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Remarkable Examples of Double Diastereodifferentiation: Application to the Eudistomin and Eudistomidin Alkaloids

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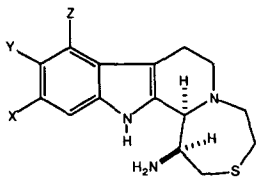
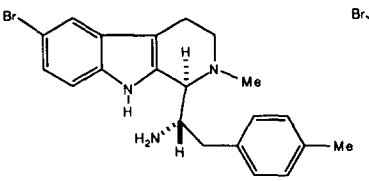
Abstract: Nucleophilic addition of chiral enolates **1** and ent-**1** with chiral iminium ion **2a** occur with total stereochemical control.

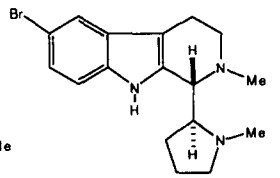
The unique oxathiazepine ring system and promising biological activity associated with the Eudistomin alkaloids[2] has stimulated several investigators to study approaches[3] to the targets and has culminated in several total syntheses.[4] Eudistomidin B[5] and woodinine[6] are related β-carboline natural products isolated from the same type of marine organism. A unified approach to these various targets involving diastereoselective addition reactions of chiral enolates **1** and ent-**1** with chiral iminium ion **2a** is described herein.



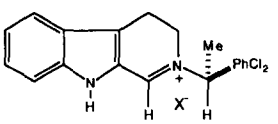
Eudistomin C: X=Br, Y=OH, Z=H
Eudistomin E: X=H, Y=OH, Z=Br
Eudistomin K: X=Br, Y=H, Z=H
Eudistomin L: X=H, Y=Br, Z=H



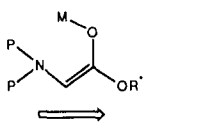
Eudistomidin B



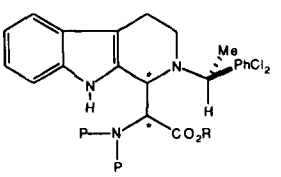
Woodinine



2a: X = Cl_2PO_2
2b: X = F

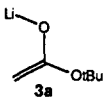
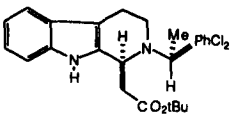
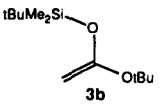
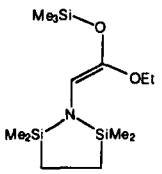
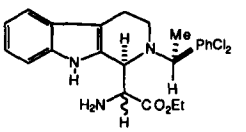
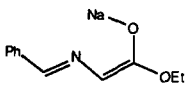


P = protecting group
1: R* = (-)-8-phenylmenthol
ent-**1**: R* = (+)-8-phenylmenthol



We demonstrated earlier that addition of achiral nucleophiles to cyclic iminium ions derived from 2,6-dichlorophenylethylamine[7] was a highly diastereoselective process.[8] Iminium ion **2a**, prepared from tryptamine in four steps (62%),[9] reacted stereospecifically with the lithium enolate of t-butyl acetate **3a** (Table). Nucleophilic addition of silyl enol ether **3b** was counterion dependent. The silyl enol ether did not react with **2a** but did react with **2b**, wherein the counterion (X) was changed to fluoride. Only one isomer of the adduct **7** was detected. The configuration of the newly formed stereogenic center in **7** was assigned by analogy to our previous study.[8] Reaction of the iminium ion with either the lithium enolate **4a** or trimethylsilyl enol ether **4b** of the stabase protected form of ethyl

Table: Reaction of Iminium Ions 2a-b with Enolates

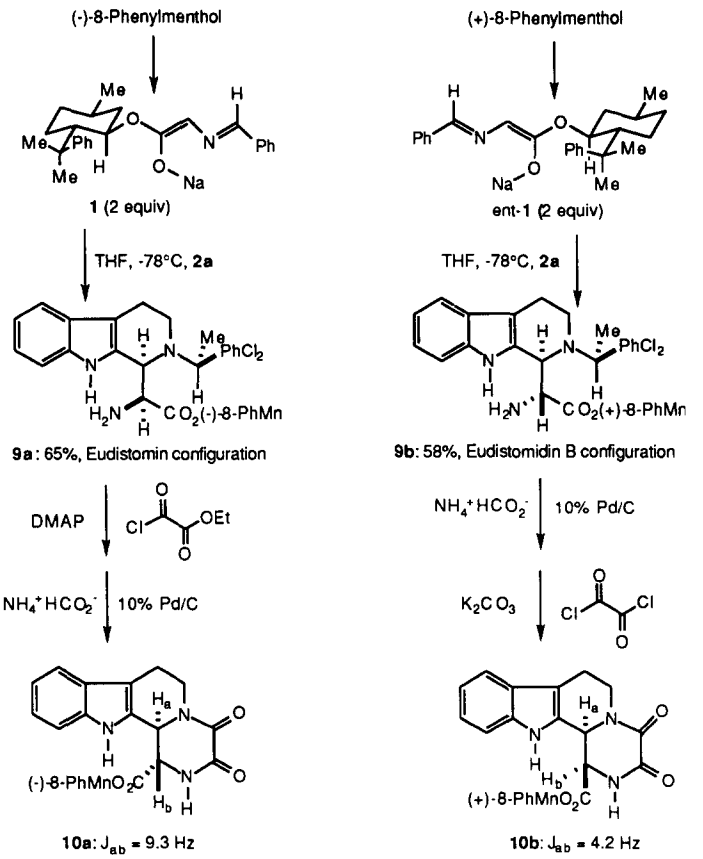
Entry	Nucleophile	Equivalents of Nucleophile	Substrate	Yield	Product
1	 **3a**	10	**2a**	48%	 **7**
2	 **3b**	4	**2a**	51%	
3	 **4a**: M=Li **4b**: M=TMS	2 5	**2a** (for M=Li) **2b** (for M=TMS)	22% 31%	 **8**: 2 stereoisomers
4	 **5**	2	**2a**	59%	

glycinate[10] afforded **8** as a 1-2:1 mixture of two stereoisomers. Again, **4b** reacted with **2b** but not **2a**. A similar mixture of isomers was obtained when **2a** underwent reaction with the the sodium enolate **5** of the benzylidene imine of ethyl glycinate.[11] Of the various glycine enolate synthons studied, the yields were best with enolate **5**.

Given that the nucleophilic additions of **3a-b** with **2a-b** were highly selective, we reasoned that the mixture of stereoisomers obtained in the reactions of **4a-b** and **5** with **2a-b** was due to a lack of control at the stereocenter adjacent to the ester moiety in **8**. The usual means of establishing control in mechanistically related aldol addition reactions is to vary the stereochemistry of the enolate. Since there is no obvious way of altering the stereochemistry of enolates derived from benzylidene imines of ethyl glycinate, we probed the face selection of reactions of chiral enolates **1**[12] and ent-**1** with chiral iminium ion **2a**.

(-) and (+)-8-Phenylmenthol[13] were acylated with α-bromoacetyl chloride, the resultant α-haloesters displaced with tetramethyl ammonium azide,[14] the azides reduced with stannous chloride,[15] and converted to the imines by condensation with benzaldehyde.[10]

In the event, the sodium enolates **1** and ent-**1** underwent stereospecific addition reactions with iminium ion **2a** affording a unique adduct in each case as measured by ^{1}H NMR and ^{13}C NMR. The stereochemistry of **9a** was assigned by acylation of the primary amine moiety with ethyl oxalyl chloride followed by hydrogenolysis and *in situ* ring closure to piperazinedione **10a**. Piperazinedione **10b** was prepared similarly from **9b**. The coupling constant of H_a and H_b in **10a** was 9.3 Hz, J_{ab} of H_a and H_b in **10b** was 4.2 Hz.[16] The coupling constants are similar in magnitude to structurally related piperazinediones[17] and are consistent with the stereochemical assignments.



The nucleophilic addition reactions of **1** and ent-**1** with **2a** constitute a remarkable example of double diastereodifferentiation.[18] The high level of stereochemical control is presumably due to the fact that the reaction involves the combination of oppositely charged species. Hence the activation energy must be very low and the transition state very early, where ground state conformational preferences of each reactant are important and determine facial selectivity with regard to that component. The stereochemistry resident in **10a** is appropriate for the Eudistomins and that of **10b** is appropriate for Eudistomidin B.

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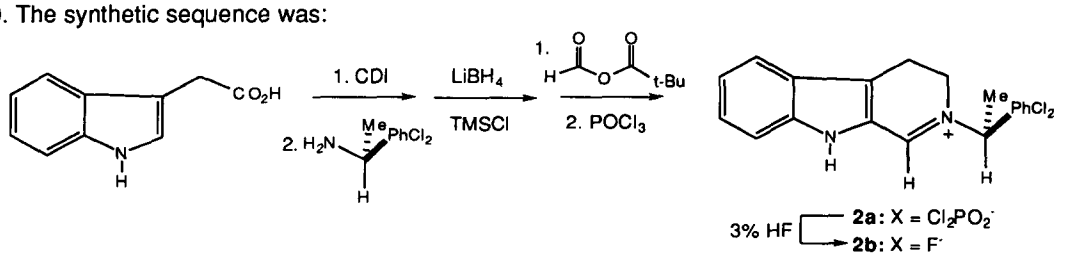
9. The synthetic sequence was:



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