46. A Short Synthesis of (±)-(*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid, a Constituent of Civet[1])

by **Cornelius Nussbaumer***

Givaudan SA, CH-1214 Vernier

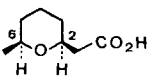
and **Georg Fráter**

Givaudan Forschungsgesellschaft AG, CH-8600 Dübendorf

(23.I.87)

The title compound has been synthesized in four steps from (±)-4-penten-2-ol *via* a novel β-alkenyloxyacrylate cyclization reaction **3**→**6** as the key step (overall yield 35%).

Introduction. – Some years ago, *Maurer et al.* [1] isolated (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**1**) in minute amounts from the glandular secretion of the civet cat *(Viverra civetta)*. The structure of this acid was deduced by spectroscopic means and also confirmed by synthesis [1]. The absolute configuration of **1** was established as (2*S*,6*S*) by comparison [2] of the natural product with an enantiomerically pure sample synthesized by *Seebach* and coworkers [3].

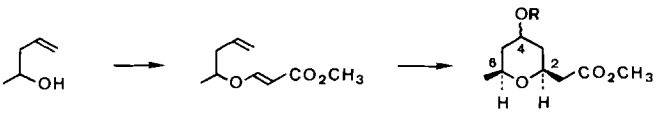


1

In the last years, several synthetic approaches to **1** have been reported [4]. We now describe a further synthesis of racemic **1**, based on a novel cyclization reaction.

Results. – Addition of (±)-4-penten-2-ol (**2**) to methyl propiolate in the presence of *N*-methylmorpholine, according to the procedure of *Winterfeldt* and *Preuss* [5], afforded the β-alkenyloxyacrylate **3** in 85% yield *(Scheme 1)*. The (*E*)-configuration of the

Scheme 1



2 **3** **4** R = $COCF_3$; **5** R = H; **6** R = SO_2CH_3

[1]) Presented in part at the 'Herbstversammlung der Schweizerischen Chemischen Gesellschaft', October 10, 1986 in Bern.

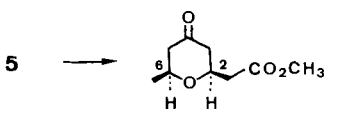
enol-ether double bond was evident from the ^{1}H-NMR spectrum of **3**, which revealed 2 doublets at 7.53 and 5.25 ppm with J = 12.5 Hz ((*Z*)-β-alkenyloxyacrylates show J = 7 Hz [5]).

Upon exposure of **3** to CF_3COOH in CH_2Cl_2 at 0°, cyclization to a mixture of labile trifluoroacetates **4** occurred which was hydrolyzed *in situ* with aqueous K_2CO_3 to a 11:1 mixture of the diastereoisomeric tetrahydropyran-4-ols **5** (overall yield 87%)[2]).

The main isomer was assigned the all-*cis*-configuration based on 400-MHz ^{1}H-NMR analysis of the corresponding mixture of the diastereoisomeric methanesulfonates **6** which was prepared in quantitative yield by treatment of **5** with MsCl in pyridine/CH_2Cl_2. The protons H–C(2), H–C(4), and H–C(6) of the major isomer each showed a vicinal coupling of 11–11.5 Hz which clearly indicates an axial position of these three protons.

Oxidation of **5** with *Jones* reagent in AcOH[3]) (0°, 30 min) gave the *cis*-oxotetrahydropyranylacetate **7** as the single product (78% yield), thus, leading to the conclusion that the minor isomer present in **5** is epimeric at C(4), and that the cyclization **3**→**4** proceeds highly stereoselective (> 99%) with respect to C(2) and C(6).

Scheme 2

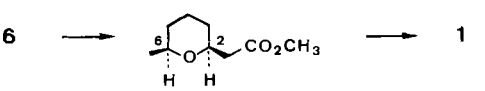


7

In contrast, cyclization of **3** with MsOH [7] in CH_2Cl_2 at 0° was less stereoselective[4]), but provided direct access to the methanesulfonates **6**, which were suitable derivatives for deoxygenation [8] of C(4). The crude cyclization product, thus, obtained (yield 94%) contained, according to ^{1}H-NMR analysis, 85% of **6** (4β/4α ratio 7:1) and 15% of a corresponding 2,6-*trans*-isomer. Fortunately, crystallization of the crude product led to separation of a diastereoisomeric mixture of **6** (4β/4α ratio 20:1) in 68% yield. This material was pure enough (*ca.* 95%) to carry out the two remaining steps.

Reductive removal of the methanesulfonyl group of **6** was effected with Zn/NaI in refluxing 1,2-dimethoxyethane [8] to afford the known [1] methyl (*cis*-6-methyltetrahydropyran-2-yl)acetate (**8**) devoid of any *trans*-isomer after chromatographic purification (60% yield).

Scheme 3



8

[2]) No attempts were made to separate the two diastereoisomers. The ratio was determined by capillary GC analysis and confirmed by integration of the signals in the 400-MHz ^{1}H-NMR spectrum of the corresponding mixture of methanesulfonates **6** (see *Exper. Part*).

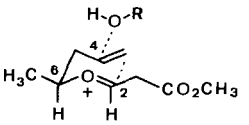
[3]) Oxidation in acetone was significantly slower. This solvent effect has previously been noted [6].

[4]) This cyclization was complete in less than 15 min, whereas cyclization of **3** with CF_3COOH in CH_2Cl_2 at 0° required 2 h for completion. By lowering the temperature, the stereoselectivity for the cyclization **3**→**6** could probably be increased.

Finally, **8** was hydrolyzed with aqueous NaOH at room temperature to acid **1** (m.p. 53–54°) in quantitative yield, the spectroscopic data of which were in good agreement with those reported by *Maurer et al.* [1].

Virtually, our approach is also suitable for the synthesis of optically active **1**, since both the (*R*)- and the (*S*)-enantiomers of the homoallylic alcohol **2** are available in high enantiomeric purity through asymmetric allylboration of acetaldehyde [9].

Discussion. – The β-alkenyloxyacrylate cyclizations **3**→**4** and **3**→**6** are probably initiated by protonation of the enol-ether double bond to give oxonium ion **a**, which then preferentially cyclizes in a chair-like conformation with the substituents at C(2) and C(6) in a *quasi*-equatorial position[5]). The predominant trapping of the developing secondary cation at C(4) on the way to the cyclization products **4** and **6** from the equatorial direction, which corresponds to an *anti*-addition across the terminal double bond, has ample precedent [12].



a

Except the acetal-olefin cyclizations studied by *Johnson* [13], which occur in an exocyclic mode with respect to the initiator and thus give carbocyclic products, oxonium-ion-initiated cyclizations have not received much attention. Recently, however, several examples of endocyclic acetal-olefin cyclizations leading to oxacyclic products have been described [14]. Much to our surprise, we could not find any previous example in the literature for enol ethers as starting units in cationic olefin cyclizations.

This β-alkenyloxyacrylate cyclization may be useful for the stereoselective construction of other 2,6-disubstituted tetrahydropyrans which form important structural elements of polyether antibiotics [15]. These studies are in progress[6]) and will be reported together with mechanistic details.

We thank Dr. *E. Billeter*, Mrs. *R. Bläuer*, Mr. *J. Märki*, Dr. *J. Schmid* (*Givaudan Forschungsgesellschaft AG*, Dübendorf) for NMR and MS measurements and Dr. *A. Dirscherl* (*F. Hoffmann-La Roche & Co. AG*, Basel) for performing the elemental analysis.

---

[5]) Similar cyclizations to tetrahydropyrans are known [10] to occur when 4-methyl-4-penten-2-ol is condensed with aldehydes under acidic conditions (*Kriewitz-Prins* reaction [11]).

[6]) A β-alkenyloxyacrylate cyclization has already found use in a stereoselective synthesis of (±)-*cis*-α-irone [16].

Experimental Part

General. Solvents and reagents: *Fluka (puriss.* or *purum)*, used without further purification except Et_2O which was distilled from $LiAlH_4$ and CH_2Cl_2 (distilled from P_2O_5). Reactions, sensitive to the atmosphere, were conducted in oven-dried (130°) glassware under an atmosphere of dry N_2. Sensitive liquids and solns. were transferred with syringes and were introduced into the reaction flask through rubber septa. Reaction temp. were measured outside the flask (bath temp.). TLC: *Merck* precoated plates, silica gel *60* F_{254}, layer thickness 0.25 mm; detection by dipping the plates into a vanillin soln. (8.35 g of vanillin, 7.25 ml of AcOH, 12.5 ml of conc. H_2SO_4, 325 ml of abs. EtOH) followed by drying with hot air. Column chromatography was performed at atmospheric pressure using *Merck* silica gel *60* (230–400 mesh). GC: *Carlo Erba GC 6000 Vega Series* instrument equipped with a *SE-30* glass capillary column (26 m × 0.3 mm), He as carrier gas (40 kPa); temp. programming: samples were injected at 70°: after 2 min, the temp. was raised 5°/min. M.p. were measured in open capillary tubes and are uncorrected. UV spectra: *Beckman 25* spectrophotometer; λ_{max} (ε) in nm. IR spectra: *Perkin-Elmer 681* spectrophotometer; in cm^{-1}. ^1H- (400 MHz) and ^{13}C-NMR (25 MHz): *Bruker AM 400* spectrometer using $CDCl_3$ solns. with TMS as internal standard; chemical shifts (δ) in ppm, coupling constants J in Hz. MS: *Varian MAT CH-5* instrument; electron energy 70 eV; relative peak intensities in % of the base peak (= 100%).

(±)-Methyl (2E)-3-(1-Methyl-3-butenyl)oxyacrylate (**3**). To a soln. of 5.30 g (63 mmol) of methyl propiolate in 50 ml of dry Et_2O were added successively 6.30 g (62 mmol) of *N*-methylmorpholine and an Et_2O soln. (20 ml) of 5.06 g (59 mmol) of 4-penten-2-ol *(Fluka, purum)*. The resulting mixture was stirred at r.t. under N_2 for 24 h, then poured into 100 ml of 0.5M aq. AcOH, and extracted with Et_2O (2 × 200 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Chromatography of the residual yellow oil on silica gel (75 g) with hexane/AcOEt 20:1, followed by bulb-to-bulb distillation (140°/15 Torr) afforded 8.52 g (85%) of **3** as a colorless, pleasant-smelling liquid (> 99% pure by cap. GC). Only traces (< 0.5%), if any, of the corresponding (*Z*)-isomer could be detected by TLC or cap. GC. TLC: R_f 0.35 (hexane/AcOEt 4:1). UV (EtOH): 235 (16600). IR (film): 3080*w*, 1715*s*, 1645*s*, 1622*s*, 1436*m*, 1330*m*, 1290*m*, 1205*s*, 1139*s*, 1062*m*, 1049*m*, 831*w*. ^1H-NMR: 1.29 (*d*, J = 6, 3 H); 2.26–2.46 (*m*, 2 H); 3.70 (*s*, CH_3O); 4.11 (*sext.*, J = 6, 1 H); 5.08–5.16 (*m*, 2 H); 5.25 (*d*, J = 12.5, O–C=CH–COO); 5.70–5.82 (*m*, 1 H); 7.53 (*d*, J = 12.5, O–CH=C–COO). ^{13}C-NMR: 19.59 (*q*); 40.55 (*t*); 50.80 (*q*); 78.78 (*d*); 97.10 (*d*); 118.22 (*t*); 133.10 (*d*); 161.75 (*d*); 168.20 (*s*). MS: 139 (3, $M^{+\cdot} - OCH_3$), 129 (5), 103 (3), 84 (16), 69 (81), 41 (100). Anal. calc. for $C_9H_{14}O_3$ (170.21): C 63.51, H 8.29; found: C 63.10, H 8.44.

*(±)-Methyl (2,6-*cis*-4-Hydroxy-6-methyltetrahydropyran-2-yl)acetate* (**5**). To a soln. of 1.70 g (10 mmol) of **3** in 25 ml of dry CH_2Cl_2 at 0° was added 4.0 ml (52 mmol) CF_3COOH (distilled from a small amount of P_2O_5) with a syringe over 2 min. The resulting soln. was stirred at 0° under N_2, until TLC indicated complete disappearance of the starting material (*ca.* 2 h). The mixture was then poured into 100 ml of a cold 1M $KHCO_3$ soln., extracted with CH_2Cl_2 (3 × 100 ml), and the combined org. extracts concentrated in vacuo. The crude trifluoroacetate **4** was dissolved in 10 ml of MeOH, and a 0.3M aq. K_2CO_3 soln. (75 ml) was added. The resulting mixture was vigorously shaken for 12 min and the pH then adjusted to 7 with AcOH. The soln. was saturated with NaCl and extracted with CH_2Cl_2 (3 × 100 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Bulb-to-bulb distillation of the crude product (130°/0.35 Torr) gave 1.64 g (87%) of **5** as a colorless, viscous liquid. Cap. GC revealed 2 peaks in a ratio of 11:1. TLC: R_f (hexane/AcOEt 1:2) 0.20 (major isomer) and 0.23 (minor isomer). IR (film): 3430*s* (br.), 1740*s*, 1640*w*, 1438*s*, 1373*s*, 1270*s*, 1200*s*, 1163*s*, 1150*s*, 1134*s*, 1081*s*, 1062*s*, 1032*s*, 1012*s*, 955*w*, 819*m*. ^1H-NMR: major isomer (all-*cis*-isomer): 1.10–1.24 (*m*, 5 H), overlapped by 1.21 (*d*, J = 6.5, CH_3–C(6)); 1.90–2.03 (*m*, H_{eq}–C(3), H_{eq}–C(5)); 2.25 (br. *s*, OH); 2.44 (*dd*, J = 6, 15.5, CH–COO); 2.62 (*dd*, J = 7.5, 15.5, CH–COO); 3.44–3.54 (*m*, H–C(6)); 3.69 (*s*, CH_3O); 3.74–3.88 (*m*, H–C(2), H–C(4)). ^1H-NMR: minor isomer: 3.685 (*s*, CH_3O); 3.90–4.00 (*m*); 4.20–4.28 (*m*). ^{13}C-NMR: major isomer (all-*cis*-isomer): 21.62 (*q*); 40.29 (*t*); 40.90 (*t*); 42.44 (*t*); 51.63 (*q*); 67.27 (*d*); 71.77 (*d*); 71.93 (*d*); 171.63 (*s*). MS: 170 (15, $M^{+\cdot} - H_2O$), 138 (9), 116 (18), 115 (20), 103 (32), 96 (38), 71 (33), 59 (53), 43 (100). Anal. calc. for $C_9H_{16}O_4$ (188.22): C 57.43, H 8.57; found: C 57.21, H 8.78.

*(±)-Methyl (*cis*-6-Methyl-4-oxotetrahydropyran-2-yl)acetate* (**7**). To a chilled soln. of 196 mg (1.04 mmol) of **5** in 4 ml of AcOH was added 1 ml (*ca.* 2 mmol) of cold (0°) *Jones* reagent [17][7]. The resulting mixture was stirred at 0° for 30 min, and then 1 ml of i-PrOH was added. The mixture was stirred for another 5 min, then poured into 50 ml of ice water, and extracted with Et_2O (2 × 100 ml). The combined org. extracts were washed with sat. $KHCO_3$ soln. (2 × 100 ml), dried ($MgSO_4$), and concentrated *in vacuo*. Bulb-to-bulb distillation of the residual oil (150°/2 Torr) yielded 151 mg (78%) of **7** as a colorless liquid. Cap. GC indicated a purity of 97.2% (t_R 15.0 min). In addition, 3 minor peaks were observed with t_R 15.5 min (0.7%), 19.1 min (1.3%), and 20.1 min (0.8%). No signals

---

[7]) Prepared by addition of 1.6 ml of conc. H_2SO_4 to a cooled soln. of 2 g of CrO_3 in 8 ml of H_2O.

attributable to the *trans*-isomer could be detected in the 400-MHz ^{1}H-NMR spectrum. TLC: R_f 0.33 (hexane/AcOEt 1:1). IR (film): 1732*s*, 1438*m*, 1377*m*, 1330*m*, 1274*m*, 1259*m*, 1220*m*, 1192*m*, 1156*m*, 1112*m*, 1068*m*, 999*m*, 836*w*. ^{1}H-NMR: 1.31 (*d*, J = 6, CH_3–C(6)); 2.18–2.47 (*m*, 2 H–C(3), 2 H–C(5)); 2.52 (*dd*, J = 5.5, 15.5, CH–COO); 2.72 (*dd*, J = 7.5, 15.5, CH–COO); 3.71 (*s*, CH_3O); 3.73–3.82 (*m*, 12 lines, H–C(6)); 4.07 (*dddd*, J = 2.5, 5.5, 7.5, 11.5, H–C(2)); irradiation of the *d* at 1.31→*dd* at 3.78 (J = 2.5, 11.5). ^{13}C-NMR: 21.97 (*q*); 41.00 (*t*); 46.70 (*t*); 49.01 (*t*); 51.78 (*q*); 73.09 (*d*); 73.21 (*d*); 170.63 (*s*); 206.09 (*s*). MS: 186 (7, $M^{+\cdot}$), 171 (5), 168 (13), 154 (28), 143 (15), 113 (81), 71 (77), 59 (56), 43 (100). Anal. calc. for $C_9H_{14}O_4$ (186.21): C 58.05, H 7.58; found: C 57.68, H 7.73.

*(±)-Methyl [2,6-*cis*-4-(Methanesulfonyl)oxy-6-methyltetrahydropyran-2-yl]acetates* (**6**). a) *Mesylation of* **5**: To a soln. of 107 mg (0.57 mmol) of **5** and 110 mg (0.96 mmol) of MsCl in 5 ml of dry CH_2Cl_2 was added 0.5 ml of pyridine. The resulting mixture was stirred at r.t. under N_2, until TLC indicated complete disappearance of the starting material (15–20 h). A soln. (1 ml) of aq. pyridine (1:1 *v/v*) was added, the mixture was stirred for 1 h at r.t. and then poured into ice water. The pH was adjusted to 2 with dil. HCl, and the aq. phase extracted with CH_2Cl_2 (2 × 100 ml). The combined org. extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The product solidified on standing (quant. yield). ^{1}H-NMR revealed the presence of 2 isomers in a ratio of 11:1. TLC: R_f (hexane/AcOEt 1:1) 0.27 (major isomer), 0.21 (minor isomer). ^{1}H-NMR: major isomer (all-*cis*-isomer): 1.23 (*d*, J = 6, CH_3–C(6)); 1.45, 1.49 (2*q*, J = 11.5, H_{ax}–C(3), H_{ax}–C(5)); 2.10–2.23 (*m*, H_{eq}–C(3), H_{eq}–C(5)); 2.45 (*dd*, J = 5.5, 16, CH–COO); 2.63 (*dd*, J = 7.5, 16, CH–COO); 3.03 (*s*, CH_3SO_2); 3.49–3.58 (*m*, 12 lines, H–C(6)); 3.70 (*s*, CH_3O); 3.80 3.89 (*m*, H–C(2)); 4.83 (*tt*, J = 5, 11.5, H_{ax}–C(4)); irradiation of the *d* at 1.23→*dd* at 3.54 (J = 2, 11). ^{1}H-NMR: minor isomer: 1.17 (*d*, J = 6, CH_3–C(6)); 3.07 (*s*, CH_3SO_2); 5.16 (*m*, H_{eq}–C(4)).

b) *Cyclization of* **3**. To a soln. of 3.404 g (20 mmol) of **3** in 50 ml of dry CH_2Cl_2 was added at 0° 5.0 ml (*ca.* 75 mmol) of MsOH with a syringe over a period of 4 min. The resulting soln. was stirred at 0° under N_2 for 30 min and then poured into 200 ml of a cold 1M $KHCO_3$ soln. The aq. phase was extracted with CH_2Cl_2 (3 × 100 ml), the combined org. extracts dried ($MgSO_4$), and concentrated *in vacuo*. The crude product (5.00 g, 94%) contained, according to ^{1}H-NMR, 85% of **6** (4β/4α ratio 7:1) and *ca.* 15% of a corresponding 2,6-*trans*-isomer. Crystallization from CH_2Cl_2/hexane afforded 3.64 g (68%) of **6** (4β/4α ratio 20:1) which was *ca.* 95% pure, m.p. 92–93°. TLC: R_f (hexane/AcOEt 1:1) 0.27 (major isomer); 0.21, 0.33 (minor isomers). IR ($CHCl_3$): 3025*m*, 1738*s*, 1438*m*, 1332*s*, 1175*s*, 938*s*. ^{1}H-NMR: see above; 2,6-*trans*-isomer: 1.25 (*d*, J = 6.5, CH_3–C(6)); 4.15–4.25 (*m*, H–C(2)). ^{13}C-NMR: major isomer (all-*cis*-isomer): 21.43 (*q*); 37.61 (*t*); 38.90 (*q*, CH_3SO_2); 39.78 (*t*); 40.66 (*t*); 51.72 (*q*); 71.49 (*d*); 71.61 (*d*); 77.38 (*d*); 170.99 (*s*). MS: 170 (42, $M^{+\cdot} - SO_2CH_3$), 127 (38), 97 (87), 96 (100). Anal. calc. for $C_{10}H_{18}O_6S$ (266.31): C 45.10, H 6.81, S 12.04; found: C 44.97, H 6.73, S 12.12.

*(±)-Methyl (*cis*-6-Methyltetrahydropyran-2-yl)acetat* (**8**). A mixture of 1.334 g (5.0 mmol) of **6** (prepared by *Method b*), 3.0 g (20 mmol) of NaI, 2.6 g (40 mmol) of Zn powder, and 30 ml of 1,2-dimethoxyethane was heated under reflux for 5 h. After cooling, the mixture was filtered through *Celite* and the flask rinsed with Et_2O. The combined filtrates were shaken with H_2O containing a small amount of $NaHSO_3$. The aq. phase was extracted a second time with Et_2O (100 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Filtration through a pad of silica gel (15 g) with pentane/Et_2O 2:1 afforded a colorless liquid which was purified by bulb-to-bulb distillation (125°/30 Torr) to give 517 mg (60%) of **8** (single peak in cap. GC). ^{1}H-NMR: 1.11–1.28 (*m*, 5 H), overlapped by 1.15 (*d*, J = 6.5, CH_3–C(6)); 1.47–1.66 (*m*, 3 H); 1.77–1.86 (*m*, 1 H); 2.39 (*dd*, J = 6, 15.5, CH–COO); 2.57 (*dd*, J = 7.5, 15.5, CH–COO); 3.42–3.52 (*m*, H–C(6)); 3.68 (*s*, CH_3O); 3.73–3.82 (*m*, H–C(2)). ^{13}C-NMR: 22.12 (*q*); 23.57 (*t*); 31.04 (*t*); 33.04 (*t*); 41.57 (*t*); 51.38 (*q*); 74.00 (*d*); 74.23 (*d*); 171.63 (*s*). IR and MS were in good agreement with the values reported in [1].

*(±)-(*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid* (**1**). To a soln. of 262 mg (1.52 mmol) of **8** in 1 ml of MeOH was added 4 ml of a 2.5M aq. soln. of NaOH (10 mmol). The resulting mixture was stirred at r.t. for 24 h and then acidified with 4N HCl. The aq. phase was extracted with CH_2Cl_2 (3 × 100 ml) after saturation with NaCl. The combined org. extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue (241 mg, quant. yield) crystallized spontaneously at 4° (m.p. 53–54°). Crystallization from pentane at −30° raised the m.p. to 54–55°. ^{1}H-NMR[8]: 1.16–1.35 (*m*, 5 H), overlapped by 1.20 (*d*, J = 6.5, CH_3–C(6)); 1.48–1.69 (*m*, 3 H); 1.80–1.90 (*m*, 1 H); 2.51 (*dd*, J = 5, 16, CH–COO); 2.58 (*dd*, J = 8, 16, CH–COO); 3.50–3.60 (*m*, H–C(6)); 3.73–3.82 (*m*, H–C(2)). IR and MS agreed with the values reported in [1].

---

[8]) For a study of the concentration dependence of the ^{1}H-NMR spectrum of (+)-**1**, see [18].

REFERENCES

[1] B. Maurer, A. Grieder, W. Thommen, *Helv. Chim. Acta* **1979,** *62,* 44.

[2] B. Maurer, W. Thommen, *Helv. Chim. Acta* **1979,** *62,* 1096.

[3] D. Seebach, M. Pohmakotr, *Helv. Chim. Acta* **1979,** *62,* 843; D. Seebach, M. Pohmakotr, C. Schregenberger, B. Weidmann, R.S. Mali, S. Pohmakotr, *ibid.* **1982,** *65,* 419.

[4] a) Y. Kim, B.P. Mundy, *J. Org. Chem.* **1982,** *47,* 3556; b) S.V. Ley, B. Lygo, H. Molines, J.A. Morton, *J. Chem. Soc., Chem. Commun.* **1982,** 1251; S.V. Ley, B. Lygo, H. Molines, *J. Chem. Soc., Perkin Trans. 1* **1984,** 2403; c) H.A. Bates, P.-N. Deng, *J. Org. Chem.* **1983,** *48,* 4479; d) Y. Masaki, Y. Serizawa, K. Nagata, K. Kaji, *Chem. Lett.* **1983,** 1601; e) M.F. Semmelhack, C. Bodurow, *J. Am. Chem. Soc.* **1984,** *106,* 1496; f) T. Gallagher, *J. Chem. Soc., Chem. Commun.* **1984,** 1554; g) F.W. Lichtenthaler, F.D. Klingler, P. Jarglis, *Carbohydr. Res.* **1984,** *132,* C1; h) E. Keinan, K.K. Seth, R. Lamed, *J. Am. Chem. Soc.* **1986,** *108,* 3474.

[5] E. Winterfeldt, H. Preuss, *Chem. Ber.* **1966,** *99,* 450.

[6] R.H. Mueller, R.M. DiPardo, *J. Org. Chem.* **1977,** *42,* 3210.

[7] A.A. Leon, G. Daub, I.R. Silverman, *J. Org. Chem.* **1984,** *49,* 4544.

[8] a) Y. Fujimoto, T. Tatsuno, *Tetrahedron Lett.* **1976,** *17,* 3325; b) P. Kočovský, V. Černý, *Collect. Czech. Chem. Commun.* **1979,** *44,* 246.

[9] P.K. Jadhav, K.S. Bhat, P.T. Perumal, H.C. Brown, *J. Org. Chem.* **1986,** *51,* 432.

[10] A. Schneider, U. Séquin, *Tetrahedron* **1985,** *41,* 949, and ref. cited therein.

[11] J. Thiem, in 'Houben-Weyl, Methoden der Organischen Chemie', Thieme, Stuttgart, 1980, Vol. VI/1a, Part 2, p. 793–799.

[12] P.A. Bartlett, in 'Asymmetric Synthesis', Ed. J.D. Morrison, Academic Press, New York, 1984, Vol. 3, Chapt. 5.

[13] W.S. Johnson, *Angew. Chem. Int. Ed.* **1976,** *15,* 9.

[14] a) H. Nishiyama, K. Itoh, *J. Org. Chem.* **1982,** *47,* 2496; b) H. Nishiyama, S. Narimatsu, K. Sakuta, K. Itoh, *J. Chem. Soc., Chem. Commun.* **1982,** 459; c) G.S. Cockerill, P. Kocienski, *ibid.* **1983,** 705; d) I.T. Kay, E.G. Williams, *Tetrahedron Lett.* **1983,** *24,* 5915; e) W.H. Bunnelle, D.W. Seamon, D.L. Mohler, T.F. Ball, D.W. Thompson, *ibid.* **1984,** *25,* 2653; f) M.L. Melany, G.A. Lock, D.W. Thompson, *J. Org. Chem.* **1985,** *50,* 3925; g) G.S. Cockerill, P. Kocienski, R. Treadgold, *J. Chem. Soc., Perkin Trans. 1* **1985,** 2093; h) L.E. Overman, A. Castañeda, T.A. Blumenkopf, *J. Am. Chem. Soc.* **1986,** *108,* 1303.

[15] J.W. Westley, Ed., 'Polyether Antibiotics', Marcel Decker, New York, 1983, Vols. I and II.

[16] C. Nussbaumer, G. Fráter, *J. Org. Chem.*, in press.

[17] K. Bowden, I.M. Heilbron, E.R.H. Jones, B.C.L. Weedon, *J. Chem. Soc.* **1946,** 39.

[18] E. Keinan, K.K. Seth, M. Sahai, E. Berman, *J. Org. Chem.* **1986,** *51,* 4288.