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The Alkylation of Menthyl Hippurate and Some Related Materials: A Reinvestigation.

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Abstract: Benzylation of chiral esters of *N*-acylglycines using various bases and additives was examined. No *C*-alkylation was observed with one equivalent of base. Diastereoselectivities were dependent on the amount of additive, the nature of the *N*-acyl group, and the chiral ester. A model to account for the degree and sense of the stereoselectivity is proposed.

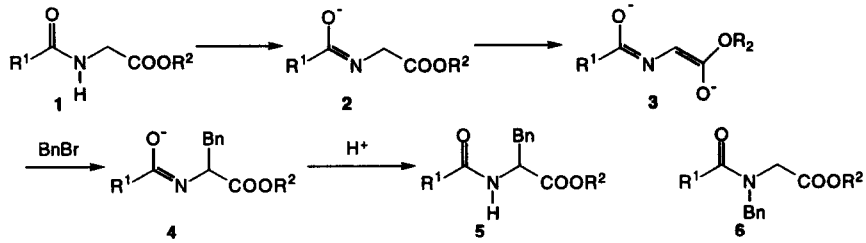
C-Alkylation of derivatized glycine esters is an important approach to the preparation of higher amino acids.[1] However, in contrast with the aldol condensation,[2] the factors that control the stereochemistry of such alkylations are still poorly understood. Standard recipes often are used with little or no understanding of the effect of the components of the reaction mixture. The deaggregation of oligomers of Li enolates by additives, such as HMPA, leads to enhanced chemical reactivity due to increased π-electron density at the α-carbon atom.[3] However, reports of highly stereoselective reactions that invoke dimers of higher order oligomers of the enolate[4] suggest a negative effect of such additives on reaction stereochemistry. Despite definitive evidence for the involvement of diisopropylamine associated with the enolate when LDA is used,[5] little attention to the choice of base is apparent.

We have recently redirected our investigations of the alkylation stereochemistry of imine derivatives of glycinates[6] to the *N*-acyl derivatives that are complicated by the presence of the N-H proton. Although Hoye[7] and Muchowski[8] have reported C-alkylation of *N*-acyl-α-aminoesters and ketones using one equivalent of base, we have been unable to effect this during our investigation of the effects of several variables (the amount and identity of the additive, and the type of base) on the *chemical* yield of alkylation of achiral methyl hippurate.[9] Contradictory evidence of other systems has been reported[10] and recently[11] more detailed information on the structure of LDA-THF has become available to aid interpretation of such data.

Chirality designed to direct the sense of induction at the new asymmetric centre may be incorporated in either or both the ester and the *N*-acyl group. The systematic elucidation of the dependence and sense of the degree of asymmetric induction on the site and nature of the existing chirality has been our principal objective.

In 1984, Bergbreiter, Newcomb, and co-workers reported[12] the first systematic study of the alkylation stereochemistry of the chiral menthyl ester of hippuric acid. Modest stereoselectivities

(5-55%de) were observed which showed little dependence on the presence or absence of an additive (TMEDA, HMPA) or on solvent (THF, Et_2O). "Dialkylated" materials were formed in some reactions, but experiments designed to determine if the obtained stereochemistry was kinetic in nature gave ambiguous results. When mono-alkylated material was alkylated a second time, the presence of a benzyl group either in the electrophile or extant in the enolate caused the *reversal* of the stereochemical sense of the reaction. No model that predicted either the sense or degree of stereochemical induction was proposed. In view of more recent information of the structure of lithium enolates[13] and on the effects of various additives on these, together with the results we have obtained for the alkylation of methyl hippurate,[9] the systematic investigation of the alkylation stereochemistry of (–)-menthyl hippurate (**1a**) and some closely related compounds was undertaken with particular attention to the base (identity, method of generation, number of equivalents), the additive (identity, number of equivalents), and the acyl protecting group.



a, R^1 = Ph, R^2 = (-)-men
b, R^1 = Ph, R^2 = 8-Phe-(-)-men
c, R^1 = c-C_6H_{11}, R^2 = (-)-men
d, R^1 = c-C_6H_{11}, R^2 = 8-Phe(-)-men
e, R^1 = Ac, R^2 = (-)-men
f, R^1 = Pival, R^2 = (-)-men

Scheme 1.

Results:

In our work with glycinate imines[6] and achiral methyl hippurate[9] significant differences between HMPA and TMEDA in the deuteration reactions and smaller differences in the chemical yields of the alkylation reactions were noted. The *method* of generation of the enolate also significantly affected the alkylation result. In the current work, experiments showed this was not a factor and the standard conditions chosen involved addition of the additive to preformed LDA before the addition of the ester.

The results of the alkylation of (–)-menthyl hippurate and some related esters are collected in Table 1. The chemical yield of *C*-alkylation for all of the reactions was estimated to be in excess of 75%. Separation of reaction mixtures was not attempted to avoid unintentional separation of diastereomers and, therefore, determination of exact yields was not possible. Treatment of **1a** (Scheme 1) with 1 equiv. of LDA and BnBr in the presence of HMPA afforded a low yield of *N*-alkylated material. This is consistent with our results for methyl hippurate.[9] Replacement of the HMPA with up to 3 equiv. of TMEDA gave no *N*- or *C*-alkylation. When 2 equiv. of each of LDA and benzyl bromide were used, efficient *C*-alkylation occurred and, as reported,[12] the major diastereomer had the *S*-configuration. The stereochemical excess was independent of the nature of the additive, but was strongly influenced by the amount of additive used. Up to 2 equivalents of additive, when used with LDA, had little effect on the reaction stereoselectivity, but the presence of more than 2 equivalents is clearly deleterious. Similar experiments with methyl iodide as the electrophile gave

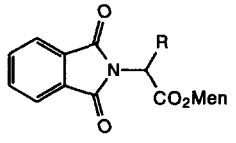
Table 1.
Benzylations of The (–)-Menthyl Ester of Hippuric Acid

Base (equiv.)	Additive (equiv.)	Product[a] (%de)[b]
LDA (1)	none	no reaction
	TMEDA (1-3)	no reaction
	HMPA (1)	**6** (*N*-alk)
LDA (2)	none	**5a** (56)
	TMEDA (1)	**5a** (49)
	TMEDA (2)	**5a** (50)
	HMPA (1)	**5a** (50)
	HMPA (>2)	**5a** (21)
	LiCl (3)	**5a** (30)
LDA (2) + TBDMS	TMEDA (1)	**5a** (20)
t-BuLi (2)	TMEDA (1)	**5a** (33)
	HMPA (1)	**5a** (27)
NaHMDS (1)	none	**6** (*N*-alk)
NaHMDS (2)	none	**5a** (10)
KOBu-*t* (2)	none	**5a** (44)[c]

[a] chemical yield of *C*-alkylated product in excess of 75%; [b] major diastereomer = *S* unless otherwise noted; [c] major diastereomer = *R*.

much lower diastereoselectivities.

When NaHMDS was used in place of LDA, the de's obtained were consistently lower. Two experiments were performed to remove the ambiguity associated with a dianionic intermediate. Generation of the enolate of the *N*-phthalyl derivative **7** with either LDA, NaHMDS, or NaH gave rise to essentially no alkylation products. If the reaction temperature was increased, significant decomposition of the enolate occurred and very complex mixtures were obtained.[14] Generation of enolate **2a** followed by sequential treatment with TBDMSiCl, a second equivalent of LDA, and then benzyl bromide gave reasonable yields of product with de's less than 10%.



7a R = H
7b R = Bn

As pointed out by Seebach,[5] the presence of diisopropylamine (DIPA) as part of the reacting complex of the enolate formed with LDA can significantly affect the reactions of such enolates. In an attempt to avoid this complication, *t*-BuLi was used to deprotonate **1a**; lower selectivities were obtained.

The use of counterions other than Li gave interesting and suggestive results. With 1 equiv. of NaHMDS and no additive, a good yield of *N*-alkylated product was obtained. Under the same reaction conditions, but using LDA as the base, no reaction occurred. Two equiv. of NaHMDS gave *C*-alkylated product with very low stereochemical bias. The potassium enolate gave a 44%de but with the opposite configuration for the major diastereomer.

Table 2.
Alkylations of Other Glycinate Derivatives With LDA.

N-Acyl group	Ester	Compound	Additive (equiv.)	Product[a] (%de)[b]
Benzoyl	8-Ph-Men	**1b**	TMEDA (2)	**5b** (85)
Cyclohexanoyl	(–)-Men	**1c**	none	**5c** (36)
	8-Ph-Men	**1d**	TMEDA (2)	**5d** (97)
Acetyl	(–)-Men	**1e**	TMEDA (2)	**5e** (30)
Pivaloyl	(–)-Men	**1f**	TMEDA (2)	**5f** (34)
Phthaloyl	(–)-Men	**7a**	none	**7b** (14)

[a] chemical yield of *C*-alkylated product in excess of 75%; [b] major diastereomer = *S*.

As shown in Table 2, changing the phenyl group of the *N*-acyl group to cyclohexyl, acetyl, or pivaloyl gave no improvement. In all cases examined, the 8-phenylmenthyl ester **1d** gave dramatically better results.

A particular problem encountered in previous investigations using the imines of glycinates was the inability to achieve aldol condensations. Only when the reaction was run in the presence of a silylating agent was an aldol product formed.[15] In the case of the *N*-acyl glycine esters, under standard aldol conditions, **1a** gave a mixture of 4 stereoisomers in a 1:1:2:2 ratio and excellent yield.

To address the question of the nature (kinetic vs. thermodynamic) of the alkylation products, diastereomerically pure **5a** (E = Bn) was mixed with an excess of dianion **3a** at -78°C and the stereochemistry of recovered **5a** determined. As no detectable racemisation was found, the observed products must represent those from a kinetically controlled process.

Discussion

The formation of kinetic products from the alkylation requires that the dianion **3a** be unable to deprotonate the monoanion **4** formed by the alkylation process. Previous experiments designed to test the kinetic nature of the products have clearly shown that one cannot generate **4** from **5** with base without causing partial racemisation[12] due to *C*-deprotonation during mixing of the reagents. Therefore, the obvious experiment of mixing the monoanion **4** with the dianion **3a** derived from menthyl hippurate would be non-productive. The experiment described above to assess this situation gives an unambiguous conclusion and allows further analysis of the alkylation results. It must be noted also that in this and previous work, the presence of dilithium enolates has been assumed on the basis of established pKa's, but no direct evidence for these has been reported.

The results can be summarised in the following way: Both formation of ester enolate (**3**), and also reaction of this enolate with the electrophile must be efficient and stereochemically defined for successful asymmetric alkylation to be possible. Initial deprotonation of amide **1a** leads to an ion (**2a**) which has been assigned the *E*-geometry.[12] A second deprotonation leads to the dienolate **3**. The formation of a 5-membered ring metallocycle involving the nitrogen atom has been invoked previously to explain the alkylations of glycinate imines and the high electron density around the nitrogen atom in **3** suggests such a structure would be favoured here as well. As in the imine case, the presence of a limited amount of HMPA or TMEDA appears to improve the reactivity of the enolate without adversely affecting the stereoselectivity, but when a threshold (2 equiv.) is exceeded, loss of stereoselectivity occurs. One possible rationale for this invokes the disruption of the metallocycle, leading to an extended enolate in which stereochemical influences are less well defined. The stereochemical

change observed when the cation is substituted from Li to Na to K lends support to this interpretation.[16] The more ionic enolates should exhibit higher tendency to form extended enolates and thus lower stereoselectivity would be expected. However, the reversal of stereochemical bias when the potassium enolate is alkylated is difficult to rationalise.

As in the alkylation of methyl hippurate, there are significant differences between TMEDA and HMPA. Notable among these is the result when one equiv. of LDA is used. In the presence of HMPA, efficient *N*-alkylation occurs whereas when TMEDA is used, there is no reaction. In alkylations using 2 equiv. of LDA and 2 equiv. of BnBr with HMPA, the post alkylation situation would appear to be identical to that used to achieve *N*-alkylation and the lack of products of both *N*- and *C*-alkylation was surprising. The explanation became evident when *N*-alkylation was attempted by adding the glycinate anion generated by addition of one equiv. of LDA and HMPA to a mixture of LiCl and the electrophile; no reaction occurred. The presence of the Li salt effectively negated the influence of the HMPA.

The effect of a proximal phenyl group as in the 8-phenylmenthyl ester is strongly reminiscent of the results obtained by Whitesell in the ene reaction of chiral glyoxalate esters.[17] In that work, it was found that the presence of an aromatic nucleus influenced the reaction stereochemistry much more than would be predicted on merely steric grounds. As noted previously, a special effect of a phenyl group was noted in our examination of the alkylation of imines of glycinate esters[6] and in previous work on menthyl hippurates.[12] Further work is required to demonstrate the generality of this effect.

A model which rationalises the absolute stereochemistry of the major diastereomer, and which has some theoretical precedence, is shown in Figure 1. The absolute configuration of (–)-menthol is 1*R*,2*S*,5*R*. It is known that the stereoelectronically preferred conformation of acetals and

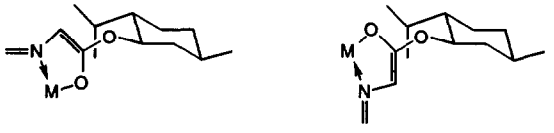


Figure 1.

dialkoxycarbonium ions is anti-gauche ("anomeric effect"). This conformation minimises the electronic repulsion between the oxygen lone pairs of electrons which are more severe in the anti-anti conformation. In acetals, the energy difference between these forms is of the order of 1.5 kcal/mol.[18] If the same consideration is applied to the enolate where the O-Li bond is covalent and the cyclohexane ring maintains its all-equatorial conformation, the enolate metallocycle containing Li atom will have the pro-R face shielded by the isopropyl group of the menthol. Use of 8-phenylmenthol which dramatically increases the influence of this group improves the stereoselectivity significantly (de = 85%). Experiments using other chiral esters are in progress to test this point.

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Experimental

Standards:
Authentic samples of the (–)-menthyl esters of *N*-acetylglycine (**1e**), *N*-pivaloylglycine (**1f**), *N*-benzoyl-D,L-phenylalanine (**5a**, *rac*), *N*-benzoyl-L-phenylalanine (**5a**), *N*-cyclohexanoylglycine (**1c**), *N*-cyclohexanoylphenylalanine (**5c**), *N*-acetylphenylalanine (**5e**), *N*-benzyl-*N*-benzoyl glycine (**6**) and the 8-phenylmenthyl ester of *N*-cyclohexanoylglycine (**1d**) were prepared for use in the HPLC analysis.

Analysis of Alkylation Mixtures by NMR and HPLC

All HPLC analyses were performed on a 10 cm C-18 reverse phase column using UV detection at 215 nm. The elution solvents were gradients of acetonitrile and 0.001% trifluoroacetic acid in water. Components of mixtures were identified by co-injection of standards. Ratios of compounds were determined from the UV extinction coefficients. Column chromatography was used to separate the components. ^1H and ^{13}C NMR were run in $CDCl_3$ solution at 300 and 75 MHz respectively on a Bruker AC300 or GE QE300 spectrometers.

(–)-Menthyl *N*-benzoyl-D,L-phenylalaninate (5a,*rac*) and (–)-Menthyl *N*-benzoyl-L-phenylalaninate (5a).

N-Benzoyl-L-phenylalanine[19] (5.4 g, 20 mmol), (–)-menthol (2.97 g, 20 mmol) and *p*-toluenesulphonic acid (2.8 g, 15 mmol) were dissolved in 150 mL of a 1:1 mixture of benzene and toluene and heated under reflux in a Dean Stark water separator for 2h. The cooled solution was filtered. The filtrate was evaporated, and the residue taken up in ether, extracted with sat. aq. $NaHCO_3$ and then with sat. brine. The dried solution was evaporated to afford 2.54 g of solid which was chromatographed using ethyl acetate to give 2.03 g (25%) of **5a**; mp. 152-153°C; ^1H NMR: 7.71 (2H, d, J = 7.1 Hz), 7.48-7.10 (7H, m), 6.67 (1H, d, J = 7.2 Hz), 5.03 (1H, q, J = 7.0 Hz), 4.72 (1H, dq, J = 4.3, 4.0 Hz), 3.24 (2H, dq, J = 6.0, 13.8 Hz), 2.00-1.00 (10H, m), 0.89 (6H, dd, J = 6.5, 16.1 Hz), 0.70 (3H, d, J= 4.9 Hz); ^{13}C NMR: 171.14, 166.74, 135.90, 134.00, 131.61, 129.56, 129.34, 128.51, 126.98, 126.92, 75.97, 53.42, 46.89, 40.70, 37.70, 34.01, 31.32, 26.09, 23.33, 21.91, 20.62, 16.24.
Anal. Calcd. for $C_{26}H_{33}NO_3$. C; 76.62, H; 8.16, N; 3.44. Found: C; 76.61, H;8.03, N; 3.27.

Using the same procedure, *N*-benzoyl-D,L-phenylalanine gave a mixture of diastereomers which was used for HPLC comparison purposes.

***N*-Cyclohexanoylglycine (–)-Menthyl Ester (1c):** To a cold solution of cyclohexanoyl chloride (1.45 g, 10 mmol) in 30 mL of dry dioxane was added a cold solution of 0.75 g (10 mmol) of glycine in 30 mL of 10% aq. Na_2CO_3. The mixture was stirred at ambient temperature for 2.5h, diluted with water (400 mL) and extracted three times with ether. The aqueous phase was acidified to pH 2 and extracted with ethyl acetate. The organic extract was washed with water, dried and evaporated to afford a solid (1.65 g) which was dissolved in 50 mL of benzene. (–)-Menthol (1.26 g, 8 mmol) and *p*-TsOH (0.4 g) were added and the solution heated under reflux for 4.5 h. The cooled solution was evaporated. The residue taken up in ether and washed with sat. $NaHCO_3$, and then water. The dried solution was evaporated to afford **1c** (1.21 g, 37%); mp. 123-124.5°C (ethyl acetate/hexane); ^1H NMR: 5.99 (1H, bs), 4.71 (1H, dd, J = 4.4, 10.9 Hz), 3.96 (2H, d, J = 5.0 Hz), 2.12 (1H, m), 2.05-1.00 (23H, M), 0.87 (3H, d, J = 5.9 Hz), 0.83 (3H, d, J = 6.6 Hz), 0.71 (3H, d, J = 6.9 Hz); ^{13}C NMR: 176.05, 169.81, 75.67, 46.89, 49.19, 41.35, 40.74, 34.08, 31.36, 29.53, 26.24, 25.67, 23.40, 21.91, 20.65, 16.31.
Anal. Calcd. for $C_{19}H_{33}NO_3$. C; 70.55, H;10.28, N; 4.33. Found: C; 70.22, H; 10.29, N; 4.21%.

***N*-Cyclohexanoylphenylalanine (–)-Menthyl Ester (5c):** In the same manner, but using L-phenylalanine in place of glycine, compound **5c** was prepared: mp. 149-150°C; ^1H NMR: 7.27 (4H, m), 7.14 (1H, d, J = 7.7 Hz), 5.98 (1H, d, J = 7.1 Hz), 4.92 (1H, q, J = 5.8 Hz), 4.77 (1H, dt, J = 4.33, 10.9 Hz), 3.15 (1H, m), 2.26-1.00 (21H, m), 0.90 (6H, dd, J = 6.5, 16.0 Hz), 0.73 (3H, d, J = 6.9 Hz); ^{13}C NMR: 175.50, 171.45, 136.61, 129.67, 128.43, 127.06, 75.92, 52.75, 47.03, 45.38, 40.85, 37.85, 34.20, 31.47, 29.74, 29.43, 26.18, 25.80, 25.71, 23.46, 22.09, 20.80, 16.37.
Anal. Calcd. for $C_{26}H_{39}NO_3$: C; 75.50, H; 9.50, N; 3.39. Found: C; 75.11, H; 9.47, N; 3.20%.

Using the same method and varying the acid chloride, the following compounds were also prepared:

***N*-Acetylglycine (–)-Menthyl Ester (1e):** mp. 64-65°C; ^1H NMR: 6.01 (1H, bs), 4.74 (1H, dd, J = 4.5, 10.9 Hz) 3.98 (2H, d, J = 5.0 Hz), 1.98 (3H, s), 1.96-1.00 (9H, m), 0.84 (6H, t, J = 6.2 Hz), 0.69 (3H, d, J = 6.9 Hz); ^{13}C NMR: 170.14, 169.68, 75.64, 46.85 41.51, 40.87, 34.01, 31.32, 26.24, 23.39, 22.81, 21.86, 20.58, 16.28.

Anál. Calcd. for $C_{14}H_{25}NO_3$. C; 65.85, H; 9.87, N; 5.49. Found: C; 65.47, H; 9.87, N; 5.32.

N-Pivaloylglycine (–)-Menthyl Ester (1f): mp. 112.5-115°C; ^{1}H NMR: 6.20 (1H, bs), 4.68 (1H, dd, J = 4.6, 10.5 Hz), 3.92 (2H, d, J = 4.9 Hz), 2.0-0.9 (9H, m), 1.12 (9H, s), 0.85 (6H, d, J = 6.0 Hz), 0.68 (3H, d, J = 6.9 Hz); ^{13}C NMR: 178.48, 169.78, 75.61, 46.83, 41.55, 40.70, 34.04, 31.29, 27.35, 26.18, 23.38, 21.84, 20.58, 16.25.

Anal. Calcd. for $C_{17}H_{31}NO_3$. C; 68.65, H; 10.51, N; 4.71. Found: C; 68.90, H; 10.48, N; 4.26%.

(–)-Menthyl N-Benzylhippurate (6): Ethyl *N*-benzylglycinate (1.0 g, 5.2 mmol) was dissolved in 3 mL of 5M HCl and heated under reflux for 1h. The solution was neutralised with solid Na_2CO_3, diluted with 15 mL of 10% Na_2CO_3, and a solution of benzoyl chloride (1 mL) in 13 mL of dioxane added. The mixture was stirred at ambient temperature for 2 h and worked up in the usual manner to afford 1.8 g of a syrup. To 1 g of this material, dissolved in 30 mL of benzene, was added 250 mg of *p*-TsOH and 500 mg of menthol. The mixture was heated under reflux for 1.5 h, cooled, neutralised with solid Na_2CO_3, filtered, and evaporated to give an oil which was chromatographed to afford **6**: ^{1}H NMR 7.6-7.0 (10H, m), 4.85-4.40 (3H, m), 4.09 (2H, ABq, J = 17.1 Hz), 2.3-0.5 (18H, m); ^{13}C NMR: 173.00, 168.62, 129.88, 128.84, 128.80, 128.54, 127.87, 127.14, 126.91, 126.65, 75.41, 53.78, 47.08, 46.37, 40.83, 34.19, 31.42, 26.21, 23.40, 21.98, 20.76, 16.30.

8-Phenylmenthyl N-Cyclohexanoylglycinate (1d): To a solution of 800 mg of *N*-cyclohexanoyl glycine in benzene (30 mL) was added 1 g of 8-phenylmenthol and 0.3 g of *p*-TsOH and the solution was heated under reflux for 2h. After the usual work-up, the syrup obtained was chromatographed to afford 1.0 g (58%) of **1d** as a syrup; ^{1}H NMR: 7.5-7.1 (5H, m), 5.24 (1H, bs), 4.86 (1H, dt, J = 4.4, 10.7 Hz), 3.32 (2H, t, J = 5.2 Hz), 2.05-0.85 (28H, m); ^{13}C NMR: 170.62, 163.92, 146.87, 122.71, 120.17, 119.95, 69.91, 45.09, 39.92, 36.36, 35.91, 34.20, 29.20, 26.05, 24.31, 24.16, 21.01, 20.50, 17.59, 16.50.

Methyl N-Phthalylglycinate: Phthalic anhydride (118.0 g, 0.8 mol), methyl glycinate, hydrochloride (100.0 g, 0.8 mol), triethylamine (112.0 mL, 81.3 g, 0.8 mol) were heated under reflux in DMF (2 L) overnight. The reaction mixture was cooled, and the solid filtered off. The filtrate was concentrated under reduced pressure to give an oil. Ethyl acetate (~1200 mL) was added to this oil, which was then washed with 5% hydrochloric acid (500 mL). The solution was concentrated under reduced pressure to give the product that was recrystallised from ethyl acetate/hexane to give 135.21g (77%). IR (KBr) ν_{max}cm^{-1} 1775, 1750, and 1730; ^{1}H NMR: 7.9 (2H, dd), 7.75 (2H, dd), 4.46 (2H, s) and 3.78 (3H, s).

Menthyl N-Phthalylglycinate (7a):

N-Phthalylglycine:[20] Finely ground phthalic anhydride (8.95 g, 0.06 mol) and glycine (4.5.g, 0.06 mol) were heated to 150° C for 0.75 h. The mixture was cooled, methanol (40 mL) was added, and the mixture filtered. The filtrate was then diluted with water (40 mL) and left to stand overnight. The product was filtered and dried to afford 10.75 g (87%); IR (KBr) ν_{max}cm^{-1} 3000 (br), 1775, and 1730; ^{1}H (d_6-DMSO) 8.0-7.8 (4H, m) and 4.33 (2H, s).^{13}C NMR (d_6-DMSO) 175.9, 174.2, 141.8, 138.4, 130.4, and 46.5 (as determined by a DEPT experiment).

Thionyl chloride (2.86 mL, 3.93 g, 33 mmol) was added to a slurry of *N*-phthalylglycine (6.15 g, 30 mmol) in chloroform (50 mL). The resultant mixture was heated under reflux for 2 h, cooled and the solution used without further purification. Menthol (4.26 g, 27 mmol) and triethylamine (4.18 mL, 3.0 g, 30 mmol) were added in chloroform solution (50 mL). The reaction was exothermic and a solid formed. The reaction mixture was kept at ~40° overnight, and then the solvent removed *in vacuo*. The resultant semi-solid material was washed with water, and then brine, and then dried, before purifying by column chromatography. Use of 4:1 hexane:ethyl acetate gave a fraction that contained 67% of the desired ester with unreacted menthol. The product was obtained by bulb to bulb distillation, bp ~200°/ 1 mm Hg, to give 4.69 g (51%); mp 75-77° C; IR (KBr) ν_{max}cm^{-1} 1774, 1747, and 1723 cm^{-1}; ^{1}H NMR 7.9 (2H, m), 7.7 (2H, m), 4.75 (1H, dt, *J* 4, 11 Hz,), 4.41 (2H, s), 2.1-0.8 (18H, overlaid with dt at 0.89 and d at 0.76); ^{13}C NMR 167.4, 166.8, 134.1, 134.1, 132.0, 123.6, 123.6, 123.5, 46.9, 40.6, 39.1, 34.1, 31.3, 26.2, 23.3, 21.9, 20.7, and 16.2.

Anal. Calcd. for $C_{20}H_{25}NO_4$. C, 69.95; H, 7.34; N, 4.08. Found: C, 70.27; H, 7.22; N, 4.25%.

General Alkylation Procedure: [The following procedure using menthyl hippurate is representative and was used in all alkylation reactions with adjustment of amounts for specific esters and bases as shown in the Tables.]

A solution of LDA was prepared by the addition of a solution of *n*-BuLi (400 μL, 2.5M, 1.0 mmol) in hexanes to a solution of diisopropylamine (140 μL, 1.0 mmol) in 2 mL of THF at -78°C. The solution was stirred for 10 min and then the additive (if any) was added in the amount indicated in the Tables. The solution was allowed to warm to room temperature and then recooled to -78°C. Menthyl hippurate (160 mg, 0.5 mmol) was dissolved in 2 mL of dry THF and then added slowly to the LDA solution and stirred for 1h. Benzyl bromide (131 μL, 1.0 mmol) in 2 mL of dry THF was added slowly and the mixture was stirred as -78°C for 1h. The reaction was quenched at -78°C with 2 mL of 2M HCl. The solution was allowed to warm to room temperature, diluted with ether, and the phases separated. The organic phase was dried and evaporated to afford material which was analysed by HPLC. Exact chemical yields could not be determined as the material still contained HMPA or TMEDA. After determination of the isomer ratio, the remainder of the material was chromatographed to obtain the pure aminoester(s) which were analysed by NMR.

Determination of Product Stability Under the Reaction Conditions:

A solution of 1.0 mmol of LDA in THF was prepared as outlined in the General Alkylation procedure. The solution was cooled to -78°C, 320 mg (1.0 mmol) of **1a** in THF was added and the mixture stirred at -78°C for 0.5h. To this solution was added a solution of authentic (–)-menthyl-L-phenylalaninate (**5a**) (196 mg, 0.5 mmol) in THF. The mixture was stirred at -78°C for 1h, quenched with aq. NH_4Cl solution and worked up in the usual manner. The mixture of **1a** and **5a** obtained was separated by chromatography (EtOAc/pet. ether) and the recovered **5a** was analysed by HPLC and NMR. The material was indistinguishable from the starting material.

References and Notes

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