# *SYNTHESIS OF ENANTIOMERICALLY PURE (5S)*-4-AZA-2-OXA-6,6-DIMETHYL-7,10-METHYLENE-5-SPIRO[4.5]DECAN-3-ONE, A NOVEL CHIRAL OXAZOLIDIN-2-ONE FROM (-)-CAMPHENE FOR USE AS A RECYCLABLE CHIRAL AUXILIARY IN ASYMMETRIC TRANSFORMATIONS

Malcolm R. Banks[a], J. I. G. Cadogan[b], Ian Gosney[a], Keith J. Grant[a], Philip K. G. Hodgson[c], and Paul Thorburn[a]

[a]Department of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, Scotland
[b]Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London SW7 2AY, England
[c]B. P. International Ltd., Sunbury Research Centre, Chertsey Road, Sunbury-on-Thames, Middlesex TW16 7LN, England

*Abstract*- By an intramolecular nitreno-mediated route (-)-camphene is transformed into a novel spiro-oxazolidin-2-one whose efficiency as a chiral auxiliary is highlighted by the excellent levels of chiral induction attained in an array of asymmetric transformations such as the Diels -Alder, conjugate addition , aldol condensation, alkylation and acylation reactions.

Preparative access to chiral oxazolidin-2-ones, whether as reagents for asymmetric manipulations[1] or as chiral derivatising agents (CDA) for the resolution of racemic amines *etc.*, employ direct cyclocarbamation of relatively expensive optically pure β-amino alcohols, or resort to the tedious separation of similarly prepared racemic analogues.[2] We have recently reported the enantiospecific synthesis of a terpenoid-derived tricyclic oxazolidin-2-one (**1**) from readily available [(1*S*)-*endo*]-(-)-borneol by a nitreno-mediated route and demonstrated its usefulness as a chiral auxiliary in a variety of asymmetric transformations[3] and as a CDA for the resolution of racemic amines, carboxylic acids and alcohols.[4] The reagent (**1**) performed well in acylation, alkylation and aldol reactions but Lewis-acid mediated Diels-Alder reactions were disappointing. The reason for this unsatisfactory diastereoselection was thought to be steric in origin and reflected the

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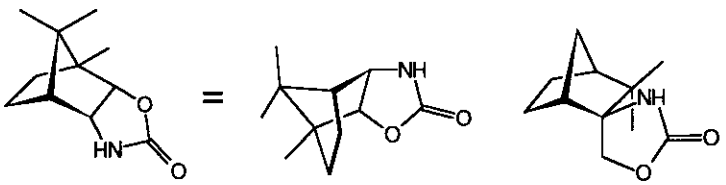
We dedicate this paper to our friend and colleague Professor Alan Katritzky, FRS on the occasion of his 65th birthday and in recognition of his many pioneering contributions to, and stentorian enthusiasm for, heterocyclic chemistry.

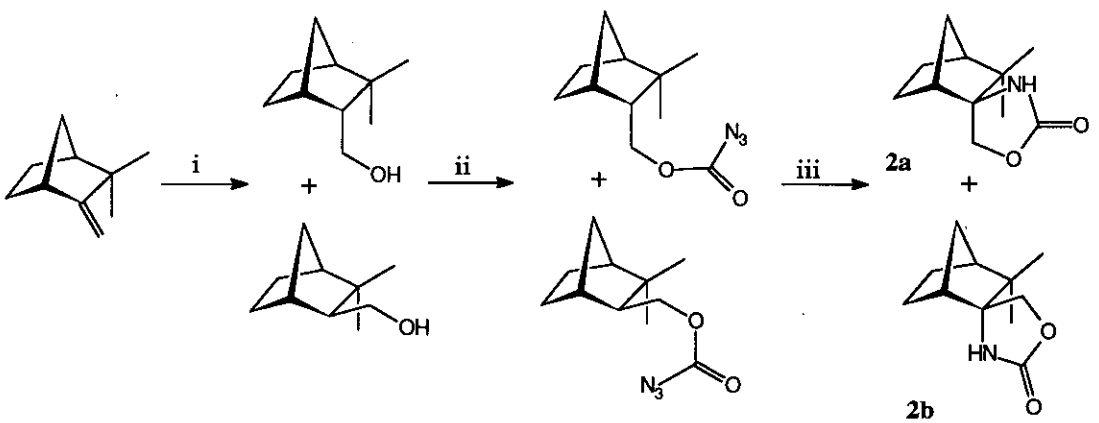
inability of **1** to provide the required topological bias to control rotameric preference in the conformations adopted by its *N*-substituted acryloyl derivatives.



**1** **2a**

With this in mind, we have designed a camphene-based oxazolidin-2-one (**2a**) with the necessary control element, *i.e.* masked *tert*-butyl group, to improve π-face discrimination and bring about very high levels of diastereoselection in Diels-Alder reactions and other asymmetric transformations. In this connection it is worth noting that due to propitious blocking of different faces of the oxazolidin-2-one ring in auxiliaries (**1**) and (**2a**), products of the opposite stereochemical sense will result in the ensuing diastereoselective processes.

For the preparation of the new chiral reagent (**2a**) in an optically pure state we used the same device of intramolecular nitrene delivery as before. This process outlined in Scheme 1 was achieved *via* hydroboration

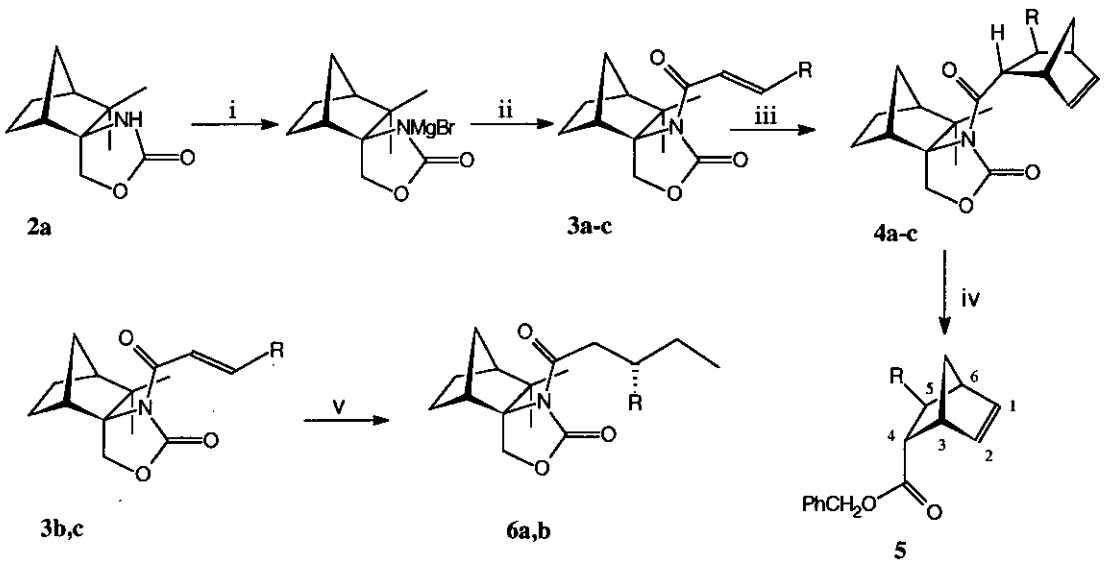


>90% (*endo:exo* 85:15)

**Scheme1**

*Reagents and conditions:* i, $BH_3$:THF then KOH, $H_2O_2$; ii, $3COCl_2$, $1.1NEt_3$ (>95%) isolate then $2NaN_3$, PTC (>95%); iii, thermolysis in TCE, 147°C, (65-70%).

of (-)-camphene[5] which yielded predominantly *endo*-camphenol in excellent yield (>90%, *endo*:*exo* 85:15). Conversion of the isomeric alcohols into their azidoformates *via* the chloroformate and subsequent thermolysis by dropwise addition to boiling 1,1,2,2-tetrachloroethane (TCE) at 2-3% concentration gave a 90% yield of an epimeric mixture of the spiro-oxazolidin-2-ones (**2a**) and (**2b**) from which **2a** was isolated in 65-70% yield after two fractional crystallisations from $CH_2Cl_2$: cyclohexane.[6] The spiro-oxazolidin-2-ones (**2a**) and (**2b**) could also be easily separated by flash chromatography on silica using ether: n-hexane as eluent.




**Scheme 2**

*Reagents and conditions:* i, MeMgBr, THF; ii, RCH=CHCOCl, -78°C, (**3a**, R=H, **3b**, R=Me, **3c**, R=Ph; yields: 29, 80, 87% respectively); iii,cyclopentadiene, 1.6 $Et_2AlCl$, $CH_2Cl_2$ -78°C; iv, 1.5 $PhCH_2OH/Bu^nLi$, THF, -78°C to room temperature; v, 4 $Et_2AlCl$, -78°C (**6a**, R=Me, **6b**, R=Ph; yields: 100, 100% respectively).

In order to prepare the chiral unsaturated carboximides (**3a-c**) as dienophiles for the Diels-Alder reactions, we adopted the method of Evans[7] whereby the oxazolidin-2-one (**2a**) was treated successively with MeMgBr and the appropriate α,β-unsaturated acid chloride in THF under carefully controlled conditions (Scheme 2). Cycloaddition of **3a-c** with freshly cracked cyclopentadiene in $CH_2Cl_2$ occurred at -78°C in the presence of 1.6 equiv. of $Et_2AlCl$ as Lewis-acid promoter to produce adducts (**4a-c**) in almost quantitative yield. From the results of these reactions shown in Table 1 it is evident that auxiliary (**2a**) induces significantly

higher levels of diastereoselection in the Diels-Alder reactions than the corresponding reactions with **1**.[8] Moreover, cleavage of **4b** and **4c** with lithium benzyl oxide afforded the 4*S*, 5*S* benzyl esters (**5b**) [91%, $[\alpha]_D = +127°$ (20°C, c = 2.44, $CH_2Cl_2$)] and (**5c**) [95%, $[\alpha]_D = +124°$ (22°C, c = 2.36, $CH_2Cl_2$)]of opposite sign to those obtained with **1** but identical to those derived with Evans' (*S*)-valinol-based oxazolidin-2-one.[7] In both cases auxiliary (**2a**) was recovered unchanged in 90% and 97%, respectively.

**Table 1.** $Et_2AlCl$-promoted reactions of dienophiles (**3a-c**) with cyclopentadiene to produce (**4a-c**) including corresponding yields for analogues derived from (**1**).

| Compound | %Yield**4a-c** (corresponding % yield for **1**) | de %* (corresponding de% for **1**) |
|---|---|---|
| **3a**, R=H | 98 (98) | >95 (60) |
| **3b**, R=Me | 99 (96) | 99 (60) |
| **3c**, R=Ph | 97 (99) | 98 (99) |

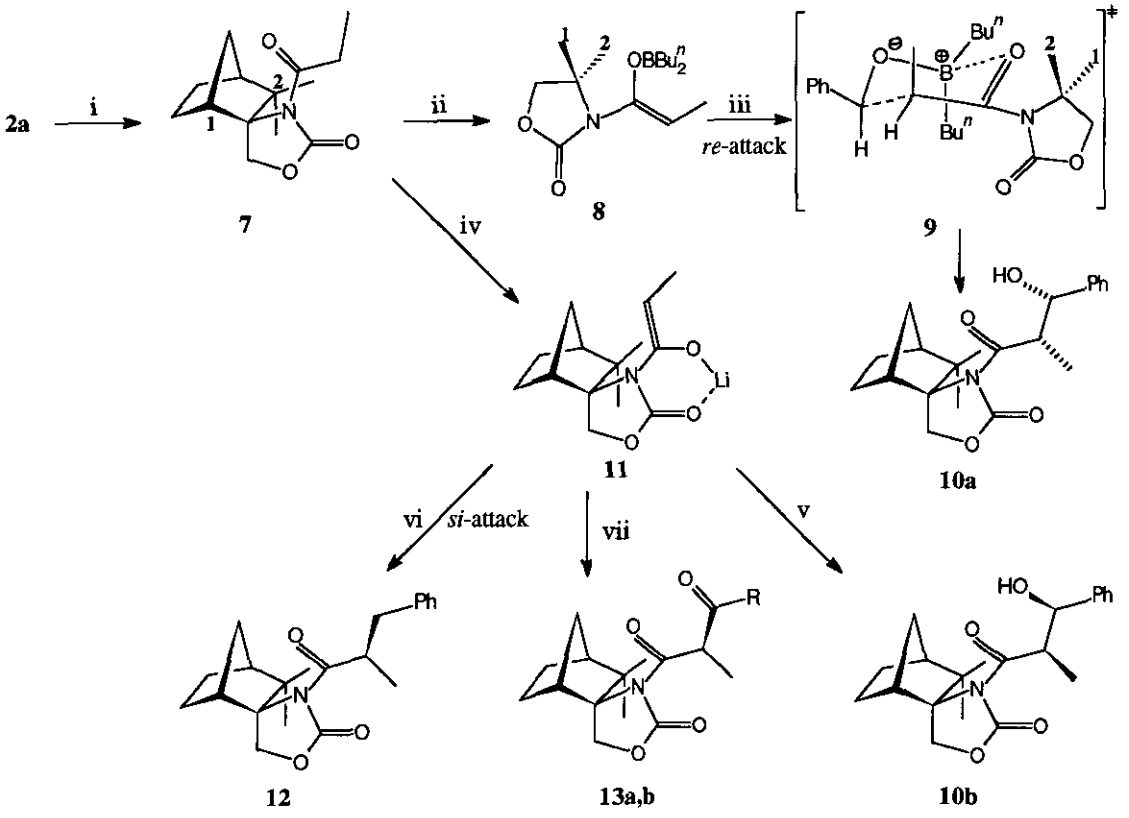
*Diastereoisomeric excesses (de) were determined by 360 MHz $^1H$ nmr spectroscopy.

With the crotonoyl and cinnamoyl derivatives (**3b**)and (**3c**) in hand we decided to investigate the stereochemical outcome of their 1,4-conjugate addition reaction with $Et_2AlCl$ (4 equiv.). Both chiral unsaturated carboximides readily underwent β-alkylation reactions from the re-face to give products (**6a**) and (**6b**) in quantitative yield with excellent diastereoselection (**6a**, de 99%; **6b**, de 90%) when compared to the corresponding adducts from **1** (11%, 43%de respectively). In each case cleavage of the adduct with lithium hydroperoxide afforded the chirally pure pentanoic acid, *e.g.* 3*S*-phenyl, in quantitative yield with almost complete recovery of the auxiliary.

On the basis of the markedly increased steric shielding provided by the new auxiliary (**2a**) *vis-à-vis* (**1**) in the foregoing reactions, we synthesised the crystalline *N*-propionyl derivative (**7**) (78% yield) as shown in Scheme 3 in order to probe its effectivness as a chiral auxiliary in aldol, alkylation and acylation reactions. The aldol condensation was studied involving both chiral boron (**8**) and lithium enolates (**11**) in reactions with PhCHO in $CH_2Cl_2$. Excellent diastereoselection was observed with the dibutylboron enolate (**8**) (de 95%) and the major aldol product (**10a**) was determined to be *erythro* by high field $^1H$ nmr spectroscopy ($J$ = 5.2 Hz) with the *threo*-products accounting for less than 5% of the crude reaction mixture. Subsequent cleavage of **10a** with lithium hydroperoxide followed by methylation with diazomethane afforded methyl

(2*S*, 3*S*)-2-methyl-3-hydroxy-3-phenyl propionate [94%,$[\alpha]_D$ = -19.2° (18°C, c = 4.4, $CH_2Cl_2$)][9] which verified the assigned stereochemistry as shown in Scheme 3.

By comparison, only moderate diastereoselectivity was found in the case of the lithium-chelated (Z)-enolate (**11**) generated from **7** with freshly prepared $Pr^i_2NLi$ (*erythro:threo* 81:19, *erythro* de 31%). A noteworthy feature of this reaction is that the *erythro*-isomer (**10a**) generated using boron is diastereomerically opposed to its isomer (**10b**) obtained with lithium as the counter-ion, this reversal in topicity arising because of the cyclic chelate (**11**).




**Scheme 3**

*Reagents and conditions*: i,3.0 M MeMgBr in $Et_2O$, THF, 0°C then -78°C, EtCOCl; ii, 1 M di-n-butylboron triflate in $CH_2Cl_2$, 0°C, $Pr^i_2EtN$; iii, -78°C, PhCHO; iv, 1.1 $Pr^i_2NLi$, 0°C,THF; v,-78°C, PhCHO; vi, -78°C, $PhCH_2Br$, NaI then -10°C; vii, -78°C, RCOCl, (**13a**, R=Me, **13b**, R=Et); yields: 90, 97% respectively).

The poor levels of stereoregulation found in the lithium enolate-mediated reaction matches those results obtained for chiral auxiliary (**1**) and PhCHO,[3] in keeping with similar results reported by other groups for

chiral auxiliaries derived from (1*S*, 2*R*)-norephedrine[10] and (+)-camphor.[11] The greater diastereoselectivity achieved with the use of the boron enolate (**8**) is comparable to the auxiliaries just mentioned and can be rationalised in terms of the Zimmerman-Traxler six-membered cyclic transition state (**9**)[12] in which only the $C_{\alpha}$-*re* face is open to attack.

It has been suggested by Heathcock[13] that the lithium cation can simultaneously coordinate three oxygen atoms in the transition state, which in turn orients the auxiliary in such a way that the two enolate faces are differentiated. On the other hand, boron bears two butyl substituents and can coordinate only two oxygens as depicted in (**9**). Since boron enolates are not very reactive species it is necessary that the aldehydic carbonyl be activated before aldol addition can occur. The required carbonyl-activation is brought about by coordination with a Lewis acid. In the absence of an external Lewis acid this activation must be provided by the boron atom and it follows that in the closed transition state (**9**) boron is coordinated with oxygen from the enolate and aldehyde and can no longer be coordinated with the oxazolidinone carbonyl group.

The opposite sense of diastereofacial bias imparted by **2a** when compared to **1** is further reflected in the alkylation of the chelated lithium enolate (**11**) with $PhCH_2Br$ at -10°C in the presence of NaI which proceeded from the less hindered *si*-face to produce α-alkylated **12** with *R*-configuration in 74% yield with a de of 84%. By comparison the analogous reaction with **1** gave the (*S*)- alkylated product in 80% yield with a de of >99%. Similarly, reaction between lithium enolate (**11**) and acyl chlorides at -78°C produced *C*-acylated derivatives (**13a**) and (**13b**) in high chemical and optical yield (**13a** de 86%, **13b** de >90%). This result compares well with the selectivity found for the associated reactions reported for **1** (R=Me, yield 88%, de 82%; R=Et, yield 89%, de >99%).[3]

On the basis of these preliminary results it is evident that the (-)-camphene-derived spirooxazolidin-2-one (**2a**) constitutes a powerful new addition to the existing armoury of preparatively useful chiral auxiliaries. For most asymmetric transformations, and especially Lewis acid-mediated Diels-Alder reactions, it offers exceptionally high levels of diastereofacial differentiation, and in this respect, it is superior to its predecessor, the likewise terpenoid-based tricyclic oxazolidin-2-one (**1**). An added benefit to **2a** is that its optical antipode is readily accessible from (+)-camphene, which in turn can be obtained from cheap (+)-α-pinene in two steps, thereby allowing preparative access to both enantiomeric products in a range of asymmetric manipulations.

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