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NEW CAMPHOR-DERIVED AUXILIARIES IN METHOXYSELENYLATION AND METHOXYBROMINATION WITH OPPOSITE DIASTEREOFACIAL SELECTIVITY. PREPARATION OF β-AMINO ALCOHOL CHIRAL SYNTHONS

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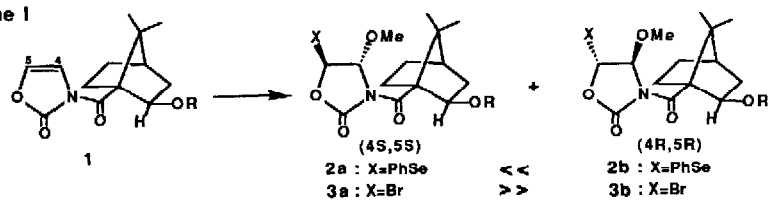
Summary: Methoxyselenylation and methoxybromination of chiral 3-acyl-2-oxazolones with PhSeCl/MeOH and Br_2/MeC(OMe)$_3$ smoothly proceed to result in highly stereoselective formation of chiral synthons for β–amino alcohols, but with ***opposite*** π-facial selectivity.

Among the extensively explored chiral auxiliaries, functionalized camphor skeletons have proved to be highly versatile in numerous asymmetric reactions, which have increasingly contributed to chiral synthesis of enantiomerically pure natural products.[1] The advantageous features of this class of templates arise chiefly from the ease of logical design of conformationally rigid derivatives and the ready availability of both enantiomers.

In this paper we wish to describe the practical utility of newly introduced 2-*exo*-hydroxy-1-apocamphanecarboxylic acid[2] (HAC) ((*1S*) or (*1R*)-7,7-dimethyl-2-hydroxybicyclo-[2.2.1]heptane-1-carboxylic acid) derivatives as chiral directors in enantioselective functionalizations of 2-oxazolone, a building block for β-amino alcohols.

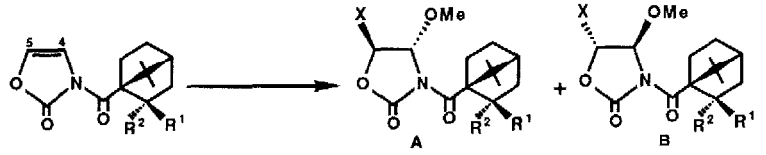
We previously developed a promising methodology to utilize 2-oxazolidinones substituted with easily replaceable unlike groups at the C_4 and C_5-positions as key intermediates for the preparation of β-amino alcohols.[3] Such versatile synthons, reactive to both ionic and radical species, could be provided by highly enantioselective introductions of functional groups such as halogeno, selenenyl, sulfenyl, alkoxy and acyloxy groups at the olefinic moiety of 2-oxazolone heterocycles. Thus, methoxyselenylation and methoxybromination with phenylselenenyl chloride/methanol and bromine/trimethyl orthoacetate[3] were performed on a series of

Scheme I



chiral 3-acyl-2-oxazolides (**1**), readily available from 2-oxazolone and 2-*exo*-alkoxy-1-apocamphanecarboxylic acids.[4] Both functionalizing reactions smoothly proceeded under mild conditions to give highly regioselective and face-differentiated addition products, trans-5-phenylselenenyl- and trans-5-bromo-4-methoxy-2-oxazolidinones (**2a,b** and **3a,b**), but surprisingly with ***opposite*** π-facial selectivity. Chiral auxiliaries examined in this face-differentiating study were 2-functionalized 1-apocamphanecarboxylic acids such as 2-*exo*- and *endo*-alkoxy[4] and 2-*exo*-alkyl derivatives[5] including the 2-oxo compound (ketopinic acid).[6]

Table 1 Diastereotopic Functionalizations of 3-Acyl-2-oxazolones.



R^1(*exo*)	R^2(*endo*)	Condition	X	Yield[a]	Ratio[b] A : B
OMe	H	PhSeCl, MeOH, 0°c, 24h	PhSe	83%	1 : 4
		Br_2, $MeC(OMe)_3$, TMSOTf, -78°c, 0.5h	Br	81	10 : 1
		Br_2, $MeC(OMe)_3$, -78°c, 0.5h	Br	89	12.5 : 1
		Br_2, $MeC(OMe)_3$, TMSOTf, 0°c, 0.5h	Br	79	5.7 : 1
OEt	H	PhSeCl, MeOH, 0°c, 24h	PhSe	84	1 : 8.3
		Br_2, $MeC(OMe)_3$, -78°c, 0.5h	Br	85	12 : 1
OPr^n	H	PhSeCl, MeOH, -50°c to r.t.	PhSe	86	1 : 8
		PhSeCl, MeOH, 0°C, 24h	PhSe	71	1 : 11
		Br_2, $MeC(OMe)_3$, TMSOTf, -78°c, 0.5h	Br	79	13 : 1
OCH_2CH_2OMe	H	PhSeCl, MeOH, 0°c, 24h	PhSe	94	1 : 19
		PhSeCl, MeOH, -20°c, 24h	PhSe	82	1 : 45
		Br_2, $MeC(OMe)_3$, -78°c, 0.5h	Br	79	17 : 1
H	OMe	PhSeCl, MeOH,- 50°c to r.t.	PhSe	81	1 : 1
		Br_2, $MeC(OMe)_3$, TMSOTf, -78°c, 0.5h	Br	36(45)[c]	1 : 1
H	OEt	PhSeCl, MeOH, 0° to r.t.	PhSe	83	1 : 1
		Br_2, $MeC(OMe)_3$, TMSOTf, -78°c, 0.5h	Br	42(16)[c]	1 : 1
Me	H	PhSeCl, MeOH, -50°c to r.t.	PhSe	69	1 : 1.5[d]
		Br_2, $MeC(OMe)_3$, -78°c, 0.5h	Br	80	1 : 1
=O		PhSeCl, MeOH, 0°C, 24h	PhSe	52	1 : 6.2
		Br_2, $MeC(OMe)_3$,T MSOTf, -78°C, 0.5h	Br	76	12 : 1

a) Isolated yields. b) The ratio was determined by ^{1}H-NMR spectra (400MHz) and both isomers were isolated to confirm the structures. c) Isolated yields of dibromo compounds.
d) Stereochemical assignment is tentative.

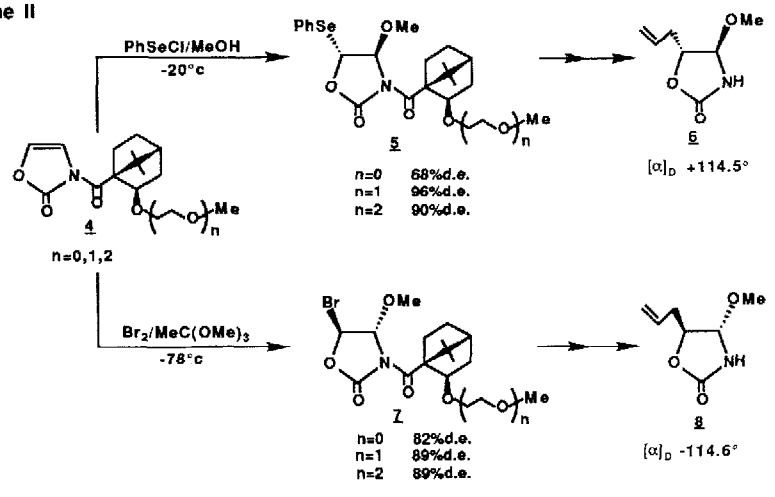
Thus, (+)-3-((*1S*)-2-*exo*-butoxy-1-apocamphanecarbonyl)-2-oxazolone (**1**, R=Bu) was treated with PhSeCl in methanol (at 0°C) to give 76% yield of (*4S,5S*)- and (*4R,5R*)-adducts (**2a**

and **2b**) in a ratio of 1 : 16, while treatment with bromine in trimethyl orthoacetate (at -78°C) gave a ratio of 12 : 1 of (*4S,5S*)- and (*4R,5R*)-isomers (**3a** and **3b**) in 85% yield, in contrast with the bromination in methanol which resulted in very poor selectivity of 1.2 : 1 even at -100°C.

Under the identical conditions, a poor diastereomeric ratio (1 : 3.8) was obtained in the methoxyselenylation of 3-(*1S*)-ketopinyl-2-oxazolone, which gave an excellent selectivity above 90%d.e. of the methoxybromo adduct as reported.[3] As indicated in Table 1, the 2-*exo*-alkoxy-1-apocamphanecarbonyl auxiliaries as well as the 2-oxo-derivative gave more or less analogous trends of opposite facial control in methoxyselenylation and methoxybromination reactions. In contrast, the 2-*endo*-alkoxy and 2-*exo*-methyl compounds gave no facial selectivity in either of the reactions, indicative of mechanistic significance of the oxygen atoms at the *exo*-position.

When (*1S*)-2-*exo*-methoxyethoxy-1-apocamphanecarboxylic acid (MOE-HAC) was used as an acyl auxiliary, the π-face discrimination was greatly improved to 96% d.e. (1 : 46) (96%yield) in the methoxyselenylation (at -20°C)[7] and above 89%d.e. (17 : 1)(79%yield) in the methoxybromination (at -78°C), though again in opposite directions of facial selection. Elongation of the 2-*exo*-substituent to methoxyethoxyethoxy group gave poorer results than the MOE derivative with regard to facial selectivity (Scheme II). Stereochemistry of the adducts thus formed was determined by free radical substitutions with allyltributyltin under UV-irradiation, followed by deacylation to 5-allyl-4-methoxy-2-oxazolidinones(**6** and **8**) of known configurations.[3]

Scheme II



This is the first example, to our knowledge, of the introduction of selenenyl and bromo functions into alkenes with *opposite* facial selectivity.[8] This provides a clean route for the preparation of β-amino alcohols in both enantiomeric forms from either of the starting isomers.

In conclusion, the presented data suggest that 2-*exo*-methoxyethoxy-1-apocamphanecarboxylic acid might be an auxiliary of choice for the preparation of chiral synthons leading to β-amino alcohols in both enantiomeric forms.

References and notes

(1) Oppolzer,W. *Tetrahedron* **1987**, *43*, 1969.

(2) Trivial name, apocamphane[6], is used in this paper for 7,7-dimethylbicyclo[2.2.1]heptane (7,7-dimethyl norbornane) skeleton for convenience.

(3) Kunieda,T.; Ishizuka,T.; Higuchi,T.; Hirobe,M. *J. Org. Chem.* **1988**, *53*, 3381

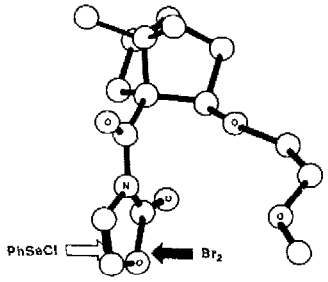
(4) Ketopinic acid methyl ester was easily reduced with L-Selectride (- 78°C,THF) to give methyl 2-*exo*-hydroxy-1-apocamphanecarboxylate exclusively, while reduction with $NaBH_4$ in the presence or absence of $CeCl_3$ resulted in poor ratios (**1** : 2 to 8 : 1) of the *exo* - and *endo*-alcohols. The *endo*-hydroxy derivative could be conveniently obtained by base-catalyzed epimerization of the *exo*-alcohol by way of retro-aldol reaction. This will be the subject of a separate paper (Ishizuka,T.; Kimura,K.; Kunieda,T.).

(5) The 2-*exo*-methyl compound was prepared in 64% by treatment of ketopinic acid with triphenylphosphonium methylides followed by hydrogenation (H_2/Pd-C).

(6) Bartlett,P.D.; Knox,L.H. *Org. Synth.* **1965**, *45*, 14, and 55

(7) The oxazolone **4** (n=1) with much enhanced reactivity afforded **5** in moderate yields (70%) and with higher selectivity (98%d.e.) at -30°C to -50°C, where no reaction occurred with 2-*exo*-methoxy and 2-*exo*-butoxy derivatives.

(8) Both reactions might involve the participation of three-membered cyclic intermediates, episeleniranium and bromonium ions, followed by anti-periplanar attack of nucleophiles.[9] The observed stereochemistry is consistent with the postulate that phenylselenenium ions approach the less hindered diastereotopic face to give thermodynamically favored intermediates, while coordination of bromine with oxygens of C_2-alkoxy substituents accelerates the attack from the sterically shielded side. The reaction paths would be depicted as in (**I**), provided that conformations determined by X-ray analysis of crystalline **4**(n=1) are operative in the reactions.[10]



(I)

Mechanistic studies to preclude other possibilities are necessary.

(9) (a) Schmid,G.H.; Garratt,D.G. *The Chemistry of Double-bonded Functional Groups. Part 2 Patai,S. Ed.*; John-Wiley & Sons: 1977 Chap. 9. (b) Paulmier,C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press, 1986: Chap. VII.

(10) Crystal data for compound **4** (n=1): orthorhombic, $P2_12_12_1$, a=9.693(2), b=21.435(6), c=7.946(2)A, Z=4. The structure was refined to R-value of 5.3%. Full details including ORTEP drawing and lists of atomic coordinates, thermal parameters, bond distances and bond angles have been deposited at the Cambridge Crystallographic Data Center. We are much indebted to Drs. N. Marubayashi and I. Ueda (Yoshitomi Research Laboratories, Fukuoka, Japan) for the X-ray analysis.

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