26. Asymmetric α-Acetoxylation of Carboxylic Esters

Preliminary Communication[1])

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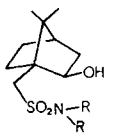
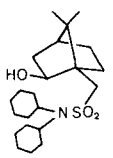
Using the readily accessible chiral auxiliaries **1–3** the sulfonamide-shielded *O*-silylated esters **5** underwent π-face-selective α-acetoxylation on successive treatment with $Pb(OAc)_4$ and $NEt_3 \cdot HF$ to give after recrystallization α-acetoxy ester **6** in 55–67% yields and in 95–100% d.e. Starting from conjugated enoates addition of RCu and subsequent acetoxylation **10**→**11**→**12** yielded α,β-bifunctionalized esters **12** with > 95% configurational control at both C_α and C_β. Nondestructive removal of the auxiliary (**6**→**7**, **6**→**8** and **12**→**13**) gave either α-hydroxy-carboxylic acids or terminal α-glycols in high enantiomeric purity. The prepared glycols **8c** and **13a** are key intermediates for previously reported syntheses of the natural products **16** and **17**, respectively.

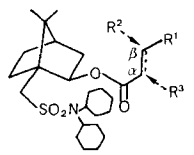
Recently, we have shown that the readily available, crystalline alcohols **1–3** are efficient and practical chiral auxiliaries for asymmetric *Diels-Alder* reactions [1], organocopper additions [2] and enolate alkylations [2]. Thus, α- and β-functionalizations of esters **I** were selectively accomplished from the least hindered π-face.



1 R = ⟨ ≡ $X_A H$
2 R = ⬡ ≡ $X_B H$



3 ≡ $X_C H$



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We report here the first extension of this principle to enantioselective preparations of α-hydroxy-carboxylic acids and terminal α-glycols which may serve as chiral building blocks in organic synthesis[2]).

Kinetically controlled *O*-silylation [7] of saturated esters **4**[3]) [*i*) LDA (1.1 mol-equiv.), THF, −78°, *ii*) Me_3SiCl (1.75 mol-equiv.)] furnished ketene acetals **5**[3]) which on successive treatment with dry $Pb(OAc)_4$ (1.1 mol-equiv., CH_2Cl_2, −15°, 15 min, then +20°, 30 min) and $NEt_3 \cdot HF$ (3.0 mol-equiv., +20°, 4 h), according to the method described by *Rubottom et al.* [9], afforded, with 88 to 96% diastereoface selection, α-acetoxyesters **6**[4]).

[1]) Presented by *W.O.* as part of a *Simonsen*-Lecture, London, November 27, 1984.

[2]) Alternative non-oxidative asymmetric preparations of α-hydroxy-carboxylic acids [3] and of terminal α-glycols [3l] [4] and their use as chiral building blocks [4a,b,d] [5] or auxiliary groups [6] have been reported.

[3]) Esters **4** were prepared by treatment of alcohols XH with $R^1CH_2COCl/AgCN$ [8]. After analogous *O*-silylation of **4**, $R^1 = CH(CH_3)(CH_2)_3CH_3$, X = cyclohexyl, ^{1}H-NMR analysis showed the presence of only one ketene acetal which differs from its isomer obtained preferentially *via* deprotonation in THF/HMPA 4:1.

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

Scheme 1

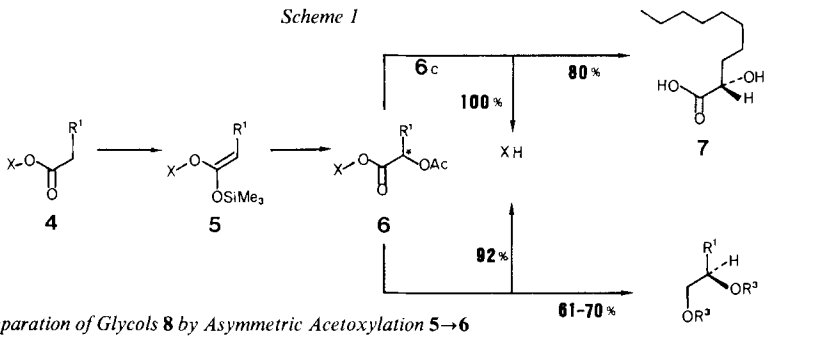


Table 1. *Preparation of Glycols* **8** *by Asymmetric Acetoxylation* **5**→**6**

Entry	Auxiliary X	R^1	d.e. [%][a]) **6** (crude)	Yield [%][b]) **6** (cryst.)	d.e. [%][a]) **6** (cryst.)	Configuration[c]) **8**
a	X_A	CH_3	88[d])	60	100[d])	(*R*)
b	X_B	C_4H_9	90.5	55	95	(*R*)
c	X_C	C_8H_{17}	96 (94)	67	98.6 (100)	(*S*)

[a]) Determined by HPLC analysis of the bis-*Mosher*-derivatives [10] **9** (values based on chiroptic comparison in parentheses [5g]. [b]) Based on ester **4**. [c]) Determined by chiroptic comparison [4b] [5g]. [d]) Determined by GC.

After crystallization the acetates **6** were obtained in fair to good yields with 95–100% diastereomeric excess *(Scheme 1, Table 1)*. Nondestructive removal of the auxiliary from **6** by saponification (K_2CO_3 (16 mol-equiv.) MeOH, 20°, 20 h) or by reduction with $LiAlH_4$ (4 mol-equiv. Et_2O, 20°, 1 h, workup with 1*N* aq. HCl) gave either hydroxy acid

Scheme 2

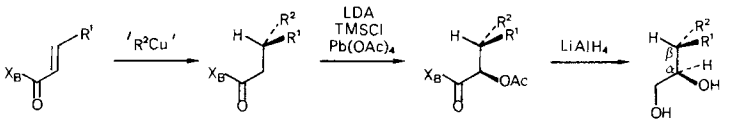
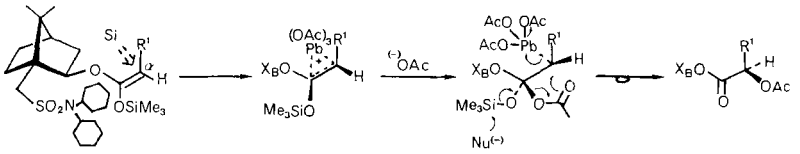


Table 2. *Preparation of Glycols* **13** *by Successive Asymmetric 1,4-Additions and α-Acetoxylations* **10**→**11**→**12**→**13**

Entry	R^1	R^2	Yield %[a]) of **12**	e.e.%[b]) **12**-C_β	(*R**,*S**)/(*R**,*R**) **12**	e.e.%[d]) **12**-C_α
a	CH_3	n-C_3H_7	–	97	94.5:5.5	92
	Crystallized (hexane)		66 (83)	98-100	99:1	98–100
b	n-C_3H_7	CH_3	–	94	6.3:93.7	94
	Crystallized (hexane)		57 (76)	> 99	0.2:99.8	> 99
c[e])	n-C_3H_7	CH_3	–	94	9:91	88
	Crystallized (hexane)		69	97–100	1.5:98.5	97–100

[a]) Based on **11** (accounting for recovered **11** in parentheses).
[b]) Determined by HPLC analyses of the (*R*)-α-naphthylethylamides [11] derived from **11** [2].
[c]) Determined by GC analyses of bisacetylated **13**.
[d]) Calculated on the basis of the analyses cited under [b]) and [c]).
[e]) The oxidation **11**→**12** was carried out in toluene; the product **12b** was deacetylated (0.3 mol-equiv, K_2CO_3, MeOH, 20°) and the resulting α-hydroxyester crystallized.

Scheme 3



5b **14** **15** **6**

7[4][5]) or glycols **8**[4]) in high enantiomeric purity. Using the antipodal inductors X_B and X_C the absolute configurations of **7** and **8** were predictably controlled in either direction (entries b/c).

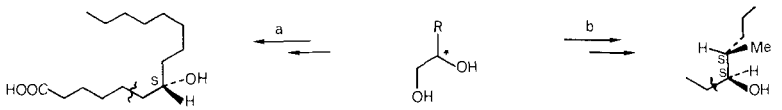
On combination of the organocopper addition **10**→**11** [2] with α-acetoxylation **11**→**12**[4]), the same auxiliary efficiently controlled the generation of two contiguous asymmetric centers of asymmetry at C_α and C_β *(Scheme 2, Table 2)*.

Comparison of entries a–c in *Table 2* illustrates the overriding topological influence of the auxiliary X over that of the adjacent center C_β. Thus, the highly enantioselective preparation of each of the four possible stereoisomers of **16** is possible by interchanging R^1 with R^2 as well as alternating X_B and X_C.

At first sight C–O bond formation appears to occur on the more hindered π-face of the *O*-silylketene acetals **5.** However, this may be rationalized by the following reaction sequence *(Scheme 3)* : *1)* attack of the electrophilic metal from the C_α-*si*-face **5b**→**14**; *2)* opening of the transient leadonium ion by acetate **14**→**15**; *3)* inversion on internal acetate/C-Pb substitution **15**→**6**[6]).

The importance of this novel asymmetric acetoxylation for the syntheses of natural products is exemplified here by the preparations of **8c** and **13a** which have served as key intermediates for the syntheses of the spore germination inhibitor **16** [5g] and of the elm-bark-beetle-pheromone **17** [4d] [5d], respectively *(Scheme 4)*.

Scheme 4



16 **8c** (*S*) R = nC_8H_{17} **17**

13a (*R*) R = (S)–$CH(CH_3)(CH_2)_2CH_3$

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[5]) During the saponification **6c**→**7** no C_α-epimerization occurred as confirmed by the reduction **7**→**8c** and HPLC analysis of the diester **9c** derived from **8c** and (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid [10].

[6]) For a postulated S_N2 substitution of a C-Pb bond by a carboxyl group see [12].

REFERENCES

[1] W. Oppolzer, C. Chapuis, G. Bernardinelli, *Tetrahedron Lett.* **1984**, *25*, 5885; W. Oppolzer, *Angew. Chem.* **1984**, *96*, 840; *ibid. Int. Ed.* **1984**, *23*, 876.

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

[3] a) P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold, P. A. D. S. Rao, *Nature (London)* **1950**, *166*, 179; b) V. Prelog, *Helv. Chim. Acta* **1953**, *36*, 308; c) D. D. Ridley, M. Stralow, *J. Chem. Soc., Chem. Commun.* **1975**, 400; d) S.-S. Jew, S. Terashima, K. Koga, *Tetrahedron* **1979**, *35*, 2337, 2345; e) A. I. Meyers, J. Slade, *J. Org. Chem.* **1980**, *45*, 2785; f) M. A. K. Patterson, R. P. Szajewski, G. M. Whitesides, *ibid.* **1981**, *46*, 4682; g) G. Frater, U. Müller, W. Günther, *Tetrahedron Lett.* **1981**, *22*, 4221; h) D. Seebach, R. Naef, *Helv. Chim. Acta* **1981**, *64*, 2704; i) H. Wynberg, E. G. J. Staring, *J. Am Chem. Soc.* **1982**, *104*, 166; j) O. Piccolo, L. Filippini, L. Tinucci, E. Valoti, A. Citterio, *Helv. Chim. Acta* **1984**, *67*, 739; k) H. C. Brown, G. G. Pai, P. K. Jadhav, *J. Am. Chem. Soc.* **1984**, *106*, 1531; l) K.-Y. Ko, W. J. Frazee, E. L. Eliel, *Tetrahedron* **1984**, *40*, 1333.

[4] a) Y. Sakito, S. Tanaka, M. Asami, T. Mukaiyama, *Chem. Lett.* **1980**, 1223; b) M. Asami, T. Mukaiyama, *ibid.* **1983**, 93; c) J. K. Whitesell, A. Bhattacharya, K. Henke, *J. Chem. Soc., Chem. Commun.* **1982**, 988; J. K. Whitesell, A. Bhattacharya, D. A. Aguilar, K. Henke, *ibid.* **1982**, 989; J. K. Whitesell, D. Deyo, A. Bhattacharya, *ibid.* **1983**, 802; d) C. Fuganti, P. Grasselli, S. Servi, C. Zirotti, *Tetrahedron Lett.* **1982**, *23*, 4269; e) G. Helmchen, R. Wierzchowski, *Angew. Chem.* **1984**, *96*, 59; *ibid. Int. Ed.* **1984**, *23*, 60.

[5] a) S. Terashima, S.-S. Jew, K. Koga, *Tetrahedron Lett.* **1978**, 4937; b) K. Mori, *Tetrahedron* **1976**, *32*, 1101; K. Mori, T. Takigawa, T. Matsuo, *ibid.* **1979**, *35*, 933; c) Y. Sakito, T. Mukaiyama, *Chem. Lett.* **1979**, 1027; d) K. Mori, H. Iwasawa, *Tetrahedron* **1980**, *36*, 2209; e) J. J. Partridge, S.-J. Shiuey, N. K. Chadha, E. G. Baggiolini, J. F. Blount, M. R. Uskoković, *J. Am. Chem. Soc.* **1981**, *103*, 1253; f) E. L. Eliel, K. Soai, W. R. Kenan, Jr., *Tetrahedron Lett.* **1981**, *22*, 2859; g) Y. Masaoka, M. Sakakibara, K. Mori, *Agric. Biol. Chem.* **1982**, *46*, 2319.

[6] S. Masamune, W. Choy, F. A. J. Kerdesky, B. Imperiali, *J. Am. Chem. Soc.* **1981**, *103*, 1566; W. Choy, L. A. Reed III, S. Masamune, *J. Org. Chem.* **1983**, *48*, 1137.

[7] R. E. Ireland, R. H. Muller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868.

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

[9] G. M. Rubottom, J. M. Gruber, R. Marrero, H. D. Juve Jr., C. W. Kim, *J. Org. Chem.* **1983**, *48*, 4940.

[10] J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543.

[11] W. H. Pirkle, J. R. Hauske, *J. Org. Chem.* **1977**, *42*, 1839.

[12] C. R. Bennett, R. C. Cambie, W. A. Denny, *Aust. J. Chem.* **1969**, *22*, 1069.