1,3,5-benzene tricarbonitrile, from which dark green single crystals with a metallic luster can be grown.[11]

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[1] a) O. Claesson, A. Lund, T. Gillbro, T. Ichikawa, O. Edlund, H. Yoshida, *J. Chem. Phys.* **1980**, *72*, 1463, and references therein; b) E. Heilbronner, H. Bock, The HMO Model and Its Appplication, Wiley, Chichester, **1979**; c) J. H. Davis, W. A. Goddard III, *J. Am. Chem. Soc.* **1977**, *99*, 4242, and references therein; d) Cf. also R. Zahradnik, J. Fabian, *Angew. Chem.* **1989**, *101*, 693–710; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 677–694.

[2] a) Cf. for example, H. Kurreck, B. Kirste, W. Lubitz, *Electron Nuclear Double Resonance Spectroscopy of Radicals in Solution*, VCH Publishers, New York, **1988**, pp. 253–277; b) N. C. Yang, A. J. Castro, *J. Am. Chem. Soc.* **1960**, *82*, 6208; cf. also D. Kearns, S. Ehrenson, *ibid.* **1962**, *84*, 739; c) ESR/ENDOR: H. van Willingen, B. Kirste, H. Kurreck, M. Plato, *Tetrahedron* **1982**, *38*, 759, and references therein; cf. also [2a] and K. Mukai, K. Ishizu, M. Nakahara, Y. Deguchi, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3363; d) W. Harrer, H. Kurreck, J. Reusch, W. Gierke, *Tetrahedron* **1975**, *31*, 625.

[3] Cf., for example, a) L. Y. Chiang, R. B. Upasani, H. S. Shen, S. P. Goshorn, C. H. Lee, *J. Chem. Soc. Chem. Commun.* **1992**, 959; b) J. R. Morton, K. F. Preston, Y. Le Page, A. J. Williams, M. D. Ward, *J. Chem. Phys.* **1990**, *93*, 2222.

[4] A CAS-on-line search with the key-words "bi/diradical" and "crystal structure" produced 32 citations, but none for a biradical in its triplet ground state. Examples of more recent crystal structures of diradicals with $S = 0$ (and a potentially temperature-dependent admixture of $S = 1$) are eightfold *tert*-butyl-substituted 2,5-dihydro-2,5-di(4-oxocyclohexadienylidene)-3,6-di(4-hydroxyphenyl)-thieno[3,2-*b*]thiophene (T. Sugimoto, M. Sakaguchi, H. Ando, T. Tanaka, Z. Yoshida, J. Yamauchi, Y. Kai, N. Kanehisa, N. Kasai, *J. Am. Chem. Soc.* **1992**, *114*, 1893), bis(1,3,2,4,6-thiaphosphatriazinyl)-1,4-phenylene (K. Bestari, G. Fergison, J. F. Gallagher, R. T. Oakley, *Inorg. Chem.* **1992**, *31*, 442; cf. also *J. Am. Chem. Soc.* **1992**, *114*, 1729). For Chichibabin and Thiele's biradicals a singlet ground state has also been proven (L. K. Montgomery, J. C. Huffmann, E. A. Jurczak, M. P. Grendze, *J. Am. Chem. Soc.* **1986**, *108*, 6004). For the complex $[Fe^{2\oplus}(mesitylene)_2][C_3(C(CN)_2)_3^{\ominus}]_2$ containing two hexacyanotriradialene anions, a triplet ground state has been detected by solid-state ESR spectra [3b].

[5] a) Preparation of **1** (according to [2d]) proceeded by reaction of the trimethylsilyl-blocked 2,6-di-*tert*-butyl-4-bromophenol with *n*-butyllithium and diethyl carbonate in *n*-hexane with addition of tetramethylethylenediamine TMEDA, followed by hydrolysis with aqueous HCl in methanol, and oxidation of the isolated bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3,5-di-*tert*-butyl)-4-oxophenylenemethane with $K_3[Fe(CN)_6]$ in a degassed water/benzene mixture. The organic phase yields a violet powder on removal of benzene. Crystal growth is achieved by slow evaporation of the green *n*-hexane solution and yields dark violet rhombusses after 2 days. At room temperature, the ESR data for the compound dissolved in toluene $g = 2.0046$ and $a_H = 0.087$ mT for the septet of the six *ortho*-ring-hydrogens; the signal intensities provide no evidence for an additional quintet expected when a monoradical impurity is present. b) Crystal structure analysis ($C_{43}H_{60}O_3 \cdot C_6H_{14}$). $M_r = 711.13\ g\,mol^{-1}$, $a = 1150.4(5)$, $b = 1770.0(9)$, $c = 2253.0(2)$ pm, $\beta = 100.62(2)^\circ$, $V = 4509(5) \times 10^6\ pm^3$ (298 K), $Z = 4$, $\rho_{calcd} = 1.047\ g\,cm^{-3}$, $\mu(Cu_{K\alpha}) = 9.4\ cm^{-1}$, monoclinic, space group $C2/c$ (no. 15 Int. Tab.). Enraf-Nonius CAD4 diffractometer, 7055 reflections within $2^\circ < 2\theta < 120^\circ$, of which 3266 are independent with $I > 0$. Structure solution with direct methods (SHELXS). $N = 3266$, $N_P = 243$, $R = 0.059$, $R_w = 0.056$, $w = 1$. The crystal proved to be partially twinned; only reflections of the main domain, which amounts to 88% of the crystal volume, have been recorded. C,O positions anisotropically refined, H positions of the biradical are detected by difference Fourier analysis and are kept on calculated positions; residual electron density $< 0.26\ e_0 Å^{-3}$. The crystal packing does not show any short intermolecular contact distances; in the biradical crystal interstices *n*-hexane molecules are found disordered along a twofold axis. Further details of the crystal structure analysis can be obtained from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, W-7514 Eggenstein-Leopoldshafen 2, on quoting the deposition number CSD-56 969, the authors, and the full journal citation.

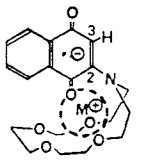
[6] Cf. H. Bock, K. Ruppert, C. Näther, Z. Havlas, H.-F. Herrmann, C. Arad, I. Göbel, A. John, J. Meuret, S. Nick, A. Rauschenbach, W. Seitz, T. Vaupel, B. Solouki, *Angew. Chem.* **1992**, *104*, 564; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 560, and references therein.

[7] a) The calculations have been performed with the program SCAMP 4.1 (T. Clark, University Erlangen) on an IBM RISC 6000 workstation. For the triplet biradical a CI wave function (6×6, 225 configurations) has been applied. The matrix elements $P_{\mu\mu} = \sum_K a_K^2 P_{\mu\mu}^K$ of the configurations K yield for the individual centers X, according to $P_{XX}^{spin} = \sum_\mu P_{\mu\mu}^{spin}$, the spin populations, and according to $P_{XX} = \sum_\mu^X P_{\mu\mu} - Z_X$, the charge orders. In addition, all structures have been geometry-optimized. b) Triplet ground state (D_3): $\Delta H_f^{AM1/CI} = 42\ kJ\,mol^{-1}$, $d_{C\cdots C} = 143$ pm, $\omega = 29^\circ$, rings: $d_{CC} = 145, 137, 150$ pm, $\sphericalangle$ CCC = 117, 124, 120, 118°, eigenvalue $\varepsilon_j(e'') = -5.56$ eV. First excited singlet state (C_2!): $\Delta H_f^{AM1/CI} = 78\ kJ\,mol^{-1}$, $d_{C\cdots C} = 147, 147, 136$ pm, $\omega = 30, 30, 90^\circ$, eigenvalues $\varepsilon_j = -5.40, -5.68$ eV. c) Closed shell singlet state (C_2): $\Delta H_f^{AM1} = 144\ kJ\,mol^{-1}$, $d_{C\cdots C} = 146, 146, 134$ pm, $\omega = 30, 30, 90^\circ$, eigenvalues -2.94 eV (unoccupied), -7.89 eV (doubly occupied).

[8] D. E. Williams, *Mol. Phys.* **1969**, *16*, 145.

[9] Cf., for example, W. Kutzelnigg, *Einführung in die Theoretische Chemie*, Vol. 1 and 2, Verlag Chemie, Weinheim, **1975** and **1978**, respectively.

[10] The dependency between spin and charge distribution, which is often complex, can be illustrated by selection the contact ion pairs of the [15]crown-5-2-aminonaphthosemiquinone radical anion (**2**), which also contains a quinoid six-membered ring as in the title compound (Fig. 1). Alkali



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metal counter cations $M^\oplus$ polarize the crown-side carbonyl group $>C^{\delta\oplus}O^{\delta\ominus}\cdots M^\oplus$ differently on account of their different effective ionic charges. Therefore, at the carbonyl oxygen negative partial charges result, which increase when the cation changes from $Cs^\oplus$ to $Li^\oplus$. The ring proton couplings $a_{H,3}$ determined by ENDOR-spectroscopy confirm that the spin density in the quinone six-membered ring increases with the negative partial charge at the oxygen centre (Scheme 2) and that its spin component therefore decreases (H. Bock, B. Hierholzer, F. Vögtle, G. Hollmann, *Angew. Chem.* **1984**, *96*, 74; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 57).

[11] J. Bretschneider, K. Wallenfels, *Tetrahedron* **1968**, *24*, 1063.

Enantioselective Synthesis of α-Amino Acetals and α-Amino Acids by Nucleophilic 1,2-Addition to Diethoxyacetaldehyde SAMP Hydrazone**

By *Dieter Enders,* Rudolf Funk, Martin Klatt, Gerhard Raabe*, and *Eric R. Hovestreydt*

Dedicated to Professor Joachim Goerdeler on the occasion of his 80th birthday

Protected, enantiomerically pure α-aminoaldehydes are of great interest as chiral synthetic building blocks because they are bifunctional, and this results in a wide range of application.[1] Although the synthesis and applications of N-protected α-aminoaldehydes are well known, the analogous carbonyl-protected compounds have attracted little attention.[2–6] The standard syntheses of carbonyl- and N-protected α-aminoaldehydes generally start from the naturally occurring α-amino acids. Asymmetric synthesis of carbonyl-protected α-aminoaldehydes has only recently become known.[7–9] One of the methods most frequently employed in this respect for the generation of the amino group is the addition of organometallic compounds to the CN double bond[10] of imines,[11] acylimines,[12] nitrones,[13] sulfen-

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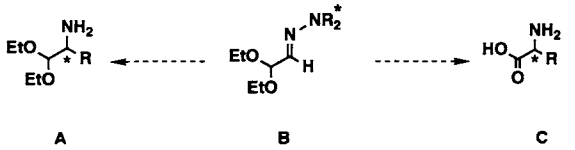
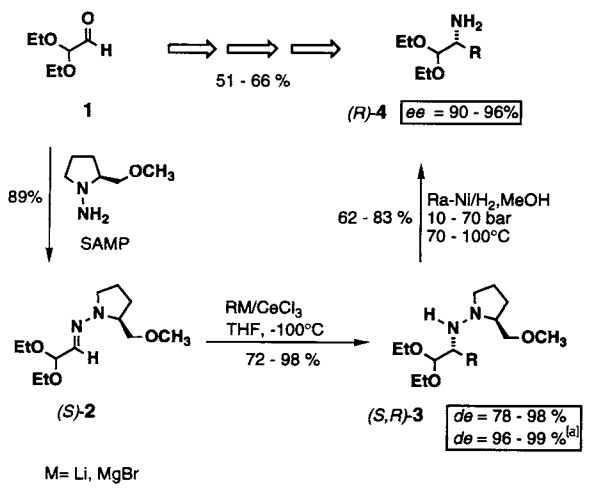
imines,[14] sulfonylimines,[15] sulfoxyimines,[16] oxime ethers,[17] and hydrazones.[8, 9, 18–21] Organolanthanoid compounds are used with increasing frequency for this purpose.[22]

We report here an enantioselective synthesis of α-amino acetals **A** starting from α-SAMP or -RAMP hydrazone acetals **B**. The key step is the diastereoselective nucleophilic 1,2-addition of organocerium and organolithium compounds to the hydrazone double bond. Oxidative transformation of the acetal into an acid group thereby provides a new, highly enantioselective entry to α-amino acids **C**.



The reaction of diethoxyacetaldehyde **1**[23] with SAMP[24] gave the SAMP hydrazone (*S*)-**2** in very good yield. The latter was treated at −100 °C with organocerium or lithium compounds in THF. The organocerium compounds were obtained according to a procedure of Imamoto et al.,[25] in which anhydrous $CeCl_3$ is treated in THF with the appropriate organolithium or Grignard reagent. The 1,2-additions, which occurred in very good yields (72–98%) and with very high diastereomeric excess (78–98%), provided the sensitive hydrazines (*S*,*R*)-**3** after aqueous workup. After chromatographic separation of the minor diastereomers, the almost diastereomerically pure hydrazines (*S*,*R*)-**3** were converted to the α-amino acetals (*R*)-**4** by reductive cleavage with Raney nickel/hydrogen in methanol. The chiral amine (*S*)-**2**-methoxymethylpyrrolidine (SMP, recovery of the auxiliary) was separated by chromatography, and after subsequent distillation (kugelrohr) the pure, colorless α-amino acetals (*R*)-**4** were obtained (Scheme 1, Table 1).



Scheme 1. Enantioselective synthesis of α-amino acetals **4**. $RM/CeCl_3$ was employed in excess (5 equiv). [a] After chromatography.

Table 1. SAMP α-amino acetals **3** (prepared by nucleophilic 1,2-addition to diethoxyacetaldehyde SAMP hydrazone) and their cleavage to **4**.

	R	$M/CeCl_3$	Yield of **3** [a] [%]	*de* [b] [%]	Yield of **4** [%]	$[\alpha]_D^{RT}$ **4** (*c*, EtOH)	*ee* [c] [%]
a	Me	Li	91	98	78	−18.9° (1.2) [d]	96.7 (*R*)
a [e]	Me	Li	92	97.5	62	+16.4° (1.0) [d]	95.3 (*S*)
b	Et [f]	MgBr	98	100 (94)	83	+1.4° (1.0)	94.0 (*R*)
c	*n*Pr [f]	MgBr	92	100 (86)	75	+8.8° (0.9)	90.0 (*R*)
d	*i*Pr	MgBr	89	100 (95)	80	−8.3° (1.2)	94.0 (*R*)
e	*n*Bu	Li	92	100 (95)	62	+8.3° (1.1)	91.0 (*R*)
f	*t*Bu	Li [g]	89	100 (78)	72	−26.0° (1.1)	94.0 (*R*)
g	Ph	MgBr	72	>96	80 [h]	+3.3° (neat)	96.0 (*R*)

[a] Yields of the major diastereomers (*R*,*S*)-**3a–h**. [b] Determined by gas chromatography (GC) (OV-1-CB, FID). The *de* values of the crude hydrazines before chromatographic purification are in parentheses. [c] Determined by ^{19}F NMR or GC analysis of the MTPA amide. The absolute configurations are in parentheses. [d] The solvent used was 0.1 N HCl. [e] RAMP was employed as chiral auxiliary. [f] Yields of both diastereomers. [g] Without addition of $CeCl_3$. [h] R = *cyclo*-C_6H_{11}.

contrast to many of the corresponding N-protected compounds, are completely configurationally stable. Even after several weeks at room temperature no loss in optical activity could be observed. The enantiomeric excess for the amino acetals (*R*)-**4** was determined in all cases by comparison with the racemates via the 3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid (MTPA) amides[26] by gas chromatography or NMR spectroscopy. The racemates were synthesized in similar fashion via the corresponding dimethylhydrazones. The absolute configuration of the α-amino acetals (*R*)-**4** could be determined by two independent methods: The optical rotation was compared with that of the known compound (*S*)-**4a**,[3] and an X-ray crystal structure analysis of the (*S*)-MTPA derivative of the compound (*R*)-**4g** gave the (*R*) configuration for the newly generated stereogenic center (Fig. 1).[27, 28] The enantiomers (*S*)-**4** are accessible by simply changing the auxiliary (RAMP instead of SAMP) (see (*S*)-**4a**, Table 1).

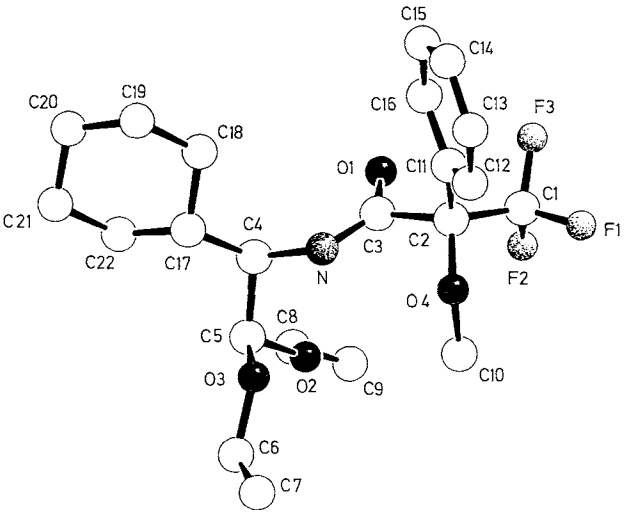
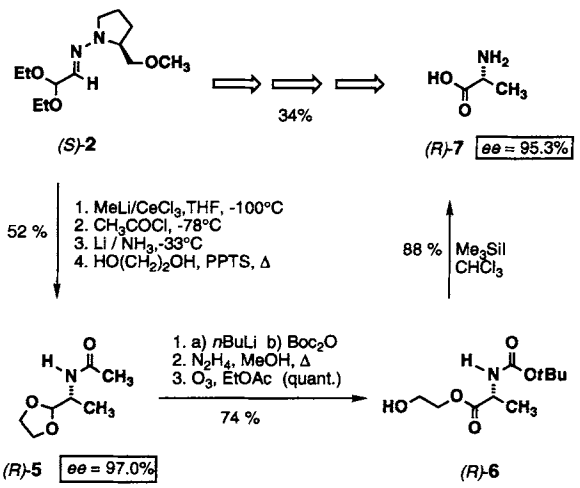


Fig. 1. Crystal structure of the MTPA amide of **4g**[7,28].

Cleavage of the N–N bond in hydrazines (*S*,*R*)-**3** by hydrogenolysis occurred with little racemization, so that the enantiomeric excess lies slightly below that of the diastereomeric excess. During hydrogenolysis of (*R*)-**3g** the phenyl ring was also hydrogenated. The α-amino acetals, in

As demonstrated in Scheme 2 for the example of the enantioselective synthesis of (*R*)-alanine (*R*)-**7**, diethoxyacetaldehyde SAMP hydrazone (*S*)-**2** can also function as an equivalent for the glycine cation, thereby permitting a new entry to α-amino acids. The key to success lies in the use of ozono-

lysis for the cleavage of the cyclic acetal with the 1,3-dioxolane structure to the hydroxyethylester, according to the method of Deslongchamps et al.[29] After addition of the organocerium compound from MeLi/$CeCl_3$ to (*S*)-**2** and trapping with acetylchloride, the N–N bond was cleaved reductively without racemization by reaction with Li/NH_3.[30] Finally, the *N*-acetyl-protected α-amino acetal was converted into the cyclic acetal (*R*)-**5** (*ee* = 97.0%) with ethylene glycol in a yield of 83%. After introduction of the *tert*-butoxycarbonyl (Boc) protecting group with $(Boc)_2O$ and hydrazinolysis, the carbamate-protected α-amino acetal was obtained. Ozonolysis, requiring only a few minutes at −78°C, gave the α-amino acid ester (*R*)-**6** quantitatively. The protecting group was removed by treatment with three equivalents of trimethylsilyliodide and the ester group hydrolyzed simultaneously. The amino acid, after purification by ion-exchange chromatography (Lewatit SP 112), was obtained in an overall yield of 34% and an enantiomeric excess of 95.3%.[31]



Scheme 2. Enantioselective synthesis of (*R*)-alanine. PPTS = pyridinium *para*-toluenesulfonate. Me_3SiI was used in excess (3 equiv).

The methods described here provide a new, highly enantioselective entry to both enantiomers of α-amino acetals and α-amino acids. Initial results show that the process is also applicable for homologous β-SAMP hydrazone acetals, thereby leading to the corresponding β-amino acetals and β-amino acids.[32]

Experimental Procedure

α-Amino acetals **4**: 5 Equiv $CeCl_3 \cdot 7H_2O$ was dried in a Schlenk flask with stirring for 2 h at 140 °C/0.1 Torr. After cooling, the anhydrous $CeCl_3$ was stirred at room temperature under argon with dry THF (3 mL mmol^{-1} $CeCl_3$) for 2 h and then for 1 h in an ultrasound bath. The colorless suspension was cooled to −78 °C and treated dropwise with 5 equiv RLi or RMgX. Upon addition of RLi a bright yellow suspension was obtained, whereas addition of RMgX caused the color to change to light gray. After the resulting suspension was stirred for 2 h at −78 °C, the reaction mixture was cooled to −100 °C (ethanol/liquid nitrogen). The SAMP hydrazone (*S*)-**2**, dissolved in THF (3 mL mmol^{-1}), was added to the suspension very slowly (10 mL h^{-1}; syringe pump). The reaction mixture was first held at −100 °C for 2 h and then allowed to warm to room temperature over ca. 15 h. The mixture was hydrolyzed with ca. 40 mL saturated $NaHCO_3$ solution, the organic phase separated, and the residue extracted several times with ether. The combined organic phases were concentrated, dissolved in 50 mL ether, washed with water, and finally dried over Na_2SO_4. After concentration, the sensitive hydrazines (*R*)-**3** were purified by flash chromatography (silica gel, ether:petroleum ether 2:1 to 1:3). A solution of the hydrazine in methanol (5–10 mL mmol^{-1}) was treated with freshly prepared Raney nickel[33] (0.5–1.0 g Ni-Al alloy per mmol of hydrazine) and hydrogenated in an autoclave with stirring at 70–100 °C and a hydrogen pressure of 70 bar for 20–60 h (monitored by thin-layer chromatography). After completion of the reaction, the catalyst was removed by filtration through celite, the solvent removed from the filtrate, the residue dissolved in ether, and the resulting ethereal solution dried over Na_2SO_4 and concentrated to dryness. The α-amino acetals were purified by flash chromatography (silica gel, anhydrous methanol) followed by removal of the methanol and distillation (kugelrohr).

α-Amino acids **7**: The product resulting from nucleophilic 1,2-addition to the SAMP hydrazone (*S*)-**2** (see above) was trapped at −78 °C with 5.5 equiv acetyl chloride and then stirred for 1 h at 0 °C. The product was worked up with 40 mL saturated Na_2CO_3 solution and ether. The hydrazines were purified by flash chromatography (silica gel, ether:petroleum ether 2:1). A solution of the *N*-acylated hydrazine in anhydrous THF (1 mL mmol^{-1}) was mixed with ammonia (15 mL mmol^{-1}) at −78 °C, and the mixture treated with clean Li wire (4 mmol mmol^{-1}). The resulting solution rapidly turned blue. The cooling bath was removed, the solution allowed to stir for 1 h at −33 °C, the reaction stopped by addition of NH_4Cl (12 mmol mmol^{-1}), and the ammonia allowed to evaporate. The residue was dissolved in 40 mL water and extracted several times with ether. After the combined organic phases were dried and concentrated, the *N*-acetylated α-amino acetals were obtained. These were dissolved in glycol (3 mL mmol^{-1}), treated with 0.1 g pyridinium *p*-toluenesulfonate (PPTS), and stirred for 3 h at 80 °C. After distillation of the volatile components, the whole was taken up in 40 mL water and extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated, and the α-amino acetals (*R*)-**5** were purified by flash chromatography (silica gel, ethyl acetate). A solution of (*R*)-**5** in anhydrous THF (5 mL mmol^{-1}) was treated with 1.1 equiv *n*BuLi at −78 °C, stirred for 4 h at this temperature, and then trapped with $(Boc)_2O$ (5 mmol mmol^{-1}). The crude solution was concentrated and the residue taken up in methanol (5 mL mmol^{-1}), treated with anhydrous hydrazine (3 mL mmol^{-1}), and stirred for 4 h at reflux. After aqueous workup and extraction with ether the α-amino acetals, protected as carbamates, were obtained. Purification was by flash chromatography (silica gel, ether:petroleum ether 2:1). The acetals were dissolved in ethyl acetate (15 mL mmol^{-1}) and treated with ozone at −78 °C (reaction followed by thin-layer chromatography). The solvent was removed to provide the pure ester (*R*)-**6**, which was allowed to react with 3 equiv Me_3SiI in $CHCl_3$ (5 mL mmol^{-1}) under argon (3–5 min). Workup was with 1 N HCl, and the amino acids were purified by ion-exchange chromatography (Lewatit SP 112, 2 N aqueous NH_3 solution).

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[1] a) M. T. Reetz, *Angew. Chem.* **1991**, *103*, 1559; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531; b) J. Jurczak, A. Golebiowski, *Chem. Rev.* **1989**, 149; c) L. E. Fisher, J. M. Muchowski, *Org. Prep. Preoced. Int.* **1990**, *22*, 399.
[2] a) E. Fischer, T. Kametaka, *Justus Liebigs Ann. Chem.* **1909**, *365*, 7; b) E. Fischer, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 1019.
[3] a) K. Balenovic, N. Bregant, D. Cerar, D. Fles, J. Jambresic, *J. Org. Chem.* **1953**, *18*, 297; b) K. Balenovic, N. Bregant, T. Galijan, Z. Stefanac, V. Skaric, *ibid.*, **1956**, *21*, 115.
[4] M. Gacek, K. Undheim, *Tetrahedron* **1974**, *30*, 4233.
[5] a) S. Kano, T. Yokomatsu, H. Iwasawa, S. Shibuya, *Heterocycles* **1987**, *26*, 2805; b) S. Kano, T. Yokomatsu, H. Iwasawa, S. Shibuya, *Chem. Lett.* **1987**, 1531.
[6] G. Bringmann in *The Alkaloids, Vol. 29* (Ed.: A. Brossi), Academic Press, New York, **1987**, p. 141.
[7] G. Bringmann, J. P. Geisler, *Synthesis* **1989**, 608.
[8] M. Thiam, F. Chastrette, *Tetrahedron Lett.* **1990**, *31*, 1429.
[9] A. Alexakis, N. Lensen, P. Mangeney, *Tetrahedron Lett.* **1991**, *32*, 1171.
[10] K. Harada in *The Chemistry of the Carbon Nitrogen Double-Bond* (Ed.: S. Patai), Interscience, London, **1970**.
[11] Reviews: a) D. J. Hart, D.-C. Ha, *Chem. Rev.* **1989**, *89*, 1447; b) M.-J. Brown, *Heterocycles* **1989**, *29*, 2225; c) Y. Yamamoto, *Acc. Chem. Res.* **1987**, 243. Recent examples: d) S. Laschat, H. Kunz, *Synlett* **1990**, 51; e) M. T. Reetz, R. Jaeger, R. Drewlies, M. Hübel, *Angew. Chem.* **1991**, *103*, 76; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 103; f) K. Tomioka, I. Inoue, M. Shindo, K. Koga, *Tetrahedron Lett.* **1991**, *32*, 3095; g) Y. Ukaji, J. Watai, T. Sumi, T. Fujisawa, *Chem. Lett.* **1991**, 1555; h) G. Cainelli, D. Giacomini, E. Mezzina, M. Pannuzio, P. Zarantonello, *Tetrahedron Lett.* **1991**, *32*, 2967; i) R. Annunziata, M. Cinquini, F. Cozzi, P. G. Cozzi, *ibid.*, **1992**, *33*, 1113.
[12] a) P. Münster, W. Steglich, *Synthesis* **1987**, 223; b) R. Kobes, K. Papadopoulos, W. Miltz, D. Enders, W. Steglich, H. Reuter, H. Puff, *Tetrahedron* **1985**, 1693; c) P. Ermert, I. Meyer, C. Stucki, J. Schneebeli, J. P. Obrecht, *Tetrahedron Lett.* **1988**, *29*, 1265.
[13] a) Z.-Y. Chang, R. M. Coates, *J. Org. Chem.* **1990**, *55*, 3475; b) M. A. Schwartz, X. Hu, *Tetrahedron Lett.* **1992**, *33*, 1689.
[14] C. Fuganti, P. Grasselli, G. Pedrocchi-Fantoni, *J. Org. Chem.* **1983**, *48*, 909.
[15] a) F. A. Davis, M. A. Giangiordano, W. E. Starner, *Tetrahedron Lett.* **1986**, *27*, 3957; b) J. Siske, S. M. Weinreb, *J. Org. Chem.* **1990**, *55*, 393.
[16] D. H. Hua, S. W. Miao, J. S. Chen, S. Iguchi, *J. Org. Chem.* **1991**, *56*, 4.

[17] H. Fujioka, M. Fuji, Y. Okaichi, T. Yoshida, H. Annoura, Y. Kita, Y. Tamura, *Chem. Pharm. Bull.* **1989**, *37*, 602.
[18] H. Takahashi, H. Inagaki, *Chem. Pharm. Bull.* **1983**, *31*, 4295, and references therein.
[19] D. A. Claremon, P. K. Lumma, B. T. Phillips, *J. Am. Chem. Soc.* **1986**, *108*, 8265.
[20] a) D. Enders, H. Schubert, C. Nübling, *Angew. Chem.* **1986**, *98*, 1118; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1109; b) D. Enders, D. Bartzen, *Liebigs Ann. Chem.* **1991**, 569.
[21] a) S. E. Denmark, T. Weber, D. W. Piotrowski, *J. Am. Chem. Soc.* **1987**, *109*, 2224; b) S. E. Denmark, T. Weber, J. P. Edwards, *Synlett*, **1989**, *1*, 20.
[22] G. A. Molander, *Chem. Rev.* **1992**, 29.
[23] H. Stetter, K. H. Mohrmann, *Synthesis* **1981**, 129.
[24] a) D. Enders in *Asymmetric Synthesis, Vol. 3*, (Ed.: J. D. Morrison), Academic Press, Orlando, FL, USA **1984**, p. 275; b) D. Enders, P. Fey, H. Kipphardt, *Org. Synth.* **1987**, *65*, 173, 183; b) D. Enders, P. Fey, H. Kipphardt, *Org. Prep. Proced. Int.* **1985**, *17*, 1.
[25] a) T. Imamoto, N. Takiyama, K. Nakamura, *Tetrahedron Lett.* **1985**, *26*, 4763; b) T. Imamoto, Y. Sugiura, *J. Organomet. Chem.* **1985**, *C21*, 285; c) T. Imamoto, Y. Sugiura, N. Takiyama, *Tetrahedron Lett.* **1984**, *25*, 4233; d) T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka, M. Yokoyama, *J. Org. Chem.* **1984**, *49*, 3904.
[26] J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512.
[27] Suitable crystals were obtained from EtOAc/cyclohexane (2:1) at $-20\,^{\circ}C$. Monoclinic, space group $P2_1(4)$, $a = 10.758(5)$, $b = 10.336(4)$, $c = 11.720(6)$ Å, $\beta = 113.73(4)^{\circ}$. The cell volume is 1193.0(9) Å^3, $Z = 2$ and $M_r = 431.5$, leading to a density $\varrho_{calc} = 1.201\ g\,cm^{-3}$. The total number of electrons per unit cell $F(000) = 460$, $Mo_{K\alpha}$ irradiation ($I = 0.71069$ Å, graphite monochromator), $m = 0.91\ cm^{-1}$. Siemens R3m/V four-circle diffractometer, 2 θ-θ scans, 23 °C. A total of 2241 independent reflections ($+h + k \pm l$) were recorded, of which 1074 were observed ($I > 2\sigma(I)$), $R_m = 0.07$, $\sin\theta/\lambda_{max} = 0.597$. The structure solution was obtained using direct methods (Siemens SHELXTL PLUS) and the refinement using the XTAL3.0 program[28]. Positions of hydrogen atoms were calculated. A total of 270 parameter refinements were used, $R = 0.073$ ($R_w = 0.029$), residual electron density 0.5 e Å^{-3}. Further details of the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information GmbH, D-W-7514 Eggenstein-Leopoldshafen 2 (FRG) on quoting the depository number CSD-56669, the names of the authors, and the journal citation.
[28] *XTAL3.0 User's Manual* (Eds.: S. R. Hall, J. M. Stewart), Universities of Western Australia und Maryland, **1990**.
[29] P. Deslongchamps, P. Atlani, D. Frehel, A. Malaval, C. Moreau, *Can. J. Chem.* **1974**, *52*, 3651.
[30] a) C. Nübling, *Dissertation*, Technische Hochschule Aachen, **1987**; b) S. E. Denmark, O. Nicaise, J. P. Edwards, *J. Org. Chem.* **1990**, *55*, 6219.
[31] All new compounds gave correct elemental analysis and NMR, IR, and mass spectra.
[32] D. Enders, M. Klatt, R. Funk, unpublished.
[33] *Organikum*, 16th ed., VEB Deutscher Verlag der Wissenschaften, Berlin, **1986**.

Enantioselective Aldol Reactions with a Phosphoenolpyruvate Equivalent: Asymmetric Synthesis of 4-Hydroxy-2-oxocarboxylic Acid Esters**

By *Dieter Enders*,* *Hubert Dyker*, and *Gerhard Raabe*

Dedicated to Professor Rudolf Hoppe on the occasion of his 70th birthday

The aldol reaction is the preferred method for the stereoselective synthesis of 1,3-dioxygenated building blocks.[1] Enantiofacial differentiation in the enolates can be diastereoselectively controlled by covalently bound auxiliaries, which permit formation of one or two stereogenic centers with high selectivity and predictable configuration.

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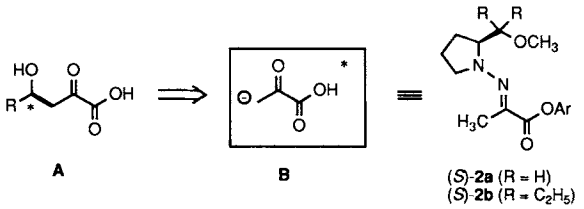
Enzyme-catalyzed aldol reactions are used in nature, for example, in the stereoselective formation of monosaccharides. The transfer of the pyruvate unit as phosphoenolpyruvate (PEP) to aldoses with the generation of 4-hydroxy-2-oxocarboxylic acids **A** in the biosynthesis of ulosonic acids[2] and sialic acids[3] is one of the most important synthetic routes of this type. Aldolases, which catalyze this reaction, have recently been used in the biocatalytic synthesis of natural and unnatural higher monosaccharides from PEP or pyruvate and aldehydes.[4-8]

Several achiral metalated pyruvic derivatives (d^2 synthons **B**) have been used as chemical equivalents for PEP in imitation of the synthetic principle used in nature.[9] Stereoselective reactions of these reagents are nevertheless limited to diastereoselective aldol reactions with enantiomerically pure aldehydes.[9g-9i]



We recently reported on the development of an enantiomerically pure, homologous PEP equivalent[10] in which our SAMP/RAMP hydrazone method[11,12] was employed and on its use in the enantioselective synthesis of 3-substituted 2-oxacarboxylic acid esters. We now introduce an enantiomerically pure, chemical PEP equivalent, which permits the biomimetic enantioselective synthesis of 4-hydroxy-2-oxocarboxylic acid esters **A**. The key step is the diastereoselective aldol reaction of (*S*)-**2** with achiral and chiral aldehydes.

In initial investigations of the metalation and alkylation conditions, simple alkylation of SAMP hydrazone (*S*)-**2a** was examined. The uniformly (*E*) hydrazone was obtained in 96% yield as light yellow solid (m.p. 84 °C) by reaction of the appropriate pyruvic acid ester **1**[10] with (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP).[12,13] Employing the 2,6-di-*tert*-butyl-4-methoxyphenyl ester[14] to avoid the self-condensation of the corresponding azaenolate is decisive.[10]

Surprisingly, the alkylation of hydrazone (*S*)-**2a** with benzylbromide by metalation with 1.1 equivalents of lithium diisopropylamide (LDA) was incomplete. The alkylated product was isolated in 71% yield, together with 21% unreacted starting material. The use of 2.2 equivalents of LDA gave both the monoalkylated and the bisalkylated products in variable yield. Complete conversion in the alkylation (98% yield) was achieved only when 1.1 equivalents of base were employed in the presence of 2 equivalents of lithium bromide at $-78\,^{\circ}C$ in THF. Similar effects have been described for related systems.[9j,15] The aldol reaction of the SAMP hydrazone (*S*)-**2a** metalated in this manner with 3-methylbutanal at $-90\,^{\circ}C$ gave the aldol product (*S,R*)-**3a** in similar good yield, albeit with only moderate stereoselectivity (84 °% yield, *de* = 36 °%). The stereoselectivity of the aldol reaction could be increased considerably when SAMP was exchanged for the sterically more demanding auxiliary (*S*)-1-amino-2-(1-ethyl-1-methoxypropyl)pyrrolidine (SAEP)[16] (Scheme 1, Table 1).

The condensation of pyruvic acid ester **1** with the hydrazine SAEP gave the (*E*)-configurated hydrazone (*S*)-**2b**