123. 1,3-Dioxanone Derivatives from β-Hydroxy-carboxylic Acids and Pivalaldehyde. Versatile Building Blocks for Syntheses of Enantiomerically Pure Compounds. A Chiral Acetoacetic Acid Derivative

Preliminary Communication

by **Dieter Seebach*** and **Jürg Zimmermann**[1])

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich

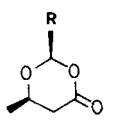
(9.VI.86)

(*R*)-3-Hydroxybutyric acid (from the biopolymer PHB) and pivalaldehyde give the crystalline *cis*- or (*R, R*)-2-(*tert*-butyl)-6-methyl-1,3-dioxan-4-one (**1a**), the enolate of which is stable at low temperature in THF solution and can be alkylated diastereoselectively (→**3**, **4**, **5**, and **7**). Phenylselenation and subsequent elimination give an enantiomerically pure enol acetal **10** of aceto-acetic acid. Some reactions of **10** have been carried out, such as *Michael* addition (→**11**), alkylation on the CH_3 substituent (→**13**), hydrogenation of the C=C bond (→**1a**) and photochemical cycloaddition (→**16**). The overall reactions are substitutions on the one stereogenic center of the starting β-hydroxy acid without racemization and without using a chiral auxiliary.

Our continuing interest in chiral building blocks derived from the readily available enantiomerically pure (3*S*)- [1–3] and (3*R*)-3-hydroxybutyrate[2]) [4] [5] has led to the investigation of 1,3-dioxanones **1**. These were, for instance, shown [6] to be versatile reagents for nucleophilic ring opening, to give, after removal of the chiral auxiliary, secondary alcohols of high enantiomeric purity.

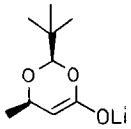
Here, we report overall enantioselective reactions at the 2-, 3-, and 4-positions of 3-hydroxybutyric acid, *i.e.* at the 5- and 6-position and on the CH_3 group of a 1,3-dioxanone **1**. For this purpose, the 2-(*tert*-butyl)-1,3-dioxanone **1a** was chosen[3]), because all its derivatives readily crystallize and react with high stereoselectivity.

The 1,3-dioxanone **1a** [6] [7] is prepared from pivalaldehyde and (*R*)-3-hydroxybutyric acid under acid catalysis.

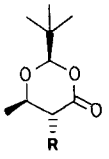


1

1a R = *t*-Bu



2



3a R = CH_3
b R = CH_2=CH–CH_2
c R = $C_6H_5CH_2$

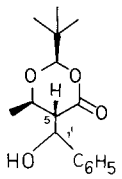
[1]) Part of the projected Dissertation of *J. Z.*, ETH Zürich.

[2]) Both enantiomers are commercially available.

[3]) 6-Methyl-2-phenyl-1,3-dioxan-4-one (m.p. 75°, one diastereomer from trimethylsilyl (*R*)-3-(trimethylsilyloxy)butanoate and benzaldehyde, CH_2Cl_2, – 75°, cat. Me_3SiOTf) is also suitable (*René Imwinkelried* and *J. Z.*, hitherto unpublished results, ETH Zürich, 1986).

The lithium enolate **2**, generated from **1a** with LDA at $-75°$ in THF, is surprisingly stable; it does not undergo β-elimination[4]) at the low temperature employed.

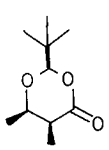
Alkylation of **2** diastereoselectively produces 5,6-*trans*-disubstituted 1,3-dioxanones **3**. The reaction of **2** with benzaldehyde gives a mixture of two products **4** (probably epimeric at the C(1′) center)[5]), the ratio of which depends to some extend upon the metal used in the enolate.



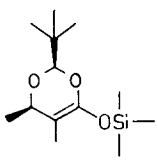
Metal on enolate	Li	MgBr	Ti[O(i-Pr)]$_3$
4a/4b	2:1	2:3	1.8:1

Diastereoisomer **4a** (J(H–C(5), H–C(1′)) = 3.3 Hz)
Diastereoisomer **4b** (J(H–C(5), H–C(1′)) = 6.2 Hz)

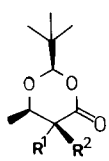
The 1,3-dioxanone method of alkylating 3-hydroxy-carboxylic acids is superior to the procedure involving dilithio-alkoxide-enolates [11]. Only 1 equiv. of strong base is necessary, the products are all crystalline, and it is possible to prepare products of either *l*- or *u*-configuration: enolate derivatives of 5,6-disubstituted 1,3-dioxanones **3** can be diastereoselectively protonated (which was not possible with the corresponding alkoxide-enolates[6])). Thus, the *trans*-5,6-dimethyl-1,3-dioxanone **3a** was converted (85% ds) to the *cis*-5,6-dimethyl isomer **5** by protonation of the silyl-enol ether **6**. It is also possible to prepare 5,5-disubstituted 1,3-dioxanones **7**.



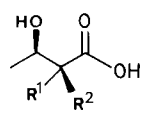
5



6



7a $R^1 = R^2 = CH_3$
b $R^1 = CH_3$, $R^2 = C_6H_5CH_2$



8

Mild acid-catalysed hydrolysis of the 1,3-dioxanones leads to the enantiomerically pure α-branched or α,α-disubstituted β-hydroxybutyric acids such as the 2-benzyl-3-hydroxybutyric acid[7]) (**8**, $R^1 = C_6H_5CH_2$, R^2 = H, from **3c**).

The enolate **2** also reacts with hetero-electrophiles. It can, for instance, be selenated with phenylselenyl chloride to give **9** which is oxidised to the selenoxide derivative,

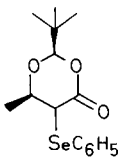
---

[4]) See the discussions in [8] [9].

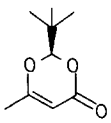
[5]) The ^3J (H–C(5), H–C(6)) values of both stereoisomers of **4** is 9.1 Hz, similar to compound **3** (10 Hz) and unlike compound **5** (4.5 Hz). Assuming that the intramolecularly H-bonded conformer prevails, we can tentatively assign the (*S*)-configuration at C(1′) to the diastereoisomer **4a** [10].

[6]) Hitherto unpublished results by *J. Z.*[1]). The diastereoselectivity was about 66% in the best case. Products of *threo*-configuration (*Fischer* nomenclature) are obtained by α-alkylation of β-hydroxy-carbonyl compounds only in cyclic cases, see for instance the γ- and δ-lactones of 3,4- and 3,5-dihydroxy-carboxylic acids [12].

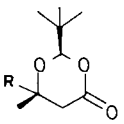
[7]) The acid **8** was converted to the (2*R*,3*R*)-configurated ethyl ester which has about the same value but opposite sign of optical rotation as the known (2*S*,3*S*)-configurated ester [11c].



9



10

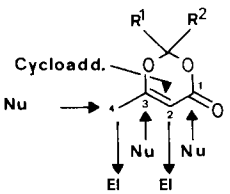


11a R = C_3H_7
b R = C_4H_9
c R = C_8H_{17}

followed by spontaneous elimination to the crystalline, chiral aceto-acetic-acid derivative **10** (*ca.* 60% overall yield from **1a**).

As indicated in *Scheme 1*, the unsaturated heterocyclic system of **10** is known to exhibit reactivity towards nucleophiles and electrophiles, and its C=C bond is susceptible to cycloadditions.

Scheme 1

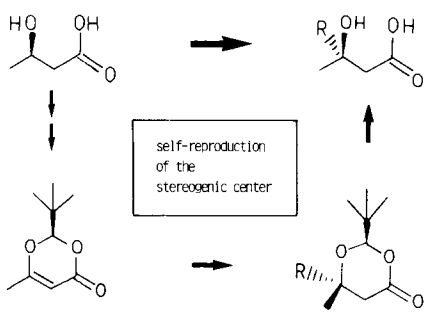


Aceto-acetate moiety of **10**

Reactivity	*Ref.*
a^1	[13]
d^2	[14]
a^3	[15]
d^4	[14]
a^4	[16]
cycloaddition	[17]

Of these different reactions, we have performed several with our chiral aceto-acetic-acid derivative **10**. Thus, the *Michael* addition of dialkyl cuprates leads to single products **11** containing a new persubstituted stereogenic center[8]). The overall process is an example of the self-reproduction of stereogenic centers [18] (see *Scheme 2*), *i.e.* the overall enantioselective alkylation at the one stereogenic center of hydroxybutyrate without using a chiral auxiliary.

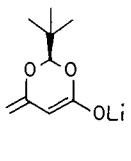
Scheme 2



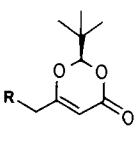
[8]) The configuration at C(4) was assigned by NMR spectroscopy, employing NOE techniques.

The alkylation[9]) of the dienolate **12** of the 1,3-dioxinone **10** takes place preferentially in the γ-position to give the products of type **13** accompanied by the formation of only a minor amount of the dialkylated compound such as **14a**[10]). The reaction with benzaldehyde led to a mixture of two diastereoisomers **15a**/**15b** 2.8:1 (yield 61%).

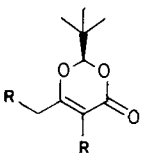
The double bond in the heterocyclic system can be diastereoselectively hydrogenated with H_2 (30 at, PtO_2): the unsaturated heterocycle **10** gives the (6*R*)-dioxanone **1a** from which it had originally been prepared. Thus, the hydrogenation takes place from the diastereotopic face opposite to the *t*-Bu group, as it is the case in the *Michael* addition.



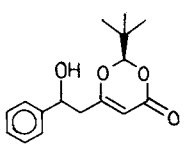
12



13a R = CH_3
b R = $C_6H_5CH_2$

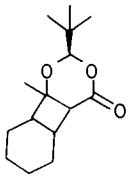


14a R = CH_3

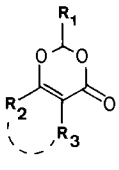


15a
15b (epimeric at C(2'))

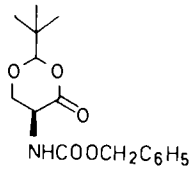
The photochemical [2 + 2] cycloaddition[11]) of the 1,3-dioxinone **10** to cyclohexene was performed using a Hg lamp to give the tricyclic derivative **16** as a mixture of diastereoisomers. There is no doubt that **10** may be a source of a myriad of enantiomerically pure products.



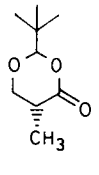
16



17



18



19a *cis*
b *trans*

There are numerous other β-hydroxy-carboxylic acids [1] [3] [5] which are available in enantiomerically pure form, and which should all be subject to application of the principle described here (see the general *Formula* **17**). For example, the *N*-benzyloxycarbonyl-protected serine[12]) forms two diastereoisomeric 1,3-dioxanones **18** in a ratio of 3:1, and the (*R*)-*'Roche'* acid gives a readily separable 1:1 mixture of the two *cis*/*trans*-isomeric 1,3-dioxanones **19**.

There are some remarkable mechanistic aspects of the reactions described. Thus, axial attack of electrophiles on the double bond of enol derivatives such as **2** and **6** might have been expected to occur on the diastereotopic face *cis* to the CH_3 and *t*-Bu groups [22]. Also, the exclusive cuprate additions to the 1,3-dioxinone **10**, containing only one sp^3

---

[9]) It is necessary to use HMPT or DMPU as co-solvent [19], otherwise no alkylation takes place. As in many other cases, DMPU has the same effect as HMPT [20].

[10]) We did not find any product monoalkylated in the 5-position of the heterocycle. *Smith* and *Scarborough* [14] reported that the acetonide derivative yields the γ- and the α-alkylated products in a ratio of 2:1.

[11]) The (–)-menthone acetate of aceto-acetic acid was also investigated in the *deMayo*-type photoaddition. We thank Dr. *Demuth, Max-Planck-Institut*, D-4330 Müllheim a.d.R., for sending us his manuscript prior to publication [21].

[12]) The acetals of the β-hydroxyamino acids (serine, threonine, phenylserine) are potential precursors of chiral 1,3-dioxinones of type **17** where R^2 = H, CH_3, or C_6H_5 and R^3 = NR_2 or H.

C-atom in the ring, from the diastereotopic face *trans* to the *t*-Bu group is surprising. As we conclude from the crystal structure of a benzodioxinone [23], the ring should have a 'Sofa' conformation, with all atoms except the tetrasubstituted C-atom in a common plane. If the *t*-Bu group would occupy a *quasi*-equatorial position in such a conformer, the nucleophilic attack should occur *cis* to that group for steric reasons. An evaluation of the role, which the involved metals might play, and of possible stereoelectronic effects does not appear reasonable to us at this stage of the investigations.

We thank Dr. *J. Winkler* (University of Chicago, USA) for inspiring discussions about *deMayo* reactions with aceto-acetic-acid enol-acetal derivatives (achiral and racemic dioxinones of type **17**), and we gratefully acknowledge the receipt of a manuscript in which a chiral, menthone-derived dioxinone is used for a *deMayo* annelation[11]) [21].

Experimental Part

The ratios of diastereoisomers were determined from the ^{1}H-NMR spectra (300 MHz) of the crude products, > 95% ds indicates that no other isomer was detected. Unless otherwise stated, the acetals **1** and **3** were deprotonated at − 75° with LDA in THF. The neat electrophile was added, and the mixture was stirred overnight at − 75°. The oxidation and elimination of the phenylseleno acetal **9** were carried out in CH_2Cl_2 at r.t. The *Michael* additions were performed using dialkyl cuprates in THF at − 75° with NH_3/NH_4Cl quenching. The dienolate from **10** was prepared by treatment with LDA/DMPU (15%-vol. of solvent) at − 75° in THF. The neat electrophile was added, and the temp. allowed to rise to 0° overnight. Hydrogenation of **10** was performed using H_2 (30 at) and PtO_2 as catalyst in AcOEt. The following list contains some experimental details and characteristic data of the compounds prepared (y = yield; ds = content of major diastereoisomer). All spectra are in agreement with the proposed structures. All $[\alpha]_D$ values refer to r.t., $CHCl_3$ soln., and c = 1–2 g/100 ml. The NMR data refer to $CDCl_3$ solns.

1a: From tech.-grade pivalaldehyde (containing *t*-BuOH) and (*R*)-3-hydroxybutyric acid [4][13]) (CH_2Cl_2, *Dowex 50 W*, azeotropic removal of H_2O), 55% y, m.p. 82.5°, $[\alpha]_D$ = − 56.6° [6].

3a: From **1** and MeI (excess), 94% y, > 95% ds, m.p. 67.0–67.5°. ^{1}H-NMR: 2.35 (*qd*, *J* = 7.2, 10.4, H–C(5)); 3.62 (*qd*, *J* = 6.1, 10.5, H–C(6)).

3b: From **1** and CH_2CHCH_2Br, 85% y, > 95% ds, $[\alpha]_D$ = − 62.5°. ^{1}H-NMR: 1.34 (*d*, *J* = 6.08, CH_3); 3.82 (*qd*, *J* = 6.08, 10.13, H–C(6)).

3c: From **1** and $C_6H_5CH_2Br$, 80% y, > 95% ds, m.p. 63.0–64.0°, $[\alpha]_D$ = − 52.9°.

4: From **1** and benzaldehyde, 68% y (crude), separation of one diastereoisomer by flash chromatography (SiO_2, hexane/Et_2O 2:1). **4a**: ^{1}H-NMR: 0.84 (*d*, *J* = 6.1, CH_3); 2.82 (*dd*, *J* = 3.3, 9.1, H–C(5)); 4.0 (*qd*, *J* = 6.2, 9.1, H–C(6)); 5.43 (*d*, *J* = 3.3, H–C(1')).

5: From **3a** (LDA, then Me_3SiCl (excess) (→**6**), then aq. NH_4F, *in situ*), 93% y (crude), 85% ds. ^{1}H-NMR: 2.7 (*qd*, *J* = 7.23, 4.78, H–C(5)); 4.18 (*qd*, *J* = 6.41, 4.78, H–C(6)).

7a: From **3a** and MeI (excess), 90% y, m.p. 38.0–39.0°, $[\alpha]_D$ = + 28.7°.

7b: From **3c** and MeI (excess), 63% y, > 95% ds, m.p. 90.0–91.0°. ^{1}H-NMR: 1.26 (*d*, *J* = 6, CH_3); 1.38 (*s*, CH_3); 4.6 (*s*, H–C(2)).

8 (R^1 = $C_6H_5CH_2$, R^2 = H): From **3c** (95% EtOH/H_2O, r.t., *Dowex 50 W*), 97% y, m.p. 123.0–124.0°, for configuration, see *Footnote 7*.

9: From **1a** and C_6H_5SeCl (addition of the enolate soln. to selenyl chloride, − 75°), variable mixture of diastereoisomers, 83% y, separation from starting material possible by flash column chromatography.

10: From mixture of diastereoisomers **9**, H_2O_2 (30%), pyridine in CH_2Cl_2, (0° with > 50 mmol runs), 82% y, m.p. 48.5°, $[\alpha]_D$ = − 217.7°. ^{1}H-NMR: 1.05 (*s*, *t*-Bu); 2.05 (*s*, CH_3); 5.0 (*s*); 5.35 (*s*).

11a: From **10** and $(C_3H_7)_2CuLi$, > 95% ds. ^{1}H-NMR: 4.92 (*s*, H–C(2)).

11b: From **10** and $(C_4H_9)_2CuLi$ (1.1 equiv.), 85% y, > 95% ds. ^{1}H-NMR: 1.24 (*s*, CH_3); 2.48 (*d*, *J* = 15.9, H–C(5)); 2.65 (*d*, *J* = 15.9, H–C(5)); 4.92 (*s*, H–C(2)). For configuration, see *Footnote 8*.

11c: From **10** and $(C_8H_{17})_2CuLi$ (3.5 equiv.), 66% y, > 95% ds, $[\alpha]_D$ = + 2.4°.

13a: From **10** and MeI (excess), 55% y after chromatographic separation from **14a** (ratio 5:1). ^{1}H-NMR: 1.05 (*s*, *t*-Bu); 1.14 (*t*, CH_3); 2.31 (*q*, CH_2); 5.02 (*s*); 5.28 (*s*).

---

[13]) Available from *Marlborough Biopolymers Ltd.*, Elta House, Yarm Road, GB-Stockton-on-Tees, Cleveland TS18 3RX.

13b: From **10** and $C_6H_5CH_2Br$, 58% y. ^{1}H-NMR: 1.06 (*s*, *t*-Bu); 2.46–2.96 (*m*, CH_2CH_2); 4.90 (*s*); 5.18 (*s*); 7.0–7.3 (*m*, arom. H).

14a (By-product of **13a**): 12.5% y. ^{1}H-NMR: 1.05 (*s*, *t*-Bu); 1.14 (*t*, CH_3); 1.82 (*s*, CH_3); 2.38 (*m*, CH_2); 4.95 (*s*, H–C(2)).

15: From **10** and C_6H_5CHO, 60% y, 70% ds. ^{13}C-NMR (major (minor) diastereoisomer): 23.77; 34.12; 42.52 (42.81); 71.11; 96.77 (97.06); 105.89 (106.13); 125.53 (125.62); 127.92 (128.01); 128.50; 142.51; 163.1; 171.76.

16: By irradiation (450-W Hg low-pressure lamp) of a 0.05M soln. of **10** in hexane with cyclohexene (4 equiv.), 74% y, mixture of diastereoisomers, acetal H-atoms (H–C(2)) in ^{1}H-NMR: 4.88, 5.23, 5.36, and 5.57 ppm.

18[14]: From commercial *N*-benzyloxycarbonyl-protected (*S*)-serine and pivalaldehyde (C_6H_6, pyridinium (*p*-toluenesulfonate), azeotropic removal of H_2O), 30% y, 75% ds, major diastereoisomer (crystallization from Et_2O), m.p. 106.0°, $[\alpha]_D = +8.7°$.

19[14]: From commercially available ethyl (*S*)-3-hydroxy-2-methylpropionate (hydrolysis to acid *cf.* [4]) and acetalization with pivalaldehyde (C_6H_6, pyridinium (*p*-toluenesulfonate), azeotropic removal of H_2O, *cf.* [6]). **19a**: 28% y, m.p. 42.0–45.0°. ^{1}H-NMR: 1.35 (*d*, CH_3); 2.80 (*m*, H–C(5)); 4.95 (*s*, H–C(2)). **19b**: 32% y, m.p. 71.0–73.0°. ^{1}H-NMR: 1.15 (*d*, CH_3); 2.60 (*m*, H–C(5)); 4.85 (*s*, H–C(2)). Assignment by NOE-NMR measurements.

REFERENCES

[1] D. Seebach, M. A. Sutter, R. H. Weber, M. F. Züger, *Org. Synth.* **1984,** *63,* 1.

[2] G. Cainelli, F. Manescalchi, G. Martelli, M. Panunzio, L. Plessi, *Tetrahedron Lett.* **1985,** *26,* 3369.

[3] J. Ehrler, F. Giovannini, B. Lamatsch, D. Seebach, *Chimia* **1986,** *40,* 172.

[4] D. Seebach, M. F. Züger, *Helv. Chim. Acta* **1982,** *65,* 495; D. Seebach, M. F. Züger, *Tetrahedron Lett.* **1984,** *25,* 2747.

[5] J. W. Scott, in 'Asymmetric Synthesis', Eds. J. D. Morrison and J. W. Scott, Academic Press, New York, 1984, Vol. 4, pp. 1–226.

[6] D. Seebach, R. Imwinkelried, G. Stucky, *Angew. Chem.* **1986,** *98,* 182; *Angew. Chem. Int. Ed.* **1986,** *25,* 178.

[7] P. Aeräs, K. Pihlaja, *Tetrahedron Lett.* **1970,** 4095.

[8] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976,** 734.

[9] M. Eyer, D. Seebach, *J. Am. Chem. Soc.* **1985,** *107,* 3601.

[10] C. H. Heathcock, in 'Asymmetric Synthesis', Ed. J. D. Morrison, Academic Press, New York, 1984, Vol. 3, pp. 115–118.

[11] a) J. L. Herrmann, R. H. Schlessinger, *Tetrahedron Lett.* **1973,** 2429; b) G. A. Kraus, M. J. Taschner, *ibid.* **1977,** 4575; c) G. Fráter, *Helv. Chim. Acta* **1979,** *62,* 2825, 2829; d) D. Seebach, D. Wasmuth, *ibid.* **1980,** *63,* 197.

[12] H. M. Shieh, G. D. Prestwich, *J. Org. Chem.* **1981,** *46,* 4319; A. R. Chamberlin, M. Dezube, *Tetrahedron Lett.* **1982,** *23,* 3055; H. M. Shieh, G. D. Prestwich, *Tetrahedron Lett.* **1982,** *23,* 4643; D. Seebach, H.-F. Chow, R. F. W. Jackson, K. Lawson, M. A. Sutter, S. Thaisrivongs, J. Zimmermann, *J. Am. Chem. Soc.* **1985,** *107,* 5292; D. Seebach, H.-F. Chow, R. F. W. Jackson, M. A. Sutter, S. Thaisrivongs, J. Zimmermann, *Liebigs Ann. Chem.* **1986,** in press.

[13] Y. Yamamoto, Y. Morita, *Chem. Pharm. Bull.* **1984,** *32,* 2555.

[14] A. B. Smith, III, R. Scarborough, *Tetrahedron Lett.* **1978,** *44,* 4193.

[15] A. B. Smith, III, P. A. Levenberg, P. J. Jerris, R. M. Scarborough, P. M. Wovkulich, *J. Am. Chem. Soc.* **1981,** *103,* 1501.

[16] R. K. Boeckmann, A. J. Thomas, *J. Org. Chem.* **1982,** *47,* 2823.

[17] S. W. Baldwin, G. F. Martin, D. S. Nunn, *J. Org. Chem.* **1985,** *50,* 5720.

[18] D. Seebach, R. Naef, G. Calderari, *Tetrahedron* **1984,** *40,* 1313; D. Seebach, J. D. Aebi, R. Naef, Th. Weber, *Helv. Chim. Acta* **1985,** *68,* 144; D. Seebach, R. Imwinkelried, Th. Weber, in 'Modern Synthetic Methods 1986', Ed. R. Scheffold, Springer-Verlag, Berlin–Heidelberg–New York–Tokyo, 1986, Vol. 4, pp. 125–260.

[19] M. W. Rathke, D. Sullivan, *Tetrahedron Lett.* **1972,** 4249; J. L. Herrmann, G. R. Kieczykowski, R. H. Schlessinger, *ibid.* **1973,** 2433.

[20] T. Mukhopadhyay, D. Seebach, *Helv. Chim. Acta* **1982,** *65,* 385; *Chimia* **1985,** *39,* 147.

[21] M. Demuth, *Pure Appl. Chem.* **1986,** *58,* in press.

[22] D. A. Evans, in 'Asymmetric Synthesis', Ed. J. D. Morrison, Academic Press, New York, 1984, Vol. 3, pp. 2–110.

[23] J. E. Jørgensen, A. B. Hansen, *Acta Crystallogr., Sect. B* **1982,** *38,* 991.

[14]) We thank *U. Gysel* and *B. Giesinger* for experimental assistance.