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ASYMMETRIC INDUCTION AT C(β) AND C(α) OF N-ENOYL SULTAMS BY 1,4-HYDRIDE ADDITION/ENOLATE TRAPPING[1]

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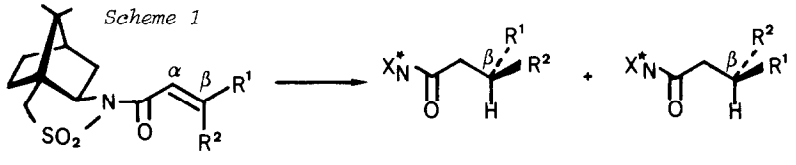
Abstract: Conjugate addition of L-Selectride to α,β-enoyl sultams 1 and 4 followed by electrophilic trapping of the resulting enolates gave in one operation saturated imides with high β- and/or α- stereodifferentiation.

Recently excellent stereoface differentiation was observed on Pd-catalyzed hydrogenations of α,β-olefinic imides 1 to provide, after saponification of products 2, β-substituted carboxylic acids in high enantiomeric purity[2] (e.g. Scheme 1, entry a).

Scheme 1



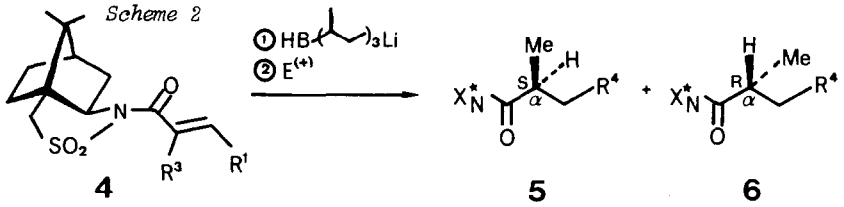
1 **2** **3**

Entry	R^1	R^2	E/Z of 1	Reaction conditions	Yield % [2 + 3]	Ratio 2 : 3
a[2]	nC_3H_7	CH_3	99 : 1	H_2, Pd/C	95	98 : 2
b	nC_3H_7	CH_3	99 : 1	L - Selectride	75	5 : 95
c	C_2H_5	CH_3	100 : 0	- " -	72	3 : 97
d	nC_4H_9	CH_3	98 : 2	- " -	90	5 : 95
e	CH_3	nC_4H_9	1 : 99	- " -	97	5 : 95
f	CH_3	$CH(OMe)_2$	99 : 1	- " -	41	5 : 95

In continuation of this work we report here 1,4-hydride additions[3] to the conjugated imides 1 which proceed with efficient but strikingly opposite π-face discrimination.Thus, treatment of imides 1 with lithium tri-*s*-butylborohydride (L-Selectride^R) (1.2 eq) in toluene at -85° to -40° afforded 1,4-adducts 3 usually in 72 to 94% yield and in 90 to 94% diastereomeric excess (Scheme 1, entries b-e)[4]. No 1,2 additions were observed except on reduction of the sterically more hindered acetal 1f[4] which gave 3f[4] in only 41% yield.

We then adressed the issue of combining the nucleophilic β-addition with electrophilic trapping of the transient enolates[5]. Scheme 2 depicts the results of studies which focus on the generation of an α-positioned stereocenter.Starting from the α-substituted acryloyl sultam 4g[4] successive addition of L-Selectride and sat aq. NH_4Cl provided the (R)-α-methyl imide 6g[4] in 86% d.e. which was increased to 92% d.e. by crystallization. It thus appears that both, formation and protonation, of the enolate intermediate occur in a highly stereoselective manner. Accordingly,alternation of the enolate E/Z-ratio should entail opposite product topicities.

Scheme 2



4 5 6

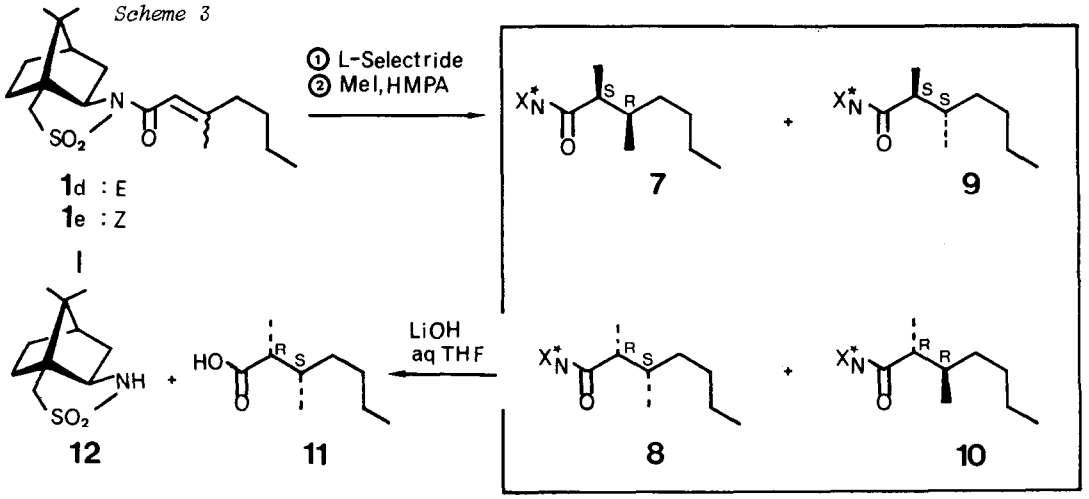
Entry	R^1	R^3	Electrophile $E^{(+)}$	R^4	Yield % * [5 + 6]	Ratio* 5 : 6
g	H	nC_3H_7	aq. NH_4Cl	C_2H_5	85 (72)	7 (4) : 93 (96)
h	C_2H_5	CH_3	- " -	C_2H_5	85 (65)	91(98) : 9 (2)
i	CH_3	CH_3	- " -	CH_3	95	90 : 10
j	CH_3	H	Me I	CH_3	84	≤ 1 : 99

* values after crystallization in parentheses

In agreement with this postulate (*vide infra*) 5h[4] (which is the (α-S)-epimer of 6g) was obtained in 82% d.e. (raised to 96% d.e. by crystallization) on subjecting the α,β-disubstituted enoyl sultam 4h[4] to the above hydride-addition/protonation tandem. Comparison of entries i and j exemplifies the option to direct the developing α-configuration by permutation of R^3 and the electrophile. Thus starting from 4i[4] a face-selective protonation of an α-methyl-substituted enolate gave the α-(S)product 5i[4], whereas methylation(MeI/HMPA) of the α-unsubstituted enolate derived from 4j[4] provided the α-(R)-epimer 6j[4] in >98% d.e.. The higher level of stereodifferentiation observed on methylation compared to protonation parallels results obtained with racemic enolates[5].

Having achieved good β- (1 → 2 or 3) or α- (4 → 5 or 6) stereodifferentiation we then explored the possibility of inducing two asymmetric centers at C(β) and C(α) in one synthetic operation. Our results are summarized in Scheme 3.

Scheme 3

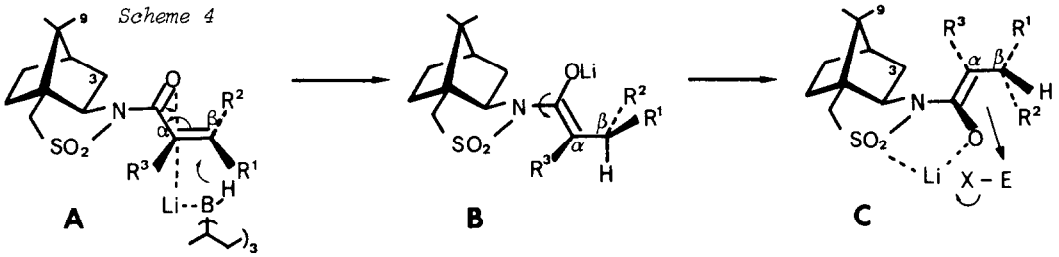


Entry	1d/1e (E/Z)	Yield 7 to 10	Ratio crude 7/8/9/10	Yield cryst. 7 to 10	Ratio cryst. 7/8/9/10
k	98 : 2	82 %	1:90:5: 4	64 %	0:99:0: 1
l	1 : 99	76 %	13: 4:0:83	55 %	0: 2:0:98

Sequential treatment of the (E)-imide 1d[4] with L-Selectride and MeI/HMPA gave a stereoisomer mixture from which the major (syn)-(2R,3S)-isomer 8[4] (90%) was obtained in 99% purity after flash chromatography/crystallization. Alternatively, the (Z)-imide 1e[4] when subjected to the same reaction conditions afforded the (anti)-(2R,3R) product 10[4] with somewhat lower α-induction; nevertheless, its stereoisomeric purity was raised to 98% by flash chromatography-crystallization. These examples show the capacity of the sultam unit to control the generation of center C(β) corresponding to the (E)/(Z)-ratio of olefinic imides 1d/1e; subsequent formation of center C(α) is only moderately affected by C(β). Accounting for the easy availability of the antipodal camphor sultam[6] each of the four stereoisomers 7 to 10 can be individually prepared in 98 to 99% purity. In practical terms it is worth noting that the auxiliary sultam 12 was efficiently recovered by mild hydrolysis (LiOH, aq THF, 40°) of adduct 8 thus giving acid 11 *without* α-epimerization in 98% enantiomeric excess. Furthermore, all diastereoisomer ratios described here, were routinely determined by direct GC- and ^{1}-NMR analyses[4].

The stereoface differentiations observed throughout this work are consistent with the transition state topologies depicted in the Scheme 4.

Scheme 4



Based on the X-ray diffraction analysis of the corresponding crotonoyl sultam[6a] we assume that the starting enoyl sultams react in the conformation A where the carbonyl group is *anti* to the SO_2 group and *s-cis* to the C(α),C(β)-double bond; the β-stereodifferentiation is then dictated by lithium coordination and hydride attack from the less hindered bottom face to generate enolate B[7]. By contrast we have ascribed previously the opposite π-face selection on Pd-catalyzed hydrogenations of imides 1 to a conformation with *syn*-disposed C=O/SO_2 groups[2].

To explain the α-stereodifferentiation found on protonation and methylation of the transient enolates we have to consider 1)their (E)/(Z)-configurations as well as 2)their conformations.

1)In line with stereochemical studies of conjugate reductions of enones[8] we postulate the enoyl-*s-cis*-conformation A to translate into the enolate configuration B. This is supported by a comparison of entries g and h (Scheme 2). Accordingly, conjugate reduction of α-substituted **acryloylsultam 4g should yield the (E)-enolate B** (R^1-R^2 = H, R^3 = C_3H_7) , whereas the β-substituted enoyl sultam 4h would be transformed to the (Z)-isomer B (R^1,R^2 = H,C_2H_5, R^3 = CH_3) . In complete agreement with this hypothesis 4g and 4h yielded as major products 6g and 5h, respectively, which possess the same substitution pattern but the opposite α-configuration. This exemplifies a new selective route to either (E) or (Z) enolates *via* permutation of the α,β-substituents in a carbonyl-conjugated precursor.

2) Consistent with the observed α-configurations of products 6g, 5h, 8 and 10 we assume that the enolates B are reorganized to give the more stable conformers C where the enolate- and SO_2 oxygens are chelated by the lithium counterion; subsequently, the electrophile approaches predominantly opposite to the auxiliary-shielded C(α)-top face.

Entries k and l (Scheme 3) are particularly interesting as they reflect the counterplay of inductive effects provided by the sultam auxiliary and by the C(β)-center. Accounting for eclipsed C-C/C(β)-H bonds in C and for an electrophile approach *anti* to the larger group R^1 or R^2 [5,9] the C(β)- versus auxiliary bias should match when R^1=*n*Bu, R^2=Me (entry k) but mis-match when R^1=Me, R^2=*n*Bu (entry l). In agreement with this model the conversion 1d → 8 displays a higher α-stereodifferentiation (entry k, 88%d.e.) than the transformation 1e → 10 (entry l, 74%d.e.). From the practical standpoint it is noteworthy that in the latter case the intrinsic α-topological influence of the auxiliary overrides that of the C(β)-center[10]; thus, given its easy purification crystalline 10 was obtained in 100%d.e. at C(α) and 96% d.e. at C(β).

In summary we have described here the predictable and versatile generation of two contiguous asymmetric centers in one operation and exemplified a new stereoselective approach to enolates. Further extensions of this methodology are presently under investigation.

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4 All new compounds were characterized by IR, ^{1}H-NMR(360 MHz), and MS. The following procedures are representative: Acylsultams: 1 and 4 (E/Z-ratios by GC) were prepared from sultam 12 by a) successive treatment with NaH and the enoyl chloride[2] (1b, 1c, 4g - 4j), b)successive treatment with Me_3Al (1.1eq, r.t.) and the corresponding methyl enoate (toluene, 80°, 24h, 1d, 1f), or c) acylation with Me_3Al/methyl-2-heptinoate followed by addition of Me_2CuLi to the heptinoylsultam (1e).-Hydride Addition/Enolate Trapping:L-Selectride (1.2eq) was added over 10 min to the enoyl sultam in toluene (entries b to f, k, l) or Et_2O (entries g to i) or THF (entry j) at -85°. 10 min later → -40° over 30 min, kept at -40° for 20 min, protonated at -40° by addition of sat. aq NH_4Cl in one portion or methylated (entries j,k,l) after recooling to -80° by addition of MeI (7eq), HMPA (2.4eq) then → 0° over 2h, then 0°, 3h, then sat. aq. NH_4Cl.- Saponification: 1.3N LiOH (10eq) in H_2O/THF 1:2 at r.t./3d (5h) or at +40°/7d (8).- Diastereoisomer Assignments and Purities: Capillary GC and ^{1}H-NMR: entries a to e: comparison with ref [2]; entry f: in analogy to entries a - e; entries g,h: saponification of 5h to (+)-(S)-2-methylpentanoic acid and its chiroptic comparison as well as by GC of its (S)-α-naphthylethylamide; entries i,j: acylation of 12 with authentic (±)- as well as (+)-(S)-2-methylbutyric acid and GC-comparison; entries k,l: GC-separation of all isomers 7 to 10. Absolute configuration at C(β) based on entries d,e, on C(α) based on GC-determination of *syn/anti* ratio (7+8):(9+10), 1) prepared from 1d or 1e, 2) prepared from authentic mixtures of (2R*,3S*)- and (2R*,3R*)-2,3-dimethylheptanoic acid [5a]. GC of (S)-α-naphthylethylamides derived from 11 and its stereoisomers. Obs. $[\alpha]_D$-values (20°, solvent, c=g/100 ml): Free acid, obtained by saponification of 5h (90% d.e.): +14.3° ($CHCl_3$, 1.0), lit: G.I. Fray, R. Robinson , *Tetrahedron*, 1962, *18*, 261. Acid 11: -40.8° (CH_2Cl_2,1.7). Melting points of recrystallized (hexane) products: 6g: 174°, 5h: 118°, 6j: 190°, 8: 105°, 10: 88°.

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7 The β-addition of L-Selectride to 1b was stereorandom in the presence of 15-crown-5.

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