The Unexpected Reorganizations of a β-Lactone Aldolate to 1,3-Dioxan-4-ones in the Reaction of 4-(1-Methylethyl)-3-[(phenylthio)methyl]-1-oxetan-2-one Lithium Enolate with Acetaldehyde

Víctor Oswaldo Nava-Salgado*[a] and Waldemar Adam[b]

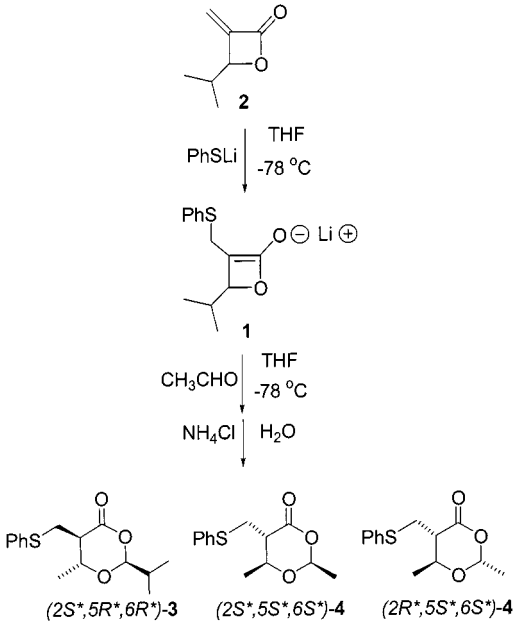
Keywords: β-Lactone aldolate / Aldol reactions / Lactones / Lithium enolates / Aldehydes

The lithium enolate 4-(1-methylethyl)-3-[(phenylthio)methyl]-1-oxetan-2-one (**1**), generated from the conjugate addition of lithium thiophenolate to α-methylene-β-lactone **2**, reacts with acetaldehyde to give the 1,3-dioxan-4-ones **3** and **4** as unexpected aldol products. These products result from unusual aldol reorganization processes, which entail a complex cascade of aldol additions, retroaldol cleavages and translactonizations. The configurations of the products have been determined by NOE experiments.

Introduction

The chemistry of β-lactones has been widely explored for synthetic purposes by numerous research groups.[1] β-Lactone lithium enolates are quite persistent at low temperature (−78 °C) and react with a variety of electrophiles to give the corresponding α-substituted β-lactones.[2] α-Methylene β-lactones, which have been shown to be quite attractive as valuable building blocks in organic synthesis,[3] have recently been prepared in enantiomerically pure forms.[4] They also function as precursors for β-lactone enolates by conjugate addition of soft nucleophiles; for example, we have described recently the generation of thiomethyl- and ester-functionalized β-lactone enolates by the addition of thiolates[5] and ester enolates[6] to α-methylene β-lactones.

The β-lactone enolates, which are conveniently generated from the corresponding β-lactones by treatment with lithium diisopropylamide in tetrahydrofuran at −78 °C,[7] but undergo electrocyclic ring opening above −50 °C,[8] react with aldehydes to give the corresponding α-hydroxymethylated β-lactone adducts in excellent yields (85−95%).[9] When the (phenylthio)methyl-substituted β-lactone enolate **1**, derived from the Michael-type addition of lithium thiophenolate to the α-methylene β-lactones **2**, was treated with acetaldehyde, along with the 1,3-dioxan-4-one **3**, **4** was unexpectedly obtained, in which the isobutyraldehyde at the acetal functionality has been replaced by an acetaldehyde,



Scheme 1. Condensation of β-lactone enolate **1** with acetaldehyde

(Scheme 1). We report herein the experimental details of this unusual reorganization of aldolates, and suggest a mechanism to rationalize this novel result.

Results and Discussion

The product ratio of the 1,3-dioxan-4-ones **3** and **4**, determined by ^{1}H NMR spectroscopy of the crude product mixtures as well as of the isolated products after silica-gel chromatography, was shown to depend on the amount of acetaldehyde employed and the temperature of the aldol reaction (Table 1). The maximum amount of 2-isopropyldioxanone **3** vs. 2-methyldioxanones **4** (58:42) was obtained by using 0.9 equiv. of acetaldehyde (Table 1, entry 1). When the amount of acetaldehyde was increased to 1.5 equiv., the **3**:**4** product ratios of 50:50 and 34:66 were obtained at −40 °C (entry 2) and ca. 20 °C (entry 3) as final temperature

[a] Instituto de Química, Universidad Nacional Autonoma de México,
Circuito Exterior, Ciudad Universitaria, 04510 México D.F., México
Fax: (internat.) + 52-5/616-2203
E-mail: navasavo@servidor.unam.mx
URL: http://iqunam.iquimica.unam.mx
[b] Institut für Organische Chemie der Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany
Fax: (internat.) + 49-(0)931/888-4756
E-mail: adam@chemie.uni-wuerzburg.de
URL: http://www-organik.chemie.uni-wuerzburg.de

  1434−193X/00/0714−2529 $ 17.50+.50/0

Table 1. Reaction of the β-lactone enolate **1** with acetaldehyde; β-lactone enolate **1** was prepared by the addition of PhSLi to β-lactone **2** at −78 °C

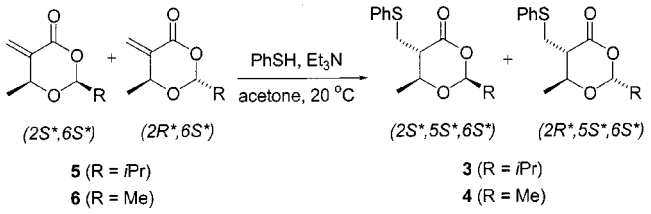
Entry	CH_3CHO[a] (equiv.)	Temp.[b] (°C)	Product ratio[c] (**3**:**4**)	Yield[d] (%)
1	0.9	ca. 20	58:42	41
2	1.5	−40	50:50	40
3	1.5	ca. 20	34:66	63
4	2.0	ca. 20	0:100	55

[a] Addition temperature −78 °C. − [b] Protonation by aqueous NH_4Cl solution. − [c] Determined by ^1H NMR spectroscopy on the crude product mixtures as well as on the isolated material after silica-gel chromatography; the (2*S**,5*S**,6*S**):(2*R**,5*S**,6*S**) ratio of **4** was determined to be 50:50 by ^1H NMR spectroscopy on the crude product mixtures, mass balance 78−80%; the **3**:**4** ratio was normalized to 100% conversion, error ca. 5% of the stated values. − [d] Yield of isolated material after silica-gel chromatography.

before aqueous workup, which display a definitive temperature dependence. Complete conversion into the dioxanones **4** was achieved by the use of two equiv. of acetaldehyde and warming to ca. 20 °C before hydrolytic workup (entry 4). The (2*S**,5*S**,6*S**)/(2*R**,5*S**,6*S**) diastereomeric ratio of the dioxanone **4** was ca. 50:50 in all cases, as shown by ^1H NMR spectroscopy.

To confirm the identity of the dioxanones, authentic samples of **3** and **4** were prepared by the conjugate addition of thiophenol to a (2*S**,6*S**)/(2*R**,6*S**) mixture of the corresponding 5-methylenedioxanones **5** and **6** (Scheme 2, Table 2). The latter were obtained from the acid-catalyzed reaction of α-methylene-β-hydroxybutanoic acid with acetaldehyde or isobutyraldehyde.[10]

The configurations of the dioxanones (2*S**,5*R**,6*R**)-**3** and (2*S**,5*S**,6*S**)-, (2*R**,5*S**,6*S**)-**4** were established unambiguously by NOE experiments (Figure 1). Thus, the most significant signal enhancements were observed upon irradiation (both directions) of the H-2 proton of the dioxane ring with the H-6 proton or the substituent at this position, as well as upon irradiation of the H-6 proton with the methylene group at the position 5. Another important enhancement was observed for the equivalent diastereomers (2*S**,5*R**,6*R**)-**3** and (2*R**,5*S**,6*S**)-**4** on irradiation of the



Scheme 2. Synthesis of dioxanones **3** and **4**

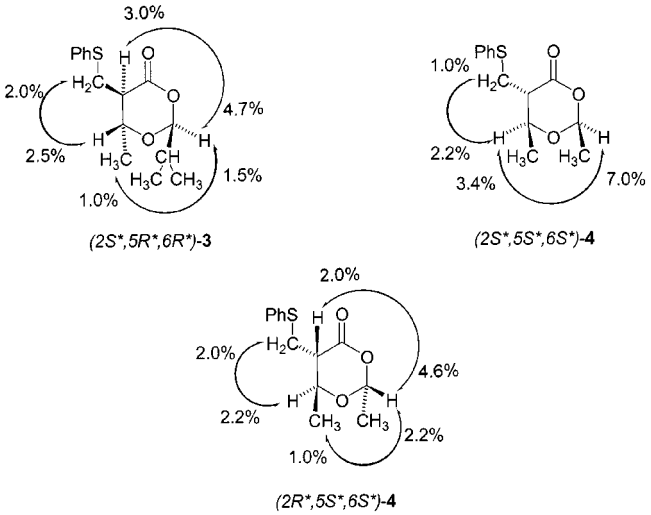


Figure 1. Configurational assignment of the 1,3-dioxan-4-ones **3** and **4** by NOE spectroscopy.

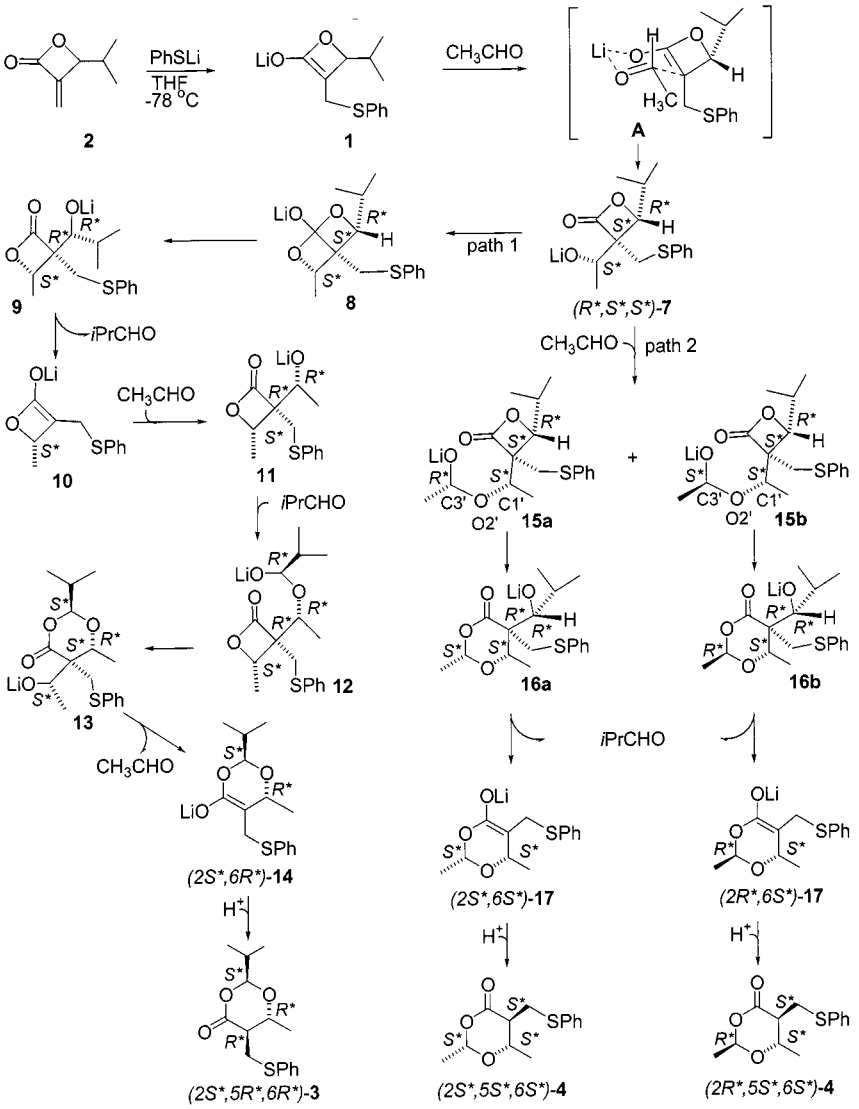
H-2 and H-5 protons, which suggests a preferred boat conformation for these compounds.

The mechanism in Scheme 3 has been proposed to rationalize the complex formation of the dioxanones **3** and **4**. First the β-lactone enolate **1** reacts with acetaldehyde, with efficient stereocontrol, via the transition state **A** to give the aldol adduct **7**; the latter serves as a common intermediate in the two competitive paths 1 and 2 (see Scheme 3). In analogy with other aldol reactions,[11] and the known aldol condensation of β-lactone enolates with aldehydes,[9] the configuration of the aldol adduct **7** is dictated by an *anti* attack relative to the substituent on the β position through lithium-ion coordination of the enolate and the carbonyl group of the aldehyde. Although the isomer (*R**,*S**,*S**) is

Table 2. Base-catalyzed nucleophilic conjugate addition of thiophenol to 5-methylenedioxanones **5** and **6**; triethylamine (0.1 equiv.) was used as base catalyst in acetone at 20 °C for 1 h, 100% conversion

Entry	R	Diastereoisomeric ratios (*dr*)[a] **5,6** (2*S**,6*S**):(2*R**,6*S**)	**3,4** (2*S**,5*S**,6*S**):(2*R**,5*S**,6*S**)[b]	Yield[c] (%)
1	Me	89:11	89:11	86
2	*i*Pr	90:10	90:10	99

[a] Determined by ^1H NMR analysis on the crude product mixtures, normalized to 100% conversion, error ca. 5% of the stated values, mass balance 78−80%. − [b] Diastereoisomers 2*S**,5*S**,6*S** and 2*R**,5*S**,6*S** are mirros images of 2*R**,5*R**,6*R** and 2*S**,5*R**,6*R**. − [c] Yield of isolated material after silica-gel chromatography.



Scheme 3. Mechanistic cascade

expected to be almost the only product, the formation of the isomer (*R**,*S**,*R**) cannot be totally excluded,[9] although this isomer leads to the corresponding enantiomeric products under the same mechanistic cascade. At acetaldehyde amounts near to one equiv., the aldol adduct (*R**,*S**,*S**)-**7** translactonizes by way of the intermediate **8** to the aldol adduct **9** (path 1). The latter undergoes a complex sequence of retroaldol cleavage (*i*PrCHO), aldol additions (CH_3CHO and *i*PrCHO), ring expansion and aldol reversion (CH_3CHO) through the inferred but likely intermediates **10**−**14** to afford, on final protonation with aqueous NH_4Cl, the dioxanone (2*S**,5*R**,6*R**)-**3**. Note that in this dioxanone, the acetaldehyde and isobutyraldehyde units are in the reverse positions as would be expected when enolate **1** is allowed to react with acetaldehyde. The mechanistic reason for the stereoselectivity of this product is still not clear and will be the subject of further studies. The competitive reaction in path 2 involves the addition of another equivalent of acetaldehyde to the aldol adduct **7** in a nonstereoselective manner to produce a 50:50 mixture of the acetaldehyde double-addition products **15a**,**b**, which differ only in their newly formed C-3′ stereogenic center. Their ring expansion by attack of the alcoholate ion at the carbonyl group of the β-lactone affords the dioxanone intermediates **16a**,**b**. A retroaldol reaction (*i*PrCHO) occurs subsequently to give the (2*S**,6*S**)- and (2*R**,6*S**)-1,3-dioxanone enolates **17**, which, after protonation with aqueous NH_4Cl, afford the observed dioxanones (2*S**,5*S**,6*S**)- and (2*R**,5*S**,6*S**)-**4**. When an excess of acetaldehyde (two equiv.) is used at room temperature (Table 1, entry 4), only the diastereomeric 1,3-dioxan-4-ones **4** are produced, with complete suppression of the dioxane **3**. A related unusual reorganization by way of a cascade of aldol, retroaldol and transacetalization processes has been reported in the reaction of lithium enolates of 2,6-dialkyl-1,3-dioxan-4-ones with aldehydes.[12]

In conclusion, the present complex transformation of the α-alkoxymethyl-β-lactone intermediate **7**, which is readily accessible by the stereoselective aldol reaction of α-thiomethyl-β-lactone enolate **1** with acetaldehyde, to the

1,3-dioxan-4-ones (2*S**,5*R**,6*R**)-**3** and (2*S**,5*S**,6*S**)-, (2*R**,5*S**,6*S**)-**4** are the first observed unusual reorganizations of alkoxymethyl-β-lactone intermediates.

Experimental Section

General: All reactions were performed in oven-dried glassware under a positive pressure of argon or nitrogen gas. The air- and moisture-sensitive enolate solutions were transferred by means of a syringe into the rubber-septum-capped reaction vessels. − ^{1}H NMR (250 MHz): Bruker AC 250 ($CHCl_3$, at δ = 7.26 as internal standard). − ^{13}C NMR (63 MHz): Bruker AC 250 ($CHCl_3$, at δ = 77.0 as internal standard). Elemental analyses were performed at the Analytical Division of the Institute of Inorganic Chemistry (University of Würzburg). For column chromatography, Merck silica-gel (230−400 mesh) was employed. Commercial grade reagents were used without further purification, except when indicated. THF was distilled from a sodium/benzophenone mixture immediately prior to use, and CH_2Cl_2 from P_2O_5. Petroleum ether was distilled from P_2O_5, and only the fraction which came over between 30−50 °C was used for the silica-gel chromatography.

General Procedure for the Generation of the β-Lactone Enolate 1 and Subsequent Reaction with Acetaldehyde (Scheme 1): A 50-mL, two-necked, round-bottomed flask was equipped with an inlet adapter for argon or nitrogen gas and a rubber septum. It was charged with 5 mL of dry THF and thiophenol (43.7 mg, 0.40 mmol), cooled in an ice bath, and subsequently a *n*-butyllithium solution (1.56 M in hexane, 0.28 mL, 0.43 mmol) was added rapidly by means of a syringe. After 15 min, the ice bath was replaced with a dry ice/acetone bath (−78 °C), and a solution of β-lactone **2** (50.0 mg, 0.40 mmol) in 1 mL of THF was added dropwise by means of a syringe over a period of 1 min; the syringe was then rinsed with THF (2 × 0.2 mL). After 30 min of stirring, a solution of acetaldehyde (15.7 mg, 0.36 mmol) in 1 mL THF was added slowly over a period of 1 min. The resulting solution was stirred at −78 °C for 1 h, allowed to warm to room temperature (ca. 20 °C) and then treated with 10 mL of saturated, aqueous NH_4Cl solution. After 5 min, the aqueous phase was separated and extracted with diethyl ether (3 × 20 mL), the combined organic phases were dried over $MgSO_4$, filtered, and concentrated (ca. 20 °C/ 20 Torr). The **3**:**4** ratio was 58:42 and the (2*S**,5*S**,6*S**):(2*R**,5*S**,6*S**) ratio of **4** was 50:50, as determined by NMR analysis of the characteristic H-2 protons of the 1,3-dioxan-4-ones, i.e., (2*S**,5*R**,6*R**)-**3**-H [δ = 5.17 (d)], (2*S**,5*S**,6*S**)-**4**-H [δ = 5.62 (q)] and (2*R**,5*S**,6*S**)-**4**-H [δ = 5.53 (q)] in the crude product mixture. The residue was purified by silica-gel chromatography to yield 26.4 mg (24%) of (2*S**,5*R**,6*R**)-**3** and 17.2 mg of a mixture of (2*S**,5*S**,6*S**)- and (2*R**,5*S**,6*S**)-**4** (17%) as light-colored oils, total yield 41%. According to this procedure, additional experiments were carried out with 1.5 and 2.0 equiv. of acetaldehyde and the protonation with aqueous NH_4Cl solution at −40 and ca. 20 °C. The product ratios and yields are reported in Table 1.

(2*S,5*R**,6*R**)-3:** IR (CCl_4): ṽ = 3060 cm^{-1}, 2960, 2920, 1740, 1465, 1380, 1230, 1160, 910. − ^{1}H NMR: δ = 0.98 (d, *J* = 6.8 Hz, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 1.37 (d, *J* = 6.4 Hz, 3 H), 1.95 (dsept, *J* = 4.4, 6.8 Hz, 1 H), 2.60 (dt, *J* = 5.0, 6.9 Hz, 1 H), 3.04 (dd, *J* = 7.2, 13.8 Hz, 1 H), 3.49 (dd, *J* = 5.0, 13.7 Hz, 1 H), 4.23 (qui, *J* = 6.5 Hz, 1 H), 5.17 (d, *J* = 4.7 Hz, 1 H), 7.18−7.48 (m, 5 H). − ^{13}C NMR: δ = 16.1 (q), 16.2 (q), 19.5 (q), 32.0 (d), 33.2 (t), 46.3 (d), 71.0 (d), 100.3 (d), 126.7 (d), 128.6 (d), 129.6 (d), 135.3 (s), 170.3 (s). − $C_{15}H_{20}O_3S$ (280.4): calcd. C 64.25, H 7.18, S 11.02; found C 64.03, H 7.18, S 10.62.

(2*S,5*S**,6*S**)- and (2*R**,5*S**,6*S**)-4:** IR (CCl_4): ṽ = 3040 cm^{-1}, 2950, 2900, 1725, 1460, 1390, 1225, 1065, 900. − $C_{13}H_{16}O_3S$ (252.3): calcd. C 61.88, H 6.39; found C 61.92, H 6.60.

(2*S,5*S**,6*S**)-4:** ^{1}H NMR: δ = 1.38 (d, *J* = 6.4 Hz, 3 H), 1.40 (d, *J* = 5.1 Hz, 3 H), 2.61 (dt, *J* = 5.0, 6.9 Hz, 1 H), 3.05 (dd, *J* = 6.9, 13.8 Hz, 1 H), 3.48 (dd, *J* = 5.0, 13.8 Hz, 1 H), 4.24 (quint, *J* = 6.6 Hz, 1 H), 5.62 (q, *J* = 5.1 Hz, 1 H), 7.20−7.45 (m, 5 H). − ^{13}C NMR: δ = 19.7 (q), 20.6 (q), 33.3 (t), 46.3 (d), 71.2 (d), 94.5 (d), 126.8 (d), 129.1 (d), 129.9 (d), 135.2 (s), 170.0 (s).

(2*R,5*S**,6*S**)-4:** ^{1}H NMR: δ = 1.35 (d, *J* = 6.1 Hz, 3 H), 1.40 (d, *J* = 5.1 Hz, 3 H), 2.72 (ddd, *J* = 3.8, 4.9, 10.0 Hz, 1 H), 3.24 (dd, *J* = 3.8, 13.6 Hz, 1 H), 3.54 (dd, *J* = 4.9, 13.6 Hz, 1 H), 4.10 (dq, *J* = 6.1, 10.1 Hz, 1 H), 5.53 (q, *J* = 5.2 Hz, 1 H), 7.20−7.45 (m, 5 H). − ^{13}C NMR: δ = 20.0 (q), 21.1 (q), 32.8 (t), 48.2 (d), 74.0 (d), 100.5 (d), 127.0 (d), 129.2 (d), 130.4 (d), 135.2 (s), 169.1 (s).

General Procedure for the Addition of Thiophenol to the 5-Methylene-1,3-dioxan-4-ones 5 and 6 (Scheme 2): To a solution of the particular 5-methylene-1,3-dioxan-4-one (1.00−1.50 mmol) and thiophenol (1.00−1.50 mmol) in 5 mL of acetone was added 20.0 mg (0.19 mmol) of triethylamine. The reaction mixture was stirred for 1 h at room temp. (ca. 20 °C), the solvent was evaporated (ca. 20 °C at 20 Torr), and the residue was purified by silica-gel chromatography to yield the 5-(phenylthio)methyl-1,3-dioxan-4-ones **3** and **4**. The yields and diasteroisomeric ratios are given in Table 2.

Acknowledgments

We are grateful to the Consejo Nacional de Ciencia y Tecnología (CONACYT, Proy. I27396-E), the Deutsche Forschungsgemeinschaft (SFB 347) and the Fonds der Chemischen Industrie for financial support. V. O. N.-S. thanks the DAAD for a doctoral fellowship (1991−1995).

[1] For recent reviews of β-lactone chemistry, see: H. W. Yang, D. Romo, *Tetrahedron* **1999**, *55*, 6403−6434; A. Pommier, J.-M. Pons, *Synthesis* **1993**, 441−459. For lead references on β-lactone chemistry, see: J. A. Marshall, H. Faubl, *J. Am. Chem. Soc.* **1970**, *92*, 948−955; W. Adam, J. Baeza, J.-C. Liu, *J. Am. Chem. Soc.* **1972**, *94*, 2000−2006; S. Mageswaran, M. U. S. Sultanbawa, *J. Chem. Soc., Perkin Trans. 1* **1976**, 884−890; B. Ganem, G. W. Holbert, L. B. Weiss, K. Ishizumi, *J. Am. Chem. Soc.* **1978**, *100*, 6483−6491; J. Mulzer, A. Pointer, A. Chucholowski, G. Brüntrup, *J. Chem. Soc., Chem. Commun.* **1979**, 52−54; J. I. Luengo, M. Koreeda, *Tetrahedron Lett.* **1984**, *25*, 4881−4884; G. E. Renzoni, T. K. Yin, F. Miyake, W. T. Borden, *Tetrahedron* **1986**, *42*, 1581−1584; R. L. Danheiser, Y. M. Choi, M. Menichincheri, E. J. Stoner, *J. Org. Chem.* **1993**, *58*, 322−327; C. Palomo, J. I. Miranda, A. Linden, *J. Org. Chem.* **1996**, *61*, 9196−9201; A. M. Warshawsky, M. V. Patel, T.-M. Chen, *J. Org. Chem.* **1997**, *62*, 6439−6440; O. Dirat, C. Kouklovsky, Y. Langlois, *J. Org. Chem.* **1998**, *63*, 6634−6642; H. W. Yang, D. Romo, *Tetrahedron Lett.* **1998**, *39*, 2877−2880; F. Machrouhi, J. L. Namy, *Tetrahedron* **1998**, *54*, 11111−11122; M. Shindo, Y. Sato, K. Shishido, *J. Am. Chem. Soc.* **1999**, *121*, 6507−6508.

[2] J. Mulzer, T. Kerkmann, *J. Am. Chem. Soc.* **1980**, *102*, 3620−3622; J. Mulzer, A. Chucholowski, O. Lammer, I. Jibril, G. Huttner, *J. Chem. Soc., Chem. Commun.* **1983**, 869−871; A. Griesbeck, D. Seebach, *Helv. Chim. Acta* **1987**, *70*, 1320−1325; R. L. Danheiser, J. S. Nowick, *J. Org. Chem.* **1991**, *56*, 1176−1185.

[3] W. Adam, L. Hasemann, V. O. Nava-Salgado, B. Nestler, E.-M. Peters, K. Peters, F. Prechtl, H. G. von Schnering, *J. Org. Chem.* **1991**, *56*, 5782−5785; W. Adam, V. O. Nava-Salgado, E.-M. Peters, K. Peters, H. G. von Schnering, *Chem. Ber.* **1993**,

126, 1481−1486; W. Adam, L. Hasemann, *Chem. Ber.* **1990**, *123*, 1449−1451; W. Adam, L. Hasemann, *Tetrahedron Lett.* **1991**, *32*, 7033−7036.

[4] W. Adam, V. O. Nava-Salgado, B. Wegener, E. Winterfeld, *Chem. Ber.* **1993**, *126*, 1509−1510; W. Adam, P. Groer, C. R. Saha-Moeller, *Tetrahedron: Asymmetry* **1997**, *8*, 833−836.

[5] W. Adam, V. O. Nava-Salgado, *J. Org. Chem.* **1995**, *60*, 578−584.

[6] V. O. Nava-Salgado, E.-M. Peters, K. Peters, H. G. von Schnering, W. Adam, *J. Org. Chem.* **1995**, *60*, 3879−3886.

[7] J. Mulzer, T. Kerkmann, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 466−468; *Angew. Chem.* **1980**, *92*, 470−471.

[8] J. Mulzer, T. Kerkmann, *J. Am. Chem. Soc.* **1980**, 102, 3620−3622.

[9] J. Mulzer, A. Chucholowski, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 777−778; *Angew. Chem.* **1982**, *94*, 788−789.

[10] D. Seebach, R. Imwinkelried, G. Stucky, *Helv. Chim. Acta* **1987**, *70*, 448−464; D. Seebach, R. Imwinkelried, G. Stucky, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 178−180; *Angew. Chem.* **1986**, *98*, 182−184.

[11] D. A. Evans, J. V. Nelson, T. R. Taber, *Top. Stereochem.* **1982**, *13*, 1−115; T. Mukaiyama, *Org. React.* **1982**, *28*, 203−331; C. H. Heathcock, in *Asymmetric Synthesis* (Ed.: J. D. Morrison), Academic Press, New York, **1984**; Vol. 3, Chapter 2, pp 111−212.

[12] J.-M. Lapierre, M. Gautschi, G. Greiveldinger, D. Seebach, *Chem. Ber.* **1993**, *126*, 2739−2746.

Received February 7, 2000
[O00049]