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SIMPLE CAMPHOR DERIVATIVES AS CHIRAL AUXILIARIES FOR ASYMMETRIC CONJUGATE ADDITION

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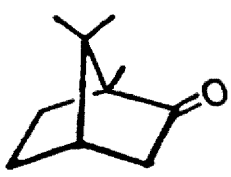
Abstract - The chiral enoates, 4, readily available in two simple steps from (+)-camphor, undergo asymmetric conjugate addition with the Gilman reagent $LiBu_2Cu$. Chemical yields are high (70-90%) and in the case of the naphthyl-substituted enoate 4e excellent diastereoselectivity (95% d.e.) is observed. 3-Methyl-heptan-1-ol of correspondingly high enantiomeric purity is obtained by reduction of the conjugate adduct with lithium aluminium hydride.

The use of the chiral pool of natural products as starting materials for total synthesis and in the development of new methodology for asymmetric carbon-carbon bond formation continues to attract intense and widespread interest[1]. Of the cheaply available members of the chiral pool, laevorotatory camphor, 1, has recently provided a convenient starting point for the enantiospecific total synthesis of steroids[2], while Oppolzer[3a,b] has demonstrated excellent diastereoselectivity in the Diels-Alder and conjugate addition reactions of the camphor-based enoates 2 and Helmchen[3c] has used the chiral propionate 3 to good effect in asymmetric alkylations. The synthesis of 2 and 3 requires several steps from (+)-camphor, however.



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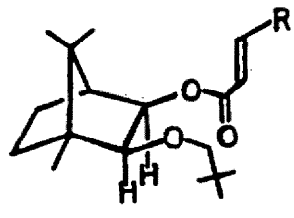
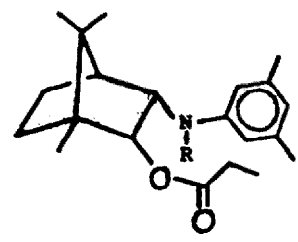
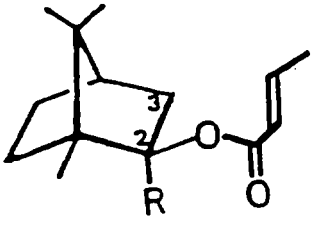


	R
2a	H
b	Et
c	Bu



3 R = SO_2Ph

In the course of synthetic projects involving some typical reactions of α,β-unsaturated esters, we became interested in the development of easily available chiral auxiliaries which could induce asymmetry in the 1,3-dipolar and Diels-Alder cycloadditions and in the conjugate addition of organometallics. Inspection of CPK molecular models suggested that simple camphor derivatives such as 4 might be suitable, taking advantage of a sufficiently bulky substituent R to shield one diastereoface of the double bond and of the well-known preference of the enoate moiety for the coplanar transoid conformation[4]. In this paper we present our results on the conjugate addition of organocopper species to such substrates.



4

4	R
a	H
b	CH_3
c	C_6H_5
d	$CH_2C_6H_5$
e	

The synthesis of the required enoates was trivial, involving a Grignard reaction to give the endo-substituted alcohols which were then esterified with crotonyl chloride using the method of Kaiser and Woodruff[5]. All of the tertiary alcohols were easily obtained pure on a multi-gram scale (50-75% yield) and the yields of the corresponding esters were also acceptable (see Experimental). The chemical yields of the conjugate additions were uniformly high (70-90% isolated yield) provided that purified CuI was used in the preparation of the cuprate reagent[6]. In line with our initial hypothesis, increasing the bulk of the substituent R in 4 led to an increase in the diastereomeric excess (d.e.) obtained upon the 1,4-addition of $LiBu_2Cu$ in diethyl ether to the enoates 4a-e. The results are collected in the Table, the d.e. values being measured by integration of appropriate pairs of signals in the 270 MHz ^1H NMR spectra of the conjugate adducts in the presence of the shift reagent $Eu(fod)_3$. The lowest-field portion of such a spectrum (a pair of naphthalene doublets) of the conjugate adduct of 4e (95% d.e.) is shown in Fig. 1A. For comparison, the corresponding spectral region for a case in which the d.e. value was close to zero (addition of $BuCu.BF_3.Et_2O$ to 4e) is also shown, Fig. 1B.

Table. Isolated chemical yields and diastereomeric excess (d.e.) for the conjugate addition of $LiBu_2Cu$ to the chiral enoates 4a-e.

Enoate	R = H	CH_3	C_6H_5	$CH_2C_6H_5$		1-naphthyl	
Chemical yield %	90	81	77	73	71	75	74
d.e. %	0	50	60	33	45	87	95
Reaction temp. °C	-25	-25	-25	-25	-78	-25	-78

It may be noted that chromatography does not enhance the d.e. values to any significant extent since d.e. values measured on the crude reaction products were in all cases near-identical to those measured on the chromatographically purified adducts. Reduction of the adducts with lithium aluminium hydride in THF then allowed recovery of the auxiliary and provided optically active 3-methyl-heptan-1-

ol, the enantiomeric excess and absolute configuration being checked by polarimetry (see Experimental).

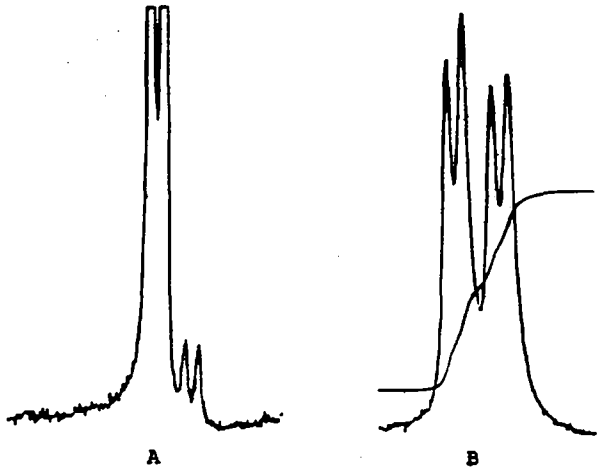


Figure 1. Portion of the aromatic region of the 270 MHz ^{1}H NMR spectrum of the conjugate adduct of 4e in the presence of Eu(fod)$_3$.
A: Addition of $LiBu_2Cu$ (95% d.e.)
B: Addition of $BuCu.BF_3.Et_2O$ (d.e. = 0).

As shown in the Table, a steady increase in d.e. was obtained upon increasing the bulk of the group R in 4 from H through methyl to phenyl. Use of a benzyl group led, somewhat surprisingly, to a drop in d.e. while the 1-naphthyl substituent in 4e induced a satisfying and synthetically useful d.e./e.e. of 95%, the 3-methyl-heptan-1-ol obtained after LAH reduction having the (S)-configuration[7].

The use of copper iodide which had been carefully purified via its dimethyl sulfide adduct[6] for the preparation of the cuprate reagent was critical for high chemical and optical yields. The cuprate solutions prepared at ca. -40°C from the purified iodide and slightly less than two equivalents of BuLi were clear, homogeneous and near-colourless, slight turbidity being noted upon cooling to -78°C. All the enoates were added at this temperature and the reaction mixture allowed to warm up slowly until TLC analysis indicated the onset of the conjugate addition reaction. For substrates 4a-c, no rection was observed below -25°C and these reactions required several hours at this temperature for completion. The benzyl-substituted enoate 4d and its 1-naphthyl counterpart 4e were anomalous in this respect, as these substrates reacted completely after only 30 minutes at -78°C (TLC analysis of an aliquot which had been removed from the reaction mixture and quenched). Further, it was noted that addition of substrates 4a-c to the cuprate solution at -78°C led to the immediate development of a bright yellow colour and formation of a precipitate, both colour and precipitate disappearing slowly as the reaction mixture was allowed to warm up and conjugate addition began. The same yellow colour was also observed upon addition of 4d and 4e, but in these cases no precipitate formed and the colour faded after a short time at -78°C (TLC at this point indicating near-total consumption of the enoate and formation of the conjugate addition product). The 1-naphthyl substituted ester 4e reacted most rapidly, reaction being complete after only 10 minutes at -78°C.

The observations that the benzyl substituent induces a poorer d.e. than methyl at -25°C and that the sterically most encumbered enoate (4e) reacts the most rapidly deserve further comment. As far as the benzyl substituent is concerned,

NMR spectroscopy indicates free rotation at ambient temperature ((in contrast to the situation in 4c and 4e) and we have no computational evidence for a single preferred conformation. The relatively poor d.e. obtained thus probably reflects reaction of a conformer (or conformers) in which the ester double bond is not efficiently "shielded" by the substituent. Recently, Ullenius and coworkers[8] have published the results of a careful low-temperature ^{1}H and ^{13}C NMR study of the conjugate addition of Gilman reagents to enoates. These workers propose the initial formation, at temperatures below -35°C, of two equilibrating species, one being an olefin-copper π-complex and the other involving complexation to the carbonyl oxygen. The former complex was suggested to lie on the reaction pathway to the conjugate addition product. Our results suggest similar behaviour for the present substrates, circumstantial evidence being the formation of the precipitates from 4a-c at low temperature. If these precipitates are indeed the complexes referred to above then their precipitation would be expected to retard the conjugate addition reaction, and the enhanced rate of reaction observed for 4d and 4e may therefore simply be due to higher complex solubility. An alternative explanation is that the rate of any (insoluble ?) complex formation from 4d and 4e is appreciably lower than that of the conjugate addition reaction.

In this respect, we have noted a distinct difference in behaviour when 4e was allowed to react with the "higher order" cuprate[9] Li_2Bu_2CuCN at -78°C. After addition of 4e to five equivalents of the cyanocuprate, TLC showed complete disappearance of the enoate after ca. 15 minutes and formation of some conjugate addition product. Quenching the reaction at this point and subsequent work-up, however, led to recovery of the bulk of the enoate (ca. 15% conversion) and virtually no asymmetric induction according to the usual NMR analysis. With the other enoates, Li_2Bu_2CuCN did give d.e. values which were only slightly lower than those obtained with the Gilman cuprate. These observations have not been further pursued due to the generally better performance of the Gilman reagent, but are also perhaps consistent with the formation and equilibration of the complexes referred to above.

Of the organocopper reagents we have studied so far, the classical Gilman cuprate has proved vastly superior in terms of asymmetric induction. This result is in direct contrast to the findings of Oppolzer[3b] who obtained optimum chemical and optical yields by addition of the Yamamoto reagents[10] $RCu.BF_3.Et_2O$ (sometimes modified by addition of PBu_3) to enoates 2b and 2c. Our own attempts to use such reagents on 4b-d resulted in poor diastereoselectivity (see, e.g., Fig. 1B) and low chemical yields since these tertiary esters are, not unexpectedly, prone to elimination upon exposure to Lewis acids, even at -78°C.

Although recent years have seen great progress in the clarification of the solution structures of the organocopper reagents used in the present work[11], such knowledge, perhaps coupled to some insight on the ground-state conformational preferences of the reactant partner, is usually insufficient to allow confident prediction/rationalisation of the actual outcome of an asymmetric conjugate addition reaction[12]. Nevertheless, we feel that some comments regarding the ground-state structure of the naphthyl-substituted enoate 4e and the corresponding alcohol precursor are in order.

The naphthyl-substituted alcohol corresponding to 4e shows temperature-dependent ^{1}H NMR behaviour consistent with slow rotation or flipping of the naphthyl moiety at ambient temperature. Heating the sample to 333K (in $CDCl_3$) leads to one set of sharpened peaks, while cooling to 213K shows the presence of two "frozen-out" conformers in roughly 2:1 ratio. The barrier to interconversion calculated using the DNMR 5 simulation program[13], is ca. 50 $kJmol^{-1}$. The spectrum of the ester 4e, however, shows no change over the same temperature range and is

consistent with the presence of a single rotamer, assuming the barrier to interconversion is higher than that in the alcohol for steric reasons. Molecular mechanics calculations on 4e (using the MMPI program [14]) predict the lowest-energy conformer to be that shown in Fig. 2.

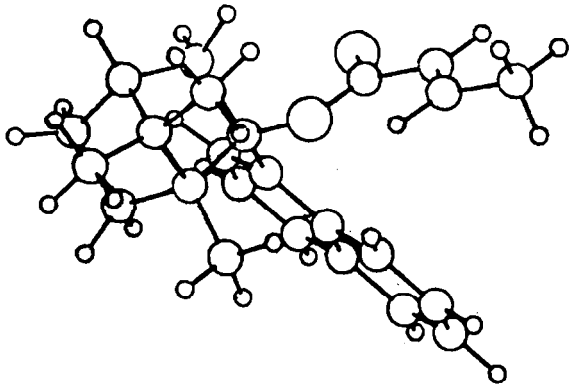


Figure 2. Calculated MMPI lowest-energy conformer of ester 4e.

In this conformation, with sufficiently slow rotation of the enoate moiety about the carbon-oxygen single bonds, the large naphthalene unit effectively shields one face of the double bond and the enoate adopts the expected planar transoid arrangement. Attack by the cuprate on the "free" diastereoface should thus lead to the (S)-configuration at the new chiral centre, and this is indeed observed (see Experimental). The design of new chiral auxiliaries analogous to 4e and their use in the synthesis of natural products is now being investigated.

Finally, we note that suitably substituted esters of type 4 show considerable promise as substrates for asymmetric 1,3-dipolar cycloaddition reactions[15]. The results will be reported elsewhere.

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EXPERIMENTAL

General remarks - ^{1}H NMR spectra were obtained at 270 MHz on a Bruker WH-270 instrument using $CDCl_3$ as solvent and TMS ($\delta = 0$) as internal standard. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; J, coupling constant in Hz. Assignments of individual camphor proton signals were made on the basis of ref. 21 and after extensive spin-decoupling experiments. IR spectra were run on a Nicolet MX-10 FT-IR spectrometer and only the structurally most important peaks (ν_{max} in cm^{-1}) are listed. Mass spectra were run on a Finnigan 1020 GC/MS instrument. Optical rotations [α_D] were measured on a Perkin Elmer 141 polarimeter at the sodium D line and ambient temperature. Melting points were determined using a Reichert Thermovar apparatus. Flash chromatography was carried out using Merck silica gel 60 (230-400 mesh). Diethyl ether and tetrahydrofuran (THF) were dried and distilled under nitrogen from sodium-benzophenone ketyl immediately prior to use. Copper iodide was purified according to House (ref. 6) and the purified material, which was used as soon as possible, was stored under argon in a brown glass bottle. Butyllithium (Aldrich, 1.55M in hexanes) was used as received. All reactions were run using septum-capped, flame- or oven-dried flasks under balloon pressure of argon, solvents and reagent solutions being transferred via syringes which had been oven-

dried (140°C) for several hours and cooled in a desiccator over P_2O_5. Reaction temperatures were measured externally. Yields refer to isolated, chromatographically and spectroscopically homogeneous materials. The alcohols used for esterification were prepared essentially according to the literature (refs. 16 through 20) except that THF was used instead of diethyl ether as solvent for the Grignard reactions. The isolated yields of the alcohols are listed below, together with the detailed procedure for the 1-naphthyl substituted alcohol. All the crotonate esters were prepared according to a standard literature procedure[5], using two equivalents of crotonyl chloride. Details for the preparation of ester 4e are given below.

Alcohols. (R in RMgX, isolated yield, lit. ref.): CH_3, 75%, 17; C_6H_5, 65%, 18; $CH_2C_6H_5$, 69%, 19.

Esters. (R in 4, isolated yield): H, 80%; CH_3, 70%; C_6H_5, 75%; $CH_2C_6H_5$, 68%. All the esters showed a strong IR band at around 1715 cm^{-1} and had 270 MHz ^1H NMR and mass spectra fully consistent with the proposed structures.

1-naphthyl-substituted alcohol. A Grignard reagent was formed from 1-bromonaphthalene (15.1g, 73 mmol) and magnesium turnings (1.75g, 72 mg-atom) in dry THF (20 ml). The solution was stirred at RT and a solution of (+)-camphor (10g, 66 mmol in 10 ml dry THF) was added via syringe. The resultant mixture was refluxed under argon for 24 hr, then cooled and poured into a mixture of ether and NH_4Cl aq. The organic layer was separated, washed with water, brine, and then dried over Na_2SO_4. Removal of solvents gave a crystalline residue which consisted of the desired product contaminated with unreacted camphor and naphthalene, both of which were removed by careful sublimation at reduced pressure. (Attempts to purify the alcohol directly by silica gel flash chromatography usually resulted in extensive elimination to olefinic products). The solid residue after sublimation was twice recrystallised from aqueous ethanol to yield the desired alcohol (8.3g, 45%) m.p. 121-123°C (lit. 122-124°C, ref. 20); $[\alpha]_D$ -38°, c = 0.3, benzene (lit. -42°, c = 15, benzene, ref. 20); MS: m/z 262 ($M-H_2O$), 65%; 219, 100%; NMR (333K): δ 8.8, 1H, m; 7.7, 3H, m; 7.4, 3H, m (naphthalene); 2.8, 1H, bd, J 15, H 3-exo; 2.4, 1H, d, J 15, H 3-endo; 1.9, 1H, btr, J 3, H 5-exo; 1.7, 1H, bm, H 4; 1.4, 1H, m, H 5-endo; 1.3, 3H, s, methyl; 1.2, 3H, s, methyl; 1.1, 2H, m, H 6-exo,H 6-endo; 0.9, 3H, s, methyl. The temperature-dependence of the NMR spectrum is discussed in the text.

Ester 4e was prepared according to Kaiser and Woodruff[5]. Thus, the 1-naphthyl-substituted alcohol (1.4g, 5 mmol) was dissolved under argon in dry THF (10 ml) and stirred at RT during the addition of BuLi (3.55 ml of 1.55M, 5.5 mmol). After 45 min. freshly distilled crotonyl chloride (1.05g, 10 mmol) in dry THF (5 ml) was added dropwise via syringe. The resultant mixture was refluxed for 6 hr then cooled in an ice-bath and hydrolysed by addition of water (10 ml). The aqueous phase was extracted with three 10-ml portions of ether and the combined organics dried over Na_2SO_4. Removal of solvents gave a solid residue which was purified by flash chromatography (5% ether in pentane) followed by recrystallisation from ether-pentane. Yield 0.7g, 40%, m.p. 139-141°C. $[\alpha]_D$ -139°, c = 0.67, CH_2Cl_2; IR: 1710 cm^{-1}; MS: m/z 262 ($M - C_4H_6O_2$), 60%; 219, 100%; NMR: δ 8.6, 1H, m; 7.8, 3H, m; 7.4, 3H, m (naphthalene); 6.9, 1H, dq, J 16 and 7, vinyl; 5.9, 1H, dq, J 16 and 1.5, vinyl; 3.0, 1H, d, J 15, H 3-endo; 2.6, 1H, dtr, J 15 and 3.5, H 3-exo; 2.0, 1H, tr, J 3.5, H 5-exo; 1.8, 3H, dd, J 7 and 1.5, methyl; 1.8-1.7, 2H, bm, H 5-endo and H4; 1.4, 2H, m, H 6-exo and H 6-endo; 1.3, 3H, s, methyl; 1.2, 3H, s, methyl; 0.9, 3H, s, methyl.

General procedure for the conjugate additions. Purified CuI (5 mmol) was slurried under argon in dry diethyl ether (10 ml) and cooled with rapid stirring to -40°C. BuLi (9.9 mmol of 1.55M) was added dropwise via syringe and the resultant mixture (usually clear, homogeneous and near-colourless) was stirred at -40°C for 20 min. The cuprate solution was then cooled to -78°C and a solution of the appropriate ester (1 mmol) in dry ether (5 ml) was added dropwise via syringe. For enoates 4a-c, the resultant mixture was allowed to warm up with stirring to -25°C and the reaction vessel then sealed and placed in the freezer (-25°C) overnight; esters 4d and 4e were observed to react completely (TLC) after ca. 30 min. at -78°C but stirring was nevertheless continued for 2 hr. at -78°C. When the reaction was complete according to TLC analysis, the reaction mixture was quenched by addition of NH_4Cl aq. and the resultant mixture transferred to a separating funnel containing more NH_4Cl solution and ether. A few drops of 25% ammonia were added and air was bubbled through the mixture until the solids had been digested and the aqueous layer had turned deep blue. The ethereal layer, colourless to pale yellow, was separated and washed with water, then brine and then dried over Na_2SO_4. After removal of solvent, the residue was purified by flash chromatography (usually eluting with 5% ether in pentane). The isolated yields of the conjugate addition products are given in the Table. Data for the conjugate adduct of ester 4e: syrup; MS: m/z 262 ($M - C_8H_{16}O_2$), 75%; 219, 100%; NMR (major diastereomer, 95% d.e.): δ 8.60, 1H, m; 7.75, 3H, m; 7.40, 3H, m (naphthalene); 2.96, 1H, d, J 15, H 3-endo; 2.50, 1H, dtr, J 15 and 3.5, H 3-exo; 2.32, 1H, dd, J 15 and 6, 2.05, 1H, dd, J 15 and 7.5 (α to carbonyl); 1.95, t, J 3.5, H 5-exo; 1.80, 3H, bm, H 5-endo, H4 and methine (decoupling of this multiplet collapses the methyl doublet at 0.69 to a singlet); 1.42, 2H, m, H 6-exo and H 6-endo; 1.29, 3H, s, methyl; 1.23, 6H, complex m, methylenes; 1.19, 3H, s, methyl; 0.98, 3H, s, methyl; 0.85, 3H, distorted t, J 7, Bu-methyl; 0.69, 3H, d, methyl.

Attempts to remove the minor diastereomer by chromatography or by recrystallisation have so far proved fruitless. The adduct mixture is extremely soluble in all the common organic solvents.

Reduction of the conjugate adduct of ester 4e. Lithium aluminium hydride (0.23g, 6mmol) was added under argon to dry THF (10 ml) at 0°C. The conjugate adduct of ester 4e (1.22g, 3 mmol) in dry THF (5 ml) was added via syringe and the resultant mixture refluxed with stirring overnight. After standard work-up (ref. 22) and flash chromatography (eluting with 30% ether in pentane) (S)-3-methyl-heptan-1-ol of ca. 95% optical purity was obtained. Yield o.36g, 92%. This procedure also allowed recovery of the camphor auxiliary after flash chromatography.
NMR (after D_2O shake): δ 3.67, 2H, m (α to hydroxyl); 1.57, 2H, m (methine and 1H β to hydroxyl); 1.38, 1H, m (β to hydroxyl); 1.29, 6H, complex m (methylenes); 0.89, 3H, d, J 6.6 overlapping 3H, distorted t, J 6.6 (two methyls). Assignments made after spin-decoupling experiments.
MS: m/z 112, 2%; 84, 58%; 70, 80%; 55, 100% (see ref. 23).
$[\alpha]_D$ -2.91, c = 4.0, CH_2Cl_2 (lit. -3.07, neat, see ref. 7).

REFERENCES

1. See, for example, Seebach, D. and Hungerbühler, E. in "Modern Synthetic Methods 1980", Salle and Sauerländer 1980, pp. 91 - 171 and Hanessian, S. "Total Synthesis of Natural Products: The 'Chiron' Approach", Pergamon Press, 1983.
2. Stevens, R.V., Gaeta, F.C.A. and Lawrence, D.S. J. Am. Chem. Soc. (1983) 105 7713.
3. (a) Diels-Alder reactions: Oppolzer, W., Chapuis, C., Dao, G.M., Reichlin, D. and Godel, T. Tetrahedron Lett. (1982) 4781 and references therein (b) Conjugate addition reactions: Oppolzer, W., Moretti, R., Godel, T., Meunier, A. and Löher, H. ibid. (1983) 4971 and references therein (c) Chiral propionates: Helmchen, G. and Schmierer, R. ibid. (1983) 1235 and references therein.
4. See, for example, Dale, J. "Stereochemistry and Conformational Analysis", Universitetsforlaget - Verlag Chemie 1978, pp. 83 - 84.
5. Kaiser, E.M. and Woodruff, R.A. J. Org. Chem. (1970) 35 1198.
6. House, H.O., Chu, C-Y., Wilkins, J. M. and Umen, M. J. J. Org. Chem. (1975) 40 1460.
7. Hashimoto, S., Yamada, S. and Koga, K. J. Am. Chem. Soc. (1976) 98 7450.
8. Hallnemo, G., Olsson, T. and Ullenius, C. J. Organometal. Chem. (1985) 282 133.
9. For a comprehensive review, see Lipshutz, B.H., Wilhelm, R.S. and Kozlowski, J.A. Tetrahedron (1984) 40 50005 and references therein.
10. Yamamoto, Y., Yamamoto, S., Yatagai, H., Ishihara, Y. and Maruyama, K. J. Org. Chem. (1982) 47 119.
11. For a very recent NMR study, see Lipshutz, B.H., Kozlowski, J.A. and Breneman, C.M. J. Am. Chem. Soc. (1985) 107 3197.
12. See, however, ref. 3b.
13. Stephenson, D.S. and Binsch, G. QCPE (1978) 12 365.
14. Allinger, N.L. and Yuh, Y. QCPE (1976) 12 318.
15. Stern, K., Olsson, T. and Tanner, D. Unpublished results.
16. Gream, G.E., Wege, D. and Mular, M. Aust. J. Chem. (1974) 27 567.
17. Dimmel, D.R. and Fu, W.Y. J. Org. Chem. (1973) 38 3778.

18. Coxon, J. M., Steel, P. J., Coddington, J. M., Rae, I. D. and Jones, A. J. Aust. J. Chem. (1978) 31 1223.

19. Sisti, A. J. and Rusch, G. M. J. Org. Chem. (1974) 39 1182.

20. Bredt, J. and Dussier, H. J. Prakt. Chem. (1918) 98 96.

21. See, for example, Wehrli, F. W. in "NMR Spectroscopy, New Methods and Applications", ACS Symposium Series 191 (1982) Levy, G. C., Ed., p.25 for a complete assignment of the NMR signals of camphor itself.

22. Fieser, L. F. and Fieser, M. "Reagents for Organic Synthesis" Wiley, 1967 p. 584.

23. The 270 MHz ^{1}H NMR and the mass spectral data as well as the TLC mobility of this substance were identical to those of racemic material prepared from methyl crotonate via conjugate addition of $LiBu_2Cu$ (Et_2O, $-25^{\circ}C$) followed by reduction of the adduct with lithium aluminium hydride, as described in the Experimental section.