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Exploiting Steric Shielding: Tuning Terpenoid-Derived Oxazolidin-2-ones as Chiral Auxiliaries for the Diels-Alder Reaction

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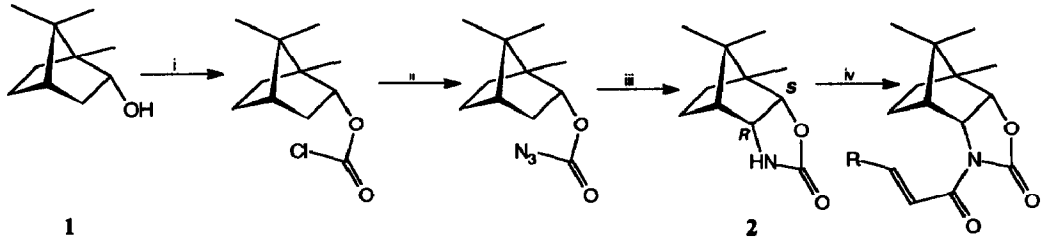
Abstract: Preparative methodology is described for access to three different terpenoid-derived oxazolidin-2-ones **4**, **8**, and **11**, of which the latter, obtained from camphene in four steps, provides virtually complete asymmetric induction when acting as a chiral auxiliary in Diels-Alder cycloaddition reactions with cyclopentadiene.

Following the seminal work by Evans[1] on the development of chiral oxazolidin-2-ones as auxiliaries in asymmetric reactions there have been numerous efforts[2] to design more efficient variants including a recent report by us[3] on the promising use of the enantiomerically pure 4,5-disubstituted oxazolidinone **2** which is sterically constrained by the rigid bornyl system. Preparative access to **2** was achieved by a nitrene-mediated three-step sequence from (-)-borneol **1** as depicted in Scheme 1 and although high levels of asymmetric induction were observed with **2** in alkylation, acylation and aldol reactions, Diels-Alder reactions were much less effective (Table 1) due to insufficient π-topological bias provided by the auxiliary when bearing acryloyl substituents.



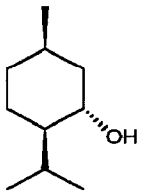
1 **2**

Scheme 1. *Reagents and conditions*:(i) phosgene, triethylamine, toluene-ether, 0°C, 4h; (ii) sodium azide, tetrabutylammonium bromide, dichloromethane-water, 25°C, 4h; (iii) flash vacuum thermolysis (300°C, 0.02 mmHg); (iv) *n*-butyl lithium, or methylmagnesium bromide followed by the appropriate α,β-unsaturated acid chloride (R = H, Me, Ph).

In this letter we describe the preparation of other likewise terpenoid-based oxazolidin-2-ones with the aim of introducing the necessary control element to bring about improved π-face discrimination in Diels-Alder reactions. For each new homochiral reagent the same synthetic protocol as used for **2** was employed and involved chloroformylation of the terpene alcohol followed by conversion into the corresponding azidoformate

and thermolysis under flash vacuum conditions[4] or in boiling 1,1,2,2-tetrachloroethane (TCE). In the final step to the required chiral dienophiles for use in asymmetric Diels-Alder reactions, the isolated oxazolidin-2-ones were functionalised at nitrogen with the appropriate α,β-unsaturated acid chloride by prior treatment with *n*-butyl lithium, or alternatively, methylmagnesium bromide to avoid polymerisation which could be a problem with acryloyl chloride.

The first terpene alcohol to be used as starting material was inexpensive *iso*-menthol **3** which was converted readily into the desired azidoformate in quantitative yield. Unfortunately when subjected to flash vacuum thermolysis, the latter gave rise to a mixture of two oxazolidin-2-ones **4** and **5** from nitrene insertion at C-2 and C-6, together with the six-membered oxazinone **6** originating from nitrene attack on the *iso*-propyl group, in the ratio of 7:1:2 respectively. The major oxazolidinone **4** could be isolated, albeit as a thick syrup (51%), but further applications of this auxiliary were not pursued when attempts to functionalise it resulted in the formation of thick gums which proved extremely difficult to purify.



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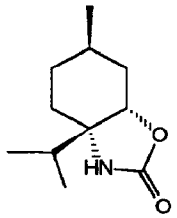

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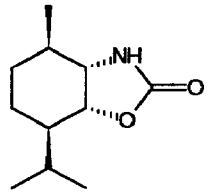

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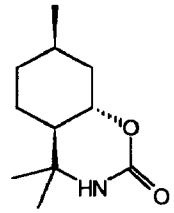

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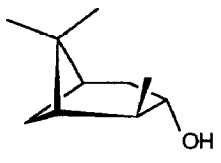
Greatly improved crystallinity was found from the same sequence of reactions when (-)-3-pinanol **7** was used as starting material. Thermolysis of its azidoformate under flash vacuum conditions (300°C, 0.02 mmHg) afforded a mixture consisting of oxazolidin-2-ones **8** and **9** in the ratio 3:1, reflecting the tendency of the nitrene intermediate to insert preferentially into *tertiary* C-H bonds compared with *secondary* C-H bonds. The major isomer could be easily isolated in 65% yield as colourless crystals (m.p. 155.5-156.0°C; $[\alpha]_D = -71.5°$ (c = 3.36, CH_2Cl_2)) following trituration with diethyl ether and recrystallisation from ethyl acetate.



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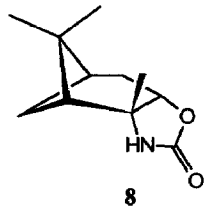

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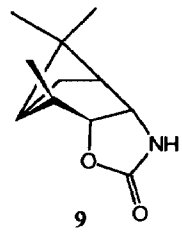

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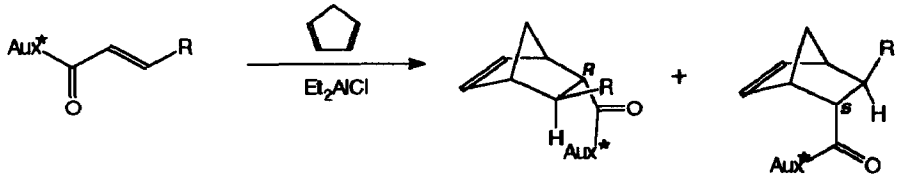
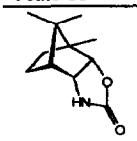
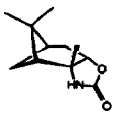
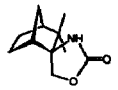
Disappointingly, the sterically crowded oxazolidin-2-one **8** imparted only poor levels of asymmetric induction in Et_2AlCl-mediated Diels-Alder cycloadditions of its *N*-acryloyl, *N*-crotonoyl, and *N*-cinnamoyl derivatives with cyclopentadiene (Table 1). This outcome is reflected in the X-ray structure of **8** (Fig. 1a) at 150K which establishes that both of its faces, and in consequence, those of the acrylate derivatives, are hindered to a similar degree, one by the methyl substituent adjacent to nitrogen and the other by the bridging methylene group of the four-membered ring of the terpenoid moiety.

Table 1. Diastereoselection in Lewis-acid catalysed Diels-Alder Cycloadditions of Chiral Acrylate Derivatives of Oxazolidin-2-ones **2**, **8**, and **11** with Cyclopentadiene

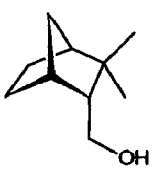


A **B**

Auxiliary Aux*H	R	Temp (°C)	Yield (%)	*endo*:*exo*	*endo* d.e.[a] A(*R*):B(*S*)
	H	-78	98	96:4	59
	Me	-78	96	100:0	71
	Ph	-20	99	100:0	99
2					
	H	-78	92	93:7	25
	Me	-78	100	97:3	33
	Ph	-20	96	95:5	32
8					
	H	-78	98	>99:1	95
	Me	-78	99	>99:1	99
	Ph	-78	97	>99:1	99
11					

[a]Determined by 360MHz ^{1}H NMR spectroscopy.

For this reason we chose *endo*-camphenol **10** (prepared from (-)-camphene by hydroboration followed by treatment with KOH/H_2O_2)[5] as the starting material and by a similar reaction process, albeit decomposition of the azidoformate in boiling TCE, to our pleasure obtained in 70% yield after recrystallisation from CH_2Cl_2/cyclohexane the spiro-oxazolidin-2-one **11** in enantiomerically pure form as a colourless crystalline compound (m.p. 226-227°C, $[\alpha]_D$ = +48°(c = 5.1,CH_2Cl_2)) whose structure was confirmed by X-ray crystallography (Fig.1b).The sole formation of **11** is notable when compared to the two previous processes, but can be explained by the overwhelming bias for nitrene insertion at C-3 to form a five-membered ring and the more sterically demanding option of attack at C-4 to afford a much less favoured six-membered ring.



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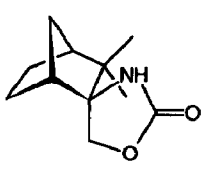
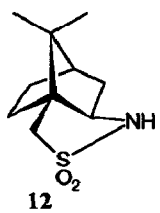


11



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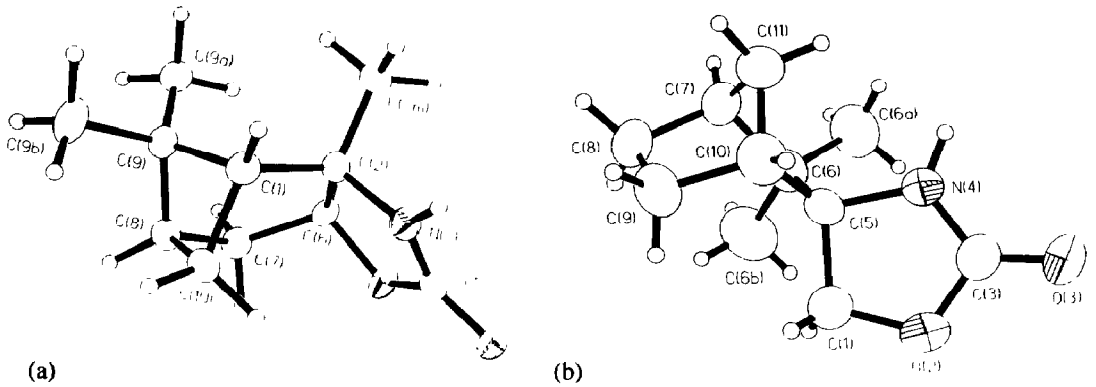
The efficiency of **11** as a chiral control element in the corresponding Diels-Alder reactions of its acrylate derivatives with excess cyclopentadiene are also given in Table 1. From the data it is evident that cycloaddition is regulated with much higher diastereoselectivity than that previously obtained with **4** and **8**. In each case *endo*-diastereoselection is *virtually complete* (in favour of adduct **A**), and to our knowledge, well in excess of levels attained by conventional chiral oxazolidin-2-ones[6] derived from amino acids, and even Oppolzer's camphor sultam **12**[7], which requires temperatures as low as -130°C to bring about a comparable outcome for the acryloyl (R = H) dienophile.



(a) (b)

Figure 1. ORTEP drawings of (a) oxazolidin-2-one **8** derived from (-)-pinanol, and (b) spirooxazolidin-2-one **11** derived from *endo*-camphenol.

This exceptional quality of asymmetric induction imparted by spirooxazolidin-2-one **11** is undoubtedly the result of propitious shielding of one of its faces by the masked *tert*-butyl group (see Fig. 1b), an effect that is extended to its acrylate derivatives such that cyclopentadiene can approach from one direction only.

Thus, we have successfully developed a powerful new addition to the panoply of chiral oxazolidin-2-ones for asymmetric chemical conversions. Work is now in progress to exploit and expand the synthetic usefulness of this new reagent and details will be reported in due course.

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