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TETRAHEDRON: *ASYMMETRY*

A new chiral oxazoline derived from camphor and its conversion to (*R*)-2-methylalkanoic acids

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Abstract

(1*S*,5*R*,7*R*)-(–)-10,10-Dimethyl-3-ethyl-4-oxa-2-azatricyclo[5.2.1.$0^{1,5}$]dec-2-ene **2** was prepared in 95% yield from (1*S*)-1-amino-2-*exo*-hydroxyapocamphane **1**. The chiral oxazoline could be alkylated (LDA/THF/–78°C/RX, RX = ethyl, *n*-propyl, *n*-butyl iodides or benzyl bromide) to **3** in 95% yield and >95% diastereoselectivity, and the products hydrolysed to (*R*)-2-methylalkanoic acids **4** (43–47% yield, 93–98% e.e.).

Among the methodologies utilising a stoichiometric equivalent of a chiral auxiliary, the alkylation of chiral oxazolines has retained its importance in the armoury of asymmetric synthesis. Introduced by Meyers[1–3] in the mid 1970s, the methodology enables the preparation of chiral 2-alkylalkanoic acids in excellent yields and enantiopurity. Although the elegant and pioneering studies of Meyers and co-workers have defined an area of asymmetric synthesis which is as exciting as it is utilitarian, scope for elaboration remains, if only by virtue of the importance of the process: for clearly, a diverse pool of auxiliaries—in both enantiomeric forms wherever possible—only enhances the value of an asymmetric synthetic methodology. We set out to design a new chiral oxazoline based on a proven chiral framework—that of camphor—and in the event developed a methodology that offered considerable advantages over existing ones.

The Meyers methodology[1–3] relies on the diastereoselective alkylation of a chiral 2-ethyloxazoline anion, the oxazoline moiety thus serving as a chiral carboxyl protecting group and the anion as a masked enolate. Initial work by the Meyers group on (4*S*,5*S*)-2-ethyl-4-methoxymethyl-5-phenyl-1,3-oxazoline indicated that a combination of three factors was essential for good stereoselectivity (Scheme 1): the kinetically controlled formation of the (*Z*)-azaenolate, the presence of the C_5-phenyl group and the chelation of the lithium counterion by the C_4-methoxymethyl group. The formation of the (*Z*)-azaenolate—non-equilibrating with the (*E*)-form—allows for the play of facial selectivity, which is then partly defined by the steric hindrance offered by the

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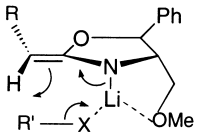
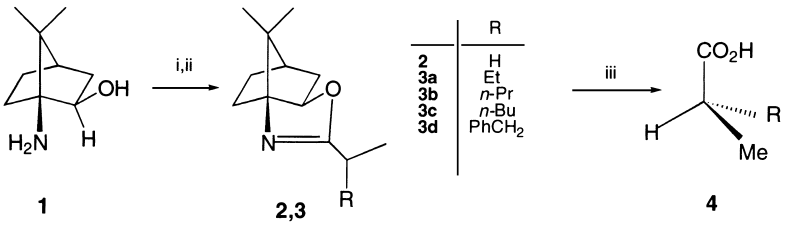
C_5-phenyl group on the 'top' face. Furthermore, the above chelation of the counterion was deemed equally critical, as it allowed the alkyl halide to be guided to the 'bottom' face via coordination of the halide atom to the lithium ion: in the absence of this interaction, presumably, steric hindrance by the C_4-substituent would dominate with a resulting loss of facial selectivity.



Scheme 1.

Such are the broad contours of the Meyers methodology. A consideration of the mechanism leads to a key conclusion: the fact that both the C_5-phenyl and C_4-methoxymethyl groups are required indicates that the C_5-phenyl group is not by itself efficient in blocking the 'top' face of the azaenolate (Scheme 1). Clearly, a larger group than phenyl at C_5 may obviate the necessity for the above chelation-guided process at the 'bottom' face of the azaenolate. In principle, a geometrically defined azaenolate in conjunction with efficient blocking of one face of this enolate—whether at C_4 or C_5—should provide high selectivity. The present studies address these possibilities (indeed, more recent work has indicated that a *t*-butyl group at C_5 can meet the above criterion: naphthalene appended with a chiral oxazoline derived from *t*-leucinol added alkyl lithium in excellent diastereoselectivity.[4] However, we are not aware of the extension of these studies to include simple alkylation processes, so their generality has apparently not been defined).

The camphor framework has inspired the design of several chiral auxiliaries analogous to the oxazoline, most notably the oxazolidinone[5] but also the imidazolidinone[6] and the oxazinone,[7] not to mention[8] the sultam. The analogues were mostly derived from either 3-amino-2-hydroxyapocamphane or 1-amino-2-hydroxyapocamphane. In the present studies, an oxazoline was prepared starting from the known[5b,9,10] (1*S*,2*R*,4*R*)-1-amino-2-hydroxyapocamphane **1** (Scheme 2), obtained via $NaBH_4$ reduction of (1*S*)-(+)-1-aminoapocamphane, derived from the commercially available (1*S*)-(+)-camphorsulphonic acid via oxidation to (1*S*)-(+)-ketopinic acid[11] and a Curtius rearrangement[9,10] of its azide. Treatment of amino alcohol **1** with ethyl iminopropionate hydrochloride[1–3] and a large excess of sodium bicarbonate in refluxing chloroform for 48 h, afforded (1*S*,5*R*,7*R*)-10,10-dimethyl-3-ethyl-4-oxa-2-azatricyclo[5.2.1.$0^{1,5}$]dec-2-ene **2** in 95% yield (Scheme 2). The oxazoline **2** was characterised spectroscopically: the IR showed absorption at 1630 cm^{-1}, ascribed to C=N; the ^1H NMR showed a doublet of a doublet at δ 4.12 ascribed to OC*H*; the ^{13}C NMR showed resonances at δ 169.8 (C_3), 88.5 (C_5) and 81.0 (C_1); and a satisfactory high resolution mass was obtained.



Scheme 2. (i) EtOC(Et)=NH/$NaHCO_3$; (ii) LDA/THF/–78°C/RX; (iii) Ac_2O/Δ–KOH/MeOH/Δ–H_3O^+

The alkylations of the chiral oxazoline **2** were investigated via lithium diisopropylamide mediated deprotonation in tetrahydrofuran solution at –78°C.[1–3] The alkyl halides employed were ethyl, *n*-propyl and *n*-butyl iodides, and benzyl bromide (Scheme 2). The alkylations were generally complete in 2 h, and yielded only one diastereomeric product **3** as far as could be discerned by NMR, in 95% yield (Table 1). However, when the reaction was performed at –20°C two diastereomeric products were discernible, as indicated by the resonance of the (O-C-H) proton at C_5: this appeared as a doublet of a doublet in the δ 4.04–4.16 region with a mean separation of 0.05 ppm between the diastereomers; the diastereomeric excess was consistently 33% at –20°C. All the alkylated products **3** were characterised by IR, ^{1}H and ^{13}C NMR, and high resolution mass spectra.

Table 1
Yields and diastereomeric excesses (d.e.) obtained for the alkylation of the oxazoline **2** with RX at –78°C, and yields and enantiomeric excesses obtained for the hydrolyses of the alkylated oxazolines **3** to the carboxylic acids **4**

RX	Oxazoline	% yield	% d.e.	Acid	% yield	% e.e. (*)
EtI	**3a**	95	> 95	**4a**	43	97 (78)[2]
n-PrI	**3b**	95	> 95	**4b**	47	98 (72)[2]
n-BuI	**3c**	95	> 95	**4c**	43	94 (75)[2]
$PhCH_2Br$	**3d**	95	> 95	**4d**	45	93 (74)[2]

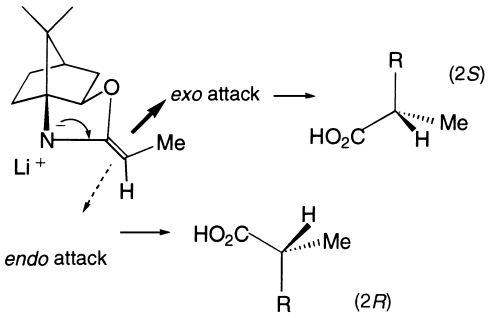
(*) refer to reported e.e. values for the alkylation-hydrolysis of (4*S*,5*S*)-2-ethyl-4-methoxymethyl-5-phenyl-1,3-oxazoline at –98 °C (–78 °C for *n*-BuI and $PhCH_2Cl$);[1-3] e.e.'s were determined from specific rotations and reported[3,8] [α] values; oxazolines **2** and **3** were purified chromatographically over neutral Al_2O_3 (EtOAc-hexane), and acids **4** by distillation; all compounds were characterised spectroscopically, and additionally by high resolution mass for new ones.

The hydrolyses of the alkylated oxazolines **3** were then investigated, previous reports[1–3] having indicated that these could be accompanied by considerable racemisation. Indeed, the hydrolysis of the benzyl derivative **3d** in 6N HCl furnished only racemic 2-methyl-3-phenylpropanoic acid; with 6N or 18N H_2SO_4 an enantiomeric excess of only 40% was realised. It seemed likely[1–3] that the racemisation occurred during the slow cleavage of the partially hydrolysed intermediates, particularly the hydroxyamide derived by cleavage of the O–C_3 bond in **3d**. This was avoided by cleaving the oxazoline ring with refluxing acetic anhydride over 24 h to obtain the putative *N*-acetyl-*O*-acyl derivative of the amino alcohol **1** ('acyl' as derived from **4**): this was not isolated but hydrolysed further in refluxing methanolic KOH to the final products, the 2-methylalkanoic acids **4** and the *N*-acetyl derivative of **1** (Scheme 2). The acids **4** were thus obtained in around 45% yield (after distillation), and characterised by their physical constants, ^{1}H NMR spectra and

specific rotations. The above *N*-acetyl derivative was isolated and hydrolysed with refluxing 6N HCl for 12 h to recover the chiral auxiliary, the amino alcohol **1** in 60% yield.

The specific rotations showed that the e.e. values for the acids **4** obtained as above were in the range 93–98% (Table 1). Thus, although the yields of **4** are moderate as compared to the Meyers methodology[1–3] (~45% vs 62–84%), the e.e. values are substantially higher in the present method (~95% vs. ~75%). Also to be considered is that the reported methodology[1–3] in some cases employs lower temperatures for the alkylation than in the present case (Table 1).

From the known[1–3] correlation of configuration and rotational sign for **4**, the presently obtained forms—being levorotatory—must possess the *R* configuration at C_2. This suggests a transition state for the alkylation of the oxazoline **2** as depicted in Scheme 3: the (*Z*)-azaenolate suffers electrophilic attack at the face that corresponds to the *endo* side of the camphane moiety. Molecular models indicate that the alternative face is severely hindered by the *gem*-dimethyl bridge (C_{10}): its methyl group *syn* to the oxazoline moiety looms over one face of the azaenolate; also, the overall rigidity of the camphane framework ensures that this steric shielding cannot easily be overcome by simple deformations. Interestingly, the (C_{10}) bridge corresponds to the C_5-substituent, and the C_6-methylene bridge (in **2**) to the C_4-substituent, in Meyers oxazoline (cf. Scheme 1). Also noteworthy is that the camphane skeleton ensures that the above two bridging substituents in the present oxazoline **2** are mutually *gauche* rather than *anti* as in the Meyers case (Scheme 1). Clearly, the origins of the stereoselectivity in these two cases are different.



Scheme 3.

A temperature dependence study indicated that the temperature at which the alkylation was performed—rather than the temperature at which the deprotonation was performed—determined the stereoselectivity. Thus, deprotonation of the oxazoline **2** as above at either –78°C or –20°C, followed by alkylation with *n*-butyl iodide at –78°C, afforded the (hex-2-yl)oxazoline **3c** in high diastereoselectivity (d.e. >95%, by NMR). However, deprotonation of **2** at –78°C followed by alkylation (*n*-BuI) at –20°C furnished **3c** in very low diastereoselectivity (d.e. ~30%, by NMR). These results most likely indicate a weighted equilibrium favouring the *Z*-form of the oxazoline anion over the *E*-form at –78°C, followed by preferential 'underside' alkylation (Scheme 3). The alternative would involve a selective—but temperature independent and hence unlikely—formation of the *Z*-form.

In fact, the above results accord well with the detailed results of the Meyers group,[1–3] which showed that the temperature of metallation did not affect the stereoselectivity in the case of LDA (although it did in the case of *n*-BuLi). The present mechanism departs from the Meyers mechanism in allowing for equilibration between the (*E*)- and (*Z*)-azaenolates, with the latter

being more stable and so prevailing at lower temperatures (it may well be that the internal chelation prevents isomerisation of the azaenolate in the Meyers oxazoline).

In summary, a novel chiral oxazoline has been introduced, which compares favourably with available analogues. Its utility in the synthesis of chiral 2-alkylalkanoic acids has been demonstrated. Both the first alkylation step and the subsequent hydrolysis step are characterised by very high stereoselectivity, although the hydrolysis occurs in relatively moderate yields. Further work that would extend the scope of the present study is planned.

Acknowledgements

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