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Control of Relative Stereochemistry in the Cycloadditive Route to β-Hydroxy Carbonyls. Stereoselective Exo Aldol Reactions of Δ^2-Isoxazolines

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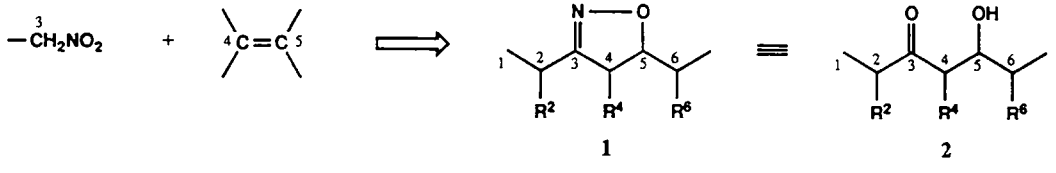
Summary: Aldol reactions with lithium exo-azaenolates derived from fused isoxazoline **10** and a variety of aldehydes have been investigated in the presence and absence of $ZrCp_2Cl_2$. The lithium azaenolate exhibits good (aldehydes) to excellent (ketones) face selectivity, but the syn/anti selectivity is poor. The zirconium enolate exhibits both high face selectivity, which is reversed from the lithium azaenolates, and high syn selectivity. Deoxygenation of the Zr-promoted aldol products complements direct azaenolate alkylation because it provides the opposite diastereomer. Methylation of dianions derived from **12** and **13** also provides access to the aldol products derived from **10**, and the stereoselectivities of these alkylations are either reinforced or eroded by the hydroxy-bearing stereogenic center.

Introduction: Isoxazolines are an important class of heterocycles because they are stable equivalents of β-hydroxy ketones.[2] The formation of an isoxazoline **1** by an olefin/nitrile oxide cycloaddition reaction[3] followed by transformation of the isoxazoline into a β-hydroxy ketone **2** constitutes a strategic alternative to the aldol and related reactions (Figure 1). If stereochemistry can be controlled at the centers on (C4, C5) and adjacent to (C2, C6) the isoxazoline ring, then a powerful method for the stereocontrolled preparation of heteroatom-containing carbon chains is available. Control of relative stereochemistry at the stereocenters on the isoxazoline ring (C4 and C5) is readily accomplished either by a nitrile oxide cycloaddition reaction with a disubstituted olefin or by a cycloaddition with a monosubstituted olefin followed by Jäger alkylation.[2b] Relative stereochemistry at C5 and C6 can be controlled either by cycloaddition of a nitrile oxide with a chiral alkene,[4] or by nucleophilic addition to (or reduction of) a 5-acyl (or 5-formyl) isoxazoline.[5] In addition to these tactics to control relative stereochemistry, practical methods to prepare optically pure isoxazolines are now available.[6]

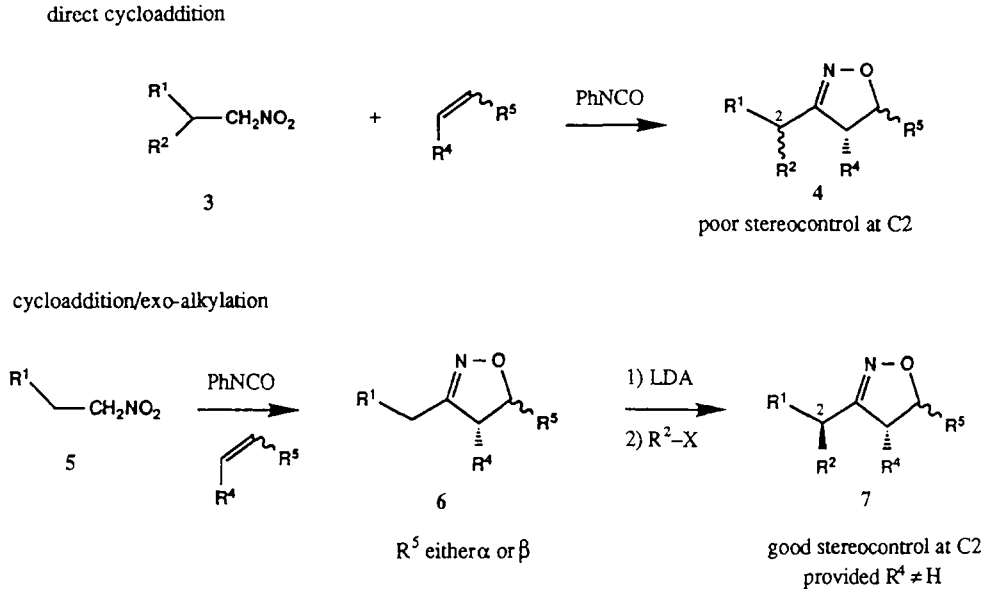
Figure 1. The Cycloadditive Route to β-Hydroxy Carbonyls



The control of relative stereochemistry at C2 is an important and challenging task—important because there are relatively few ways to prepare α,α′-disubstituted β-hydroxy ketones,[7] and challenging because nitrile oxides generated from chiral nitro compounds **3** typically cycloadd to alkenes with little or no stereoselectivity (Figure 2, top).[8] We have recently introduced a method to control stereochemistry at C2 that involves cycloaddition of an alkene with an achiral nitrile oxide

(generated from an achiral nitro compound **5**), followed by stereoselective alkylation of an exo-azaenolate derivative of the resulting isoxazoline **6** (Figure 2, bottom).[9] Alkylated isoxazolines **7** are formed with stereoselectivities ranging from 85/15 for small alkylating agents like methyl iodide to >97/3 for alkylating agents like benzyl bromide and isopropyl iodide. The presence of a substituent R^4 is essential for the success of this method because it controls both the regio- and stereoselectivity in azaenolate generation, and the stereoselectivity in azaenolate alkylation. Substituents R^5 are tolerated in either configuration, and have little effect on the stereochemistry of the alkylation. A model that rationalizes these features is outlined in Figure 3. The R^4 substituent: 1) kinetically retards formation of the otherwise more favorable endo-azaenolate, 2) ensures that the *Z*-azaenolate is formed (the *E*-azaenolate has unfavorable $A^{1,3}$-interactions between R^1 and R^4), and 3) directs approach of the alkylating agent to the opposite face of the isoxazoline ring.

Figure 2. Stereocontrol at C_2



The reactions of carbonyl compounds with isoxazoline exo-azaenolates should form α,α′-disubstituted β,β′-dihydroxyketones **9** via the intermediacy of isoxazolines **8** (Figure 4).[10-13] Because these molecules are useful in the stereocontrolled preparation of polyol chains,[7] we have investigated the synthetic potential of this aldol-type reaction, and our salient results follow.

Figure 3. Stereochemical Model

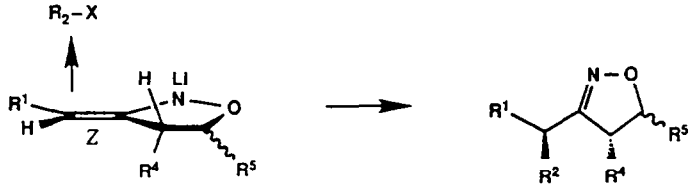
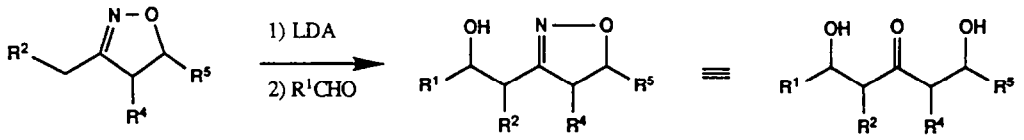


Figure 4. Exo Aldol Reactions of Δ^2-Isoxazolines

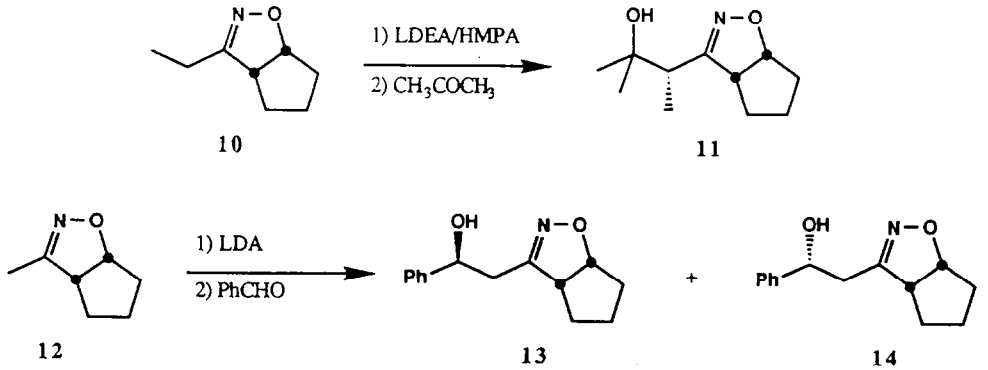


8 9

Aldol Reactions of Lithium and Zirconium Azaenolates: To survey the proposed aza-aldol reactions, we selected isoxazoline **10** because it was readily available from nitropropane and cyclopentene (Mukaiyama reaction[14]), and because the generation and reactions of the derived azaenolate were carefully studied in our previous alkylation work.[9] The azaenolate was formed by dropwise addition of **10** to a THF solution of lithium diethylamide and HMPA at –78 °C. To ensure complete deprotonation, the reaction mixture was maintained overnight at –78 °C. Fused isoxazolines like **10** were not required for highly stereoselective alkylations, and we presume that they are not required for the following aldol reactions, but we have not determined this experimentally. The assignment of stereostructures to the aza-aldol products involves some interesting chemistry, which is discussed in the next section.

The study was initiated by a brief investigation that combined reaction partners in which only two (instead of four) possible stereoisomers could be formed (Scheme 1). To probe the stereochemistry at the isoxazoline, we added acetone to the lithium azaenolate derived from **10** (**10-Li**). A single product **11** (64% isolated yield) formed as evidenced by capillary GC and analytical HPLC analysis. The stereochemistry of **11**[15] is in accord with the model: acetone approaches the *E*-azaenolate on the face opposite the cyclopentyl ring. To probe the stereochemistry at the carbonyl, we repeated the previously reported addition of benzaldehyde to the lithium azaenolate derived from **12**.[16] Two separable stereoisomers, **13** and **14**, formed in a ratio of 67/33 (60% isolated yield).

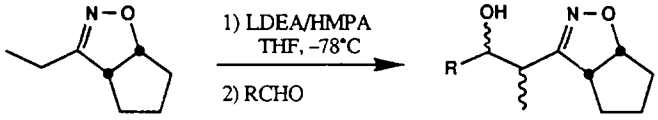
Scheme 1



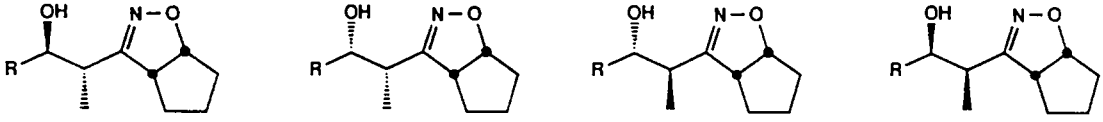
10 11 12 13 14

Next we added a series of four aldehydes (propanal, benzaldehyde, 2-methylpropanal, and 2,2-dimethylpropanal) to the lithium azaenolate **10-Li**. After 1 h at –78 °C, the reactions were quenched with water. The results of these experiments are summarized in Table 1. Experiments indicated that the products were formed under kinetic control.[17] With one exception (entry d), all four possible products were formed in each case. The diastereomer ratios were determined by capillary GC and analytical HPLC analysis of the crude reaction mixtures. The yields listed in Table 1 represent combined yields of all four products after MPLC. Retention times of the diastereomers differed significantly, and we obtained each of the products in Table 1 in pure form.

Table 1.



10 **15/16**



15-anti **15-syn** **16-anti** **16-syn**

	RCHO	**15-anti**	**15-syn**	**16-anti**	**16-syn**	Yield
no additive						
a	EtCHO	40	36	4	20	46%
b	*i*-PrCHO	43	37	3	17	53%
c	PhCHO	44	35	8	13	58%
d	*t*-BuCHO	51	30	n.d.	19	63%
$ZrCl_2Cp_2$ additive						
a	EtCHO	n.d.	n.d.	12	88	42%
b	*i*-PrCHO	n.d.	4	8	89	39%
c	PhCHO	n.d.	1	6	93	58%
c	PhCHO (no HMPA)	n.d.	n.d.	n.d.	100	31%
d	*t*-BuCHO	n.d.	n.d.	6	94	24%

n.d. = not detected

According to the formalism of the model (Figure 3), products **15-anti** and **15-syn** result from top face attack of the *Z*-azaenolate, and products **16-anti** and **16-syn** result from bottom face attack. The direction of this face selectivity is in accord with expectations, but the magnitude (**15/16** ≈ 4/1) is somewhat lower than expected based on our alkylations,[9] and on the model reaction in Scheme 1. There is little variation in face selectivity as a function of aldehyde structure. The minor products **16-anti/16-syn** form with modest to good syn selectivity (see especially **16d-syn**), as expected from a chair transition state model applied to a *Z*-azaenolate. In contrast, the major products **15-anti/15-syn**

exhibit low selectivity, with a very slight preference for anti isomers. The anti/syn ratio of the major products does not vary much with aldehyde structure.

To alter the selectivity, we next surveyed various additives in the aldol reaction of **10-Li** with benzaldehyde. Attempted transmetallations with $ZnCl_2$, $B(OEt)_3$, $SnCl_2$, and $SnCl_4$ were not productive; in general, starting isoxazoline **10** was recovered in variable yields, and no aldol adducts were formed. Although $Ti(OiPr)_4$ showed some promise, the best results were obtained with $ZrCp_2Cl_2$.[18] The general procedure was similar to that described above, except that 1.1 equivalents of $ZrCp_2Cl_2$ was added to the azaenolate solution 10 min prior to the addition of the aldehyde. The same sequence of reactions was conducted, and the product ratios and isolated yields are reported in Table 1 (bottom). The yields in this sequence were somewhat lower than with the lithium azaenolate (Table 1, top), especially with branched aldehydes.

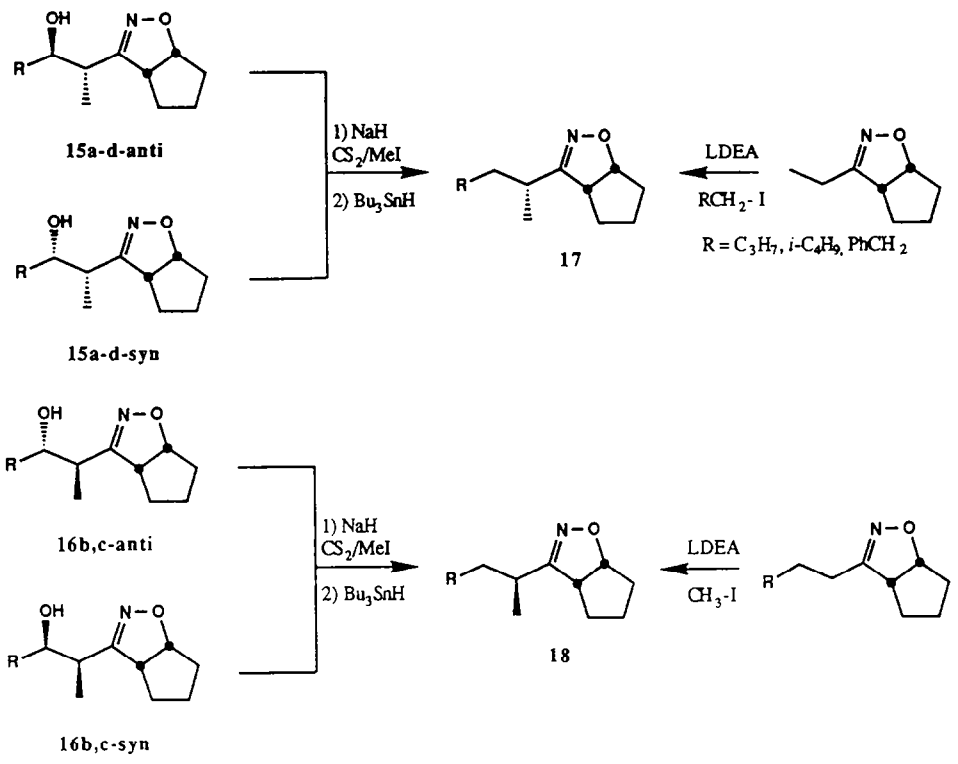
Two trends emerge when the results in the top and bottom of Table 1 are compared. The zirconium enolate: 1) exhibits higher syn-selectivity that the lithium azaenolate, and 2) exhibits a high face selectivity that is reversed from the lithium azaenolate. The first trend was expected since it is known that zirconium enolates of esters and ketones show high syn selectivity regardless of enolate geometry.[18] The second trend was not expected, and if the model in Figure 3 still applies, then products **16** result from attack of the aldehyde on the more hindered face of the *Z*-Zr-azaenolate. Since we have no structural information on this postulated intermediate, we cannot comment on the origins of this stereochemical reversal. It is also possible that the model does not apply to Zr-promoted reactions.[19] The formation of the proposed Zr-azaenolate may be accompanied by isomerization from *Z* to *E* (although the *Z*-azaenolate suffers from severe $A^{1,3}$ strain between the enolate methyl and the cyclopentyl ring). Products **16** would then form from normal top face attack. Experiments designed to probe whether the azaenolate geometry was altered by zirconium did not succeed.[20]

We also conducted one experiment with the Zr-azaenolate in the absence of HMPA with benzaldehyde as the electrophile. Although the stereoselectivity increased (**16**-syn was the only detectable aldol product), the yield decreased to 31% (from 58%, Table 1, bottom, entry c). This decrease is due at least in part to competing endo deprotonation on the isoxazoline in the absence of HMPA.[9] We also conducted the model experiments outlined in Scheme 1 with the $ZrCp_2Cl_2$ additive. Acetone failed to react with the intermediate derived from **10**, while benzaldehyde reacted with the intermediate derived from **12** to give a 77/23 mixture of **13/14** (54% combined yield).[21] In the absence of HMPA **13/14** formed in a ratio of 54/46 (40% combined yield).

Structural Assignments: By using a combination of chemical interconversions and spectroscopy, we were able to propose stereochemical assignments for all four products **15-anti/syn** and **16-anti/syn**. These assignments were later supported by several x-ray crystal structures.

A series of deoxygenation experiments that is summarized in Scheme 2 grouped the four products into two pairs of hydroxy epimers, differing in the face selectivity of attack of the aldehyde. The deoxygenations were accomplished by tin hydride reduction of the corresponding xanthate esters (Barton-McCombie reaction[22]). Twelve of the fifteen aldol products were deoxygenated to give products that were correlated with authentic samples **17, 18** derived from exo-azaenolate alkylation. The only assumption in this analysis is that all the alkylations proceed with the same stereochemistry, as was established in our previous study.[9]

Scheme 2



The pairs of epimers were then assigned syn/anti stereochemistry based on established proton-proton coupling constant trends for β-hydroxy carbonyls.[12] The pair of isomers with $J_{1,2}$ larger than 5 Hz was assigned anti stereochemistry, and the pair with $J_{1,2}$ smaller than 5 Hz was assigned syn. The observed couplings and the complete assignments obtained by integrating the deoxygenation results are outlined in Table 2. Coupling constants were not useful in the **d** series; the bulky *t*-butyl group disrupts the conformational preferences.[23] Here assignments were based on similarities in product ratios, chemical shifts of related protons, and retention times on chromatography.

Table 2

^{1}H NMR Vicinal Coupling Constants ($J_{1,2}$ in Hz) for

15-anti/syn and 16-anti-syn

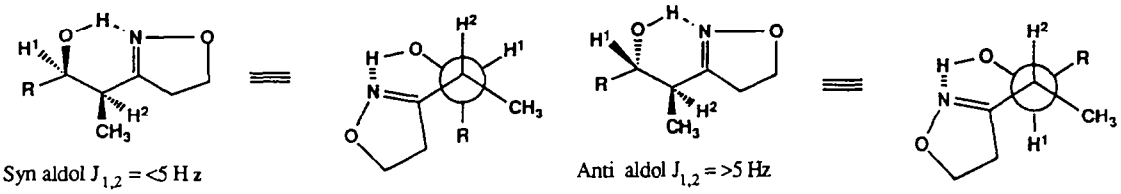
Entry	R	15-anti	15-syn	16-anti	16-syn
a	Et	5.6	3.2	6.2	2.6
b	*i*-Pr	5.8	3.1	6.2	2.4
c	Ph	6.8	4.5	7.2	3.4
d	*t*-Bu	1.8	1.4	a	1.2

a) product not formed

Although the consistency in the trends with products **a-c** gave us confidence that the assignments were correct, we were concerned that the analysis was not foolproof. The assignment of $J_{anti} > J_{syn}$ usually assumes that aldol conformers containing intramolecular hydrogen bonds dominate in solution.

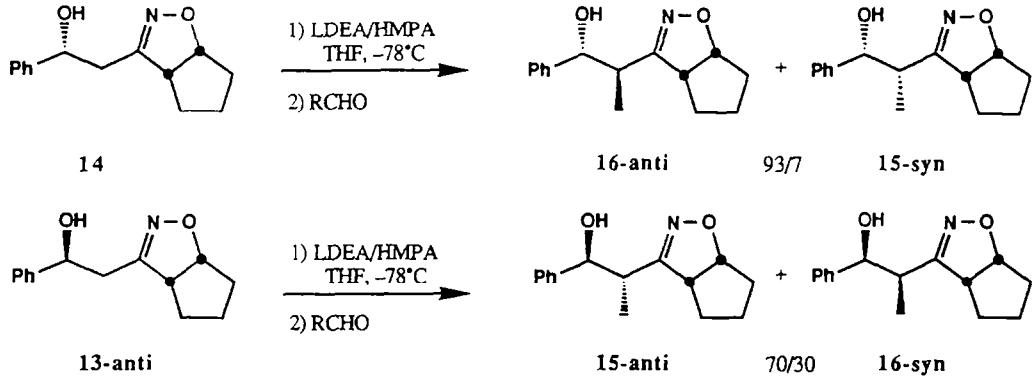
and that these conformers dictate coupling constants by virtue of dihedral angles. Because the isoxazoline nitrogen is a poor Lewis base, we were concerned about the validity of this assumption. The required conformers of isoxazolines **15/16** are depicted in Figure 5.

Figure 5



The first break towards a secure syn/anti structure assignment came when suitable crystals of **14** were grown, and the x-ray structure was solved.[24] Figure 6a contains a view of this structure. Indeed, in the solid state, the isoxazoline nitrogen and the hydroxy group are not suitably oriented to form an intramolecular hydrogen bond. With the structure of **14** secure, this compound could readily be correlated with **16-anti/15-syn** by formation of the dianion of **14** (2.4 equiv LDEA), and alkylation with methyl iodide (Scheme 3). Two products formed in a ratio of 93/7. To assign stereostructures, we apply two models to the dianion of **14** (Figure 7). Our model for alkylation of such exo-azaenolates predicts attack of methyl iodide opposite the C4 substituent in a *Z*-azaenolate. To predict the effect of the hydroxy-bearing stereocenter, we apply the Seebach-Fráter model for related dianion alkylations:[25] this model predicts attack opposite the phenyl group in the chelated (*Z*) dianion. Thus, the models reinforce each other, and indeed the selectivity in methylation of **14** is higher than typical methylations in which the side-chain stereocenter is absent. Thus we can confidently assign the major product as **16-anti**.

Scheme 3



As the model predicts alkylation of **13** gives **15-anti/16-syn** with much lower selectivity (70/30). Here, the Seebach-Fráter model and our model work against each other, and it is not easy to predict the major diastereomer from our present knowledge of stereoselectivity. The coupling constant analysis (later confirmed by x-ray) indicates that **15-anti** predominates, and thus

Figure 6a (14)

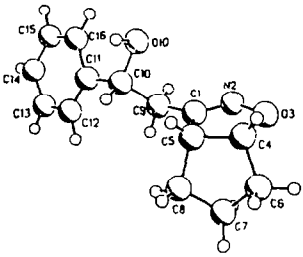


Figure 6b (15-anti)

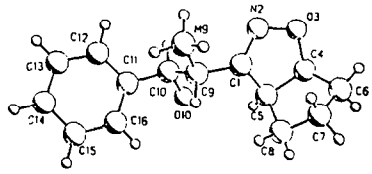
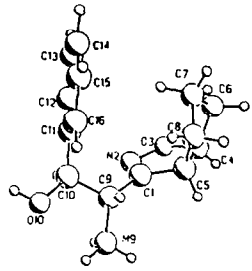


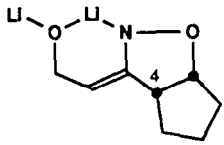
Figure 6c (16-syn)



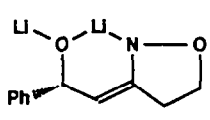
(numbering is arbitrary)

the directing effect of the isoxazoline ring is somewhat greater than that of the hydroxy-bearing stereogenic center. This qualitative analysis is an application of the principles of double asymmetric induction.[26] In a normal double asymmetric induction experiment, two chiral reagents are reacted, and stereochemical predictions are made based on the reaction of each chiral reagent with an appropriate achiral model of the other. In Scheme 3, only one reagent is chiral (**14** or **15**), but it contains two stereodirecting elements that are sufficiently remote from each other that they can be treated independently.[27] Thus, one generates the two model reactions outlined in Figure 8 to anticipate the outcome of the alkylations in Scheme 3. Neither model reaction was actually conducted, but the first reaction should give a level of selectivity of about 85/15 based on our past (mono-anion) methylations. The second model was not attempted because it is difficult to generate exo-azaenolates of isoxazolines lacking C4-substituents (endo deprotonation occurs). The results of Scheme 3 actually predict the outcome of this reaction: the anti product should be favored, but in a ratio not exceeding about 85/15.

Figure 7. Product Models



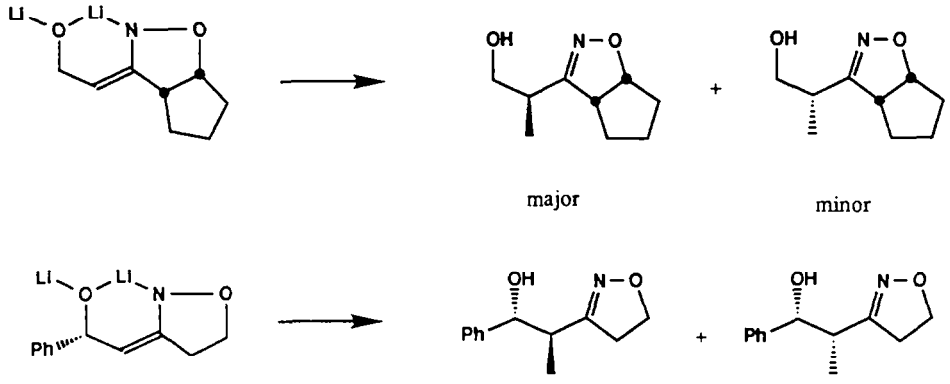
exo-azaenolate model
MeI attacks face opposite C4 substituent



Seebach-Frater model
MeI attacks face opposite Ph

Figure 8. Model Reactions for Double Asymmetric Induction

predicted outcomes of model reactions based on selectivities in Scheme 3

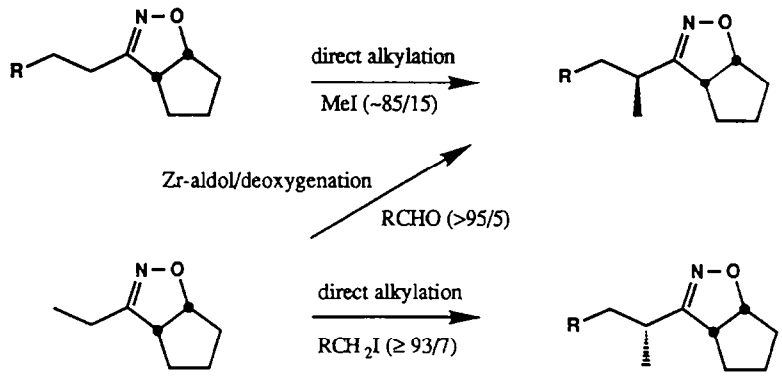


The last tiles in this stereochemical mosaic were placed when suitable crystals of both **15-anti** and **16-syn** were obtained, and x-ray crystal structures were determined. These structures are shown in Figure 6b and 6c, respectively. Neither compound is suitably oriented to form an intramolecular hydrogen bond in the solid state. Both compounds have very similar orientations about the C9-C10 bond, except the orientation of the two substituents (CH_3 and CH(OH)Ph) is reversed. This is because H9 must reside in the crowded position near C4 of the isoxazoline. It is not immediately apparent from these structures that the coupling constant trend in Table 2 should be valid because both isomers have rather large H-C9-C10-H dihedral angles (**15-anti** = 178°, **16-syn** = 176°). Nonetheless, the rigorous structural proofs now confirm that assignment of syn/anti stereostructures by the magnitude of J is applicable. Other rotamers about the C9-C10 bond than those identified in the solid state must be significantly populated in solution.

Conclusions: The aldol reactions of exo azaenolates derived from isoxazolines show promise for the stereocontrolled synthesis of heteroatom-bearing carbon chains. Lithium azaenolates exhibit modest (aldehydes) to good (ketones) facial selectivities, but low syn/anti selectivities. Zirconium azaenolates exhibit high face selectivity, which is opposite from the lithium azaenolates, and also high syn selectivity. Thus adducts with stereochemistry as represented in **16-syn** are available. This reversal in face selectivity is also useful in alkylation reactions because deoxygenation of the aldol products (**16-syn** and **16-anti**) produces the opposite diastereomer from that formed on direct alkylation of the isoxazoline. Thus, either diastereomer is available starting from the same isoxazoline (see Figure 9).

Stereochemical assignments were initially made by a combination of chemical interconversions and spectroscopy, and later secured by x-ray. Although intramolecular hydrogen bonds are not formed in the three crystal structures that were obtained, the standard coupling constant trend ($J_{anti} > J_{syn}$) still applies. The interpretation of the levels of stereoselectvity in the methylations of **13** and **14** relies on an application of the double asymmetric induction model that should be generally applicable in reactions of achiral reagents with chiral reagents that bear two separate stereodirecting elements.

Figure 9. Stereocontrolled Side Chain Introduction by Aldol and Alkylation



Experimental

General: All reactions were run under a nitrogen atmosphere. Temperatures of reactions are bath temperatures. Cooling was obtained by using a FLEXI-COOL (flexible cooling probe) apparatus available from FTS Systems Inc. Tetrahydrofuran (THF), diethyl ether, and benzene were distilled under nitrogen from sodium-benzophenone. Mass spectra for the diastoreomers were virtually identical, and data are reported only for one isomer of each set. NMR spectra were recorded at 300 MHz in $CdCl_3$.

General Procedure for Aldol Reaction of the Zirconium and Lithium Enolates of the Isoxazoline 10. [3*S,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*syn*-2-hydroxy-1-methyl-2-phenyl-ethyl)-4*H*-cyclopent[d]-isoxazole (16-syn).**

To a solution of diethylamine (0.23 ml, 2.4 mmol) in dry THF (3 mL) at 0 °C was added butyllithium (1.6 ml, 2.2 mmol, 1.4 M in hexane). After 15 minutes, hexamethylphosphoric triamide (HMPA) was added, and the mixture was cooled to –80 °C. Isoxazoline **10** (278 mg, 2 mmole) in dry THF (2 mL) was added, and the reaction mixture was then stirred for 20 h at -80 °C. Next, 1.2 equivalent of a 0.16 M solution of $ZrCl_2Cp_2$ was added in THF . The resultant red solution was allowed to stir at –78 °C for 1 h, and benzaldehyde (240 μL, 2.4 mmol) was added rapidly via syringe. The mixture was stirred for 1 h at –80 °C, poured into dilute NH_4Cl, and extracted with Et_2O (3x). The organic phase was washed with H_2O (4x) and brine, dried over $MgSO_4$, and concentrated. The crude product was then purified by MPLC (EtOAc/hexane, 1/2.5) to give 283 mg, 58%, of the separable diastereomers **16c-syn/16c-anti/15c-syn/15c-anti** in a 6/93/1/0 ratio as determined by gas chromatography and HPLC. The order of the diastereomers is the order of HPLC elution. The generation of lithium azaenolate and the benzaldehyde quench were perfomed under exactly the same reaction conditions, but omitting the addition of 1.2 equivalent of a 0.16 M solution of $ZrCl_2Cp_2$. The diasteromeric ratio from the lithium azaenolate was 8/13/35/44 (58% isolated yield). After separation, pure **16c-syn** was recrystallized from 2% EtOAc in hexane at –4 °C, and the structure was determined by X-ray diffraction: mp 105-106 °C: ^1H NMR of **16c-syn**: δ 7.36 (5 H, m), 5.18 (1 H, t, collapses to d on exchange with D_2O, J = 3.4 Hz), 4.99 (1 H, m), 3.60 (1 H, bt, J = 8.6 Hz), 3.30 (1 H, d, exchanges with D_2O), 2.65 (1 H, dq, J = 3.4, 7.1 Hz), 2.06 (1 H, m), 1.68 (4 H, m), 1.31 (1 H, m), 1.05 (3 H, d, J = 7.1 Hz); IR (thin film): 3434, 2959, 2870, 1451, 1109, 1013, 916, 897, 726, 702 cm^{-1}; MS, *m/e*: 245, 226, 212, 198, 186, 170, 138, 149, 139.

[3*S,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*anti*-2-hydroxy-1-methyl-2-phenyl-ethyl)-4*H*-cyclopent[d]-isoxazole (16c-anti).**

^1H NMR δ 7.35 (5 H, m), 4.98 (1 H, m), 4.82 (1 H, dd, collapse to d on exchange with D_2O, J = 7.2 Hz), 3.77 (1 H, d, J = 5.4 Hz), 3.61 (1 H, bt, J = 8.6 Hz), 2.74 (1 H, m, when irradiated at 1.07 collapses to doublet, J = 7.2 Hz), 2.94 (1 H, m), 1.62 (4 H, m), 1.20 (1 H, m), 1.07 (3 H, d, J = 7.1 Hz); IR (thin film): 3440, 2961, 2870, 1453, 1198, 1067, 916, 768, 700 cm^{-1}; MS, *m/e* calcd. for $C_{15}H_{16}NO$ ($M^+ - H_2O$): 226.1232, found: 226.1232. Anal. Calcd. for ($C_{15}H_{16}NO$); C, 73.44; H, 7.81; N, 5.71. Found: C, 73.24; H, 7.81; N, 5.62.

[3*R,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*anti*-2-hydroxy-1-methyl-2-phenyl-ethyl)-4*H*-cyclopent[d]-isoxazole (15c-anti).**
Compound **15c-anti** was recrystallized from 2% EtOAc in hexane at –4 °C to give crystals and the structure was determined by X-ray diffraction: mp 98-99 °C: ^{1}H NMR δ 7.34 (5 H, m), 4.90 (1 H, dd, J = 5.1, 8.8 Hz), 4.72 (1 H, t, collapses to d on exchange with D_2O, J = 6.8 Hz), 3.23 (1 H, bt, J = 8.6 Hz), 2.93 (1 H, d, J = 6.8 Hz, exchanges with D_2O), 2.86 (1 H, m, when irradiated at 1.15 collapses to doublet, J = 6.8 Hz), 2.08 (1 H, m), 1.82 (1 H, m), 1.66 (3 H, m), 1.45 (1 H, m), 1.15 (3 H, d, J = 7.2 Hz).

[3*R,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*syn*-2-hydroxy-1-methyl-2-phenyl-ethyl)-4*H*-cyclopent[d]-isoxazole (15c-syn).**
^{1}H NMR δ 7.37 (5 H, m), 4.94 (2 H, m), 3.26 (1 H, bt, J = 8.6 Hz), 2.65 (2 H, m, when exchanged with D_2O, collapses to 1H, m), 2.08 (1 H, m), 1.84 (1 H, m), 1.68 (3 H, m), 1.46 (1 H, m), 1.24 (3 H, d, J = 6.4 Hz).

[3*S,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*syn*-2-hydroxy-1-methylbutyl)-4*H*-cyclopent[d]isoxazole (16a-syn).**
The aldol reaction was performed with the zirconium azaenolate of **1** and propanal. The aldol products were purified by MPLC (EtOAc/hexane: 1/2.5) to give 42% of the separable diastereomers **16a-anti/16a-syn/15a-anti/15a-syn** in a 12/88/0/0 ratio as determined by gas chromatography and HPLC. (The order of the diastereomers is the order of elution.) The diastereomeric ratio from the lithium azaenolate was 4/12/40/36 (in a 46% isolated yield): ^{1}H NMR δ 4.99 (1 H, m), 3.87 (1 H, ddd, J = 2.6, 4.3, 8.1 Hz), 3.65 (1 H, bt, J = 8.6 Hz), 2.96 (1 H, d, exchanges with D_2O), 2.43 (1 H, dq, J = 2.6, 7.1 Hz), 2.08 (1 H, m), 1.90-1.30 (7 H, m), 1.13 (3 H, d, J = 7.2 Hz), 0.97 (3 H, t, J = 7.4 Hz); IR (thin film): 3422, 2963, 2938, 1684,1460, 1375, 974, 957 cm^{-1}; MS, *m/e* calcd. for $C_{19}H_{14}NO_2$ ($M^+ - C_2H_5$): 168.1025, found: 168.1025.

[3*S,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*anti*-2-hydroxy-1-methylbutyl)-4*H*-cyclopent[d]isoxazole (16a-anti).**
^{1}H NMR δ 4.97 (1 H, m), 3.65 (2 H, m), 3.02 (1 H, d, exchanges with D_2O), 2.45 (1 H, m), 2.08 (1 H, m), 1.94 (1 H, m), 1.9-1.30 (7 H, m), 1.18 (3 H, d, J = 7.2 Hz), 0.99 (3 H, t, J = 7.4 Hz).

[3*R,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*anti*-2-hydroxy-1-methylbutyl)-4*H*-cyclopent[d]isoxazole (15a-anti).**
^{1}H NMR δ 4.99 (1 H, m), 3.58 (2 H, m), 2.60 (1 H, m, when irradiated at 1.24 shows doublet, J = 5.6 Hz), 2.23 (1 H, d, J = 6.4 Hz, exchanges with D_2O), 2.08 (1 H, m), 1.94 (1 H, m), 1.8-1.35 (6 H, m), 1.23 (3 H, d, J = 7.1 Hz), 0.99 (3 H, t, J = 7.4 Hz).

[3*R,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*syn*-2-hydroxy-1-methylbutyl)-4*H*-cyclopent[d]isoxazole (15a-syn).**
^{1}H NMR δ 4.99 (1 H, dd, J = 5.1, 8.8 Hz), 3.72 (1 H, m, collapses to ddd when exchanged with D_2O, J = 3.2, 5.0, 8.1 Hz), 3.64 (1 H, dt), 2.54 (1 H, dq, J = 3.2, 7.1 Hz), 2.19 (1 H, bs, exchanges with D_2O), 2.08 (1 H, m), 1.89 (1 H, m), 1.80-1.30 (6 H, m), 1.18 (3 H, d, J = 7.1 Hz), 0.99 (3 H, t, J = 7.4 Hz).

[3*S,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*syn*-2-hydroxy-1,3-dimethylbutyl)-4*H*-cyclopent[d]isoxazole (16b-syn).**
The aldol reaction was performed with the zirconium azaenolate of **1** and 2-methylpropanal. The aldol products were purified by MPLC (EtOAc/hexane: 1/2.5) to give a total of 39% of the separable diastereomers **16b-syn/16b-anti/15b-anti/15b-syn** in a 8/88/0/4 ratio as determined by gas chromatography and HPLC. (The order of the diastereomers is the order of elution.) The diastereomeric ratio from the lithium azaenolate was 3/17/43/37 (53% isolated yield): ^{1}H NMR δ 4.99 (1 H, dd, J = 5.1, 8.8 Hz), 3.66 (1 H, dt, J = 8.6 Hz), 3.57 (1 H, m), 3.08 (1 H, d, J = 2.8 Hz, exchanges with D_2O), 2.62 (1 H, dq, J = 2.3, 7.0 Hz), 2.08 (1 H, m), 1.72 (5 H, m), 1.46 (1 H, m), 1.18 (3 H, d, J = 7.1 Hz), 1.08 (3 H, d, J = 6.5 Hz), 0.92 (3 H, d, J = 6.8 Hz); IR (thin film): 3476, 2959, 2872, 1462, 1375 cm^{-1}; MS, *m/e* calcd. for $C_{12}H_{20}NO_2$ (M^+): 210.1494, found: 210.1494.

[3*S,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*anti*-2-hydroxy-1,3-dimethylbutyl)-4*H*-cyclopent[d]isoxazole (16b-anti).**
^{1}H NMR δ 4.98 (1 H, m), 3.66 (1 H, bt, J = 8.6 Hz), 3.44 (1 H, q, J = 6.4 Hz), 2.84 (1 H, d, J = 7.1 Hz), 2.61 (1 H, m), 2.08 (1 H, m), 1.89 (2 H, m), 1.72 (3 H, m), 1.43 (1 H, m), 1.18 (3 H, d, J = 7.0 Hz), 0.94 (6 H, two overlapping

doublets, J = 6.3, 6.3 Hz).

[3*R,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*anti*-2-hydroxy-1,3-dimethylbutyl)-4*H*-cyclopent[d]isoxazole (15b-anti).**
^{1}H NMR δ 4.98 (1 H, dd, J = 5.1, 8.8 Hz), 3.62 (1 H, bt, J = 8.6 Hz), 3.30 (1 H, m), 2.91 (1 H, m), 2.31 (1 H, d, exchanges with D_2O), 2.08 (1 H m), 1.96 (1 H, m), 1.70 (4 H, m), 1.47 (1 H, m), 1.22 (3 H, d, J = 7.1 Hz), 0.94 (6 H, d, J = 6.7 Hz).

[3*R,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*syn*-2-hydroxy-1,3-dimethylbutyl)-4*H*-cyclopent[d]isoxazole (15b-syn).**
^{1}H NMR δ 5.00 (1 H, dd, J = 5.1, 8.8 Hz), 3.61 (1 H, bt, J = 8.6 Hz), 3.38 (1 H, m), 2.66 (1 H, dq, J = 3.2, 7.0 Hz), 2.21 (1 H, d, J = 3.6 Hz), 2.08 (1 H, m), 1.87 (1 H, m), 1.70 (4 H, m), 1.48 (1 H, m), 1.17 (3 H, d, J = 7.0 Hz), 1.04 (3 H, d, J = 6.5 Hz), 0.90 (3 H, d, J = 6.8 Hz).

[3*S,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*syn*-2-hydroxy-1,3,3-trimethylbutyl)-4*H*-cyclopent[d]isoxazole (16d-syn).**
The aldol reaction was performed with the zirconium azaenolate of **1** and 2,2-dimethylpropanal. The aldol products were purified by MPLC (EtOAc/hexane: 1/2.5) to give 24% of the separable diastereomers **16d-anti/16d-syn** in a 6/94 ratio as determined by gas chromatography and HPLC. (The order of the diastereomers is the order of elution.) The diastereomeric ratio from the lithium azaenolate was **15d-syn/16d-syn/15d-anti** 30/19/51 (63% isolated yield): ^{1}H NMR δ 4.97 (1 H, dd, J = 5.1, 8.8 Hz), 3.67 (2 H, m), 2.78 (1 H, d, J = 3.5 Hz), 2.71 (1 H, dq, J = 1.2, 7.1 Hz), 2.08 (1 H, m), 1.72 (4 H, m), 1.44 (1 H, m), 1.18 (3 H, d, J = 7.1 Hz), 0.99 (9 H, s); IR (thin film): 3474, 2955, 2870 cm^{-1}; MS, *m/e* calcd. for $C_{12}H_{20}NO_2$ ($M^+ - CH_3$): 210.1494, found: 210.1494.

We did not isolate sufficient quantities of **16d-anti** for characterization.

[3*R,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*anti*-2-hydroxy-1,3,3-trimethylbutyl)-4*H*-cyclopent[d]-isoxazole (15d-anti).**
^{1}H NMR δ 4.98 (1 H, dd, J = 5.1, 8.8 Hz), 3.61 (1 H, bt, J = 8.6 Hz), 3.43 (1 H, dd, J = 1.8, 6.0 Hz), 2.18 (1 H, d), 2.09 (1 H, m), 1.89 (1 H, m), 1.71 (3 H, m), 1.44 (1 H, m), 1.20 (3 H, d, J = 7.1 Hz), 0.99 (9 H, s).

[3*R,4α,5α]-3a,5,6,6a-Tetrahydro-3-(*syn*-2-hydroxy-1,3,3-trimethylbutyl)-4*H*-cyclopent[d]-isoxazole (15d-syn).**
^{1}H NMR δ 4.93 (1 H, dd), 3.65 (1 H, bt, J = 8.6 Hz), 3.28 (1 H, m), 2.78 (1 H, dq, J = 1.4, 7.2 Hz), 2.08 (1 H, m), 1.97 (1 H, m), 1.71 (3 H, m), 1.44 (1 H, m), 1.33 (3 H, d, J = 7.2 Hz), 0.90 (9 H, s).

[3*R,4α,5α]-3a,5,6,6a-Tetrahydro-3-(2-hydroxy-1,3,3-trimethylbutyl)-4*H*-cyclopent[d]isoxazole (11).**
The aldol reaction was performed with the lithium azaenolate of **10** and acetone. The aldol product was purified by flash chromatography (EtOAc/hexane: 1/2.5) to give **11** (60% isolated yield) as the sole product as determined by gas chromatography and HPLC: ^{1}H NMR δ 4.97 (1 H, dd, J = 4.5, 8.9 Hz), 3.66 (1 H, bt, J = 8.6 Hz), 2.50 (2 H, m), 2.09 (1 H, m) 1.92 (1 H, m), 1.72 (3 H, m), 1.43 (1 H, m), 1.26 (3 H, s), 1.25 (3 H, s), 1.21 (3 H, d, J = 7.3 Hz); IR (thin film): 3376, 2963, 1688, 1115 cm^{-1}; MS, *m/e* calcd. for $C_{10}H_{16}NO_2$ ($M^+ - CH_3$): 182.1181, found: 182.1181.

[3*R,4α,5α]-3a,5,6,6a-Tetrahydro-3-(2-hydroxy-2-phenylethyl)-4*H*-cyclopent[d]isoxazole (14).**
The aldol reaction was performed with the zirconium azaenolate of isoxazoline **12** and benzaldehyde. The aldol products were purified by MPLC (EtOAc/hexane: 1/2) to give partially separable **13/14** in 54% total isolated yield, with a 77/23 diastereomeric ratio as determined by gas chromatography and HPLC: ^{1}H NMR (minor diastereomer) δ 7.40 (5 H, m), 5.12 (1 H, m), 5.03 (1 H, m), 3.52 (1 H, bt, J = 8.8 Hz), 3.27 (1 H, d), 2.71 (1 H, dd, J = 9.2. 16.6 Hz), 2.60 (1 H, dd, J = 3.2, 16.6 Hz), 2.07 (1 H, m), 1.67 (4 H, m), 1.40 (1 H, m); IR (thin film): 3382, 3062, 3031, 2955, 2870, 1605, 1493, 1056 cm^{-1}; MS, *m/e* calcd. for $C_{14}H_{17}NO_2$ (M^+): 231.1259, found 231.1260.

[3*S,4α,5α]-3a,5,6,6a-Tetrahydro-3-(2-hydroxy-2-phenylethyl)-4*H*-cyclopent[d]isoxazole (13).**
^{1}H NMR (major diastereomer) δ 7.42 (5 H, m), 5.12 (1 H, m), 5.01 (1 H, m), 3.74 (1 H, bt, J = 8.6 Hz), 2.67 (2 H, m), 2.07 (1 H, m), 1.69 (4 H, m), 1.42 (1 H, m); IR (thin film): 3374, 3062, 3031, 2954, 2869, 1561, 1494, 1453, 1430, 1049, 920 cm^{-1}; MS, *m/e* calcd. for $C_{14}H_{17}NO_2$ (M^+): 231.1259, found 231.1260.

General Procedure for the Deoxygenation by Xanthate Formation and Tributyltin Hydride Reduction.

[3*S,4α,5α]-3a,5,6,6a-Tetrahydro-3-(1,3-dimethylbutyl)-4*H*-cyclopent-[d]isoxazole (18b).** Alcohol **16b-syn** (124 mg, 0.59 mmol) was added dropwise in THF (2 mL) to a suspension of NaH (70 mg, 2.95 mmol) in THF (2 mL). After stirring at ambient temperature for 2 h, carbon disulfide (0.1 mL) was added. Methyl iodide (0.2 mL) was added very rapidly to the resulting yellow solution after 15 min. The reaction mixture was allowed to stir at ambient temperature for 30 min, poured into water, extracted with methylene chloride (3 times), dried with $MgSO_4$, and concentrated to give 182 mg crude oil: ^{1}H NMR δ 6.15 (1 H, dd, J = 3.6, 8.8 Hz), 4.99 (1 H, dd, J = 4.5, 8.8 Hz), 3.58 (1 H, bt, J = 8.6 Hz), 3.07 (1 H, m), 2.59 (3 H, s), 2.17 (1 H, m), 2.08 (1 H, m), 1.90 (1 H, m), 1.72 (3 H, m), 1.50 (1 H, m), 1.20 (3 H, d, J = 7.1 Hz), 0.96, 0.95 (6 H, two doublets overlapping, J = 6.8, 6.8 Hz). The crude xanthate was then heated to reflux with Bu3SnH (0.24 mL, 0.89 mmol), and catalytic amount of AIBN in dry benzene (4 mL). After 1 h, the reaction mixture was concentrated, and subsequent MPLC (hexane/EtOAc, 10/1) separation gave 101 mg, 88% yield of **18b**, identical to a sample prepared by alkylation of **10** with isobutyl iodide: ^{1}H NMR δ 4.98 (1 H, dd, J = 4.7, 8.8 Hz), 3.58 (1 H, bt), 2.56 (1 H, m), 2.08 (1 H, m), 1.84 (1 H, m), 1.66 (4 H, m), 1.48 (1 H, m), 1.30 (1 H, m), 1.13 (3 H, d, J = 7.1 Hz), 0.89, 0.88 (6 H two doublets overlapping, J = 6.3, 6.3 Hz); IR (thin film): 2957, 2870, 1466, 897 cm^{-1}; MS, *m/e* calcd. for $C_{12}H_{21}NO$ (M^+): 195.1623, found 195.1623. Anal. calcd. for ($C_{12}H_{21}NO$): C, 73.80; H, 10.84; N, 7.17. Found: C, 73.69; H, 10.69; N, 7.07.

Xanthate from **16b-syn**: ^{1}H NMR δ 5.90 (1 H, t, J = 6.3 Hz), 5.10 (1 H, m), 3.68 (1 H, bt, J = 8.6 Hz), 3.24 (1 H, m), 2.58 (3 H, s), 2.06 (2 H, m), 1.88 (1 H, m), 1.70 (4 H, m), 1.55 (1 H, m), 1.22 (3 H, d, J = 7.3 Hz), 1.00 (3 H, d, J = 6.8 Hz), 0.96 (3 H, d, J = 6.8 Hz).

Xanthate from **16c-anti**: ^{1}H NMR δ 7.37 (5 H, m), 6.78 (1 H, d, J = 8.7 Hz), 4.90 (1 H, m), 3.47 (1 H, bt, J = 8.6 Hz), 3.12 (1 H, m), 2.55 (3 H, s), 1.89 (2 H, m), 1.47 (3 H, m), 1.35 (3 H, d, J = 6.9 Hz), 0.68 (1 H, m).

Xanthate from **15a-anti** : ^{1}H NMR δ 5.83 (1 H, m), 4.71 (1 H, dd, J = 4.3, 8.8 Hz), 3.41 (1 H, bt, J = 8.6 Hz), 2.81 (1 H, m), 2.13 (3 H, s), 1.93 (1 H, m), 1.7-1.2 (8 H, m), 1.21 (3 H, d, J = 7.1 Hz), 0.77 (3H, t).

Xanthate from **15b-anti**: ^{1}H NMR δ 5.78 (1 H, dd, J = 5.3 , 7.1 Hz), 4.99 (1 H, dd, J = 4.7, 8.3 Hz), 3.62 (1 H, bt, J = 8.6 Hz), 3.01 (1 H, m), 2.58 (3 H, s), 2.19-2.03 (2 H, m), 1.94 (1 H, m), 1.70 (3 H, m), 1.44 (1 H, m), 1,28 (3 H, d, J = 7.1 Hz), 0.98, 0.97 (6 H, two doublets overlapping, J = 6.7, 6.7 Hz).

Xanthate from **16c-syn**: ^{1}H NMR δ 7.36 (5 H, m), 6.78 (1 H, d, J = 8.7 Hz), 4.90 (1 H, m), 3.47 (1 H, bt, J = 8.6 Hz), 3.12 (1 H, m), 2.55 (3 H, s), 1.89 (2 H, m), 1.47 (3 H, m), 1.35 (3 H, d, J = 6.9 Hz), 0.68 (1 H, m).

Xanthate from **15b-anti**: ^{1}H NMR δ 5.85 (1 H, d, J = 4.0 Hz), 5.00 (1 H, dd, J = 4.0, 8.7 Hz), 3.85 (1 H, bt, J = 8.6 Hz), 2.91 (1 H, m), 2.57 (3 H, s), 2.07 (1 H, m), 1.9-1.6 (4 H, m), 1.50 (1 H, m), 1.31 (3 H, d, J = 6.9 Hz), 1.05 (9 H, s).

Xanthate from **15a-syn**: ^{1}H NMR δ 5.84 (1 H, m), 4.67 (1 H, dd, J = 4.8, 8.7 Hz), 3.16 (1 H, bt), 2.94 (1 H, m), 2.13 (3 H, s), 1.94 (1 H, m), 1.7-1.15 (7 H, m), 1.17 (3 H, d, J = 7.1 Hz), 0.79 (3 H, t, J = 7.4 Hz).

Xanthate from **15d-syn**: ^{1}H NMR δ 5.85 (1 H, dd, J = 4.7, 7.1 Hz), 4.98 (1 H, dd, J = 4.0, 8.7 Hz), 3.81 (1 H, dt, J = 8.6 Hz), 2.92 (1 H, m), 2.56 (1 H, s), 2.20-2.0 (2 H, m), 1.8-1.6 (4 H,m), 1.45 (1 H, m), 1.28 (3 H, d, J = 7.1 Hz), 1.00, 0.99 (6 H, two doublets overlapping, J = 6.8, 6.8 Hz).

Xanthate from **15b-syn**: ^{1}H NMR δ 5.77 (1 H, d, J = 4.3 Hz), 5.02 (1 H, dd, J = 4.7, 8.3 Hz), 3.67 (1 H, bt, J = 8.6 Hz), 2.98 (1 H, m), 2.59 (3 H, s), 2.07 (1 H, m), 1.90 (1 H, m), 1.71 (3 H, m), 1.47 (1 H, m), 1.38 (3 H, d, J = 7.2 Hz), 1.04 (9 H, s).

[3*R,4α,5α]-3a,5,6,6a-Tetrahydro-3-(1-methylbutyl)-4*H*-cyclopent-[d]isoxazole (17a).** Compound **17a** was prepared from the deoxygenation of both **15a-anti** and **15a-syn**. It was also prepared from the exo-alkylation of isoxazoline **1** and propyl iodide followed by MPLC separation (EtOAc/hexane, 1/10): ^{1}H NMR δ 4.99 (1 H, dd, J = 4.3, 8.8 Hz), 3.61 (1 H, bt, J = 8.6 Hz), 2.49 (1 H, m), 2.06 (1 H, m), 1.83 (1 H, m), 1.8-1.3 (8 H, m), 1.19 (3 H, d, J = 7.0 Hz), 0.92 (3H, t, J = 7.4 Hz); IR (thin film): 2959, 2934, 2888, 1497, 1399, 972, 943, 909 cm^{-1}; MS, *m/e* calcd. for $C_{11}H_{19}NO$ (M^+): 181.1467, found: 181.1467. Anal. Calcd. for ($C_{11}H_{19}NO$): C, 72.88; H, 10.56; N, 7.73. Found: C, 72.89, H, 10.63; N, 7.76.

[3*R,4α,5α]-3a,5,6,6a-Tetrahydro-3-(1,3-dimethylbutyl)-4*H*-cyclopent-[d]isoxazole (17b).** Compound **17b** was prepared from the deoxygenation of both **15b-anti** and **15b-syn**. It was also prepared from the exo-alkylation of isoxazoline **1** and isobutyl iodide followed by MPLC separation (EtOAc/hexane, 1/10) : ^{1}H NMR δ

4.97 (1 H, dd, J = 4.5, 8.6 Hz), 3.58 (1 H, bt, J = 8.7 Hz), 2.53 (1 H, m), 2.03 (1 H, m), 1.83 (1 H, m), 1.66 (3 H, m), 1.45 (2 H, m), 1.27 (1 H, m), 1.17 (3 H, d, J = 6.9 Hz), 0.91 (3 H, d, J = 6.6 Hz), 0.88 (3 H, d, J = 6.6 Hz); IR (thin film): 2957, 2870, 1468, 897 cm^{-1}; MS, *m/e* Calcd. for $C_{12}H_{21}NO$ (M^+): 195.1623, found: 195.1623.

[3*R,4α,5α]-3a,5,6,6a-Tetrahydro-3-(1,3,3-trimethylbutyl)-4*H*-cyclopent-[d]isoxazole (17d).** Compound **17d** was prepared from the deoxygenation of both **15d-syn** and **15d-anti** followed by MPLC separation (EtOAc/hexane, 1/10): ^1H NMR δ 4.98 (1 H, dd, J = 4.7, 9.3 Hz), 3.60 (1 H, bt, J = 8.7 Hz), 2.48 (1 H, m), 2.08 (1 H, m), 1.90 (1 H, m), 1.67 (5 H, m), 1.47 (1 H, m), 1.24 (3 H, d, J = 6.7 Hz), 0.93 (9 H, s); IR (thin film): 2955, 2869, 1468, 1366, 895 cm^{-1}; MS, *m/e* calcd. for $C_{13}H_{23}NO$ (M^+): 209.1780, found: 209.1779. Anal. Calcd. for ($C_{13}H_{23}NO$): C, 74.59; H, 11.07; N, 6.69. Found: C, 74.40, H, 11.02; N, 6.70.

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