *primary* halides, several conclusions can be reached. The original model proposed to explain the observed stereoselectivities involved an association of the π-systems of the enolate and the alkylating agent (Figure 1). In this arrangement, the steric influences imparted by the camphor moiety at the transition state are most severe for *si* face attack. The reduction in de for the *p*-nitrobenzyl case suggests that π-association, if occurring, is favored by an electron-rich system in the alkylating agent. Thus benzyl, *o*- and *p*-methyl and *p*-fluoro, and 1-naphthylmethyl all gave very high de values (the Hammett σ constant, for these substituents are all either positive or very weakly negative) while *p*-cyano, *p*-nitro, and *p*-trifluoromethyl derivatives gave more drastically reduced values. The unexpectedly low de's obtained with *p*-methoxy and *p*-*tert*-butyl derivatives suggests than an additional, opposing effect is operating in these cases. If the two π-systems are eclipsed at the transition state, any steric effect that impedes this association should result in a reduced de value. Both the methoxy and *tert*-butyl groups must possess significant steric bulk above and below the plane of the aromatic ring which clearly should lead to the observed lower de values. It is crucial to note that the low de obtained when ethyl bromoacetate was used as the electrophile indicates that the reactivity of the alkylating agent is not a primary determining factor in the selectivity. It is also important to note that when (bromomethyl)-cyclohexane was used as a model for benzyl bromide, the alkylating agent was recovered unchanged.

An alternative model involves complexation of the π-system with the Li atom of the enolate. The fact that electron-rich π-systems in the alkylating agent favor high selectivities suggests association with a positive center. Literature precedent exists for such π–Li association even in donor solvents like THF.[16-20] In particular, recent

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(16) Nagase, S.; Houk, K. N. *Tetrahedron Lett.* **1982**, *23*, 19.
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(19) Willard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462.

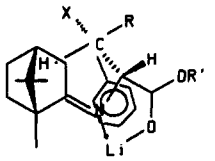

Figure 2. π association with benzyl halides.

results by Duhamel[9] using achiral glycine imines and *chiral* electrophilic species, in which the chirality resides in the leaving group, lend strong support to the concept of association of an electron-rich center (oxygen in that case) with the lithium atom of the enolate. Whether one views the stereoselectivity as arising from π–π or π–Li association, the conclusion that electron-rich systems should increase association remains constant. In the former case, the presence of electron-donating substituents will favor increased C–X bond-breaking at the transition state and therefore attraction with the electron-rich enolate π-system. In the π–Li case, the higher π-electron density in the alkylating agent would favor association with the electropositive Li atom prior to the alkylation step. The presence of HMPA and diisopropylamine in our reaction system is troublesome as their strong coordinating properties would make the π–Li association seem improbable. However, a difference of less than 2 kcal/mol in the energies of the diastereomeric transition states is sufficient to drastically change the selectivity obtained and thus very weak interactions can still be effective. Recent work by McGarvey[21] has demonstrated that the inclusion of HMPA can change a chelated enolate to an extended one, presumably due to HMPA occupying the coordination sites on the lithium atom. Nevertheless, our previous studies[7] have shown the requirement for HMPA to achieve good chemical yields, perhaps as a deaggregation agent. The stereoselectivities we observe are best explained by the conformation shown in Figure 2. At this time, the nature of the association, π–π or π–Li, cannot be specified.

The large difference in stereoselectivity between benzylic and allylic halides can be attributed to the strength of the interactions, which is correlated with the π-electron density in the alkylating agent. The weak electron-withdrawing power of the fluorine substituent (σ = 0.06) is insufficient to reduce the stereoselectivity (entry 7, Table I). Whether the low de obtained with propargyl bromide reflects a reduced interaction or the lower steric demands of the linear alkyne is not clear. The lower selectivity observed in entries 17 and 19 (Table I) relative to the case of allyl bromide itself implies that, as in the aromatic cases, further congestion adversely affects the interaction and thus favors conformation A (Figure 1). When the association is overridden by steric factors, the relatively smaller size of the allylic systems leads to a *reduction* in the observed de relative to the saturated examples.

The results using *secondary* allylic and benzylic halides are especially interesting. Assuming that substitution occurs with inversion of configuration on the electrophile, that *re* face attack on the enolate is preferred, and that the π-systems of **1a** and the alkylating agent are associated, one enantiomer of the electrophile must have the saturated substituent positioned toward the camphor, while the other enantiomer will have it positioned under the exocyclic *tert*-butoxy group. A difference in the activation energies for these two diastereomeric transition states would lead to a kinetic resolution of the alkylating agent. As shown in Figure 3, a preference for the latter should exist. The size of the preference will reflect the steric bulk of the group required to lie under camphor.

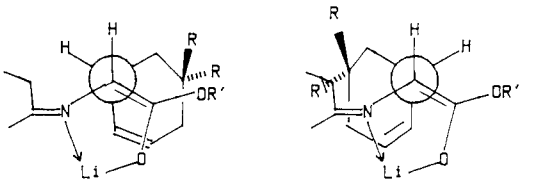

Figure 3. Kinetic resolution with secondary halides.

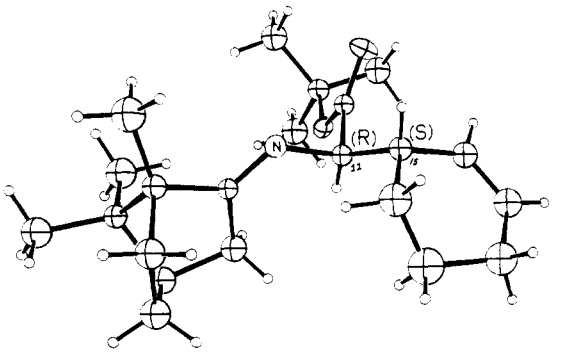

Figure 4. ORTEP drawing of compound **25**.

Table IV. Summary of Crystal Data, Intensity Collection, and Structure Refinement for Compound 25

mol form	$C_{22}H_{35}NO_2$
M_r	345
cell constants (Å)	11.498 (4), 10.370 (3), 18.179 (7)
cell volume (Å^3)	2167.6 (13)
crystal system	orthorhombic
space group	$P2_12_12_1$
Z, $F(000)$	4, 760
ρ_i/ρ_o (g cm^{-3})	1.06, 1.10
crystal dimensions (mm)	0.19 × 0.23 × 0.33
abs coeff (cm^{-1})	0.36
radiation	Mo $K_{\alpha,\lambda}$ = 0.171069 A°
monochrometer	highly oriented graphite
temp (°C)	21
2θ angle (deg)	4–45
scan type	coupled (crystal)/2 (counter)
scan width	$K_{\alpha 1}$ – 1 to $K_{\alpha 2}$ + 1°
scan speed (deg/min^{-1})	variable, 2.02–4.88
bkgd time/scan time	0.5
total reflections measured	1775 ($+h$, $+h$, $+l$)
unique data used	1200 [$I > 3\sigma(I)$]
no. of parameters (NP)	124
$R = (\sum\|\|F_o\| - \|F_c\|\|/\sum\|F_o\|)$	0.0926
$R_w = [\sum_w(\|F_o\| - \|F_c\|)^2/\sum_w\|F_o\|^2]^{1/2}$	0.1026
$\Delta\rho_{max}$	0.3
shift error (max)	0.1

In the event, 1 equiv of all bromides of this type with the exception of 1-phenylpropyl bromide and 3-bromo-1-butyne (entries 5 and 8, Table II) reacted rapidly with **1a** at −78 °C to give chemical yields of products of 55% or less, but *only* two of the four possible diastereomers were formed (de 60–80%). The formation of only two of the four possible diastereomers requires that one of the two newly created chiral centers be (within the limits of detection) optically pure. As we have previously outlined,[10] hydrogenation of **25** led to a diastereomeric mixture of **22**, demonstrating that the optically pure center is C15. The tenative conclusion that the absolute configuration of **25** should be 11*R*,15*S* has been fully confirmed by a single-crystal X-ray structure determination (Figure 4, Table IV).

The double chiral induction noted for the alkylation of **1a** with 1-phenethyl bromide was evident in the other secondary allylic halides. Alkylation of 2 equiv of the

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racemates resulted in increased yields of product in each case and increased stereoselectivity in two cases (Table II). The dramatic increase in the chemical yield of **26** with 2 equiv of alkylating agent suggests a much more efficient kinetic resolution in this instance due to the bulk of the substituents (cf. Figure 3). Other products related to **25** and **26** (e.g. derived from 3-bromo-1-methylcyclohexene) could not be obtained due to our inability to prepare the requisite bromides.

The effect of reaction temperature is variable. In some instances, increasing the temperature had no significant effect on the stereoselectivity (entries 1 and 1a, Table II) while in other cases (entries 4 and 4a) increasing temperature leads to a reduction in selectivity. It is tempting to note that those cases where a negative correlation between temperature and selectivity occurs involve the alkylating agents for which we invoke the π-association. Further evidence on this point is required. In all cases, the use of chlorides required reaction temperatures of −20 °C or higher. Comparison of the stereoselectivities obtained with bromides and chlorides is tenuous due to this difference.

The results presented suggest further work is in progress. Examination of the effect of different cations, replacements for HMPA, and NMR studies of the enolate ions should allow a more definitive answer to the question of association.

Experimental Section

Unless other wise noted, infrared spectra were run as neat liquids. The NMR spectra were run at 300 MHz for ^1H, 75 MHz for ^{13}C, and 188 MHz for ^{19}F in $CDCl_3$ solution. Values in brackets are for the minor diastereomer. The ^{13}C NMR signals are listed in order of C1 through C14 followed by the signals due to the R group. ^{19}F NMR shifts were measured relative to internal trifluoroacetic acid. Optical rotations were measured at 24 °C in 95% ethanol solution with $c = 10$ unless otherwise noted. Gas chromatographic analyses were performed on a 1.5 ft × $^1/_8$ in. column packed with 5% OV-101 on Chromosorb W. Mass spectra were run in the field ionization mode (FIMS). Solvents were removed under reduced pressure and the drying agent used was anhydrous magnesium sulfate. Column chromatography utilized silica gel 60 and 20% ether in petroleum ether as eluant unless otherwise noted. Microanalyses were performed by Galbraith Laboratories, Knoxville TN.

Materials. Imine 1 was prepared as reported previously.[7] Methallyl bromide was prepared by a literature method[22] (bp 82–100 °C), 3-bromocyclohexene[23] and 3-bromo-1-butyne[22] were also prepared by literature methods. 1-Phenylpropyl bromide was prepared from the corresponding alcohol by using trimethylsilyl chloride–lithium bromide according to Olah[24] and had bp 70 °C (14 mm) (lit.[23] bp 46–50 °C (0.2 mm)). 5-Bromo-3,3-dimethylcyclohexene and *p*-methoxybenzyl bromide were prepared as outlined below. The remaining alkylating agents were commercially available and used as received.

5-Bromo-3,3-dimethylcyclohexene. DIBAL-H reduction of 5,5-dimethyl-2-cyclohexenone[25] according to Masamune[26] afforded the unsaturated alcohol (71%, not purified). The alcohol was converted to the bromide according to a literature procedure[22] in 71% yield: bp 90–92 °C (26 mm); ^1H NMR (60 MHz) δ 5.9–5.5 (m, 2 H), 4.95–4.45 (m, 1 H), 2.3–1.55 (m, 4 H), 1.00 (s, 3 H), 0.85 (s, 3 H).

***p*-Methoxybenzyl Bromide.** To 50 mL of ether was added 3.0 g (21.7 mmol) of *p*-methoxybenzyl alcohol, followed by 14.4 g (45.3 mmol) of carbon tetrabromide. To the stirred solution was added 11.4 g (45.3 mmol) of triphenyl phosphine slowly. Stirring was continued for 1 h while a precipitate developed. The mixture was filtered, concentrated, and passed through a short column of silica gel using ether as eluant. The eluant was concentrated and the residue distilled to give the bromide (2.7 g, 60%), bp 77–80 °C (0.8 mm) (lit.[27] bp 128–130 °C (15 mm)).

Three examples follow to illustrate the general procedures used for the alkylations and Michael additions.

Alkylation with a Benzylic Halide. LDA (8.5 mmol) was prepared at 0 °C by addition of 1.43 mL of 2.5 M *n*-BuLi in hexane to a solution of 0.362 mL of diisopropylamine in 10 mL of THF under nitrogen at 0 °C, and then the solution was cooled to −78 °C. Imine 1 (2.0 g, 8.3 mmol) in 10 mL of THF was added, the reaction was stirred for 10 min, and then a mixture of 1.62 g (8.3 mmol) of *p*-cyanobenzyl bromide in 10 mL of THF was added. After being stirred for 1 h at −78 °C, 10 mL of water was added, the mixture was allowed to warm to room temperature, and the layers were separated. The aqueous layer was extracted with ether, and the combined organic phases were dried and concentrated to give 2.36 g (75%) of crude 11 which was purified by chromatography over a short column of silica gel (20% ether/petroleum ether). Unreacted halide eluted with the solvent front, followed by 11. Further elution with ether afforded no unreacted imine.

11: IR 1153, 1683, 1737, 2958 cm^{-1}; ^1H NMR δ 7.41 (AB q, 4 H), 4.00 [4.09] (dd, 1 H, J = 9.5, 3.9 Hz), 3.29 (dd, 1 H, J = 4.0, 13.3 Hz), 3.12 (dd, 1 H, J = 9.8, 13.3 Hz), 2.25 (bd, 1 H), 1.95–1.48 (m, 4 H), 1.42 [1.45] (s, 9 H), 1.15–1.00 (m, 2 H), 0.95 (s, 3 H), 0.87 (s, 3 H), 0.74 (s, 3 H); ^{13}C NMR 53.9, 185.0, 35.9, 43.5, 27.2, 31.8, 47.0, 19.4, 18.9, 11.5, 66.6, 170.9, 81.0, 28.0, 159.9, 134.5, 131.2, 131.1, 114.8, 114.5, 37.8. ^{19}F NMR of (+)-MPTA derivative of *p*-cyanophenylalanine *tert*-butyl ester: 8.72 [8.58].

Anal. Calcd ($C_{24}H_{32}N_2O_2$): C, 75.75; H, 8.47; N, 7.36. Found: C, 75.53; H, 8.43; N, 7.21. FIMS, m/z 380.

Alkylation with 2 equiv of a Secondary Allylic Halide. Using the above alkylation procedure exactly, but substituting 2.7 g (17 mmol) of 3-bromocyclohexene, there was obtained 1.9 g (66%) of **25**: mp 80–81 °C (hexane); $[\alpha]_D$ + 70.7° (c 1.78); IR 1147, 1678, 1731, 2938 cm^{-1}; ^1H NMR δ 5.8–5.45 (m, 2 H), 3.63 [3.61] (d, 1 H, J = 9 Hz), 2.90–2.76 (m, 1 H), 2.55–2.29 (m, 1 H), 2.05–1.10 (m, 12 H), 1.42 [1.44] (s, 9 H), 0.97 [0.99] (s, 3 H), 0.91 [0.92] (s, 3 H), 0.77 [0.74] (s, 3 H); ^{13}C NMR 54.1, 184.7, 36.4, 43.9 [43.9], 27.5, 32.3, 47.3, 19.4, 18.9, 11.5, 70.3, 170.9, 80.5, 28.1, [28.0], 128.9, 128.2, 37.9, 25.3, 24.9, 20.9.

Anal. Calcd ($C_{22}H_{35}NO_2$): C, 76.47; H, 10.21; N, 4.05. Found: C, 76.21; H, 10.83; N, 4.09. FIMS, m/z 345.

Spectroscopic data for a selected number of alkylation products follow. The data for remaining materials is available as supplementary material.

6: $[\alpha]_D$ + 79.1° (c 2.3); IR 1152, 1684, 1736, 2958 cm^{-1}; ^1H NMR δ 7.19–6.98 (m, 4 H), 4.00 (dd, 1 H, J = 10.32, 3.6 Hz), 3.25 (dd, 1 H, J = 13.5, 3.6 Hz), 3.06 (dd, 1 H, J = 13.6, 10.35 Hz), 2.38 (s, 3 H), 2.25–2.15 (m, 2 H), 1.73–1.41 (m, 3 H), 1.45 (s, 9 H), 1.10–0.90 (m, 2 H), 0.96 (s, 3 H), 0.84 (s, 3 H), 0.72 (s, 3 H); ^{13}C NMR 53.7, 184.6, 35.7 [35.6], 43.5, 26.9, 32.3, 46.8, 19.1 [19.4], 18.6 [18.9], 11.2 [11.5], 65.7, 171.3, 80.7, 27.9, 137.1, [136.7], 130.4 [130.9], 129.7 [130.1], 126.5 [125.9], 125.6 [125.1], 43.2, 19.8 [19.6].

Anal. Calcd ($C_{24}H_{35}NO_3$): C, 74.76; H, 9.15; N, 3.63. Found: C, 74.49; H, 8.79; N, 3.74. FIMS, m/z 385.

10: mp 60–64 °C; IR 1066, 1125, 1327, 1678, 1744, 2955 cm^{-1}; ^1H NMR δ 7.20 (AB q, 4 H), 4.00 (dd, 1 H, J = 10.0, 3.7 Hz), 3.31 (dd, 1 H, J = 3.7, 13.3 Hz), 3.11 (dd, 1 H, J = 10.0, 13.3 Hz), 2.11 (bd, 1 H), 1.95–1.50 (m, 4 H), 1.43 [1.45] (s, 9 H), 1.1–1.0 (m, 2 H), 0.96 [0.91] (s, 3 H), 0.85 [0.82] (s, 3 H), 0.74 (s, 3 H); ^{19}F NMR 15.05 [14.93]; ^{13}C NMR 53.9, 185.4, 35.9, 43.5 [43.7], 27.1 [27.3], 31.8, 47.0, 19.3 [19.4], 18.8, 11.4 [11.3], 66.2, 170.6, 81.1, 28.0, 38.5, 143.2, 130.1, 129.9, 126.1, 124.8, 124.7. ^{19}F NMR of (+)-MPTA derivative of *p*-(trifluoromethyl)phenylalanine *tert*-butyl ester: 14.85 [14.79], 8.66 [8.54].

Anal. Calcd ($C_{24}H_{32}F_3NO_2$): C, 68.06; H, 7.61; N, 3.30. Found: C, 67.89; H, 8.08; N, 3.15. FIMS, m/z 423.

26: IR 1147, 1682, 1739, 2952 cm^{-1}; ^1H NMR δ 5.70–5.48 (m, 2 H), 3.59 [3.52] (d, 1 H, J = 9 Hz), 2.91–2.75 (m, 1 H), 2.50–2.48

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(m, 1 H), 1.98–1.50 (m, 7 H), 1.48 (s, 9 H), 1.48–1.00 (m, 3 H), 0.98 (s, 3 H), 0.90 (s, 3 H), 0.87 (s, 3 H), 0.76 (s, 3 H); ^{13}C NMR 54.0, 184.5, 36.3, 43.9, 27.5 [27.4], 32.3 [32.1], 47.1, 19.4, 18.9, 11.5, 70.3, 170.8, 80.6, 28.0, 127.3, 126.9, 39.3 [38.5], 37.0, 29.2, 25.3, 25.2.

Anal. Calcd ($C_{24}H_{39}NO_2$): C, 77.16; H, 10.52; N, 3.74. Found: C, 77.18; H, 10.13; N, 3.55. FIMS, m/z 373.

Transaminations. (a) Of Imine 11. To a cooled solution of sodium hydroxide (0.23 g, 5.75 mmol) in 50 mL of methanol were added 0.35 g of acetic acid and 0.40 g of hydroxylamine hydrochloride, followed by 2.0 g (5.26 mmol) of imine 11. The solution was stirred for 24 h at ambient temperature, the solvent removed, and the residue chromatographed. Elution with ether gave 0.87 g (97%) of camphor oxime. The eluting solvent was then changed to methanol and 1.11 g (86%) of *p*-cyanophenylalanine *tert*-butyl ester was obtained: mp 57–62 °C (hygroscopic); IR 1156, 1368, 1558, 1607, 1730, 2226, 2981, 3391 (br) cm^{-1}; ^{1}H NMR 7.5 (AB q, 4 H), 3.64 (m, 1 H), 3.0 (doublet of AB q, 2 H, J = 7.7, 5.85 Hz), 2.86 (br s, 2 H), 1.42 (s, 9 H); ^{19}F NMR of (+)-MPTA amide 8.72, [8.58].

The amino ester was too hygroscopic to allow elemental analysis.

Anal. Calcd ($C_{24}H_{25}F_3N_2O_4$): C, 62.33; H, 5.44; N, 6.05. Found: C, 61.89; H, 5.38; N, 5.96. FIMS, m/z 462.

(b) Of Imine 23. Use of the above procedure on imine **23** afforded **33**: 62%, $[\alpha]_D$ −30.8° (c 1.06); IR 1155, 1250, 1728, 2975 cm^{-1}; ^{1}H NMR δ 7.45–7.23 (m, 5 H), 3.53 [3.45] (d, 1 H, J = 6 Hz [7.5] Hz), 3.13 (dq, 1 H, J = 7.0, 7.0 Hz), 1.59 (bs, 2 H), 1.36 (s, 9 H), 1.32 (d, 3 H, J = 7.0 Hz); ^{13}C NMR 174.0, 143.5, 128.4, 128.0 [128.2], 126.7, 81.1, 60.9, 46.8, 28.0 [28.2], 15.6.

Anal. Calcd ($C_{14}H_{21}NO_2$): C, 71.45; H, 8.99; N, 5.95. Found: C, 71.31; H, 8.65; N, 6.08. FIMS, m/z 235.

Michael Reaction Procedure. Use of the above procedure exactly, but omitting the HMPA and using dimethyl ethylidenemalonate as the electrophile, afforded 99% of **30** after correcting for the recovered imine.

30: IR 1150, 1259, 1369, 1677, 1735, 2962 cm^{-1}; ^{1}H NMR δ 4.30–4.10 (m, 4 H), 3.88 [3.85] (d, 1 H, J = 10 Hz), 3.72 [3.75] (d, 1 H, J = 10 Hz), 3.05–2.80 (m, 1 H), 2.60–1.67 (m, 6 H), 1.44 [1.46] (s, 9 H), 1.43–1.28 (m, 7 H), 1.14 (d, 3 H, J = 7 Hz), 0.98 [0.97] (s, 3 H), 0.94 (s, 3 H), 0.79 [0.76] (s, 3 H); ^{13}C NMR 54.2 [54.4], 186.6, 36.3 [36.8], 44.1, 29.0, 32.0, 47.4 [46.5], 19.6, 19.2, 11.4, 65.8, 170.1, 80.9, 28.1, 169.4, 168.6, 61.0 [61.4], 51.8, 29.2, 14.3 [14.8].

Anal. Calcd ($C_{23}H_{37}NO_6$): C, 65.22; H, 8.80; N, 3.31. Found: C, 65.98; H, 8.92; N, 2.83. FIMS, m/z 423.

Conversion of 30 to 32. Compound **30** (2.97 g, 7 mmol) in 30 mL of methanol was stirred for 5 h at ambient temperature with a solution of 1.1 g of potassium hydroxide in 20 mL of water. The solution was concentrated, acidified, and extracted with chloroform. The dried extracts were evaporated to give a white solid whose spectra identified it as the monomethyl ester of **30**. This material was heated under vacuum at 110–120 °C for 2 h and the yellow liquid obtained was transaminated with hydroxylamine acetate in methanol as described above. Chromatography of the crude product using 20% ether/petroleum ether eluted all the byproducts and lactam **32** was obtained by washing the column with 10% hydrochloric acid, basification of the washings with 2 N sodium hydroxide, and extraction with chloroform. There was obtained 0.32 g (32%) of lactam **32**: mp 85–90 °C; $[\alpha]_D$ 7.5° (c 2); IR (KBr) 1166, 1226, 1367, 1698, 1735, 2977, 3106, 3207 cm^{-1}; ^{1}H NMR δ 4.15 (dd, 1 H, J = 8, 0.5 Hz) [3.72 (d, 1 H, J = 6 Hz)], 2.90–2.43 (m, 2 H), 2.17–1.67 (m, 1 H), 1.53 (s, 9 H), 1.34 [1.15] (d, 3 H, J = 7 Hz); ^{13}C NMR (22.64 MHz) 177.9 [177.1], 170.7 [169.6], 82.1 [81.9], 60.6 [63.2], 37.9 [38.2], 32.6 [34.1], 27.9, 15.7 [20.0].

Anal. Calcd ($C_{10}H_{17}NO_3$): C 60.28; H, 8.60; N, 7.03. Found: C 59.84; H, 8.54; N, 6.68. FIMS, m/z 199.

Catalytic Hydrogenation of 18 and 25. To a hydrogen saturated mixture of 0.05 g of 10% Pd on charcoal and 15 mL of 95% ethanol was added via syringe 500 mg of **18** or **25** in 10 mL of the same solvent. The mixture was stirred under hydrogen until the gas was no longer consumed (2–3 h). The mixture was filtered through Celite and concentrated. Chromatography on a short silica gel column with ether gave **18a** and **22** from **18** and **25**, respectively.

18a: 71%; IR 2957, 1736, 1684, 1156 cm^{-1}; ^{1}H NMR δ 3.78 [3.74] (dd, 1 H, J = 11.4, 5.1 Hz), 2.48–2.40 (m, 1 H), 2.03–1.58 (m, 6 H), 1.47 (s, 9 H), 1.43–1.21 (m, 4 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 0.96 (t, 3 H, J = 7 Hz), 0.80 (s, 3 H); ^{13}C NMR 184.2, 171.8, 80.5, 65.0 [64.6], 53.9, 47.2, 43.9, 36.1, 35.0 [35.8], 32.3 [31.9], 28.0, 27.5 [27.4], 19.5 [19.4], 19.3, 18.9, 13.8, 11.4 [11.3].

Anal. Calcd ($C_{19}H_{33}NO_2$): C, 74.22; H, 10.81; N, 4.56. Found: C, 74.31; H, 10.93; N, 4.39. FIMS, m/z 307.

22: 95%; ^{1}H NMR δ 3.52 [3.48] (d, 1 H, 9 Hz), 2.5–2.2 (m, 1 H), 2.1–1.6 (m, 11 H), 1.42 [1.43] (s, 9 H), 1.52–0.70 (m, 6 H), 0.97 (s, 3 H), 0.90 [0.91] (s, 3 H), 0.75 [0.73] (s, 3 H); ^{13}C NMR 184.2, 171.4, 80.5, 71.6, 54.1, 47.3, 43.9, 40.6, 36.4 [35.9], 32.4 [32.1], 30.1 [30.2], 28.9 [26.7], 28.2 [28.3], 27.7, 26.1 [26.0], 19.6, 19.1, 11.6; IR: 2929, 1737, 1682, 1141 cm^{-1}.

Anal. Calcd ($C_{22}H_{37}NO_2$): C, 76.03; H, 10.73; N, 4.03. Found: C, 76.21; H, 10.83; N, 4.09. FIMS, m/z 347.

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Supplementary Material Available: Spectroscopic data for **2**, **7–9**, **12–14**, **17**, **18**, **20**, **21**, **23**, **27–29**, **31a**, and **31b** and crystallographic analysis of **25** (14 pages). Ordering information is given on any current masthead page.