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ASYMMETRIC ALKYLATIONS OF N-ACYL DIHYDROPYRIMIDINONES

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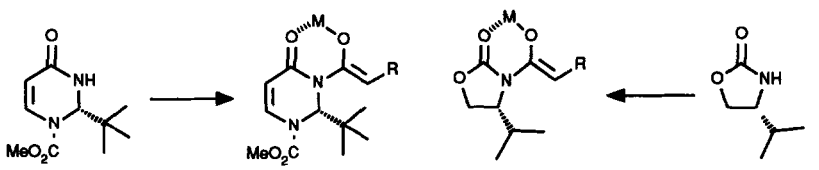
Abstract: Enantiomerically pure dihydropyrimidin-4-one **1** has been employed as a chiral auxiliary for enantioselective alkylation reactions Acylation of **1**, followed by enolate formation, alkylation and acyl cleavage, affords α-alkylated carboxylic acids in high chemical yield and enantiomeric purity

Auxiliary-mediated asymmetric alkylation reactions directed at the formation of chiral carboxylic acid derivatives have received a great deal of attention in recent years, and elegant approaches to these compounds have been developed [1] In a previous paper we presented our results concerning the synthesis of enantiomerically pure dihydropyrimidin-4-one **1** and its use as a *reagent* for the synthesis of enantiomerically pure β-aryl-β-amino acids [2] In this report we present our recent results on the use of **1** as a *chiral auxiliary* for asymmetric alkylations

The similarity of **1** to the Evans-type reagents **2**[1a] (see below for comparable deprotonated *N*-acyl analogs) led us to speculate that the chiral acetal center would provide excellent stereoselection in alkylation



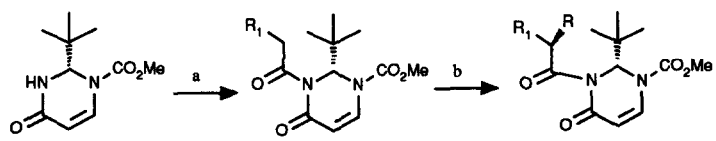
1 **2**

reactions of enolates derived from an *N*-acylated derivative As reported for similar α,β-unsaturated heterocycles,[3] the MM2 minimized structure of **1** indicates that the ring atoms are nearly coplanar, with the exception being the acetal carbon, which supports the *t*-butyl group in an axial orientation [4] In analogy with

the work of Evans, we reasoned that deprotonation of *N*-acylated **1** would cleanly provide *Z*-enolate[5] in which the reactive sp^2 carbon is rigidly configured in proximity to the auxiliary chiral center, thus providing an avenue for highly diastereoselective alkylation reactions.

To investigate these ideas, pyrimidinone **1** was *N*-acylated with propionyl and butyryl chloride in high yield via the procedure employed for the synthesis of mandelate derivatives (Scheme 1)[2] While the butyryl derivative **3** is an oil, the *N*-propionyl analog **4** demonstrates high crystallinity and is isolated by crystallization rather than chromatography Imide enolates were formed on exposure of these substrates to the sodium salt of hexamethyldisilazane[6] (1 1 eq, -78°C, 2 hr) Table I presents the results of our alkylation experiments Product ratios were assessed by NMR and GC Ethylation, allylation, propargylation and benzylation proceed in at least 94% diastereomeric excess for the enolates tested The sterically undemanding methylation reaction (Entry e) proceeds with good diastereoselection (86% d e) and in excellent yield (90%)

Scheme 1



1 **3** R = Et, **4** R = Me **5a-h**

a) 1) *n*-BuLi, 2) RCH_2COCl, b) 1) $NaN(TMS)_2$, 2) R_1X

Table I

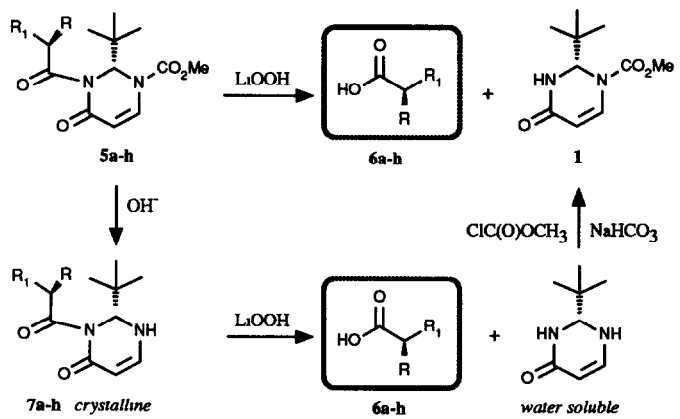
entry	R	R_1X (equivalents, temperature, time)	diastereomic ratio of 5 crude	diastereomic ratio of 5 isolated	isolated yield
a	Me (4)	ethyl iodide (4, -78°C, 6 h)	97 3	99 1	44%
b	Me (4)	allyl iodide (2, -78°C, 4 h)	99 1	98 2	95%
c	Me (4)	propargyl bromide (2, -78°C, 4 h)	99 1	100 0	86%
d	Me (4)	benzyl bromide (1 2, -23°C, 2 h)	99 1	150 1	93%
e	Et (3)	methyl iodide (5, -78°C, 5 h)	93 7	99 1	90%
f	Et (3)	allyl iodide (2, -78°C, 4 h)	98 2	98 2	87%
g	Et (3)	propargyl bromide (2, -78°C, 4 h)	99 1	255 1	80%
h	Et (3)	benzyl bromide (1 2, -23°C 2 h)	99 1	100 0	83%

The diastereomeric mixtures are obtained as oils which can be subjected to flash chromatography[7] to afford the diastereomeric ratios and chemical yields reported (Table I) Deacylation can be accomplished cleanly with LiOOH[8] to afford the expected optical series of alkylated acids (**6a-h**) in high yield with concomitant recovery of **1** in excellent yield and stereochemical purity The acids are obtained without attendant racemization as demonstrated by the magnitude of optical rotation observed in the hydrolysis adducts[9]

Alternatively, hydrolysis with 1 equivalent of methanolic hydroxide reagent[10] at 0°C (15 min) selectively removes the carbomethoxy group without interfering with the stereochemical integrity of the

heterocycle [11] These secondary amines **7a-h** tend strongly toward crystallinity, presenting an alternate strategy for achieving optically pure acyl derivatives (Scheme 2) Thus, the cold alkylation reaction mixture is treated with 1 0 eq 80% methanolic KOH and allowed to warm to 0°C After 20 min, the decarbomethoxylated heterocycle is extractively isolated with ethyl acetate and recrystallized to high diastereomeric purity The acyl group is then cleaved via LiOOH treatment and extractively isolated from the acidified aqueous phase with ethyl acetate Under these conditions, the water soluble heterocycle can be recovered from the aqueous layer via treatment with sodium bicarbonate and methyl chloroformate This sequence has the advantage that no chromatographic isolation is required, either to enrich the major isomer or to separate the acyl derivative from the chiral steering group

Scheme I



In summary, homochiral heterocycle **1** is amenable to functionalization with acyl derivatives and provides excellent stereo-directing capabilities in enolate alkylations We believe the ease of preparation of **1**, its economic preparation in either enantiomeric series,[12] and the crystallinity of **1** and key derivatives make it a valuable addition to auxiliary mediated asymmetric technology [13] Particularly appealing is the possibility of employing this methodology without the necessity of chromatographic separations for diastereomeric enrichment or auxiliary separation Further investigations into the chemistry of **1** are underway and will be reported in due course [14]

Notes and References

‡ American Cancer Society Junior Faculty Research Awardee, 1987-90

(1) (a) Evans, D A in *Asymmetric Synthesis*, Vol 3, Morrison, J D , Ed , Academic Press New York, 1984, p 1-110 (b) Oppolzer, W *Tetrahedron* **1987**, *43*, 1969-2004 (c) Meyers, A I *Acc Chem Res* **1978**, *11*, 375-81

(2) Konopelski, J P , Chu, K S , Negrete, G N *J Org Chem* **1991**, *56*, 0000

(3) For example see Seebach, D , Zimmermann, J , Gysel, U , Zeigler, R , Ha, T K *J Am Chem Soc* **1988**, *110*, 4763-4772

(4) For a recent discussion of a similar conformational bias, see Brown, J D , Foley, M A , Comins, D L *J Am Chem Soc* **1988**, *110*, 7445-7, and references therein

(5) Evans, D A , Takacs, J M *Tetrahedron Lett* **1980**, 21, 4233-6

(6) The use of LDA resulted in severely reduced yields and poor selectivity

(7) Isolated diastereomeric ratios and yield correspond to material obtained from simple flash chromatographic isolation Separation of isomers was not optimized

(8) Evans, D A , Britton, T C , Ellman, J A *Tetrahedron Lett* **1987**, *28*, 6141-6144

(9) Literature rotation of (*S*)-2-methyl-3-phenylpropionic acid (derived from **5d**) $[\alpha]_D$ = +17 87 (c = 5 03, EtOH) (Kenyon, J , Phillips, H , Pittman, V P *J Chem Soc* **1935**, 1072) Observed $[\alpha]_D$ = +17 7 (c = 2 37, EtOH) Literature rotation of (*R*)-2-methyl-butyric acid (derived from **5e**) $[\alpha]_D$ = -18 (c = 5 3, EtOH) (Asahira, Y , Shimizu, T *Nippon Yakugaku Kaishi* **1922**, *1*, 479) Observed $[\alpha]_D$ = -20 7 (c = 0 77, EtOH)

(10) We have employed aqueous solutions of LiOH, NaOH, KOH, and K_2CO_3 with equal success

(11) GC analysis indicates a 3-5% loss of stereochemical integrity at the newly-formed chiral center

(12) Currently (*S*)-asparagine is at approximately one-half the cost of (*S*)-valine or (*S*)-phenylalanine on a gram basis The difference is greater for the (*R*)-isomers, with (*R*)-asparagine at one-fourth the cost of the others

(13) Other advantages of **1** are its UV absorption characteristics, which allows easy detection on thin layer chromatography, and its lack of resonances in the aliphatic region of the ^1H NMR spectum In certain cases we have been able to judge the diastereomeric purity of the alkylation reaction by direct observation of resonances of the diastereomers formed in the reaction

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