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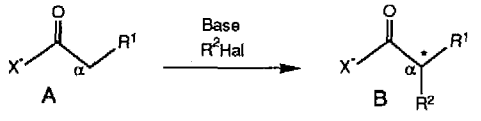
ASYMMETRIC ALKYLATION OF N-ACYLSULTAMS: A GENERAL ROUTE TO ENANTIOMERICALLY PURE, CRYSTALLINE C(α,α)-DISUBSTITUTED CARBOXYLIC ACID DERIVATIVES.

Wolfgang Oppolzer*, Robert Moretti and Silvia Thomi
Département de Chimie Organique, Université de Genève, CH-1211 Genève 4, Switzerland

Abstract.-Successive treatment of acylsultams 2 with *n*BuLi or NHMDS and primary alkyl halides, followed by crystallization, gave pure C(α)-alkylation products 4 and, *via* their non-destructive cleavage, enantiomerically pure alcohols 5 or carboxylic acids 6 .

Face-selective alkylations of chiral enolates rank among the most important methods for asymmetric carbon-carbon bond formation [1,2]. In particular, since 1980 the generation of an 'acyclic' stereogenic center α to a carbonyl group (A → B) has been impressively addressed [2] (Scheme 1).

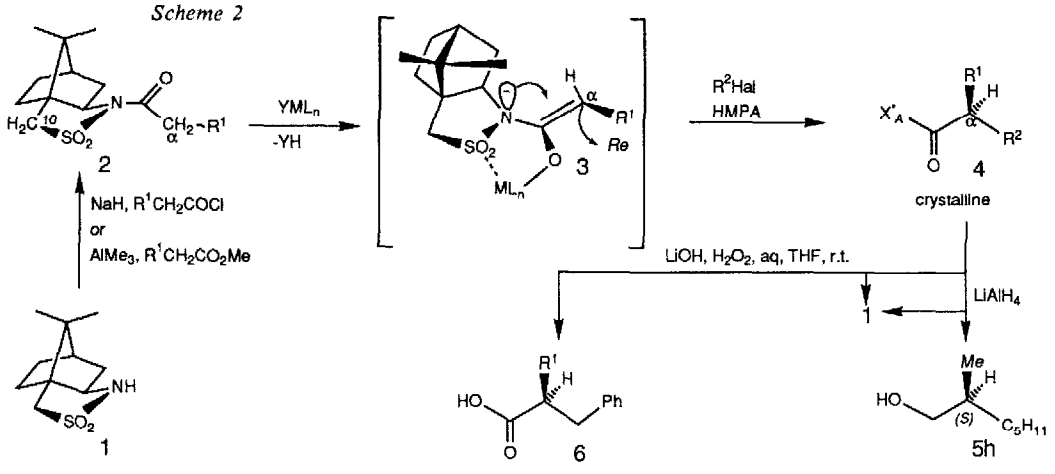
Scheme 1



However, among the published protocols only very few are compatible with the use of non-activated alkyl halides [2b-2e] and none of them provides products B which can be generally purified by crystallization.

We report here a practical solution of these problems as outlined in Scheme 2 and the Table [3].

Scheme 2



Acylsultams 2, readily accessible from inexpensive auxiliary 1 [4], were initially treated with lithium hexamethyldisilazide (LHMDS, as well as with lithium cyclohexylisopropylamide) followed by an alkyl halide/HMPA. Under these reaction conditions the formation of C(10)-alkylated by-products was inevitable.

Table: Asymmetric Alkylations : 2 → 4

		R^1	R^2	Hal	YMLn (Base)	Yield [%] Crude	d.e. [%] Crude	Yield [%] Cryst.	d.e. [%] Cryst.	Config. C (α)	M.p.
1	a	Me	$PhCH_2$	I	NHMDS	100	96.5	89	98.4	*S*	119-120
2	a	Me	$PhCH_2$	I	KHMDS	100	92.9	--	--	*S*	--
3	a	Me	$PhCH_2$	I	BuLi	91	96.9	89	98.5	*S*	--
4	b	Me	CH_2=CH-CH_2	I	NHMDS	98	94.2	94	94.5	*S*	--
5	b	Me	CH_2=CH-CH_2	I	BuLi/10%ICA	82	96.6	74	96.6	*S*	140-142
6	c	Me	Me_2C=$CHCH_2$	Br	BuLi/10%ICA	82	98.8	70	>99	*S*	87-89
7	d	Me	HC≡CH-CH_2	Br	BuLi	82	98.3	78	>99	*S*	133-135
8	e	Me	$tBuO_2CCH_2$ [a]	Br	NHMDS	--	98.5	77	>99	*S*	146-148
9	f	Me	$ZNMeCH_2$ [a,b]	Cl	NHMDS	--	72.7	58	>99	*S*	145-147
10	g	Me	$MeOCH_2$ [a,b]	Br	NHMDS	--	74	67	>99	*S*	118-120
11	h	Me	C_5H_{11}	I	BuLi	88	97.7	81	98	*S*	43-45
12	i	Me	$Me_2CH(CH_2)_3$	I	NHMDS	89	99	81	>99	*S*	65-67
13	j	Me	CH_2=CMe-$(CH_2)_2$	I	NHMDS	--	--	82	--	-	--
14	k	$PhCH_2$	Me	I	NHMDS	93	90.1	83	97.5	*R*	178-180
15	k	$PhCH_2$	Me	I	BuLi	--	94.7	88	>99	*R*	
16	l	CH_2=CH-CH_2	Me	I	BuLi	--	95.4		98.5	*R*	186-189
17	m	C_5H_{11}	Me	I	BuLi	--	96.1		98.1	*R*	95-96
18	n	Et	$ZNMeCH_2$	Cl	BuLi	47(99) [c]	88.7	34(87) [c]	>99	*S*	101-102
19	o	OCH_2Ph	$PhCH_2$	I	LHMDS	88	98.2	68	98.2	*S*	114-115
20	p	OMe	$PhCH_2$	I	NHMDS	81	99.0	--	--	*S*	163-165

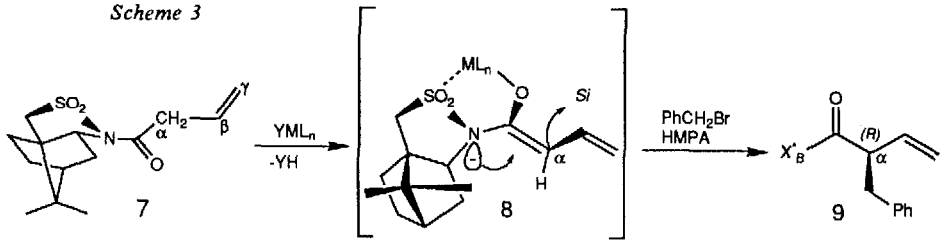
a) Alkylation in the presence of $(n\text{Bu})_4NI$ (0.1 mol-equiv.); b) Alkylation in the absence of HMPA;
c) Yield in parenthesis based on recovered 2.

This competitive deprotonation/alkylation at C(10) was efficiently prevented by decreasing and even avoiding the build-up of *sec.* amine (employing *n*BuLi with 0.1 mol-equiv. of cyclohexylisopropylamine, entries 5,6, or rather *n*BuLi alone, entries 3, 7, 11, 15-18). Clean C(α)-alkylation also resulted from the use of sodium hexamethyldisilazide (NHMDS, entries 1, 4, 8-10, 12-14, 20) as a base, presumably owing to the increased reactivity of enolate 3, M = Na relative to 3, M = Li. This also holds for the potassium enolate 3, M = K which, however, reacts in a less face-selective manner (c.f., entries 1-3). Excellent π-face differentiations were observed on deprotonation of 2, R^1 = Me with either *n*BuLi or NHMDS in THF, followed by alkylation with benzylic, allylic, propargylic and C(α)-alkoxycarbonyl halides (i.e., activated alkylation reagents, entries 1-8) in the presence of HMPA. Analogous alkylations with $ClCH_2NMeCO_2Bn$ [5] or $MeOCH_2Br$, in the presence of Bu_4NI and in the absence of HMPA, were less selective but yielded pure products 4 after FC/crystallization (entries 9, 10, 18). It is particularly worth noting that non-activated primary alkyl iodides (except homoallylic halides) reacted smoothly to give products 4 in high yield and diastereomeric purity (entries 11, 12, 13). Alkylations of various acylsultams 2 (R^1 = $PhCH_2$, CH_2CH=CH_2, C_5H_{11}) with methyl iodide were equally successful (entries 14-17).

The more acidic C(α)-benzyloxy- and methoxy-acylsultams 2o and 2p underwent efficient and π-face-selective deprotonation/alkylation reactions (using LHMDS or NHMDS, entries 19, 20) providing access to enantiomerically pure glycolic acid derivatives.

The absolute configuration at C(α) of 4 was easily directed in either sense by interchanging R^1 with R^2 (e.g., 4a/4k, 4b/4l, 4h/4m) as well as by using sultam 1 or its antipode [4b] as the auxiliary. The latter option is demonstrated by the benzylation of *N*-(3-butenoyl)sultam 7. LHDMS or NHDMS were equally suitable because of the relatively low basicity of transient dienolate 8, which was cleanly alkylated at C(α) providing crystallized *(R)*-product 9 (80% yield, m.p. 167 - 168°C, 98.9% d.e.).

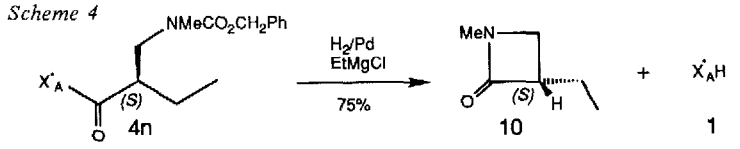
Scheme 3



In general, products 4 could be separated from their C(α)-epimers by chromatography and, more remarkably, purified by crystallization. Thus, pure 4 was obtained by rapid FC (removal of very apolar and polar impurities) and crystallization (4a-4d, 4f-4i, 4n-4p) or rather by direct crystallization (4e, 4k, 4l, 4m, 9).

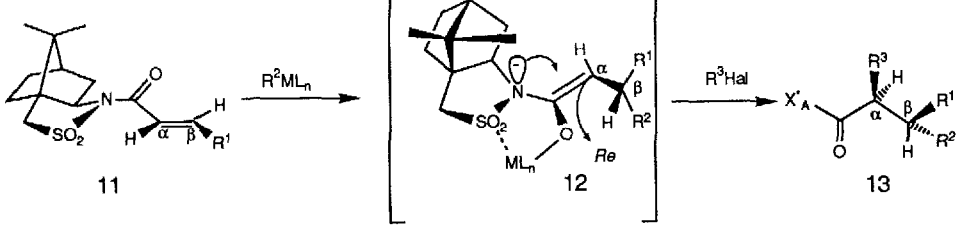
The depicted diastereomeric excess (d.e.) values of crude and purified 4 were determined by comparison (GC) with either the pure C(α)-epimer, obtained by alternating R^1 and R^2 (*vide supra*), or with mixture of epimers, prepared by Me_3Al mediated acylation of sultam 1 [6] with a racemic methylester (4g, 4o, 4p, 9). The C(α)-epimers are clearly distinguishable not only by GC (the *(S)*-isomer being eluted first) but also by ^1H- and ^{13}C-NMR. Absolute configurations of 4m and 4n were rigorously assigned *via* comparison with authentic samples [7,8]. Non-destructive cleavage by reduction ($LiAlH_4$) or hydroperoxide-assisted saponification [9] provided sultam 1 and enantiomerically pure alcohol 5h or carboxylic acids 6a (R^1 = Me) and 6o (R^1 = OCH_2Ph); their optical rotations are in agreement with published values [10]. The conversion of amidoalkylation product 4n to an enantiomerically pure 3-substituted β-lactam 10 (Scheme 4) has been reported elsewhere [8].

Scheme 4



The observed topicity is consistent with a kinetically controlled formation of chelated *(Z)*-enolates 3 (Scheme 2), alkylated from the bottom face, opposite to the lone electron pair on the nitrogen atom, in analogy to alkylations 12 → 13 (Scheme 5) [7,11].

Scheme 5



Thus, complementary to the 1,4-addition reactions of enoylsultams 11 [7,11], *simple deprotonation of saturated* acylsultams 2 provides chiral *(Z)*-enolates 8 and 12 allowing the overall enantiospecific formation of a carbon-carbon bond at C(α) relative to a carbonyl group. This work exemplifies once more the general utility of sultam 1 (and its antipode) as a practical chiral auxiliary [8a,12]. Applications and extensions e.g., to asymmetric syntheses of α-amino acids will be published in due course.

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REFERENCES AND NOTES

1) Review: 1) D.A. Evans, 'Asymmetric Synthesis', Ed. J.D. Morrison, Academic Press, New York 1984, Vol. 3, Part B, p.2. Cyclic enolates: A.I. Meyers, B.A. Lefker, K.T. Wanner, R.A. Aitken *J. Org. Chem.* 1986, *51*, 1936; D. Seebach, R. Imwinkelried, T. Weber 'Modern Synthetic Methods' Ed. R. Scheffold, Springer, Berlin-Heidelberg, 1986, vol. 4, p.125.

2) a) D.A. Evans, J. Bartroli, T.L. Sih, *J. Am. Chem. Soc.* 1981, *103*, 2127; D.A. Evans, M.D. Ennis, D.J. Mathre, *ibid.*, 1982, *104*, 1737; S.G. Davies, *Pure & Appl. Chem.* 1988, *60*, *13*. b) P.E. Sonnet, R.R. Heath, *J. Org. Chem.* 1980, *45*, 3137; D.A. Evans, J.M. Takacs, *Tetrahedron Lett.* 1980, *21*, 4233; c) E. Ade, G. Helmchen, G. Heiligenmann, *ibid.*, 1980, *21*, 1137; R. Schmierer, G. Grotemeier, G. Helmchen, A. Selim, *Angew. Chem.* 1981, *93*, 209; *Angew. Chem. Int. Ed. Engl.* 1981, *20*, 207; G. Helmchen, R. Wierzchowski, *Angew. Chem.* 1984, *96*, 59; *Angew. Chem. Int. Ed. Engl.* 1984, *23*, 60; d) L. Guoqiang, M. Hjalmarsson, H.-E. Högberg, K. Jernstedt, T. Norin, *Acta Chem. Scand.* 1984, *B 38*, 795; e) Y. Kawanami, Y. Ito, T. Kitagawa, Y. Taniguchi, T. Katsuki, M. Yamaguchi, *Tetrahedron Lett.* 1984, *25*, 857; M. Enomoto, Y. Ito, T. Katsuki, Y. Yamaguchi, *ibid.*, 1985, *26*, 1343.

3) All new compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and MS. The following procedures are representative: Deprotonation/alkylation: 1M *n*BuLi (hexane, 1 mol-equiv.) was added over 1 h to a solution of 2 (THF, 5 ml/mmol) at -78°; alternatively, a 1 M solution of NHDMS or LHDMS (THF) was added over 10 min. Stirring the mixture at -78°C , 1h, addition of the alkylating agent (3 mol-equiv.) in HMPA (3 mol-equiv., except entries 9,10), then stirring either at -78°C, 16h (entry 14), -60°C, 16h (entries 3,4), -45°, 16 h (entry 19), 0°C, 2h (entry 18), or otherwise, while slowly warming up to r.t., quenching with water and extraction (Et_2O) afforded crude 4, usually crystallized from MeOH. Hydroperoxide-assisted saponification: 30% aq. H_2O_2 (8 mol-equiv.) and $LiOH.H_2O$ (4 mol-equiv.) were added at 0°C to a solution of 4 in THF/H_2O (4:1). Stirring at 0°C, 1h, then at r.t., 16h, acidification (HCl), extraction (CH_2Cl_2), evaporation of the dried extracts and trituration of the residue with pentane furnished insoluble auxiliary 1 (93 - 96%). The soluble carboxylic acid was purified by distillation (6a) or FC (6o).

4) a) W.Oppolzer, C. Chapuis, G. Bernardinelli, *Helv. Chim. Acta* 1984, *67*, 1397; b) M. Vandewalle. J. Van der Eycken, W.Oppolzer, C. Vullioud, *Tetrahedron*, 1986, *42*, 4035; c) F.A. Davis, J.C. Towson, M.C. Weismiller, S. Lal, P.J. Carroll, *J. Am. Chem. Soc.* 1988, *110*, 8477.

5) Bayer A.G., *Belg. Patent*, 1962, 621,378; *Chem. Abstr.*, 1963, *59*, 9816.

6) W. Oppolzer, J.-P. Barras, *Helv. Chim. Acta* 1987, *70*, 1666.

7) W. Oppolzer, G. Poli, A.J. Kingma, C. Starkemann, G. Bernardinelli, *Helv. Chim. Acta* 1987, *70*, 2201.

8) a) W.Oppolzer, *J. Pure & Appl. Chem.* 1988, *60*, 39; b) W. Oppolzer, H. Bracher, to be submitted to *Helv. Chim. Acta.*

9) E.J. Corey, S. Kim, S. Yoo, K.C. Nicolaou, L.S. Melvin, Jr, D.J. Brunelle, J.R. Falck, E.J. Trybulski, R. Lett, P.W. Sheldrake, *J. Am. Chem. Soc.* 1978, *100*, 4620; D.A. Evans, T.C. Britton, J.A. Ellman, *Tetrahedron Lett.* 1987, *28*, 6141; W. Oppolzer, A.J. Kingma, *Helv. Chim. Acta*, in press.

10) $[\alpha]_D$ values (°C, solvent, c = g/100 ml): 5h: obs. = -13.1° (20°, $CHCl_3$, c = 1.15); lit. = -4.01° (25°, neat, 31% e.e.), P.D. Levene, M. Kuna, *J. Biol. Chem.*, 1941, *140*, 255. 6a: obs. = +29.3° (20°, $CHCl_3$, c = 1.15); lit. = +25.2° [2d]. 6o: obs. = -80.9° (25.6°, EtOH, c = 2.2); lit. = -81° [2e].

11) W. Oppolzer, G. Poli, *Tetrahedron Lett.*, 1986, *27*, 4717. W. Oppolzer, G. Poli, C. Starkemann, G. Bernardinelli, *Tetrahedron Lett.* 1988, *29*, 3559.

12) Review: W.Oppolzer, *Tetrahedron*, 1987, *43*, 1969; Erratum, *ibid.*, 1987, *43*, 4057.

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