Synthesis *via* Oxazolines. A Highly Stereoselective Synthesis of (±)-*cis*-2-Methyl Cyclopentanecarboxylic Acid, *via* a Kinetically Controlled Cyclization

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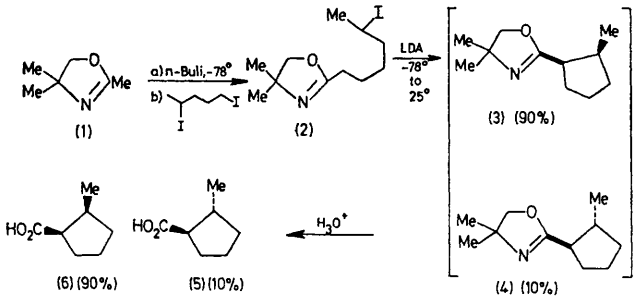
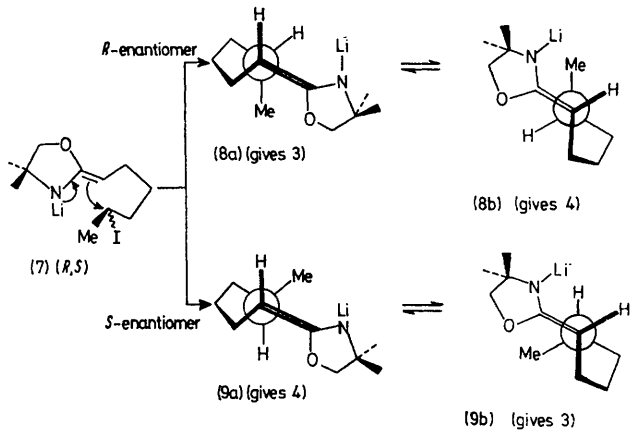
Summary A kinetically controlled cyclization using the lithio-salt of an oxazoline and 1,4-di-iodopentane gave *cis*- and *trans*-2-methyl cyclopentanecarboxylic acid in the ratio 9:1.

THE utility of 2-oxazolines as a source of acetic acid homologues has been previously reported.[1] We now describe a synthesis of 2-methyl cyclopentanecarboxylic acids [(**5**) and (**6**)] which is highly stereoselective, furnishing the thermodynamically less favoured *cis*-isomer (**6**) over the *trans*-isomer (**5**) in a ratio of 9:1. Although 2-methylcyclopentanecarboxylic acid has been prepared by a number of routes, all give either mainly the *trans*-acid (**5**) or an approximately equal mixture of both.[2] The significance of the present method lies in the fact that the *cis*-isomer is formed *via* a kinetically controlled cyclization step under conditions which do not epimerize the product to the more stable *trans*-isomer.

The scheme is initiated by metallation (n-BuLi, −78°, THF) of the oxazoline (**1**) and alkylation with 1,4-di-iodopentane (−78°) producing the iodoalkyl oxazoline (**2**). Without isolation of the latter, lithium di-isopropyl amide



(LDA) is then added (−78°) and cyclization to the cyclopentyl oxazolines occurs as the solution slowly (3—4 h) reaches ambient temperature.† Quenching the reaction mixture and extraction with ether gave (**3**) and (**4**) in a ratio of 9:1.‡ Hydrolysis (3N HCl, 3·5 h) of this mixture furnished (**5**) (10%) and (**6**) (90%) in 95% yield [70% overall based on (**1**)]. The n.m.r. spectrum showed the methyl doublet of (**5**) at 1·12 p.p.m. (broad, unresolved) and that of (**6**) at 0·98 p.p.m. (sharp) in a ratio of 1:9. Furthermore, v.p.c. of the acid mixture also showed (**6**) and (**5**) in a ratio of 9:1. The major component (**6**) was readily collected from the v.p.c. instrument and proved to be pure *cis*-acid (**6**), thus precluding any epimerization during the gas chromatographic analysis. The unusually high degree of stereoselectivity in the cyclization step may be rationalized by consideration of the lithio-salt (**7**), which is a racemate with respect to the carbon bonded to the iodine, and its possible conformations in approaching the transition state. By employing rotomer structures for the two conformers of the *R*-enantiomer, it is clear that (**8a**) possesses less non-bonded interactions than (**8b**) and therefore should approach the



transition state more readily. Alternatively, the *S*-enantiomer should reach the transition state faster as conformer (**9b**). Enantiomers (**8a**) and (**9b**) lead to racemic *cis*-cyclopentyloxazoline (**3**), whereas (**8b**) and (**9a**) lead to racemic (**4**).

The results tend to indicate that the lithio-salt (**7**) is a rigid species with the lithium firmly bound to the nitrogen and its steric requirements, including solvation, are sufficiently large to render significant differences in the non-bonded interactions in (**8a**) and (**9a**). This effect may carry significant implications in the synthesis of cyclic compounds from acyclic precursors.

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† The lithio-salt of (**1**) reacts rapidly with primary iodides at −78° and does not react with secondary halides until the temperature reaches −50° or higher. Thus, the initial alkylation step gives only (**2**).

‡ Pure *cis*-(**3**) and *trans*-(**4**) were collected from the v.p.c instruments: satisfactory i.r. and n.m.r. spectra and elemental analyses were obtained.

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