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Camphor-Derived Alcohols: An Anomalous Reaction of 3-Hydroxycamphor and the Influence of Internal Alkoxides on the Alkylation Stereochemistry of Glycinate Imines[1]

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ABSTRACT

Attempted imine formation between 3-hydroxycamphor and tert. butyl glycinate led to 8, the substitution product at the 3-position. Zinc-acetic acid treatment of 8 afforded 3-acetoxycamphor. Alkylation of the imine from from norcamphor and tert. butyl glycinate gave no stereoselection. Alkylation of the imine from from 10-hydroxymethylcamphor and tert. butyl glycinate gave stereoselectivities inferior to those obtained from the imine of camphor itself (1), but aldol condensation with benzaldehyde, a reaction not possible with 1, was effected in 71% yield.

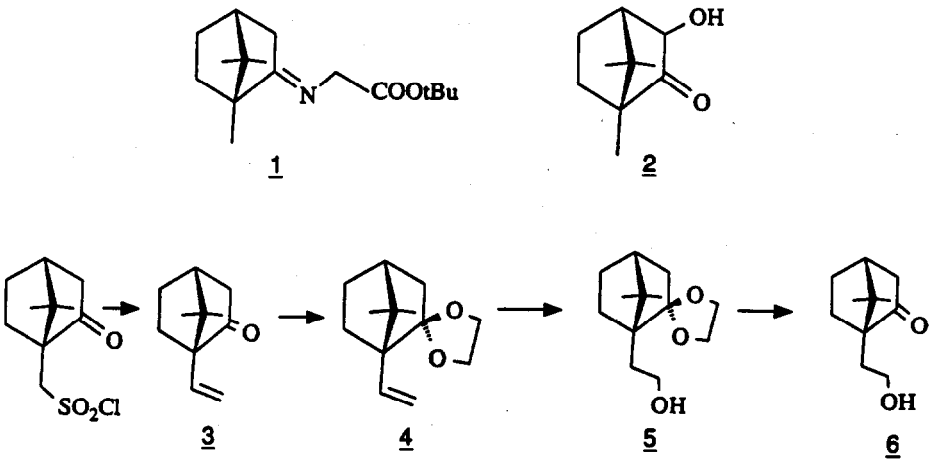
For the past five years, we have been engaged in the examination of various aspects of alkylation reactions of the imine (1) derived from camphor and *tert.*-butyl glycinate. Our results which have been fully documented[3] indicate a surprising dependency of the alkylation stereochemistry on the electronic nature of the electrophilic species which does not seem to exist in the alkylations of other glycine imines.[4] One further unexpected result of this work has been our inability to effect aldol condensations on the anion of 1. Such a reaction would provide a route to amino alcohols which holds some promise of allowing stereochemical control, both in the relative (threo *vs.* erythro) and absolute (R *vs.* S) sense. We had expended considerable effort on this reaction using benzaldehyde as a test case with uniformly unencouraging results.[3c] These failures in the case of 1 parallel the results obtained by Stork[5] on other imines of glycinate esters. Stork attributed these failures to the soft nature of the anions.

Recently reactions of 1 and other imines of glycine, including aldol condensations with benzaldehydes having an electron withdrawing group (e.g. p-NO_2), have been reported to proceed under phase transfer conditions.[6] Also, results have been reported by several groups which suggested that enolates of imines possessing other chelating sites might behave significantly differently from enolates of imines like 1. Aldol condensations and alkylations of imines of ketopinic acid[7] and hydroxypinanone[4] have been reported and it seemed that the presence of an hydroxy group in the derivatizing agent might affect the alkylation reaction and thus afford more information on the stereochemical pathway. The reactive intermediate would necessarily be a dianion, which might change the reactivity of the imine anion significantly. In addition, the three methyl groups on camphor have always been assumed to be the important stereochemical feature which causes the asymmetric induction. However, to our knowledge, no direct evidence on this point has been obtained. To examine these questions, the preparation and alkylation of the imines of norcamphor and two hydroxylated derivatives 2 and 6 of camphor with *tert.*-butyl glycinate were attempted and the results obtained in these reactions form the subject of this paper.

RESULTS AND DISCUSSION

3-Hydroxycamphor (2) (a 5:1 mixture of *endo* and *exo* stereoisomers) was prepared as outlined in the literature[8]. This molecule has been prepared by oxidation of the enolate of camphor by a number of oxidants[9], but apparently has found no use in synthesis. 10-

Hydroxymethylcamphor (6) was prepared by the method outlined in Scheme 1. Direct hydroboration of 3 using 9-BBN afforded a very low yield of 6 which was accompanied by an inseparable impurity. This difficulty was avoided by protection of the ketone as the ketal 4, followed by hydrolysis to the ketone 6 after the hydroboration had been accomplished. It was necessary to use 3 equivalents of 9-BBN to effect the complete hydroboration of 4. A very recent report on the use of rhodium catalysis of hydroboration reactions[10] suggests that this procedure may avoid the necessity for ketone protection.

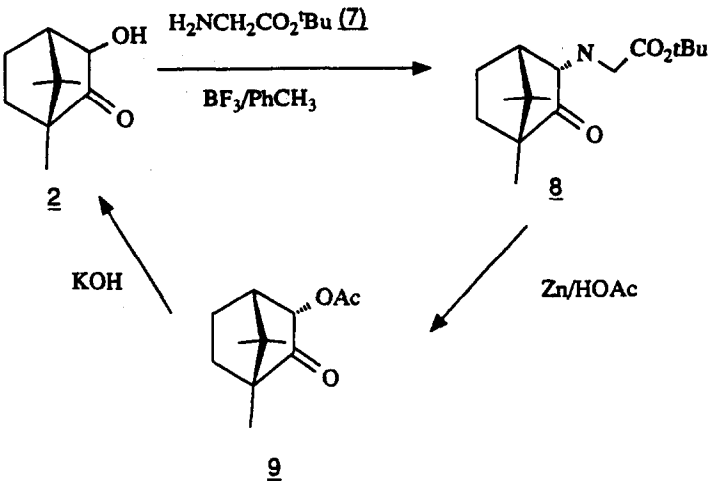


1 2 3 4 5 6

Scheme 1

In previous work, we had found it necessary to activate the camphor carbonyl as the thione before it could be condensed with *tert.*-butyl glycinate (7). Recent reports[6a,c] on successful condensations of this kind on molecules closely allied to camphor led us to reexamine this process and we can now report that the imine derived from 7 and camphor or camphor derivative 6 can be formed readily and directly using BF_3 catalysis. When the reaction was tried with 2, an unexpected reaction occurred which is detailed in the following paragraphs. (Scheme 2)

Attempted BF_3-catalyzed condensation of 2 with 7 led to the formation of a compound whose IR spectrum showed one carbonyl stretching absorption (1740 cm^{-1}), no apparent C = N absorption, and a weak absorption which could be attributed to either OH or NH (3320 cm^{-1}). The ^1H NMR spectrum showed that the camphor moiety was intact, that 7 had been incorporated into the molecule (presence of N-CH_2 and O^{t}Bu groups) and that an electronegative substituent was still present at C3. The absorption of the proton at C3 (a singlet at 2.86 ppm) suggested that only the *exo* stereoisomer of the compound was present since the C-3 proton of the *endo* isomers show significant coupling to the proton at C-4. The ^{13}C NMR spectrum confirmed these facts and also showed that two carbonyls were present, one of which was clearly an ester (δ 171.6) and the other was a ketone (218.4; compare camphor at 218.6). No imine carbon was evident (δ = 170). Furthermore, a 2-D proton-carbon correlated NMR spectrum clearly linked the proton signals at δ = 3.43 (glycinate CH_2 group), 2.86 and 2.12 with the carbon signals at δ = 51.8(t), 69.1(d) and 59.9(d) respectively. This clearly indicates that C-3 is substituted and that the substituent is less deshielding than an oxygen atom. All the available data supported the structure 8 (Scheme 2) as the product. Formally 8 arises from substitution of the OH group by the amino group of 7. The hydrochloride salt of 8 was also prepared and its spectra were consistent with the assigned structure. In this case, the protons of the



Scheme 2

methylene group of the glycine residue were non-equivalent and were split into an AB quartet.

For comparison purposes, the spectra of camphor oxime, *endo* 3-bromo camphor and 3-hydroxycamphor oxime were taken. The ^{13}C NMR are given in Table 1 along with that of 8. From these it can be seen that the oxime of 2 seems to form normally, but reaction of 2 with 7 proceeds by a completely different route. The stereochemistry of the substitution suggests that it occurs with inversion - i.e. by an Sn2 mechanism. To our knowledge, such a transformation on the camphor nucleus is unprecedented, especially as it requires attack of the nucleophile from the *exo* face. Nucleophilic displacements of groups as reactive as triflates[11] from the 3-*endo* position on camphor are unknown. An alternative explanation might involve the consecutive intermediacy of the ene-diol, 2-hydroxyepicamphor, its imine with 7 and re-tautomerization to the camphor form (Scheme 3). Such sequences are well documented in α-hydroxyketone systems.[12] However, in the absence of supportive data, it seems unproductive to speculate further.

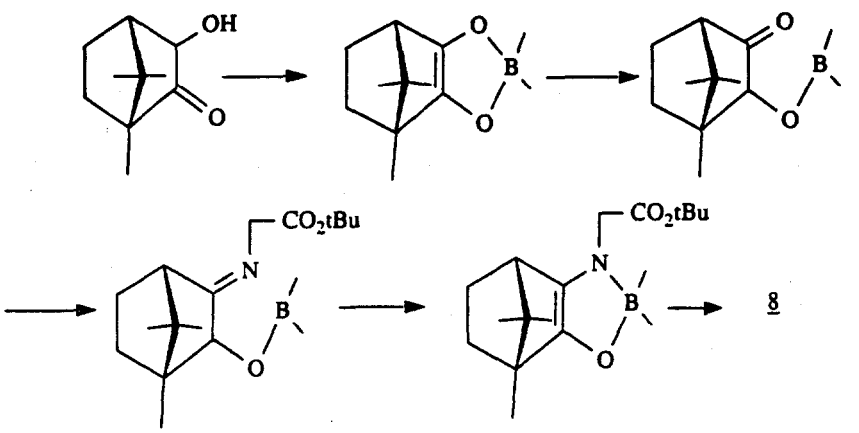
In an effort to verify the structural assignment, 8 was treated with zinc metal in acetic acid with the expectation of generating camphor. In the event, no camphor could be detected but a new compound was formed whose spectroscopic characteristics showed that the glycinate moiety had been removed. Furthermore, the C-3 proton had shifted from 2.86 to 5.22 and was now split into a doublet. This fact in combination with the presence of a three proton singlet at 2.13 suggested the structure 9. The ^{13}C and DEPT NMR spectra were in full accord with this structure and the assignment was easily confirmed by its hydrolysis to 3-hydroxycamphor 2, the starting material for the reaction sequence. The stereochemistry of the substitution also indicates an inversion process. The apparent complete absence of camphor from the crude product is extraordinary as is the formation of the acetate under these conditions. We can only rationalize the formation of 9 if the zinc is used to activate the glycinate moiety to substitution by acetic acid instead of functioning as an electron source for the reduction of 8.

Table 1.

^{13}C NMR chemical Shifts and multiplicities for the Camphor carbons of 2, 8 and related compounds

	Shift (Mult)[a]						
Carbon #	camphor,	2 (en)	2 (ex)	8	camphor oxime	3-bromo camphor	2-hydroxy camphor oxime
1	57.4 (s)	58.5		50.4	51.7	57.4	51.2
2	218.6 (s)	220.6		218.4	169.5	212.3	168.4
3	43.2 (t)	74.7	77.4(d)	69.1(d)	33.0(t)	53.8(d)	74.1(d)
4	43.6 (d)	48.7	49.4	59.9	43.7	49.4	50.1
5	27.3 (t)	18.0	25.3	24.2[c]	27.2	22.2	26.0
6	30.2 (t)	32.7	28.7	26.5[c]	32.5	30.3	25.5
7	46.8 (s)	43.2		44.3	48.2	45.7	45.8
8[b]	19.9 (q)	20.1	21.1	16.1	19.4	19.8	18.9
9[b]	19.3 (q)	18.9		19.2	16.5	19.7	18.4
10	9.5 (q)	9.4		14.0	11.0	9.5	12.8

[a] Unless otherwise noted, the multiplicities are unchanged from those of camphor.
[b] Values in these rows may be interchanged
[c] Values may be interchanged

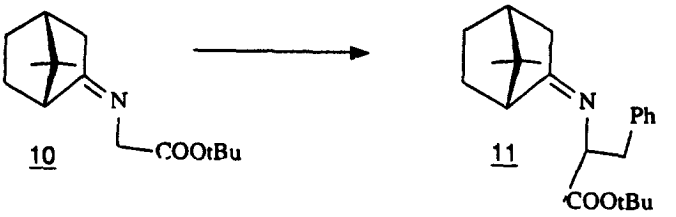


Scheme 3

Condensation of 7 with racemic norcamphor gave the imine 10 which was very unstable to hydrolytic conditions and which could not be chromatographed. Distillation afforded 10 as a 5:1 mixture of stereoisomers about the C=N bond. The methylene group of the glycine residue appeared as a broadened singlet in the minor isomer and an AB quartet in the major isomer. Molecular models suggest that the Z isomer should be the predominant one. The isomeric composition of imine 10 was expected to cause some difficulty in the analysis of its alkylation products, but the highly biased nature of the mixture encouraged us to continue.

Alkylation studies

Alkylations of 10 with benzyl bromide were chosen for study (Scheme 4), since this gave the "best" results (de > 98%) when 1 was employed.[3a,c] It was found that the work-up and purification used routinely to isolate the alkylation products from 1 completely hydrolyzed imine 11. Since the norcamphor used was racemic, the hydrolyzed aminoester was also necessarily racemic and no measure of the stereoselectivity of the reaction could be obtained. Therefore, resort was made to NMR measurements made on the crude reaction mixture. This mixture contained HMPA as well as lithium salts and other byproducts and therefore the accuracy of the determination is necessarily low. However, based on the presence of two singlets of approximately equal intensity for the *tert.*-butyl groups, and overlapping signals for the methine protons of the phenylalanine moiety which appeared to be of equal intensity, it can be stated that no significant asymmetric induction occurred in this reaction. This is the best evidence to date that the methyl groups of camphor are critical to its success in causing stereochemical differentiation. Further work is required to delineate the specific roles of C-10 and C-8.



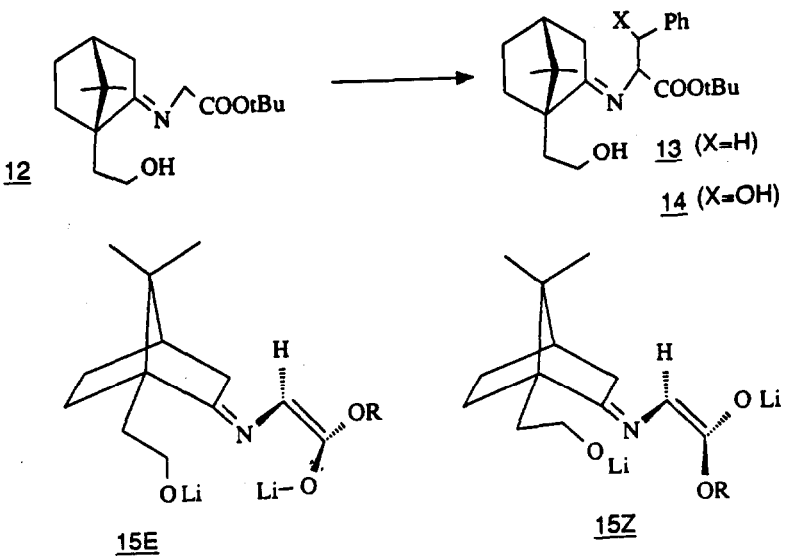
Scheme 4

Formation of the imine (12) (Scheme 5) from 6 and 7 was straightforward and gave a diastereomerically pure product according to both the ^{1}H and the ^{13}C NMR which showed only fifteen absorptions. Alkylation with benzyl bromide under the usual conditions, but using two equiv. of LDA proceeded normally. One equivalent of HMPA was required for maximum chemical yield and stereoselectivity, but in all attempts, the maximum diastereoselectivity that could be obtained was 80%. This contrasts unfavorably with the >98% de which was obtained using imine 1. It may be that the planar 5-membered N-Li-enolate chelate (15E) (Scheme 5) postulated as the dominant form of the intermediate during alkylation of imine 1 is disrupted by the presence of the O-Li at C-11. This would permit the enolate to assume the Z-configuration (15Z) which would lead to the S-configuration of 13. Alternatively it may be that the C-10 side chain hinders attack at the *re* face of the enolate thus making *si* face attack relatively more competitive.

Finally, we decided to explore an aldol reaction of glycinate 12 with benzaldehyde as a test case to determine the effect of the additional anionic site. In this case, we isolated a 71% yield of the aldol product 14 from benzaldehyde when the dianion of imine 14 was employed.

The aldol reaction creates two new chiral centers and therefore four stereoisomeric products are possible. These are the *erythro* and *threo* forms arising from each of *re* and *si* face attack of the electrophile on the enolate. The presence of the chiral camphor

moiety makes these products all diastereomers of each other. The ^{1}H NMR spectrum of the crude aldol reaction product indicated a 7:1 ratio of pairs of diastereomers as indicated by integration of the hydroxymethine proton. We successfully separated the pairs of diastereomers employing silica gel chromatography (56% yield and 15% yields respectively). Whether these are the *erythro/threo* pair resulting from *re*-face and *si*-face attack, or whether they are the *re/si* pair both having the *erythro* or *threo* configuration has not been determined. According to the ^{1}H NMR the minor pair of diastereomers appear to be present in approximately equal amounts, but the major pair seem to be present as at least a 2:1 mixture of diastereomers. It seems that the presence of a dianion in the enolate system facilitates the aldol reaction of these imine systems with benzaldehyde. In contrast the mono anion derived from 1 does not undergo an aldol reaction with benzaldehyde. The exact nature of the facilitation is unclear at this time. However, it is possible that one of the lithium atoms of the dianion system can coordinate to the aldehydic oxygen thus activating the carbonyl and making it more reactive with the imine.[13] Further work is in progress to delineate the nature and source of the effect. The results of this and related investigations will be the subject of a future report.



Scheme 5

ACKNOWLEDGEMENTS

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EXPERIMENTAL

Unless otherwise noted, infrared spectra were run as neat liquids and on a Nicolet 5-DX spectrometer. The NMR spectra were run at 300 Mz for ^1H and 75 MHz for ^{13}C in $CDCl_3$ solution. Values in brackets are for the minor diastereomer. Where DEPT editing of the carbon spectra was done, the multiplicities that would have been seen in the proton-coupled spectra are indicated. Mass spectra were run on a Varian MAT CH-5DF instrument in either the electron impact (EI) or field ionization (FI) mode. Gas chromatography was done using either a 8 ft x 1/4 in columnpacked with 20% SE-30 on Chromosorb W or a 1.5 ft x 1/8 in column packed with 5% OV-101 on Chromosorb W. Column chromatography utilized silica gel 60. Solvents were removed under reduced pressure and the drying agent used was anhydrous magnesium sulfate. Mosher esters were prepared from commercially prepared (R)-(+)-α-(trifluromethyl)phenylacetic acid using the literature procedure.[14] The preparation of imine 1[3a], D-2-oxo-7,7-dimethyl-1-vinylbicyclo[2.2.1]heptane (3)[15] were carried out as described in the literature. *endo*-3-bromocamphor was purchased from Aldrich Chemical Company. Elemental analyses were performed by Galbraith Laboratories, Knoxville Tenn.

3-Hydroxycamphor (2). This compound was prepared according to the literature[8] directions; IR: 3472, 2961, 2931, 1741, 1107cm^{-1}; ^1H NMR: 4.15 (d, 1H, J = 5 Hz) [3.69 (s, 1H)], 2.92 (s, 1H), 2.19 (t, 1H, J = 5 Hz), 1.87 (m, 1H), 1.65 (m,2H), 1.43 (m, 1H), 0.95 [0.93] (s, 3H), 0.87 [0.88] (s, 3H), 0.82 [0.86] (s, 3H); ^{13}C NMR: 220.6(s), 74.7 [77.4](d), 58.5(s), 48.7 [49.4](d), 43.2(s), 23.7 [28.7](t), 20.1 [21.1](q), 18.9(q), 18.0 [25.3](t), 9.4 [9.1](q); MS(EI): m/z = 168.

Preparation of ketal 4. A solution of 0.50g (3.05 mmol) of olefin 3, 0.29g (4.6 mmol) of ethylene glycol and 120 mg of p-toluenesulfonic acid in 10 mL dry benzene was refluxed 4 hours with azeotropic removal of water. After cooling the solution was washed with water, saturated sodium bicarbonate solution and brine. Concentration of the dried solution yielded 0.441g (70%) of 4 as a colorless oil after silica gel chromatography (30:1 petroleum ether:Et_2O); IR: 2950, 2882, 1163, 1122cm-1; ^{1}NMR: 6.03 (1H, dd, H = 17.7, 11), 5.17 (1H, dd, J = 11, 2.1), 5.10 (1H, dd, J = 17.7, 2.2), 3.84 (4H, m), 2.17 (1H, dt, 13.64, 4.09), 1.92 (1H, m), 1.71 (3H, m), 1.49 (1H, d, 13.64), 1.27 (1H, m), 1.12 (3H, S), 0.89 (3H, S); ^{13}C NMR: 136.0, 118.0, 116.6, 65.1, 64.3, 58.8, 50.0, 45.4, 45.2, 26.7, 24.4, 20.7, 20.5; MS(FI): m/z = 208.

Anal. Calcd. ($C_{13}H_{20}O_2$): C, 74.95; H, 9.67. Found: C, 74.94; H, 9.62.

Hydroboration of ketal 4. To 0.13g (0.63 mmol) of 4 in 2.5 mL THF was added 3.78 mL (1.89 mmol, 3 equivalents) of 9-BBN at 0° C under N_2. After stirring 3 hours at room temperature, 1 mL of EtOH was added followed by 1.0 mL 6N NaOH and 2 mL 30% H_2O_2 at 0° C and the solution was stirred at ambient temperature overnight. After saturation with K_2CO_3 and dilution with 10 mL Et_2O the layers were separated. The aqueous layer was extracted with 5 mL Et_2O and the combined organics were dried concentrated and chromatographed to give 100 mg (72%) of 5 as a colorless oil; IR: 3420(b), 2951, 1640, 1114cm-1; ^{1}H NMR: 3.95 (3H, m), 3.76 (1H, m) 3.65 (2H, m), 2.0 (3H, m), 1.75 (2H, m), 1.50 (1H, m), 1.38 (1H, d), 1.3 (2H, m), 1.04 (3H, s), 0.75 (3H, s); ^{13}C NMR: 116.6, 64.1, 62.4, 60.6, 53.6, 49.3, 44.9, 44.0, 28.5, 27.0, 26.5, 20.5, 20.5; MS(FI) m/z = 226.

Preparation of 10-hydroxymethyl camphor (6). A solution of 0.19g (0.84 mmol) of 5 in 3 mL THF and 6 mL 1M HCl was stirred 22 hours at room temperature. The solution was diluted with 15 mL Et_2O, washed successively with aqueous sodium bicarbonate and brine, then dried and concentrated to give a 6 as a colorless oil (0.11g, 70%) after chromatography with 1:1 petroleum ether:Et_2O; IR: 3417, 2958, 2885, 1735, 1051cm-1; ^{1}H NMR: 3.73(2H, m), 2.42 (1H, dt, J = 19, 3.2 Hz), 2.2 (1H, t, J = 4.4 Hz), 2.0 (1H, m), 1.95-1.38 (6H, m), .95 (3H, s), 0.91 (3H, s); ^{13}C NMR: 222.6, 61.6(s), 59.7(t), 48.0(s), 43.5(d), 43.3(t), 28.7(t), 26.9(t), 26.6(t), 20.1(q), 19.3(q); MS(FI): m/z = 182.

Anal. Calcd. ($C_{11}H_{18}O_2$): C, 72.48; H, 9.95. Found: C, 72.16; H, 10.07.

Formation of ketoamine 8. Camphor derivative 2 (0.5 g, 3 mmol) (5:1 *endo/exo*) was dissolved in 10 mL of dry toluene in a flask fitted with a Dean-Stark water separator and the system was purged with nitrogen. *tert.* butyl glycinate (0.43 g, 3.3 mmol) was added followed by 40 ul of $BF_3.Et_2O$. The mixture was refluxed for 8 h at which time gc analysis indicated all the starting material had been consumed. The mixture was concentrated to afford an orange oil which was chromatographed (5:1 pet. ether:ether) to give 0.588 g (70%) of an orange-tinted oil; IR: 3319(w), 2966, 1742, 1450, 1367, 1292, 1157cm^{-1}; ^{1}H NMR: 3.43 (s, 2H), 2.86 (s, 1H), 2.12 (d, 1H, J = 4.8 Hz), 1.89 (m, 2H), 1.75 (s, 1H, D_2O exchangeable), 1.40 (s, 9H), 1.35 (m, 2H), 0.98 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H); ^{13}C NMR: 218.4(s), 171.6(s), 81.3(s), 69.1(d), 59.9(d), 51.8(t), 50.4(s), 44.3(s), 28.2(q), 26.5(t), 24.2(t), 19.2(q), 16.1(q), 14.0(q); MS(FI): m/z = 281.

Anal. Calcd. ($C_{16}H_{27}NO_3$): C, 68.33; H, 9.60; N, 4.98. Found: C, 68.53, H; 9.12, N, 4.61.

The hydrochloride salt of 8 was prepared by adding a solution of 8 (40 mg, 0.14 mmol) in 2 mL of ether to 20 mL of ether saturated with HCl gas. The solution was stirred 20 min, concentrated, and the solid product recrystallized from ether to give 43 mg (97%) of a white solid, mp 84-86°C; ^{1}H NMR: *ca.* 10 (very broad, 1H), 7.20 (s, 1H), 4.11 (ABq, 2H, J = 17.4 Hz), 3.61 (s, 1H), 2.27 - 1.50 (m, 5H), 1.44 (s, 9H), 1.28 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H).

Preparation and Hydrolysis of 9. To 80 mg (0.3 mmol) of 8 in a 25 mL r.b. flask was added 3 mL of glacial acetic acid and 0.5 g of activated zinc dust. The mixture was stirred overnight at room temperature, diluted with 15 mL of water, filtered and the filtrate extracted with 3 x 30 mL of ether. The combined organic layers were washed with 3 x 15 mL of $NaHCO_3$ and 20 mL of brine. The combined aqueous washings were extracted once with ether, the combined ether phases dried and concentrated to give 41 mg (655) of 9 as an oil with the following spectroscopic characteristics; ^{1}H NMR: 5.21 (d, 1H, J = 5 Hz) [4.77 (s, 1H)], 2.42 (bs, 1H), 2.13 [2.10] (s, 3H), 1.72 (m, 3H), 1.45 (m, 1H), 1.02 [1.00] (s, 3H), 0.96 (s, 3H), 0.95 (s, 3H); ^{13}C NMR: 214.3(s), 170.3(s), 75.6(d), 58.4(s), 47.4(d), 43.5(s), 31.8(t), 20.8(q), 19.9(q), 16.8(t), 16.8(q), 9.3(q).

Hydrolysis of 12 to 2 was achieved by stirring 13 mg (0.06 mmol) of 9 in 4 mL of methanol containing 4 mg of KOH overnight. Tlc (4:1 pet. ether:ether) showed no starting acetate remaining. The methanol was evaporated, 2 mL water was added to the residue and the solution was extracted with 3 x 10 mL of ether. The dried extracts were evaporated to give 10 mg (95%) of a solid, identical in all respects with 2.

Preparation of 3-hydroxycamphor oxime. To 2 mL of absolute EtOH was added 238 gm (4.2 mmol) of KOH followed by 82 mg (1.2 mmol) of hydroxylamine hydrochloride. 3-Hydroxycamphor (100 mg, 0.6 mmol) was added, the solution refluxed for 12 h, cooled and filtered. The filtrate was acidified, extracted with 3 x 25 mL of ether, the extracts dried and concentrated to afford 81 mg (74%) of a yellow oil which was purified by chromatography (4:1 pet. ether: ether) to give 36 mg (35%) of a clear oil; ^{1}H NMR: 9.20 (bs, 1H), 4.46 (s, 1H), 3.21 (bs, 1H), 2.28 (s, 1H), 1.96 (m, 2H), 1.39 (m, 2H), 1.00 (s, 3H), 0.98 (s, 3H), 0.92 (s, 3H); ^{13}C NMR: 168.4, 74.1, 51.2, 50.1, 45.8, 26.0, 25.5, 18.9, 18.4, 12.8.

Preparation of the norcamphor imine of *tert.* butyl glycine (10). A solution of 0.589g (5.34 mmol) of norcamphor, 0.70g (5.34 mmol) *tert.* butyl glycinate (7) and 5 drops of BF_3:Et_2O was refluxed in 20 mL of dry benzene with azeotropic removal of water under nitrogen for 5 h. After cooling the dried solution was concentrated to give an oil containing the crude imine. Distillation gave pure imine (0.56g, 40%) b.p. 70 - 75° C (0.15 mm.) The ^{1}H and ^{13}C NMR indicated a mixture of diastereomers which could not be separated by chromatography since the imines hydrolyzed readily. The ratio of the diastereomers was determined to be 5:1 on the basis of integration of ^{1}H NMR spectra of the methylene imine protons. The sample was stored in the freezer under nitrogen since slow decomposition occurred at room temperature. IR: 2986, 1744, 1689, 1154cm-1; ^{1}H NMR: 3.98 [4.06] (2H, ABq, J = 11.7 Hz), 2.85 [3.0] (1H, s), 2.56 [2.50] (1H, s), 2.05 [2.3] (1H, d, J = 16), 1.8 - 1.2 (m, 16H); ^{13}C NMR: 184.5(s), 169.8(s), 81.0(s), 55.0 [55.58](t), 47.0(d), 37.8 [38.2](t), 36.8(t), 35.4 [34.8](d), 27.83 [28.0](q), 27.4 [27.1](t), 26.0 [25.2](t).

Preparation of hydroxy imine 12. A solution of 41 mg (0.225 mmol) 6 and 44 mg (0.340 mmol) *tert.* butyl glycinate (7) in 3 mL benzene was refluxed in the presence of 1 drop of BF_3:Et_2O under a Dean-Stark water trap under nitrogen. After 12 hours the solution was cooled, dried and concentrated to give 43 mg (65%) of the imine 101 after chromatography with 2:1 petroleum ether:Et_2O followed by

2:1 Et_2O:petroleum ether; IR: 3200, 2960, 1735, 1684, 1156cm-1; ^1H NMR: 3.92 (2H, s), 3.78 (1H, ddd, J = 11.2, 4.7, 2.8 Hz), 3.65 (1H, dt, J = 11, 1Hz), 2.3 (1H, d(b), J = 16.8 Hz), 2.05-1.6 (7H, m), 1.47 (9H, s), 1.3 (1H, m), 0.92 (3H, s), 0.84 (3H, s); ^{13}C NMR: 188.0(s), 168.9(s), 81.5(s), 59.6(t), 59.3(s), 54.0(t), 48.4(s), 44.2(d), 35.7(t), 30.2(t), 28.6(t), 28.1(q), 27.3(t), 19.7(q), 19.1(q); MS(FI): m/z = 295.

Alkylation reactions of Imine 10 A solution of 0.55g (2.47 mmol) imine 10 in 3 mL THF was added slowly to a solution of 2.71 mmol of LDA [prepared by adding 1.1 mL (2.71 mmol) BuLi (2.5M in hexanes) to .274g (2.71 mmol) diisopropylamine in 3 mL THF at 0^o C and stirring 15 minutes at that temperature] at -78^o C under nitrogen. After 20 minutes at that temperature 0.464g (2.71 mmol) benzylbromide in 3 mL THF was added. The reaction was quenched after 1.5 h by the addition of 5 mL H_2O (which also caused imine hydrolysis). Drying and concentration of the organic layer afforded, after chromatography (2:1 petroleum ether:ether) 0.289g (75%) phenylalanine *tert.* butyl ester. Derivatization as the Mosher amide indicated a racemic mixture as expected..

When one equivalent HMPA was added with the imine under otherwise identical conditions as above 0.33g (85%) of phenylalanine *tert.* butyl ester was obtained.

When two equivalents HMPA were added with the imine under otherwise identical conditions as above 0.237g (61%) of phenylalanine *tert.* butyl ester was obtained.

Several extraneous peaks were present in the ^1H NMR spectrum of the crude alkylated product due to the presence of HMPA, benzylbromide, and unreacted and hydrolyzed imine. However, the 8 lines due to the glycinate methine proton were found at approximately 3.92 ppm in analogy with the camphor imine.

General procedure for alkylation of hydroxy camphor imine 12.

In a flame dried 25 mL 3 neck round bottom flask was added 2 mL THF, 0.144g (1.4 mmol) of diisopropylamine and 0.57 mL (1.4 mmol) BuLi (2.5M in hexanes) at 0^o C under N_2. This LDA solution was stirred for 20 minutes at 0^o C then cooled to -78^o C at which point 0.2g (0.68 mmol) of imine 12 in 1 mL THF was added. An orange enolate solution resulted. After 30 minutes 0.128g (0.75 mmol) benzyl bromide was added in 2 mL of THF at -78^oC. After 2.5 hours at that temperature the reaction was quenched with 5 mL saturated NH_4Cl and diluted with 10 mL Et_2O. Separation, drying and concentration of the organic phase yielded 0.167g (64%) of the crystalline solid 13 whose de was 78% after chromatography with 1.5:1 petroleum ether:Et_2O. Recrystallization from petroleum ether did not improve this value.

When 1 equivalent HMPA was added along with the imine under otherwise identical conditions as above, except reaction time of 1.5 hours, 0.217g (83%) of alkylated product 13 was obtained with de = 80%

When 2 equivalent HMPA were employed as above 0.201g (77%) of alkylated product 13 was obtained with 80% de; IR: 2958, 1735, 1154, 1684cm-1; ^1H NMR: 7.3 (5H, m), 3.99 [4.03] (1H, dd, J = 10.4, 3.4 Hz), 3.78 (1H, m), 3.64 (1H, m), 3.25 (1H, dd, 12, 4), 2.95 (1H, dd, J = 14, 12), 2.2 (1H, dt, 16Hz), 1.9 - 1.4 (8H, m), 1.45 (9H, s), 0.178 (3H, s), 0.80 (3H, s); ^{13}C NMR: doubling of peaks, new peaks at 138 - 128; MS(FI): m/z = 385.

Anal. Calcd. ($C_{24}H_{35}NO_3$): C, 74.81; H, 9.09; N, 3.64. Found: C, 74.78; H, 9.39; N, 3.57.

Aldol reaction of hydroxy camphor imine 12. A solution of 0.1g (0.34 mmol) hydroxy imine 12 was added to a solution of LDA [prepared by adding .072g (0.71 mmol) diisopropylamine to 0.29 mL (0.73 mmol) BuLi (2.5M in hexanes) in one mL THF at 0^oC and stirring 20 minutes at this temperature then 5 minutes as -78^oC] and stirred 30 minutes at -78^oC. A solution of benzaldehyde [.039 mL (0.38 mmol)] in 1 mL of THF was added and the mixture was stirred at -78^oC for 1.5 hours. The reaction was quenched by addition of 1 mL H_2O followed by dilution with 15 mL diethyl ether. Phase separation, drying of the organics and concentration yielded the crude aldol product 14. NMR indicated a 7:1 ratio of pairs of stereoisomers (δ = 5.30, 5.15). After chromatography (1:1, hexane:ethyl acetate) these pairs were separated into major (76 mg, 56% yield) and minor (20 mg, 15% yield) pairs of stereoisomers. The major pair appeared to be present as approximately a 2:1 ratio of stereoisomers whereas the minor pair seemed to be present in equal amounts according to the ^1H NMR spectra.

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