Tetrahedron Letters,Vol.26,No.41,pp 5037-5040,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

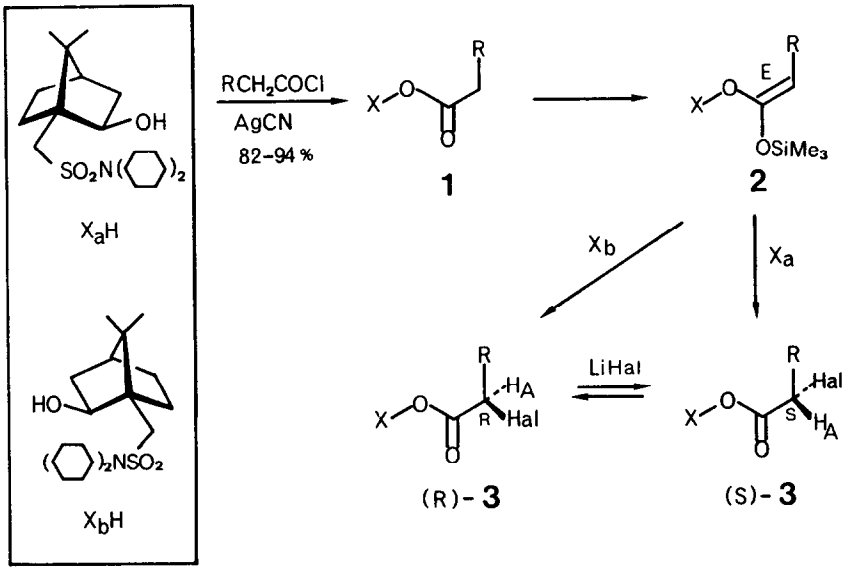
ASYMMETRIC HALOGENATION OF CAMPHOR-10-SULFONIC ACID DERIVED ESTERS: AN EFFICIENT NEW ROUTE TO ENANTIOMERICALLY PURE HALOHYDRINS AND EPOXIDES.

Wolfgang Oppolzer* and Philip Dudfield
Département de Chimie Organique, Université de Genève, CH-1211 Genève, Switzerland

Abstract: Successive treatment of chiral esters 1 with LDA/Me_3SiCl and NBS or NCS gave crystalline α-haloesters 3 which furnished halohydrins 4 and terminal epoxides 5 in high e.e..

The practical, chiral auxiliaries Xa and Xb (Scheme 1) confer high Π-face differentiation to Diels-Alder-[1] and organocopper additions of conjugated enoates[2] as well as α-alkylations[3] and -acetoxylations[3] of enolates.

Scheme 1



In conjunction with this work we report here a straightforward conversion of esters to enantiomerically pure halohydrins and terminal epoxides[4] which features an analogous Π-face selective halogenation process.

Acylation of auxiliary alcohols XH with acid chlorides in the presence of AgCN[5] furnished esters 1 in excellent yields. Kinetically controlled deprotonation/O-silylation[6] of esters 1 furnished silyl ketene acetals 2 which were then treated with N-bromosuccinimide in DME(method A) or in toluene (method B) at -78°[7]. Our results are summarized in Scheme 1 and Table 1[8].

Table 1: Asymmetric Ester Halogenation 1→(2)→3[9]

Entry	R	Hal	Method[8]	Product 3 yield % crude	d.e.%[a] crude	yield % cryst.	d.e.%[a] cryst.	Config.[b] at Cα
1	CH_3	Xa Cl	C	92	95	77	98	(S)
2	nC_4H_9	Xa Br	A	84	~90	68	>96	(S)
3	nC_4H_9	Xa Cl	C	83	95	67	>96	(S)
4	C_6H_5	Xa Cl	C	68	94	54	>96	(S)
5	$(CH_3)_2CHCH_2$	Xa Br	A	97	92	66	>96	(S)
6	(S)-$nC_3H_7CH(Me)$[c]	Xa Br	B	83	76	59	>96	(S)
7	nC_8H_{17}	X_b Br	C	91	84	68	>96	(R)
8	nC_8H_{17}	Xa Cl	C	71	96	62	>99	(S)

a) ^{1}H-NMR (360 MHz) of H_A-signal and HPLC analysis (*Merck*, Lichrosorb Si 60 (5μ), either hexane/2-propanol 270:1 or hexane/ethylacetate 20:1) by comparison with the epimer mixture obtained on treatment of 3 with LiBr or LiCl, respectively. b) assignment based on correlation with oxiranes 5; c) starting ester 1 prepared by addition of $nC_3H_7Cu.BF_3$ to (E)-MeCH=CH-C(O)-Xa.

Thus, α-bromoesters 3 were efficiently obtained in high diastereomeric excess as determined directly by ^{1}H-NMR- and HPLC analyses of the product mixtures. Furthermore, crystallization provided routinely the preferred diastereoisomer in virtually quantitative diastereomeric excess. As expected, the absolute configuration of 3 was reversed when using the antipodal inductor X_b (entry 7). The controlled generation of two contiguous centers of asymmetry using the same auxiliary is exemplified by entry 6 where Cβ has been first created by addition of *n*PrCu to the (E)-crotonate of X_aH prior to α-bromination.

The analogous α-chlorinations (entries 1,3,4,8) proceeded reliably with high diastereoface differentiation using an even more convenient one-pot procedure. Thus, successive addition of Me_3SiCl, ester 1 and NCS to a solution of LDA in THF at -78° →0° (method C) furnished the crystalline chloroesters 3 in good yields.

Reduction of both bromo- and chloroesters with $Ca(BH_4)_2$ in THF[10] followed by flash chromatography afforded the corresponding halohydrins 4 and the recovered auxiliary XH (> 90%) Scheme 2, Table 2). Cyclization of 4 with NaOMe (1.2 eq, MeOH, r.t.0.5 to 2h, extraction with pentane/water gave epoxides 5. Their high enantiomeric purities (Table 2) as determined most reliably by complexation GC[4c] (entries 1,2,3,6) match perfectly the d.e. values of α-haloesters 3 (Table 1) which indicates clean retention and inversion for the steps 3→4 and 4→5, respectively.

Scheme 2

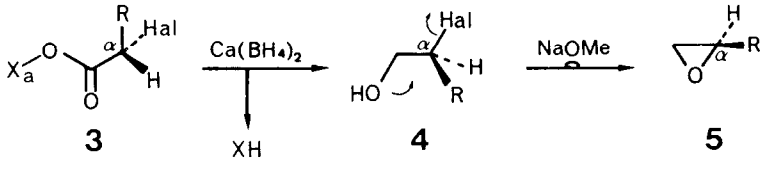


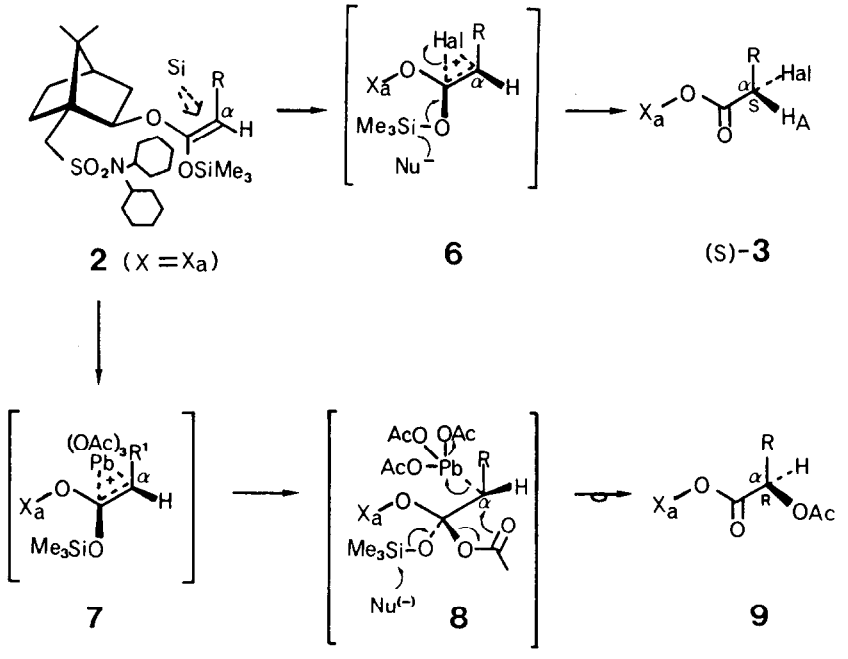
Table 2: Conversion of α-Haloesters 3 to Halohydrins 4 and Epoxides 5[9]

				Halohydrin 4	Epoxide 5		
Entry	R	X	Hal	yield %	yield %[a]	e.e. %	Config.[b,c]
1	CH_3	Xa	Cl	40	-[d]	96[b]	(R)
2	nC_4H_9	Xa	Br	73	-[d]	>98[b]	(R)
3	nC_4H_9	Xa	Cl	85	54	>98[b]	(R)
4	C_6H_5	Xa	Cl	95	67	>90[c]	(R)
5	$(CH_3)_2CHCH_2$	Xa	Br	70	86	>96[c]	(R)
6	(S)-$nC_3H_7CH(Me)$	Xa	Br	72	72	98[b,c,e]	(2R,3S)
7	nC_8H_{17}	Xb	Br	73	58	>96[c]	(S)

a) After bulb-to-bulb distillation. b) Complexation GC[4c] (Fused silica column, CHIRA METAL Ni-R-CAM/SE 54, Helium). c) Chiroptic comparison[11]. d)Yield not determined. e) GC-determination of the $(R^*,S^*)/(R^*,R^*)$ ratio of the corresponding bromohydrin 4 e.e. at C(3)= >99%.

Mechanistically, this assignment is consistent with an attack of "Hal$^+$" from the less hindered Cα-*Si*-face 2 (X=Xa) →6→ (S)-3 (Scheme 3). Furthermore, this supports our postulated topicity for the lead tetraacetate provoked α-acetoxylation of 2 (X=Xa)→7→8→9[3] which involves electrophilic addition of the metal to the Cα-*Si* face.

Scheme 3



In summary we have described herein a novel and practical enantioselective entry to halohydrins and terminal epoxides which are versatile chiral building blocks in organic synthesis [4b,4e]. Further applications and extensions of this methodology such as the preparation of enantiomerically pure α-amino acids are presently being explored.

Acknowledgements: Financial support of this work by the *Swiss National Science Foundation*, *Sandoz Ltd, Basel*, and *Givaudan SA*, Vernier is gratefully acknowledged. We thank Mr. *J.P. Saulnier*, Mr. *A. Pinto* and Mrs. *C. Clément* for NMR and MS measurements and particularly, Mr. *M. von Arx* for his technical contribution.

REFERENCES AND NOTES

[1] *W. Oppolzer, C. Chapuis, G. Bernardinelli*, Tetrahedron Lett. 25, 5585 (1984).

[2] *W. Oppolzer, P. Dudfield, T. Stevenson, T. Godel*, Helv. Chim. Acta 68, 212 (1985).

[3] *W. Oppolzer, P. Dudfield*, Helv. Chim. Acta 68, 216 (1985).

[4] Different enantioselective approaches to terminal epoxides: from α-amino- or hydroxy acids or sugars: a) *K. Mori*, Tetrahedron 32, 1101 (1976); b) *K. Mori, H. Iwasawa, Ibid.* 36, 2209 (1980); c) *V. Schurig, B. Koppenhöfer, W. Bürkle*, Angew. Chem., Int. Ed. Engl. 17, 937 (1978); d) *B. Koppenhöfer, R. Weber, V. Schurig*, Synthesis, 1982, 316; e) *Masaoka, M. Sakakibara, K. Mori*, Agric. Biol. Chem. 46, 2319 (1982). f) *K. Mori, T. Otsuka*, Tetrahedron 41, 547 (1985); g) *J. Gombos, E. Haslinger, U. Schmidt*, Chem. Ber. 109, 1645 (1976); h) *B. Seuring, D. Seebach*, Helv. Chim. Acta 60, 1175 (1977); i) *B.D. Johnston, K.N. Slessor*, Can. J. Chem. 57, 233 (1979); j) *L.R. Hillis, R.C. Ronald*, J. Org. Chem. 46, 3348 (1981); k) *D.A. Howes, M.H. Brookes, D. Coates, B.T. Golding, A.T. Hudson*, J. Chem. Research (S), 1983,9; l) *J.Mulzer, P. de Lasalle Ibid.* 1983, 10; m) *U. Schmidt, J. Talbiersky, F. Bartkowiak, J. Wild*, Angew. Chem. 92, 201 (1980); Angew. Chem., Int. Ed. Engl. 19, 198 (1980); by separation of β-hydroxysulfides: n) *W. H. Pirkle, P.L. Rinaldi*, J. Org. Chem. 43, 3803 (1978); from α-haloketones: o) *H.C. Brown, G.G. Pai*, J. Org. Chem. 48, 1784 (1983); from β-ketosulfoxides: p) *G. Solladié, G. Demailly, C. Greck*, Tetrahedron Lett. 26, 435 (1985); q) *H. Kosugi, H. Konta, H. Uda*, J. Chem. Soc. Chem. Commun. 1985, 211.

[5] *S. Takimoto, J. Inanaga, T. Katsuki, M. Yamaguchi*, Bull. Chem. Soc. Jpn. 49, 2335 (1976).

[6] *E.J. Corey, A.W. Gross*, Tetrahedron Lett. 25, 495 (1984); *G.M. Rubottom, J.M. Gruber, R. Marrero, H.D. Juve Jr, C.W. Kim*, J. Org. Chem. 48, 4940 (1983).

[7] For brominations of vinyloxysilanes see: a) *R.H. Reuss, A. Hassner*, J. Org. Chem. 39, 1785 (1974). b) *L. Blanco, P. Amice, J.M. Conia*, Synthesis 1976, 194.

[8] The following experimental procedures (carried out under argon) are representative: Method A: Me_3SiCl (14 mmol) and ester 1 (8mmol) in THF (25 ml) were added successively to a solution of LDA (prepared from diisopropylamine (8.8 mmol) and 1.6N *n*BuLi (hexane, 5.5 ml))in THF (25 ml) at -78°. The mixture was stirred at -78° for 1h and then evaporated *in vacuo* at r.t. (or alternatively, used directly as described in method C). Extraction of the residue with pentane, filtration and evaporation of the pentane solution furnished crude 2. Solid N-bromosuccinimide (8.4 mmol) was added portionwise over 10 min. to a solution of crude 2 in dry DME (80 ml) at -78° with vigorous mechanical stirring. Stirring of the mixture at -78° for 30 min. followed by aq. work-up and flash chromatography gave crude haloester 3 which was crystallized (3x) from hexane. Method B: Analogous to method A but the bromination was carried out in toluene at -78° over 3h to 36h until completion. Method C: Solid N-bromo- or N-chloro succinimide (8.4 mmol) was added in one portion to the stirred solution of *in situ*-prepared 2 in THF (as described in method A) at -78°. Warming up of the mixture to 0° over 3h, stirring at 0° for 30 min., work-up, flash chromatography and crystallization (2x hexane) gave pure haloester 3.

[9] All new compounds were characterized by IR, ^{1}H-NMR(360MHz) and MS.

[10] *J. Kollonitsch, O. Fuchs, V. Gábor*, Nature 175, 346 (1955) *V. Tolman, K. Vereš*, Collect. Czech. Chem. Commun. 37, 2962 (1972).

[11] Observed $[\alpha]_D$ 21° to 25° values (solvent, c= g/100 ml) of isolated epoxides 5. R, (absolute configuration), lit. ref. for comparison: C_6H_5(R), ref.[4p]:+ 41.6°(C_6H_6, 4.8); $(Me)_2CH_2CH_2$(R), ref. [4a]:+ 18.1° (EtOH, 1.9); $nC_3H_7CH(Me)$(2R,3S), ref.[4b]:+ 4.2°(Et_2O, 1,0); nC_8H_{17}(S), ref. [4e]: -13.9° (Et_2O, 1.2).

(Received in Germany 26 July 1985)