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Highly diastereoselective alkylation, acylation and aldol condensation of *cis*- and *trans*-(*N*-acyloyl)hexahydrobenzoxazolidin-2-ones

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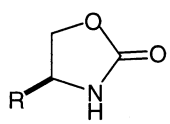
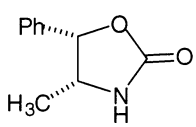
Abstract—The potential of hexahydrobenzoxazolidinones **1a–d** as chiral auxiliaries was explored. *N*-Acylation of **1a–d**, **2a–d** and **3a–d** was followed by methylation and benzylation via the corresponding sodium enolates generated by treatment with NaHMDS. Diastereoselectivities of 98% or higher were observed. The absolute configuration of the newly created stereogenic center was established by chemical correlation with 2-benzyl-1-propanol. The stereochemical results are congruent with addition to the electrophile from the less hindered face of a (*Z*)-configured enolate, the sodium cation being coordinated by both carbonyl oxygens of the substrate. *cis*- and *trans*-*N*-Propionyl derivatives **2a–d** were treated with Bu_2BOTf/Et_3N to give dialkylboron enolates **6a–d**, which were then reacted with acetaldehyde and benzaldehyde. ^1H and ^{13}C NMR analyses showed the formation of a single diastereomeric aldol addition product, whose relative configuration was ascertained as *syn* from the measurement of the $^3J_{H(2')/H(3')}$ coupling constants, and whose absolute configuration was determined by X-ray crystallographic analysis. The results are rationalized in terms of a Zimmerman–Traxler transition state, with a (*Z*)-configured enolate where boron is coordinated to the aldehyde carbonyl rather than the oxazolidinone carbonyl. Substrate **2a** was also reacted with acyl chlorides via the sodium enolate (NaHMDS). The effect of reaction conditions on *O*- versus *C*-acylation, as well as the influence of solvent and additives on diastereoselectivity, are discussed.

1. Introduction

One of the most practical methods for the enantioselective synthesis of chiral molecules involves the diastereoselective alkylation of enolates, whose C=C faces were rendered diastereotopic owing to the presence of chiral auxiliaries in the substrate.[1] The use of enantiomerically pure oxazolidin-2-one derivatives **A** and **B** as chiral auxiliaries in such asymmetric processes was first reported by Evans et al.[2] and the enormous utility of these and related oxazolidinones has been amply demonstrated.[3]



A, R = *i*-Pr, CH_2Ph, Ph, $CHPh_2$



B

In 1997 we reported[4] a convenient procedure for the preparation of both pairs of enantiomeric hexahydrobenzoxazolidin-2-ones **1a–d** from inexpensive cyclohexene oxide and (*S*)-α-phenylethylamine.[5] We now report the use of **1a–d** as effective chiral auxiliaries for the stereoselective alkylation, acylation, and aldol condensation of propionic and hydrocinnamic acids.

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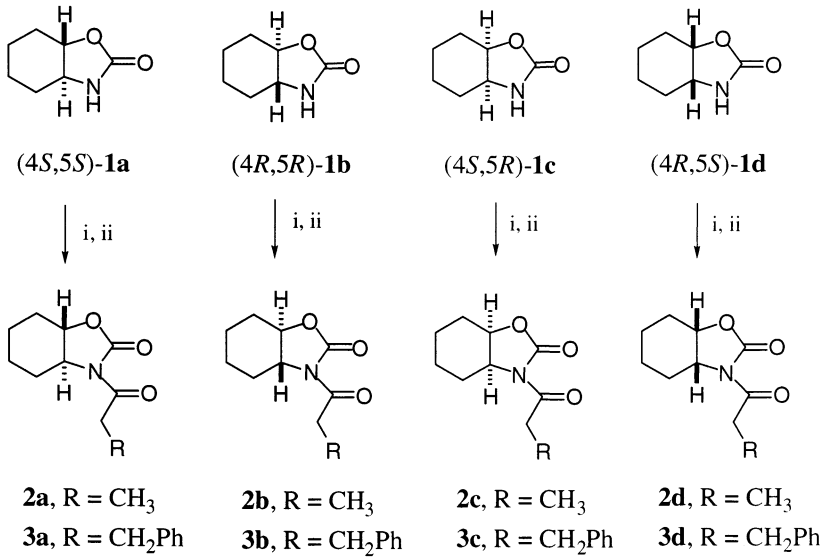
2. Results and discussion

cis- and *trans*-Hexahydrobenzoxazolidinones **1a–d** were *N*-acylated following the established protocol,[6] by treatment with *n*-butyllithium at 0°C, followed by addition (−78°C) of propionyl chloride to generate the *N*-propionyl derivatives **2a–d** (83–99% yield)[4] and of hydrocinnamoyl chloride to give **3a–d** (98–99% yield) (Scheme 1).

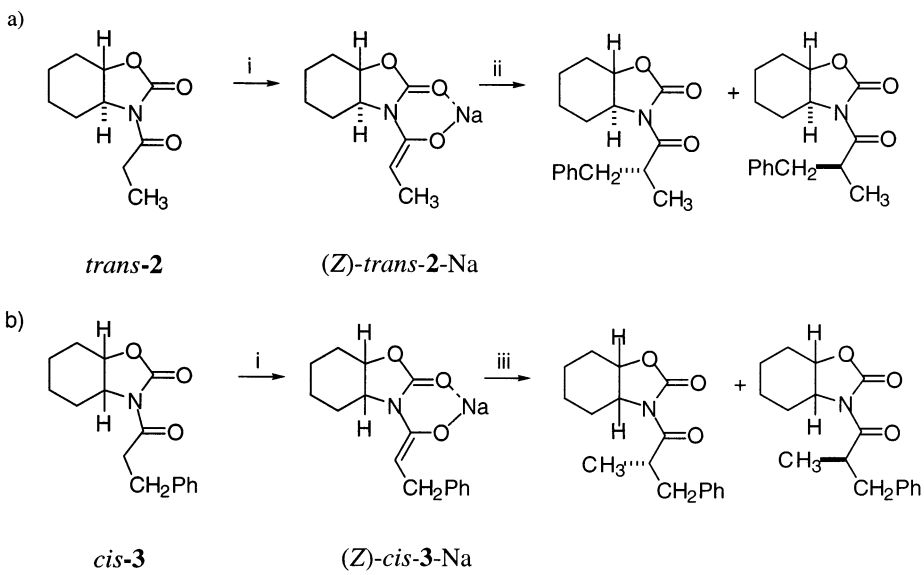
2.1. Part A. Diastereoselective alkylation of 2a–d and 3a–d

The alkylation of **2a–d** with benzyl bromide, and the alkylation of **3a–d** with iodomethane proceeded with very high diastereoselectivity, showing the potential of oxazolidinones **1** in asymmetric synthesis (Scheme 2). Enolates **2**-Na and **3**-Na were prepared by treatment of **2** and **3** with NaHMDS, at −78°C in THF, and alkylation performed at −78°C→rt, using 3–5 equivalents of electrophile. Assessment of diastereomeric product ratios (dr) was achieved by high resolution (400 MHz) ^{1}H NMR spectroscopic analysis of the crude products. As summarized in Tables 1 and 2, a single alkylated product was obtained with ds ≥ 98%.

The absolute configuration of the newly created stereogenic center at C(2′) in products *cis*- and *trans*-**4** was established by means of chemical correlation with 2-benzyl-1-propanol. Thus, reduction of (4*S*,5*S*,2′*R*)-**4** with $LiAlH_4$ afforded (*R*)-2-benzyl-1-propanol, (*R*)-**5** {$[\alpha]_D^{25} = +10.9$ ($c = 2.0$, C_6H_6); lit.[3j] $[\alpha]_D = +11.1$ ($c = 1.25$, C_6H_6)}, in 90% yield. Similarly, (4*R*,5*R*,2′*S*)-**4**, (4*R*,5*S*,2′*R*)-**4** and (4*S*,5*R*,2′*S*)-**4** were correlated with (*S*)-**5**, (*R*)-**5** and (*S*)-**5**, respectively.

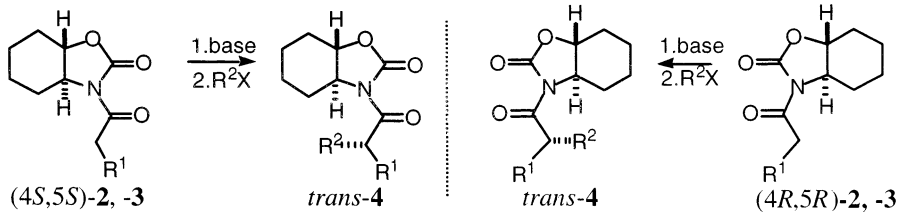


Scheme 1. *Conditions*: i, *n*-BuLi/THF, 0°C, 30 min. ii, CH_3CH_2COCl or $PhCH_2CH_2COCl$, −78°C, 1 h.



Scheme 2. *Conditions*: i, NaHMDS (2 equiv.)/THF, −78°C, 30 min. ii, $PhCH_2Br$ (3–5 equiv.)/THF, −78°C→rt, 6+24 h. iii, CH_3I (3–5 equiv.) THF, −78°C→rt, 6+24 h.

Table 1. Diastereoselectivity of alkylation of *trans*-*N*-acylated hexahydrobenzoxazolidin-2-ones[a]

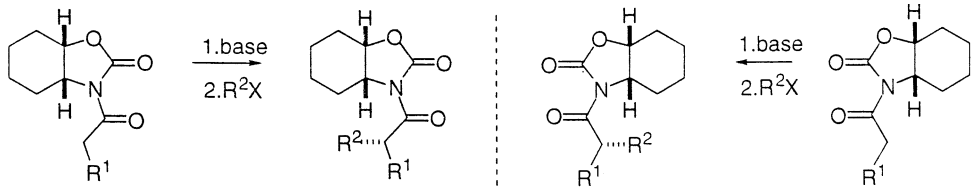


(4*S*,5*S*)-**2**, **-3** *trans*-**4** *trans*-**4** (4*R*,5*R*)-**2**, **-3**

Entry	Substrate (**2** or **3**)	R^2X	Product[b] **4**	Yield (%)	$[\alpha]_D$ **4**	Ds[c] (%)
1	(4*S*,5*S*)-**2a**	BnBr[d]	(4*R*,5*S*,2′*R*)	41	−52.3	>98
2	(4*R*,5*R*)-**2b**	BnBr[d]	(4*R*,5*R*,2′*S*)	40	+53.9	>98
3	(4*S*,5*S*)-**3a**	CH_3I	(4*S*,5*S*,2′*S*)	80	+68.8	>98
4	(4*R*,5*R*)-**3b**	CH_3I	(4*R*,5*R*,2′*R*)	78	−68.3	>98

[a] For conditions, see Scheme 2.
[b] Configuration at C(2′) established by chemical correlation. See text.
[c] Single diastereomeric product detected by ^1H NMR spectroscopy.
[d] Bn = benzyl.

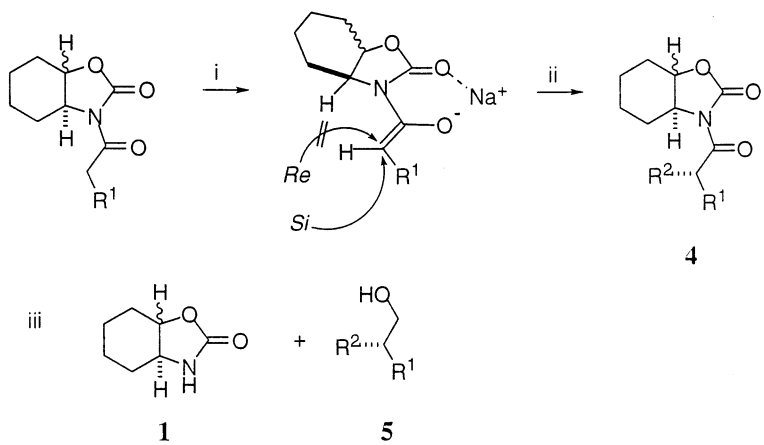
Table 2. Diastereoselectivity of alkylation of *cis*-*N*-acylated hexahydrobenzoxazolidin-2-ones[a]



(4*R*,5*S*)-**2**, **-3** *cis*-**4** *cis*-**4** (4*S*,5*R*)-**2**, **-3**

Entry	Substrate (**2** or **3**)	R^2X	Product[b] **4**	Yield (%)	$[\alpha]_D$ **4**	Ds[c] (%)
1	(4*S*,5*R*)-**2c**	BnBr[d]	(4*S*,5*R*,2′*R*)	31	+21.1	>98
2	(4*R*,5*S*)-**2d**	BnBr[d]	(4*R*,5*S*,2′*S*)	34	−20.0	>98
3	(4*S*,5*R*)-**3c**	CH_3I	(4*S*,5*R*,2′*S*)	78	+76.5	>98
4	(4*R*,5*S*)-**3d**	CH_3I	(4*R*,5*S*,2′*R*)	75	−78.2	>98

[a] For conditions, see Scheme 2.
[b] Configuration at C(2′) established by chemical correlation. See text.
[c] Single diastereomeric product detected by ^1H NMR spectroscopy.
[d] Bn = benzyl.



1 **5** **4**

Scheme 3. *Conditions*: i, NaHMDS (2 equiv.)/THF, −78°C, 30 min. ii, $R^2X = PhCH_2Br$ or CH_3I (3–5 equiv.)/THF, −78°C, rt→6+24 h. iii, $LiAlH_4$/THF, 25°C, 3 h.

The results collected in Tables 1 and 2 are consistent with the intermediacy of (*Z*)-configured enolates[7] where the sodium cation is chelated by both carbonyl oxygens, and the electrophile is incorporated from the less sterically hindered face of the enolate (Scheme 3).

Analysis of the data collected in Tables 1 and 2 also demonstrates that it is the configuration at C(4) in the substrate oxazolidinone that dictates the relative reactivity of the diastereotopic faces in the derived enolate—the chirality center at C(5) playing an inconspicuous role as stereodirecting moiety. Thus, both the *cis* and *trans* isomers of the auxiliary with, say, (*R*)-configuration at C(4) are complementary in their stereoinducing capacity to either the *cis* or *trans* isomer of the (*S*)-configured hexahydrobenzoxazolidinones.

2.2. Part B. Diastereoselective aldol addition reaction of 2a–d with aldehydes

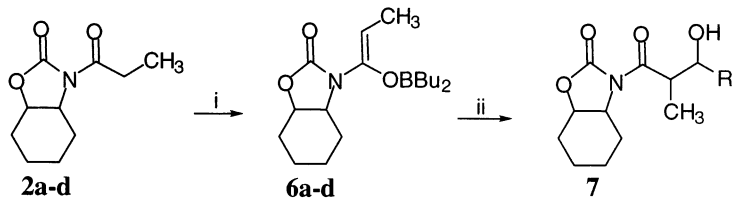
The aldol reaction is one of the most useful reactions of enolates, being a powerful tool for the stereoselective synthesis of β-hydroxy carbonyl segments.[3g,8]

cis- and *trans*-Oxazolidin-2-ones **2a–d** were treated with *n*-Bu_2BOTf and triethylamine to afford boron enolates **6a–d**, which were then reacted with acetaldehyde and benzaldehyde. ^1H and ^{13}C NMR analysis of the crude products showed the presence of a single diastereoisomeric aldol addition product **7**; the results from these experiments are summarized in Table 3.

The *syn* relative configuration for all aldol products **7** was established from the observed ^1H NMR coupling constants for the vicinal protons at the newly created stereogenic centers.[2a,d,9] Indeed, as can be seen in Table 4, $^3J_{H(2')/H(3')}$ for all products **7** fall in the range of 2.9–4.4 Hz, which is consistent with expected values for *syn* configuration. (By contrast, *anti* diastereomers exhibit coupling constants $^3J_{H(2')/H(3')} = 7–9$ Hz.[2a,d,9])

The assignment of the *absolute* configuration in aldol products **7** was possible by means of X-ray diffraction

Table 3. Diastereoselectivity of the aldol reaction of boron enolates **6a–d** with acetaldehyde and benzaldehyde[a]



Starting oxazolidinone	RCHO	Yield (%)	Ds[b] (%)	Relative[c] configuration	Absolute[d] configuration	$[\alpha]_D$ **7**
2a, *trans*-(4*S*,5*S*)	CH_3CHO	65	≥98	*syn*	(4*S*,5*S*,2′*S*,3′*R*)	+51.0
2a, *trans*-(4*S*,5*S*)	PhCHO	60	≥98	*syn*	(4*S*,5*S*,2′*S*,3′*S*)	+20.1
2b, *trans*-(4*R*,5*R*)	CH_3CHO	60	≥98	*syn*	(4*R*,5*R*,2′*R*,3′*S*)	−50.8
2b, *trans*-(4*R*,5*R*)	PhCHO	70	≥98	*syn*	(4*R*,5*R*,2′*R*,3′*R*)	−20.1
2c, *cis*-(4*S*,5*R*)	CH_3CHO	60	≥98	*syn*	(4*S*,5*R*,2′*S*,3′*R*)	+78.0
2c, *cis*-(4*S*,5*R*)	PhCHO	70	≥98	*syn*	(4*S*,5*R*,2′*S*,3′*S*)	+70.1
2d, *cis*-(4*R*,5*S*)	CH_3CHO	60	≥98	*syn*	(4*R*,5*S*,2′*R*,3′*S*)	−77.3
2d, *cis*-(4*R*,5*S*)	PhCHO	70	≥98	*syn*	(4*R*,5*S*,2′*R*,3′*R*)	−71.2

[a] Conditions: i, Bu_2BOTf (1.2 equiv.)/Et_3N, CH_2Cl_2, −78°C→rt, 30 min. ii, RCHO (2.0 equiv.), −78°C, 5.5 h, then H_2O_2, 1.5 h.
[b] Single diastereomeric product detected by ^1H and ^{13}C NMR.
[c] From $^3J_{H(2')/H(3')}$; see text.
[d] By chemical correlation and/or X-ray structure determination.

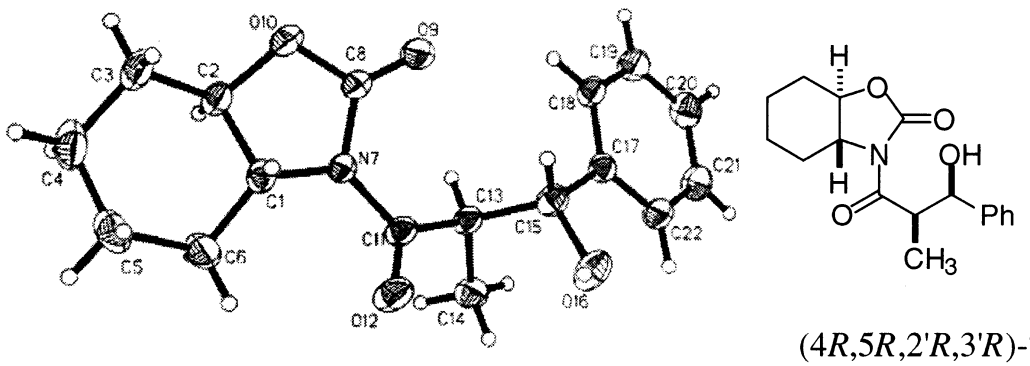
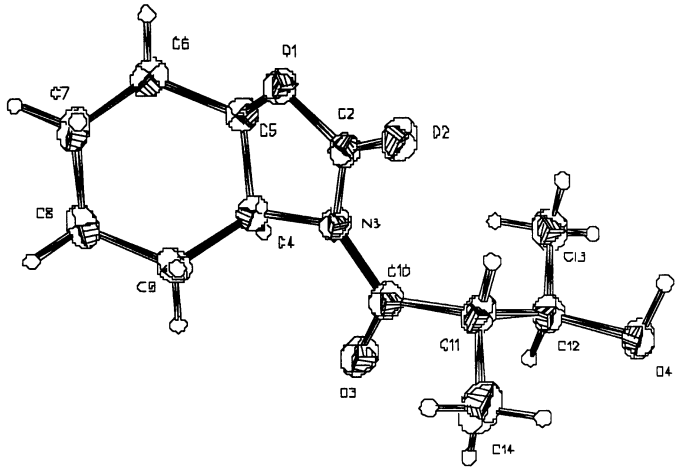
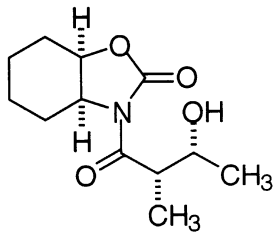


Figure 1. Structure and solid-state conformation of (4*R*,5*R*,2′*R*,3′*R*)-*N*-(3-hydroxy-2-methyl-3-phenylpropionyl)hexahydrobenzoxazolidin-2-one.

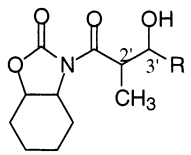




(4*S*,5*R*,2'*S*,3'*R*)-**7**

Figure 2. Structure and solid-state conformation of (4*S*,5*R*,2′*S*,3′*R*)-*N*-(3-hydroxy-2-methylbutanoyl)hexahydrobenzoxazolidin-2-one.

Table 4. ^{1}H NMR coupling constants between H(2′) and H(3′) in aldol products **7**



7

Aldol product **7**	δ H(2′) (ppm)	δ H(3′) (ppm)	$^3J_{H(2')/H(3')}$ (Hz)
(4*S*,5*S*,2′*S*,3′*R*)	3.59	4.06	2.9
(4*S*,5*S*,2′*S*,3′*S*)	4.03	5.20	2.9
(4*R*,5*R*,2′*R*,3′*S*)	3.67	4.15	2.9
(4*R*,5*R*,2′*R*,3′*R*)	4.03	5.20	2.9
(4*S*,5*R*,2′*S*,3′*R*)	3.64	4.36	3.0
(4*S*,5*R*,2′*S*,3′*S*)	4.01	5.02	4.4
(4*R*,5*S*,2′*R*,3′*S*)	3.62	4.34	3.0
(4*R*,5*S*,2′*R*,3′*R*)	4.02	5.01	4.4

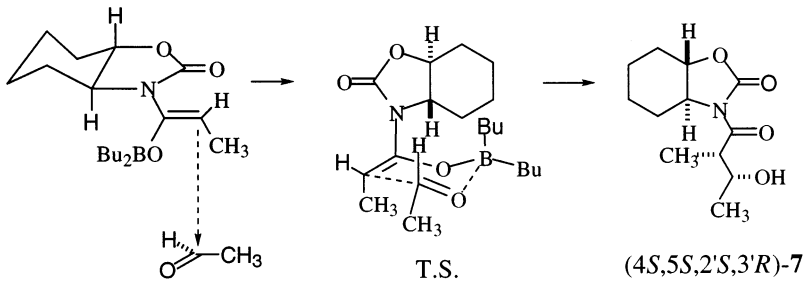
structure determination of (4*R*,5*R*,2′*R*,3′*R*)-**7** and (4*S*,5*R*,2′*S*,3′*R*)-**7**, which correspond to the addition products between *trans*-(4*R*,5*R*)-**2b** and benzaldehyde, and between *cis*-(4*S*,5*R*)-**2c** and acetaldehyde (Figs. 1 and 2).[10]

The absolute configuration of the enantiomeric products, (4*S*,5*S*,2′*S*,3*S*)-**7** and (4*R*,5*S*,2′*R*,3′*S*)-**7**, was assigned on the basis of the observed physical properties (similar melting point, opposite sign of optical rotation) and spectroscopic properties (identical ^{1}H and ^{13}C NMR). Since the *syn* relative configuration for all aldol products **7** had been determined (see Table 3), and because electrophilic addition takes place on the less hindered face of the enolate (see Table 3), the absolute configuration of the remaining aldol products in Table 3 could then be assigned with some confidence.

The observed stereoselectivity in the formation of aldol products **7** (Table 3) can be rationalized in terms of a six-membered cyclic, Zimmerman–Traxler-type transition state. Scheme 4 includes a reasonable model for an illustrative example, the addition of (*Z*)-configured[7] boron enolate (4*S*,5*S*)-**2a**-BBu$_2$ to acetaldehyde, affording (4*S*,5*S*,2′*S*,3′*R*)-**7**. It can be appreciated that the more reactive (less sterically hindered) *Re* face of the enolate adds to the *Si* face of the aldehyde, so that the methyl group adopts a pseudoequatorial position (Scheme 4).

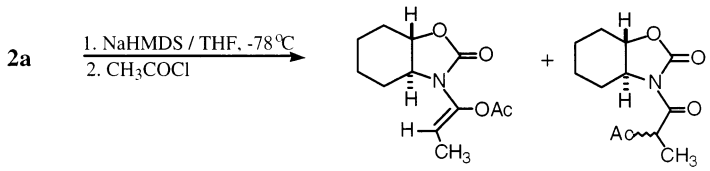
2.3. Part C. Diastereoselective *C*-acylation reaction of *trans*-(4*S*,5*S*)-2a-Na

Although the acylation reaction of enolates containing chiral oxazolidinone auxiliaries has been less exploited



Scheme 4.

Table 5. *C*- versus *O*-acylation in the reaction of **2a**-Na with acetyl chloride under various reaction conditions



Entry	CH_3COCl:THF	Time of addition (min)	Temp. (°C)	*C*- versus *O*-acylation
1	3:97	10	−78	18:82
2	3:97	1	−78	54:41
3	100:0	0	−40	89:11

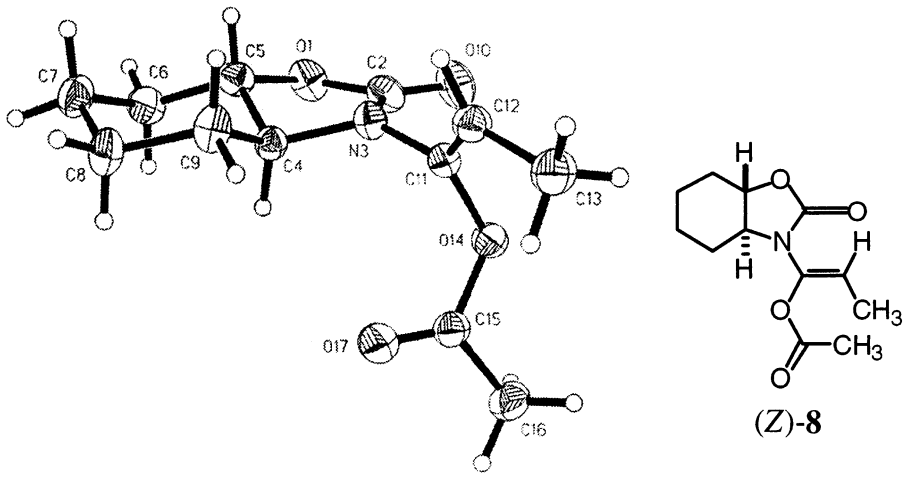


Figure 3. Structure and solid-state conformation of (4*S*,5*S*)-*N*-[1-acetoxy-(1*Z*)-propenyl]hexahydrobenzoxazolidin-2-one.

than the analogous asymmetric alkylation and aldol additions, it has been shown to be an efficient means for the enantioselective formation of chiral 1,3-dicarbonyl derivatives.[3i,11,12] In the present study, *trans*-(4*S*,5*S*)-*N*-(propionyl)hexahydrobenzoxalidin-2-one **2a** was metallated with NaHMDS,[13] and the resulting enolates were then treated with various acyl chlorides (vide infra).

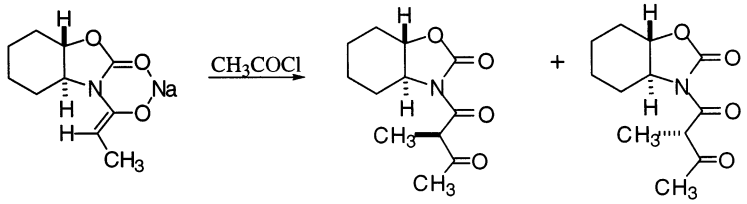
A critical issue, not always addressed in other publications in this field, is the question of *O*- versus *C*-acylation of the enolate. In our hands, when the enolate from oxazolidinone **2a** and 1.0 M NaHMDS, in THF solution, was treated with dilute CH_3COCl (slow addition), most of the reaction proceeded to afford the *O*-acylated product (entry 1, Table 5). The ratio of *C*- versus *O*-acylation improved when the dilute solution of acetyl chloride in THF was added rapidly to the enolate solution (entry 2, Table 5) and synthetically useful *C*-regioselectivity was achieved when *neat* acetyl chloride was rapidly added to the enolate (entry 3, Table 5).

The (*Z*)-configuration in *O*-acylated derivative **8** was established by means of X-ray crystallography (Fig. 3) and is in line with expectation of relative steric hindrance due to allylic $A^{1,3}$ strain.[7]

With suitable conditions for the *C*-acylation of enolate **2a**-Na, we proceeded to explore solvent and additive effects on the diastereoselectivity of the reaction. To this end, crude reaction products were analyzed by ^1H NMR spectroscopy. Most useful was the chemical shift for H(2′)—the major diastereomeric product consistently appearing at lower field ($\delta = 4.6$–4.8 ppm) relative to the minor isomer ($\delta = 4.2$–4.3 ppm) (Table 6).[14]

In THF solvent addition of $MgCl_2$ or $MgBr_2$ to the reaction had a detrimental effect both on regioselectivity and diastereoselectivity (entries 2 and 3, Table 6) of the reaction. Similarly, addition of 4-*N*,*N*-dimethylaminopyridine (DMAP) reduced the regioselectivity from an 82:18 ratio in favor of *C*-acylation, to a 45:55 ratio, with a slight predominance of *O*-acylation (entry 4 in Table 6).

Table 6. Solvent and additive effects on the diastereoselectivity in the *C*-acylation of **2a**-Na with acetaldehyde (neat)



2a-Na (4*S*,5*S*,2′*R*)-**9** (4*S*,5*S*,2′*S*)-**9**

Entry	Solvent	Additive	*C*- versus *O*-acylation	(2′*R*):(2′*S*) ratio
1	THF	–	82:18	89:11
2	THF	$MgCl_2$	46:54	58:42
3	THF	$MgBr_2$	4:96	60:40
4	THF	DMAP[a]	45:55	99:1
5	CH_2Cl_2	–	99:1	99:1
6	CH_2Cl_2	DMAP[a]	97:3	97:3

[a] DMAP = 4-dimethylaminopyridine.

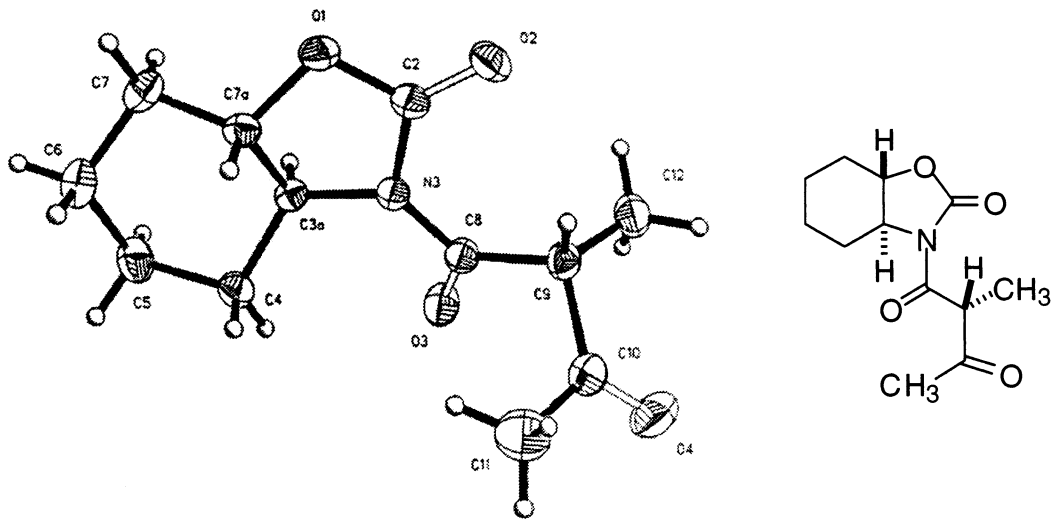
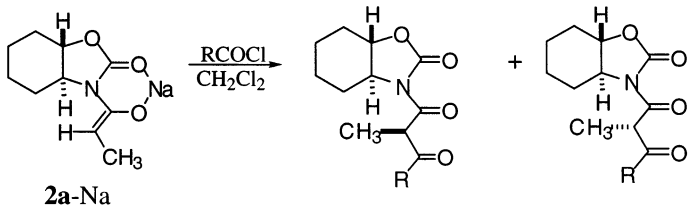


Figure 4. Structure and solid-state conformation of (4*S*,5*S*,2′*R*)-*N*-(2-acetyl-1-propionyl)hexahydrobenzoxazolidin-2-one.

By contrast, the acylation reaction *in CH_2Cl_2 solvent* was both highly regio- and diastereoselective, affording (4*S*,5*S*,2′*R*)-**9** as the only product (entry 5 in Table 6). In the presence of DMAP, both the regio- and diastereoselectivity dropped slightly, from 99 to 97% (entry 6, Table 6).

Table 7. Diastereoselectivity in the *C*-acylation of **2a**-Na with various acyl chlorides in CH_2Cl_2 solvent



2a-Na

Entry	RCOCl	*C*:*O* Acylation ratio	(2′*R*):(2′*S*) ratio	Total yield (%)
1	CH_3COCl	99:1	99:1	87
2	EtCOCl	94:6	99:1	90
3	$(CH_3)_2CHCOCl$	93:7	43:57	85
4	PhCOCl	70:30	48:52	93
5	$PhCH_2COCl$	97:3	44:56	91

The assignment of the absolute configuration in the main product was achieved by X-ray diffraction analysis (Fig. 4). The (*R*)-configuration at C(2′) is in accord with a reaction pathway involving addition on the less hindered face of the enolate; that is, the *Si* face (cf. Scheme 3 and Table 6).

Finally, several other acyl chlorides were used as electrophiles in the acylation reaction of **2a**-Na. In contrast with the observations of Koell and Luetzen,[3i] we find that increasing the steric bulk of the acyl group leads to lower diastereoselectivities (Table 7).

3. Conclusions

The high diastereoselectivities observed in the alkylation reactions of oxazolidinones **2a–d** and **3a–d** as well as the high diastereoselectivity found in aldol condensation reactions of dialkylboron enolates **6a–d** demonstrate the potential of hexahydrobenzoxazolidinones **1a–d** as chiral auxiliaries. Appropriate selection of reaction conditions (addition order, solvent and presence/absence of additives) also results in the highly diastereoselective acylation of **2a** (Part C).

4. Experimental[15]

4.1. 3*H*-Hexahydrobenzoxazolidin-2-ones (1a–d), see Ref. 4. *N*-(Propionyl)hexahydrobenzoxazolidin-2-ones (2a–d), see Ref. 4. *N*-(Hydrocinnamoyl)hexahydrobenzoxazolidin-2-ones (3a–d); general procedure

A dry two-necked flask fitted with a magnetic stirrer, a dropping funnel and a low-temperature thermometer, was charged with a mixture of **1** (0.14 g, 1 mmol) in THF (20 mL) under argon. The solution was cooled to 0°C in an ice bath before the dropwise addition of a precooled solution on *n*-BuLi (0.65 mL, 1.6 M in hexane). After 30 min the mixture was cooled to −78°C with an acetone/dry ice bath, and then a precooled solution of hydrocinnamoyl chloride (0.17 g, 1.0 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred and allowed to warm to rt and quenched with a saturated aqueous solution of NH_4Cl (5 mL). Water (25 mL) was added and the organic material was extracted with CH_2Cl_2 (3×25 mL), dried with anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate, 5:1) to give compounds **3**.

4.1.1. (4*S*,5*S*)-3a. 0.26 g (99% yield) as white crystals, mp 135–136°C, $[\alpha]_D^{25}=-77.3$ ($c=1$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.40 (m, 3H), 1.64 (dq, $^3J=7.00$ Hz, $^2J=4.40$ Hz, 1H), 1.83 (m, 1H), 1.92 (m, 1H), 2.21 (dd, $^3J=2.16$ Hz, 1H), 2.80 (m, 1H), 3.0 (m, 2H), 3.15 (m, 1H), 3.27 (m, 1H), 3.53 (dt, $^3J=3.28$ Hz, $^2J=10.96$ Hz, 1H), 3.81 (dt, $^3J=3.68$ Hz, $^2J=11.30$ Hz, 1H), 7.21–7.27 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 23.6, 23.8, 28.5, 28.8, 30.5, 38.0, 63.2, 77.4, 126.3, 128.5, 128.6, 140.6, 155.0, 174.6. IR (cm^{-1}): 1793.9, 1687.2. Mass (*m*/*z*): 197 (molecular ion), 169, 152, 142, 112, 97, 81, 74, 57 (base peak), 29. $C_{16}H_{19}NO_3$ (273) calc. 70.33% C, 6.96% H; found 70.40% C, 7.03% H.

4.1.2. (4*R*,5*R*)-3b. 0.25 g (98% yield) as white crystals, mp 134–135°C, $[\alpha]_D^{25}=+78.1$ ($c=1$, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR and mass spectrum similar to those described for (4*S*,5*S*)-**3a**.

4.1.3. (4*S*,5*R*)-3c. 0.26 g (99% yield) as white crystals, mp 60–61°C, $[\alpha]_D^{25}=+60.5$ ($c=1$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.23 (m, 2H), 1.40 (m, 1H), 1.62 (m, 3H), 2.15 (m, 1H), 2.30 (m, 1H), 2.95 (m, 2H), 3.20 (m, 2H), 4.31 (m, 1H), 4.48 (m, 1H), 7.10–7.30 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 19.0, 20.8, 26.2, 27.1, 30.3, 37.1, 53.7, 74.4, 126.1, 128.4, 128.5, 140.5, 153.7, 172.2. IR (cm^{-1}): 1803.2, 1693.5. Mass (*m*/*z*): 197 (molecular ion), 169, 152, 142, 112, 97, 81, 74, 57 (base peak), 29. $C_{16}H_{19}NO_3$ (273) calc. 70.33% C, 6.96% H; found 70.25% C, 6.80% H.

4.1.4. (4*R*,5*S*)-3d. 0.26 g (99% yield) as white crystals, mp 58–59°C, $[\alpha]_D^{25}=-59.7$ ($c=1$, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR and mass spectra similar to those described for (4*S*,5*R*)-**3c**.

4.2. *cis*- and *trans*-*N*-(2′-Benzyl-propionyl)hexahydrobenzoxazolidin-2-ones (4). General procedure

A dry two-necked flask fitted with a magnetic stirrer, dropping funnel and a low-temperature thermometer was charged with a mixture of **2** or **3** (0.25 mmol) in THF (5 mL) under argon. The solution was cooled to −78°C in an acetone/dry ice bath before the dropwise addition of a precooled solution of NaHMDS (1 M, hexane, 0.50 mmol). After 45 min at −78°C a precooled solution of benzyl bromide or methyl iodide (0.75–1.25 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred during 45 min, and then allowed to warm up to rt for 4–24 h before quenching with a saturated solution of NH_4Cl (5 mL). Water (25 mL) was added and the organic material was extracted with CH_2Cl_2 (3×25 mL), dried with anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 4:1) to yield **4**.

4.2.1. (4*S*,5*S*,2′*R*)-4. 0.057 g (41% yield) as white crystals, mp 62–63°C, $[\alpha]_D^{25}=-53.3$ ($c=1$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.9 (m, 1H), 1.0 (m. 1H), 1.1 (d, $^3J=7.0$ Hz, 3H), 1.8 (m, 2H), 2.2 (m, 1H), 2.6 (m, 1H), 2.8 (dd, $^2J=13.56$ Hz, $^3J=8.44$ Hz, 1H), 2.9 (dd, $^2J=13.56$ Hz, $^3J=8.4$ Hz, 1H), 3.4 (m, 2H), 4.0 (m, 1H), 7.2–7.3 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 17.1, 23.6, 23.8, 28.2, 40.5, 41.5, 63.0, 63.8, 81.2, 126.5, 128.0, 129.0, 139.9, 154.3, 178.5. IR (cm^{-1}): 1784.3, 1701.3. Mass (*m*/*z*): 287 (molecular ion), 243, 228, 174, 142, 118 (base peak), 91, 74, 55, 41. $C_{17}H_{21}NO_3$ (287.4) calc. 71.05% C, 7.37% H; found 70.97% C, 7.40% H.

4.2.2. (4*R*,5*R*,2′*S*)-4. 0.056 g (40% yield) as white crystals, mp 59–60°C, $[\alpha]_D^{25}=+53.9$ ($c=1$, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR and mass spectra similar to those described for (4*S*,5*S*,2*R*)-**4**.

4.2.3. (4*S*,5*S*,2′*S*)-4. 0.11 g (80% yield) as white crystals, mp 60–61°C, $[\alpha]_D^{25}=+68.8$ ($c=1$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.15 (d, $^3J=6.96$ Hz, 3H), 1.38 (m, 3H), 1.62 (d, $^3J=11.7$ Hz, 1H), 1.85 (dd, $^3J=6.0$ Hz, $^2J=8.8$ Hz, 1H), 1.92 (d, $^3J=8.0$ Hz, 1H), 2.22 (d, $^3J=11.76$ Hz, 1H), 2.55 (dd, $^2J=13.56$ Hz, $^3J=8.40$ Hz, 1H), 2.82 (m, 1H), 3.13 (dd, $^3J=7.7$ Hz, $^2J=13.56$ Hz, 1H), 3.52 (dt, $^2J=10.96$ Hz, $^3J=1.64$ Hz, 1H), 3.85 (dt, $^2J=11.72$ Hz, $^3J=3.64$ Hz, 1H), 3.99 (m, 1H), 7.17–7.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 17.6, 23.6, 23.8, 28.5, 28.9, 38.5, 40.5, 63.2, 81.3, 126.2, 128.3, 129.4, 139.6, 154.0, 178.9. IR (cm^{-1}): 1784.3, 1701.3. Mass (m/z): 287 (molecular ion), 243, 228, 174, 142, 118 (base peak), 91, 74, 55, 41. $C_{17}H_{21}NO_3$ (287.4) calc. 71.05% C, 7.37% H; found 71.08% C, 7.25% H.

4.2.4. (4*R*,5*R*,2′*R*)-4. 0.10 g (78% yield) as white crystals, mp 63–64°C, $[\alpha]_D^{25}=-68.3$ ($c=1$, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR and mass spectra similar to those described for (4*S*,5*S*,2′*S*)-**4**.

4.2.5. (4*S*,5*R*,2′*R*)-4. 0.050 g (35% yield) as a colorless oil, $[\alpha]_D^{25}=+21.1$ ($c=1$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.13 (d, $^3J=7.0$ Hz, 3H), 1.42 (m, 2H), 1.58 (m, 4H), 2.15 (m, 2H), 2.59 (dd, $^2J=8$ Hz, $^3J=6$ Hz, 1H), 3.08 (dd, $^2J=8$ Hz, $^3J=6$ Hz, 1H), 4.06 (m, 1H), 4.34 (m, 1H), 4.52 (m, 1H), 7.16–7.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 16.7, 19.0, 20.7, 26.3, 26.8, 39.3, 39.7, 53.8, 74.2, 126.3, 128.3, 129.7, 139.3, 153.5, 176.4. IR (cm^{-1}): 1784.3, 1701.3. Mass (m/z): 287 (molecular ion), 243, 228, 174, 142, 118 (base peak), 91, 74, 55, 41. $C_{17}H_{21}NO_3$ (287.4) calc. 71.05% C, 7.37% H; found 71.14% C, 7.31% H.

4.2.6. (4*R*,5*S*,2′*S*)-4. 0.04 g (30% yield) as a colorless oil, $[\alpha]_D^{25}=-20.0$ ($c=1$, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR and mass spectra similar to those described for (4*S*,5*S*,2′*R*)-**4**.

4.2.7. (4*S*,5*R*,2′*S*)-4. 0.12 g (82% yield) as white crystals, mp 40–41°C, $[\alpha]_D^{25}=+76.5$ ($c=1$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.17 (m, 5H), 1.41 (m, 1H), 1.62 (m, 3H), 2.15 (m, 1H), 2.30 (m, 1H), 2.69 (dd, $^2J=7.32$ Hz, $^3J=6.96$ Hz, 1H), 2.96 (dd, $^2J=13.38$ Hz, $^3J=7.72$ Hz, 1H), 4.05 (m, 1H), 4.18 (m, 2H), 7.16–7.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 16.8, 19.1, 20.9, 26.3, 27.2, 39.5, 40.2, 53.8, 74.2, 126.3, 128.3, 129.1, 139.3, 153.4, 176.3. IR (cm^{-1}): 1784.3, 1701.3. Mass (m/z): 287 (molecular ion), 243, 228, 174, 142, 118 (base peak), 91, 74, 55, 41. $C_{17}H_{21}NO_3$ (287.4) calc. 71.05% C, 7.37% H; found 71.15% C, 7.28% H.

4.2.8. (4*R*,5*S*,2′*R*)-4. 0.11 g (75% yield) as white crystals, mp 42–43°C, $[\alpha]_D^{25}=-78.2$ ($c=1$, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR and mass spectra similar to those described for (4*S*,5*R*,2′*S*)-**4**.

4.2.9. (*R*)-2-Benzyl-1-propanol, (*R*)-5. A dry two-necked flask provided with a magnetic stirrer and a dropping funnel was charged with a mixture of $LiAlH_4$ (13 mg, 0.70 mmol) in THF (5 mL) under argon. The solution was cooled to 0°C in an ice water bath before the dropwise addition of a precooled solution of (4*S*,5*S*,2′*R*)-**4** (100 mg, 0.35 mmol) in THF (5 mL). The reaction mixture was stirred and allowed to warm up to rt for 3 h and quenched with a saturated solution of NH_4Cl (5 mL). Water (25 mL) was added and the organic material was extracted with CH_2Cl_2 (3×25 mL), dried with anhydrous Na_2SO_4, filtered and evaporated, to afford (*R*)-**5** in 95% crude yield. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 6:1) to give (*R*)-**5** (0.04 g, 90%), $[\alpha]_D^{25}=+10.9$ ($c=2.0$, C_6H_6) [lit.[16] $[\alpha]_D^{25}=+11.1$ ($c=1.25$, C_6H_6)].

4.2.10. (*S*)-2-Benzyl-1-propanol, (*S*)-5. Following the same procedure described for the preparation of (*R*)-**5**, 100 mg (0.35 mmol) of (4*R*,5*R*,2′*S*)-**4** was reduced with $LiAlH_4$ (13 mg, 0.70 mmol) to afford (*S*)-**5** (40 mg, 90% yield), $[\alpha]_D^{25}=-10.2$ ($c=1$, C_6H_6) [lit.[16] $[\alpha]_D^{25}=+11.1$ ($c=1.25$, C_6H_6) for the (*R*) enantiomer]. ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 0.9 (d, $J=6.6$ Hz, 3H), 1.2 (broad, 1H), 2.0 (q, $J=6.6$ Hz, 1H), 2.4 (dd, $J=8.1$ Hz, $J^1=13.2$ Hz, 1H), 2.6 (dd, $J=6.2$ Hz, $J^1=13.6$ Hz, 1H), 3.6 (m, 2H), 7.2 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 16.5, 37.9, 39.8, 67.8, 125.9, 128.3, 129.2, 140.6. IR (cm^{-1}): 3368.

4.3. General procedure for aldol condensation reactions

A dry two-necked flask fitted with magnetic stirrer and low-temperature thermometer was charged with a mixture of **2** (0.50 g, 2.53 mmol) in dry CH_2Cl_2 (5.8 mL) under argon. The solution was cooled to −78°C with a dry ice/acetone bath, and then 1.2 equiv. of di-*n*-butylboron triflate was added dropwise, followed by a slow addition of 2.0 equiv. of Et_3N (0.7 mL) over 30 min. The reaction mixture was stirred and allowed to warm up to rt (15–20 min), then cooled again to −78°C before the addition of 2.0 equiv. of the aldehyde. Stirring was continued at −78°C for 5.5 h, and quenched by slow addition of 30% aqueous H_2O_2 (0.5–1.0 mL). The organic material was extracted with CH_2Cl_2 (3×25 mL), dried with anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to give aldol products **7**.

4.3.1. (4*S*,5*S*,2′*S*,3′*S*)-7. 0.46 g (60% yield) as white crystals, mp 101–102°C, $[\alpha]_D^{25}=+20.1$ ($c=1$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.10 (d, $^3J=6.96$ Hz, 3H), 1.4 (m, 3H), 1.64 (m, 1H), 1.8–2.0 (m, 2H), 2.24 (d, $^3J=11.72$ Hz, 1H), 2.81 (m, 1H), 3.27 (br. s, 1H, OH), 3.55 (dt, $^3J=3.28$ Hz, $^3J=10.96$ Hz, 1H), 3.86 (dt, $^3J=3.64$ Hz, 2H), 4.04 (dq, $^3J=2.92$ Hz, $^3J=7.0$ Hz, 1H), 5.2 (d, $^3J=2.92$ Hz, 1H), 7.22–7.43 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 11.0, 23.6, 23.8, 28.5, 28.7, 45.2, 63.2, 72.2, 81.4, 126.1, 127.3, 128.2, 141.3, 154.3, 179.7. IR (cm^{-1}): 3523, 1759, 1707. Mass (m/z): 303 (molecular ion), 286, 242, 206, 197 (base peak), 142, 105, 97, 77, 68, 57, 39. $C_{17}H_{21}NO_4$ (303) calc. 67.32% C, 6.93% H; found 67.25% C, 6.80% H.

4.3.2. (4*R*,5*R*,2′*R*,3′*R*)-7. 0.54 g (70% yield) as white crystals, mp 101–102°C, $[\alpha]_D^{25}=-20.1$ ($c=1$, $CHCl_3$). ^1H

NMR, ^{13}C NMR, IR and mass spectra similar to those described for (4*S*,5*S*,2′*S*,3′*R*)-**7**.

4.3.3. (4*S*,5*S*,2′*S*,3′*R*)-7. 0.40 g (65% yield), as white crystals, mp 61–62°C, $[\alpha]_D^{25}=+51.0$ ($c=1$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.17 (t, $^3J=7.32$ Hz, 3H), 1.36 (m, 3H), 1.62 (m, 1H), 1.87 (m, 2H), 2.20 (d, $^3J=11.76$ Hz, 1H), 2.75 (d, $^3J=2.56$ Hz, 1H), 3.00 (br. s, 1H, OH), 3.55 (dt, $^3J=3.32$ Hz, $^3J=11.0$ Hz, 1H), 3.66 (dq, $^3J=6.96$ Hz, $^3J=3.28$ Hz, 1H), 3.85 (dt, $^3J=3.68$ Hz, $^3J=11.34$ Hz, 1H), 4.16 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 11.5, 19.5, 23.5, 23.6, 28.3, 28.6, 44.0, 63.0, 67.0, 81.2, 154.5, 179.5. IR (cm^{-1}): 3456, 1780, 1698. Mass (*m*/*z*): 242 (molecular peak), 224, 198, 180, 154, 142, 124, 110, 97, 81, 69, 56, 39. $C_{17}H_{19}NO_4$ (241) calc. 59.75% C, 7.88% H; found 59.69% C, 7.75% H.

4.3.4. (4*R*,5*R*,2′*R*,3′*S*)-7. 0.37 g (60% yield), as white crystals, mp 63–65°C, $[\alpha]_D^{25}=-50.8$ ($c=1$, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR and mass spectra similar to those described for (4*S*,5*S*,2′*S*,3′*R*)-**7**.

4.3.5. (4*S*,5*R*,2′*S*,3′*S*)-7. 0.54 g (70% yield) as white crystals, mp 120–121°C, $[\alpha]_D^{25}=+70.1$ ($c=1$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.16 (d, $^3J=5$ Hz, 1H), 1.42 (m, 1H), 1.55–1.72 (m, 3H), 2.15 (m, 1H), 2.31 (m, 1H), 3.22 (br. s, 1H, OH), 4.01 (m, 1H), 4.22 (m, 1H), 4.31 (d, $^3J=2.56$ Hz, 1H), 5.01 (d, $^3J=3.24$ Hz, 1H), 7.2–7.45 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 10.9, 19.1, 20.9, 26.3, 27.0, 44.7, 53.8, 74.0, 74.5, 126.2, 127.6, 128.3, 141.5, 153.4, 176.5. IR (cm^{-1}): 3602, 1780, 1723. Mass (*m*/*z*): 303 (molecular peak), 286, 206, 197 (base peak), 142, 129, 105, 97, 77, 68, 57, 39. $C_{17}H_{21}NO_4$ (303) calc. 67.32% C, 6.93% H; found 67.30% C, 6.75% H.

4.3.6. (4*R*,5*S*,2′*R*,3′*R*)-7. 0.54 g (70% yield) as white crystals, mp 122–123°C, $[\alpha]_D^{25}=-71.2$ ($c=1$, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR and mass spectra similar to those reported for (4*S*,5*R*,2′*S*,3′*S*)-**7**.

4.3.7. (4*S*,5*R*,2′*S*,3′*R*)-7. 0.37 g (60% yield) as white crystals, mp 82–83°C, $[\alpha]_D^{25}=+78.0$ ($c=1$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.17 (d, $^3J=6.24$ Hz, 3H). 1.2 (d, $^3J=7$ Hz, 3H), 1.45 (m, 1H), 1.65 (m, 4H), 2.19–2.32 (m, 2H), 2.91 (br. s, 1H, OH), 3.63 (dq, $^3J=2.92$ Hz, $^3J=6.9$ Hz, 1H), 4.11 (m, 1H), 4.35 (m, 1H), 4.55 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 10.3, 11.0, 19.7, 20.8, 26.3, 27.0, 43.1, 53.7, 67.8, 74.5, 153.5, 177.3. IR (cm^{-1}): 3468, 1780, 1687. Mass (*m*/*z*): 242 (molecular peak), 224, 197, 153, 142, 123, 110, 97, 81, 69, 56, 39. $C_{17}H_{21}NO_4$: calc. 59.75% C, 7.88% H; found 59.74% C, 7.85% H.

4.3.8. (4*R*,5*S*,2′*R*,3′*S*)-7. 0.37 g (60% yield) as white crystals, mp 80–81°C, $[\alpha]_D^{25}=-77.3$ ($c=1$, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR and mass spectra similar to those reported for (4*S*,5*R*,2′*S*,3′*R*)-**7**.

4.3.9. (4S,5S)-*N*-[1-Acetoxy-(*Z*)-propenyl]hexahydrobenzoxazolidin-2-one, (*Z*)-8. White crystals, mp 91–92°C, $[\alpha]_D^{25}=+25.98$ ($c=1.07$, $CHCl_3$). ^1H NMR (100 MHz, $CDCl_3$) δ 1.36 (m, 3H), 1.57 (d, $J=6.92$ Hz, 3H), 1.61 (m, 1H), 1.87 (m, 2H), 2.14 (m, 2H), 2.17 (s, 3H), 3.29 (ddd, $J_{gauche}=3.46$ Hz, $J_{anti}=11.13$ Hz, $J_{anti}=11.01$ Hz, 1H), 3.83 (ddd, $J_{gauche}=3.46$ Hz, $J_{anti}=11.13$ Hz, $J_{anti}=11.31$ Hz, 1H), 5.23 (q, $J=6.92$ Hz, 1H). ^{13}C NMR (25 MHz, $CDCl_3$) δ 11.0, 20.4, 23.5, 23.8, 28.1, 28.5, 64.5, 82.1, 112.0, 136.56, 168.3. IR (cm^{-1}): 2360,1700,1772. Mass (*m*/*z*): 240 (molecular peak), 198, 180, 153, 136, 124, 109, 97, 82, 68, 56. $C_{12}H_{17}NO_4$: calc. 60.25% C, 7.11% H; found 59.85% C, 7.01% H.

4.3.10. (4*S*,5*S*,2′*R*)-*N*-(2-Acetyl-1-propionyl)hexahydrobenzoxazolidin-2-one, (4*S*,5*S*,2′*R*)-9. White crystals, mp 144–146°C, $[\alpha]_D^{25}=-159.1$ ($c=1$, $CHCl_3$). ^1H NMR (100 MHz, $CDCl_3$) δ 1.22 (d, $J=7.32$ Hz, 3H), 2.15 (s, 3H), 4.32 (q, $J=7.32$ Hz, 1H). ^{13}C NMR (25 MHz, $CDCl_3$) δ 12.8, 27.9, 53.7, 154.5, 172.3, 205.0. IR (cm^{-1}): 1794, 1724, 1682. Mass (*m*/*z*): 240 (molecular peak), 222, 197, 169, 153, 142, 124, 112, 97, 88, 81, 74, 68, 56. $C_{12}H_{17}NO_4$: calc. 60.25% C, 7.11% H; found 60.25% C, 7.21% H.

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