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Stereoselective synthesis of 3-amino-4,5-dihydroxyaldehydes—a novel preparation of *N*-acetyl-L-daunosamine[1]

Franz Effenberger* and Jürgen Roos†

Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

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Abstract

A general route for the stereoselective synthesis of 3-amino-4,5-dihydroxyaldehydes, with almost any desired configuration at the three stereogenic centers, is described by applying a combination of enzymatic and chemical steps. L-Daunosamine **1**, for example, the glycosidic fragment of many important anthracycline antibiotics has been prepared by this route starting from *O*-allyl-L-lactaldehyde (*S*)-**6a**. (*R*)-Hydroxynitrile lyase (HNL) catalyzed addition of HCN to (*S*)-**6a** yields the 2,3-dihydroxynitrile (2*S*,3*S*)-**7a** with high stereoselectivity (91% *de*) in 75% yield. The addition of allyl Grignard to the *O*-protected 2,3-dihydroxynitrile (2*S*,3*S*)-**9a** and subsequent hydrogenation of the imino intermediate leads to 4-amino-2,3-dihydroxy-1-heptene (4*S*,5*S*,6*S*)-**12a**, which after ozonization and deprotection gives *N*-acetylated L-daunosamine **14a** in a total yield of 15% referring to (*S*)-**6a**. The general applicability of this chemoenzymatic multistep procedure is demonstrated in the stereoselective synthesis of the unnatural aminodeoxy sugar (2*S*,3*S*,4*S*)-**14b**, starting from isovaleraldehyde **3**.

1. Introduction

L-Daunosamine (**1**, 3-amino-2,3,6-trideoxy-L-*lyxo*-hexose) is the glycosidic fragment of a number of important anthracycline antibiotics such as daunomycin **2a**[2] and adriamycin **2b**[3] (Fig. 1) which exhibit impressive activity against a wide range of experimental and human tumors.[2,4]

Daunosamine was found to be essential for the activity of anthracycline antibiotics and moreover, it reduces significantly their toxicity.[5] Therefore, there has been considerable interest in the synthesis of this class of sugars in recent years.[6] Most of the syntheses of L-daunosamine have been started from carbohydrate precursors. L-Rhamnose was the most widely used starting material[6,7] because it has the requisite L-configuration and is a 6-deoxy hexose. Whereas hexoses with L-configuration are uncommon in nature, certain L-pentoses occur and can readily be homologated to 2-deoxy-L-hexoses. These possibilities have been used in total syntheses of daunosamine starting from L-arabinose.[4c,8] Among the D-hexoses frequently used as precursors,

* Corresponding author. E-mail: franz.effenberger@po.uni-stuttgart.de

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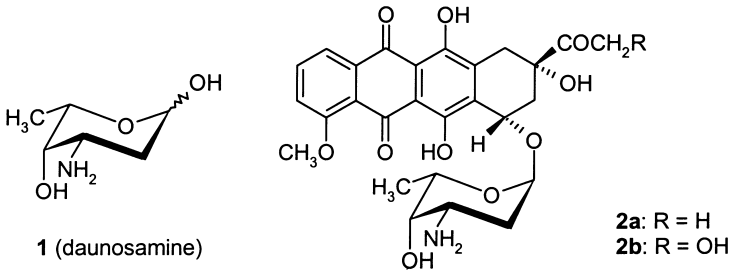
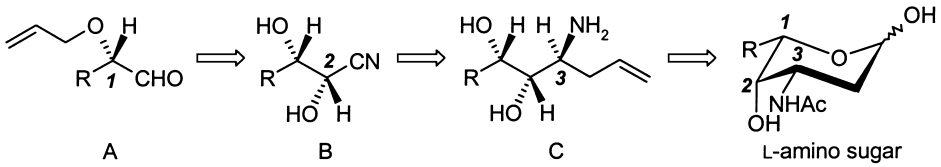


Figure 1.

which are easily available but require inversion of configuration at C-5, are methyl α-D-mannoside[4a,9] and D-glucose.[10]

Non-carbohydrate precursors such as L-tartaric acid[5c,d,11] as well as L-lactic acid and its derivatives[5b,12] have been applied as starting materials for the synthesis of daunosamine. Syntheses starting from achiral precursors, where chiral auxiliaries[13] or enzymes[4d,14] were used for introduction of the chiral centers, are also known.

In a recent publication[1] we have reported the hydroxynitrile lyase (HNL) catalyzed addition of HCN to *O*-protected α-hydroxyaldehydes A, allowing the stereoselective preparation of 2,3-dihydroxynitriles B. The diastereoselective conversion of (*R*)- and (*S*)-2-hydroxynitriles, via addition of a Grignard reagent to the cyano group and subsequent hydrogenation of the imino intermediate with sodium borohydride, to the corresponding *erythro*-1,2-amino alcohols is well known.[15] We now describe a preparation of L-daunosamine and other L-amino sugars starting from suitable aldehydes, combining the enzyme catalyzed enantioselective cyanohydrin formation and the stereoselective chemical follow-up reactions (Scheme 1).

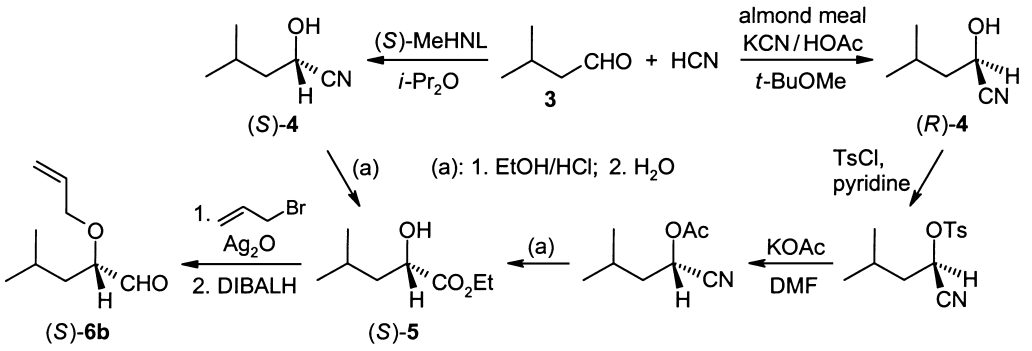


Scheme 1.

This method offers the advantage that almost any 3-amino-2,3,6-trideoxyhexose could be prepared stereoselectively referring to all stereogenic centers not only from 'chiral pool' derived precursors, but from simple aldehydes. The proposed procedure would also represent a general approach to unnatural higher homologues of 3-amino-2,3,6-trideoxyhexoses.

2. Results and discussion

Since the stereoselective synthesis of 2,3-dihydroxynitriles should be investigated not only starting from the readily accessible L-lactaldehyde,[16] we have developed two general approaches to prepare allyl-protected (*S*)-2-hydroxyaldehydes starting from aldehydes. Scheme 2 shows the two pathways exemplary for the stereoselective preparation of (*S*)-2-allyloxy-4-methylpentanal (*S*)-**6b** starting from isovaleraldehyde **3**.



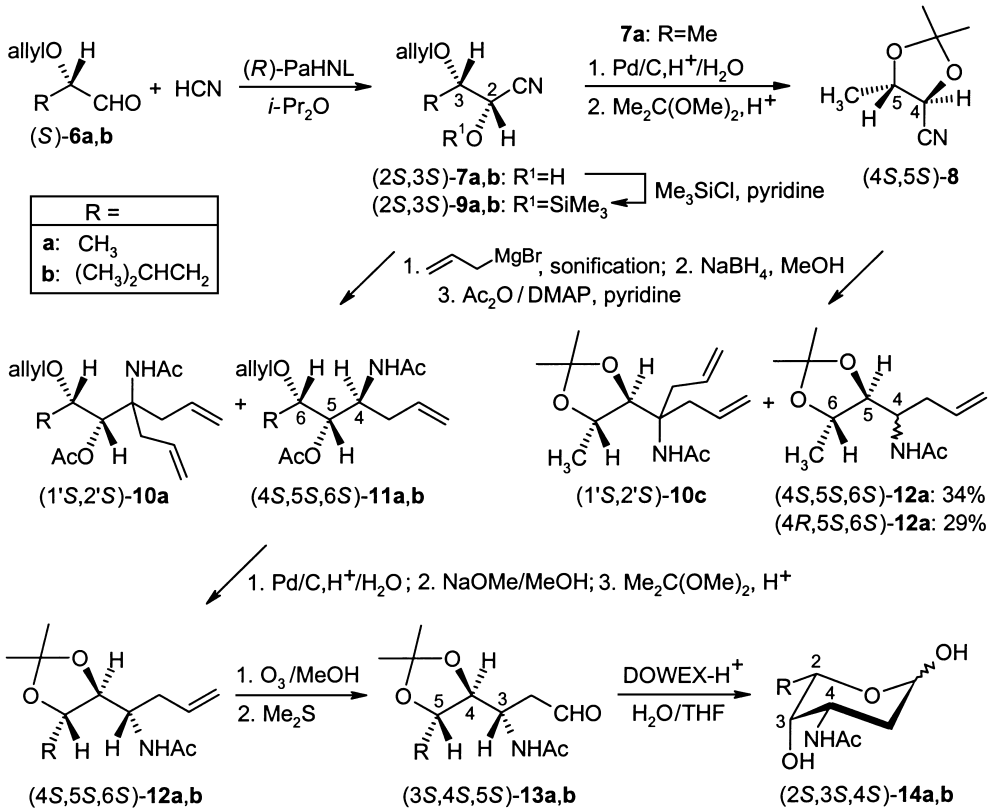
Scheme 2.

The first method involves the (*S*)-MeHNL catalyzed addition of HCN to isovaleraldehyde **3** as the key reaction.[17] The resultant (*S*)-cyanohydrin (*S*)-**4** (92% *ee*) was converted to the ethyl ester (*S*)-**5** via a Pinner reaction.[18] (*S*)-2-Allyloxy-4-methylpentanal (*S*)-**6b** was obtained in 85% yield and 92% *ee* from (*S*)-**5** by *O*-protection with allyl bromide and subsequent hydrogenation with diisobutylaluminium hydride (DIBALH). Since as an enzyme source for (*R*)-PaHNL simple almond meal can be applied, we have developed a second procedure to obtain the (*S*)-2-hydroxy ester (*S*)-**5** without using the less easily available (*S*)-MeHNL. For the (*R*)-PaHNL catalyzed enantioselective addition of HCN to aldehyde **3** defatted almond meal was used, and HCN was generated from potassium cyanide with acid.[19] Analogous to a literature procedure[20] the obtained (*R*)-cyanohydrin (*R*)-**4** (93% *ee*) was first *O*-tosylated, then reacted with potassium acetate to give the corresponding (*S*)-cyanohydrin acetate which afforded the hydroxy ester (*S*)-**5** (92% *ee*) via a Pinner reaction (Scheme 2).

The total syntheses of *N*-acetyl-L-daunosamine **14a** and the unnatural *N*-acetylated L-3-amino-deoxy sugar **14b** starting from the lactaldehyde derivative (*S*)-**6a** and aldehyde (*S*)-**6b**, respectively, are summarized in Scheme 3.

(*R*)-PaHNL catalyzes the HCN addition to (*S*)-**6a** with high stereoselectivity, giving the 2,3-dihydroxynitrile (2*S*,3*S*)-**7a** in 75% yield with 91% *de*.[1] It is also possible to start from racemic (*RS*)-**6a**, since the diastereoisomers of **7a** resulting from (*R*)-PaHNL catalyzed addition of HCN to (*RS*)-**6a** can be separated by chromatography on silica gel after removal of the allyl protecting group and subsequent isopropylidene protection. In this way, the isopropylidene-protected dihydroxynitrile (4*S*,5*S*)-**8** was isolated in 43% yield with >99% *de*.

Preliminary investigations of the reaction of silylated cyanohydrins with the Grignard reagent from 2-bromomethyl-1,3-dioxolane[21] or *Z*-2-(*tert*-butyldimethylsilyloxy)vinyl lithium[22] have shown that an addition of these organometallic compounds to a cyano group is not possible. Therefore allyl Grignard has been chosen for introducing the 'CH_2CHO' moiety. In order to perform the Grignard addition (2*S*,3*S*)-**7a** was first reacted with trimethylchlorosilane,[15a] giving the *O*-silylated (2*S*,3*S*)-**9a** in 66% yield without racemization. Although the Grignard reagent from allyl bromide is very reactive,[23] activation by sonification was necessary to react (2*S*,3*S*)-**9a** with allyl Grignard in diethyl ether as solvent. After in situ hydrogenation of the addition product with $NaBH_4$, the intermediate amino diol was acetylated to give (4*S*,5*S*,6*S*)-**11a** in 67% yield with high diastereoselectivity (diastereomeric ratio (*dr*) = 95:4:1). Due to the high activation by sonification, a second mole of Grignard reacts with the imino intermediate,[24] yielding the carbinamine derivative (1′*S*,2′*S*)-**10a** as a by-product in 10% yield, which can be separated by chromatography.



Scheme 3.

The isopropylidene-protected (4*S*,5*S*)-**8** reacts less diastereoselectively. Both diastereomers, (4*S*,5*S*,6*S*)- and (4*R*,5*S*,6*S*)-**12a**, are obtained in nearly equal amounts (Scheme 3) (*dr* = 51:49). Also in this case, the corresponding carbinamine derivative (1′*S*,2′*S*)-**10c** results as by-product in 11% yield.

The significant differences in diastereoselectivity of the hydrogenation of the imino intermediates derived from (2*S*,3*S*)-**9a**,**b** and (4*S*,5*S*)-**8**, respectively, can be explained by molecular modeling calculations[25,26] of the intermediate magnesium chelate complexes. In the case of the isopropylidene-protected intermediate, the diol is fixed in a *syn*-periplanar conformation by the dioxolane ring, allowing attack of a hydride from both sides with comparable probability. In contrast, in the silylated compounds **9**, in which an *anti*-periplanar conformation is preferred, the substituent R protects the front side. Hydride attack therefore occurs preferentially from the back, resulting in high diastereoselectivity. Thus the synthesis via the trimethylsilyloxy derivatives **9a**,**b** is preferable.

For ozonolysis, compound (4*S*,5*S*,6*S*)-**11a** had to be transformed into the isopropylidene derivative **12a**. For this purpose the allyl protecting group was removed by Pd/C in acidic medium followed by removal of the acetyl group according to Zemplén.[27] The isopropylidene protecting group was then introduced, yielding (4*S*,5*S*,6*S*)-**12a** (*dr* = 95:4:1) in 65% yield. Ozonolysis of (4*S*,5*S*,6*S*)-**12a** afforded the aldehyde (3*S*,4*S*,5*S*)-**13a** in 85% yield. Finally **13a** was deprotected and cyclized to *N*-acetyl-L-daunosamine (2*S*,3*S*,4*S*)-**14a** using an acidic ion-exchange material DOWEX in water/THF. Compound **14a** was obtained in 95% yield with an anomeric

ratio α:β = 1:1.6. The corresponding furanose derivative could be detected by ^{1}H NMR spectroscopy as a by-product.

The unnatural aminodeoxy sugar (2*S*,3*S*,4*S*)-4-acetamido-2-isobutyl-3,6-dihydroxytetrahydropyran **14b** has been synthesized analogously (Scheme 3). (*S*)-2-Allyloxy-4-methylvaleraldehyde (*S*)-**6b**, however, is a poorer substrate for (*R*)-PaHNL than (*S*)-**6a**. In this case a sixfold amount of enzyme was necessary compared to the reaction of **6a**. Under these conditions the cyanohydrin (2*S*,3*S*)-**7b** was obtained in 88% yield with 95% *ee* (referred to the new stereogenic center at C-2). The conversion of **7b** with trimethylchlorosilane to give (2*S*,3*S*)-**9b** in 64% yield proceeded without epimerization. The allyl Grignard addition to **9b**, subsequent hydrogenation and acetylation afforded (4*S*,5*S*,6*S*)-**11b** in 60% yield (*dr* = 92:4:2:2). The removal of the acetyl group in the following reaction sequence causes the low total yield of 19% for (4*S*,5*S*,6*S*)-**12b**. The configuration of (4*S*,5*S*,6*S*)-**12b** could be proved by X-ray crystallographic analysis.[26] After ozonolysis, the resulting aldehyde (3*S*,4*S*,5*S*)-**13b** was deprotected and cyclized as described for **13a** to give the aminodeoxy sugar (2*S*,3*S*,4*S*)-**14b** in 89% yield in an anomeric ratio α:β = 1:1.2.

3. Experimental

3.1. Materials and methods

Melting points were determined on a Büchi SMP-20 and are uncorrected. Unless otherwise stated, ^{1}H NMR spectra were recorded on a Bruker AC 250 F (250 MHz) and ARX 500 (500 MHz) in $CDCl_3$ with TMS as internal standard. Chromatography was performed using silica gel S (Riedel-de Haen), grain size 0.032–0.063 mm. Optical rotations were measured in a thermostated polarimeter with $l = 10$ cm. Diastereomeric excesses: GC separations were conducted with a OV 1701 column (30 m×0.32 mm), carrier gas hydrogen (0.45 bar). Enantiomeric excesses: GC separations were conducted with a Chiraldex B-TA (ICT) column (30 m×0.32 mm), carrier gas hydrogen (0.9 bar), or with a Bondex-unβ-5.5-Et-105 column (20 m), carrier gas hydrogen (0.4 bar). All solvents were dried and distilled. Reactions with organometallic compounds and trimethylchlorosilane were performed in flame-dried glassware under an argon atmosphere.

3.2. (S)-MeHNL catalyzed preparation of (S)-2-hydroxy-4-methylpentanenitrile (S)-4

The enzyme catalyzed addition of HCN to isovaleraldehyde **3** was performed as described previously[1,17] to give 83% of (*S*)-**4**; bp 99°C/13 torr; $[\alpha]_D^{20} = -24.9$ (*c* 1.5, $CHCl_3$), 92% *ee*. ^{1}H NMR (250 MHz): δ 0.98 (d, $J = 6.4$ Hz, 6H), 1.65–2.00 (m, 3H), 2.50 (br s, 1H), 4.52 (t, $J = 7.2$ Hz, 1H). For comparison see published data.[28]

3.3. Ethyl (S)-2-hydroxy-4-methylpentanoate (S)-5

A solution of (*S*)-**4** (9.4 g, 83.1 mmol) in 8 M ethanolic HCl (60 mL) in a sealed tube was heated to 90°C for 8 h, then 20 vol% water were added to hydrolyze the iminium hydrochloride formed. The reaction mixture was extracted with diethyl ether (3×50 mL). The combined extracts were washed with sat. $NaHCO_3$ solution to neutralize, dried ($MgSO_4$), and concentrated. The residue was distilled under vacuum to give 10.25 g (77%) of (*S*)-**5**; bp 79°C/11 torr; $[\alpha]_D^{20} = -7.2$ (*c* 0.75, $CHCl_3$), 92% *ee*. ^{1}H NMR (250 MHz): δ 0.95, 0.96 (2 d, $J = 6.7$ Hz, 3H), 1.30 (t, $J = 7.2$ Hz,

3H), 1.49–1.64 (m, 2H), 1.90 (sept, 1H), 2.70 (br s, 1H), 4.16–4.28 (m, 3H). Anal. calcd for $C_8H_{16}O_3$ (160.3): C, 59.98; H, 10.07. Found: C, 59.98; H, 10.19.

3.4. (S)-Allyloxy-4-methylpentanal (S)-**6b**

(i) The allyl protecting group was introduced according to Aurich et al.[16] From (*S*)-**5** (14.8 g, 92.4 mmol), allyl bromide (24.7 mL, 292 mmol), Ag_2O (65.5 g, 283 mmol), $MgSO_4$ (2.2 g, 18.3 mmol), and diethyl ether (370 mL) in 10 h was obtained 16.8 g (91%) of ethyl (*S*)-2-allyloxy-4-methylpentanoate; bp 93°C/11 torr; $[\alpha]_D^{20} = -63.6$ (*c* 1.0, $CHCl_3$), 92% *ee*. ^{1}H NMR (500 MHz): δ 0.92 (d, $J = 6.9$ Hz, 3H), 0.94 (d, $J = 6.7$ Hz, 3H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.47–1.52 (m, 1H), 1.63–1.72 (m, 1H), 1.79–1.88 (m, 1H), 3.87–4.26 (m, 5H), 5.19–5.31 (m, 2H), 5.88–5.95 (m, 1H). Anal. calcd for $C_{11}H_{20}O_3$ (200.3): C, 65.97; H, 10.07. Found: C, 65.71; H, 9.81.

(ii) The reduction was performed as described previously.[1] From ethyl 2-allyloxy-4-methylpentanoate (16.8 g, 83.9 mmol) in diethyl ether (200 mL), 1 M DIBALH solution in dichloromethane (100 mL, 100 mmol), water (15 mL) in 4 h was obtained 11.14 g (85%) of (*S*)-**6b**; bp 67°C/11 torr; $[\alpha]_D^{20} = -67.8$ (*c* 1.8, $CHCl_3$), 92% *ee*. ^{1}H NMR (250 MHz): δ 0.93, 0.95 (2 d, $J = 6.6$ Hz, 6H), 1.36–1.93 (m, 3H), 3.77 (ddd, $J_1 = 4.7$, $J_2 = 8.9$ Hz, 1H), 3.95–4.20 (m, 2H), 5.20–5.35 (m, 2H), 5.84–5.99 (m, 1H), 9.65 (d, $J = 2.2$ Hz, 1H). Anal. calcd for $C_9H_{16}O_2$ (156.2): C, 69.19; H, 10.32. Found: C, 69.35; H, 10.46.

3.5. Dihydroxynitriles (2S,3S)-**7a,b** by (R)-PaHNL catalyzed HCN addition to aldehydes (S)-**6a,b**

The enzyme catalyzed HCN addition was performed as described previously.[1]

3.5.1. 3-Allyloxy-2-hydroxybutanenitrile (2S,3S)-**7a**

Yield: 75%; $[\alpha]_D^{20} = +17.8$ (*c* 1.5, $CHCl_3$), 91% *de*. ^{1}H NMR (300 MHz): δ 1.31 (d, $J = 6.3$ Hz, 3H), 3.16 (br s, 1H), 3.77 (dq, $J = 4.5$ Hz, 1H), 4.07–4.21 (m, 2H), 4.33 (d, 1H), 5.22–5.36 (m, 2H), 5.85–5.98 (m, 1H).

3.5.2. 3-Allyloxy-2-hydroxy-5-methylhexanenitrile (2S,3S)-**7b**

Yield: 88%; bp 79°C/0.001 torr; $[\alpha]_D^{20} = -15.8$ (*c* 1.2, $CHCl_3$), 95% *ee* (referred to the stereogenic center at C-2), 87% *de*. ^{1}H NMR (500 MHz): δ 0.95 (d, $J = 6.6$ Hz, 6H), 1.39–1.45 (m, 1H), 1.56–1.62 (m, 1H), 1.74 (sept, 1H), 3.04 (br s, 1H), 3.67–3.70 (m, 1H), 4.18–4.28 (m, 2H), 4.35 (d, $J = 2.6$ Hz, 1H), 5.24–5.35 (m, 2H), 5.89–5.97 (m, 1H).

3.6. 2,2,5-Trimethyl-1,3-dioxolane-4-carbonitrile (4S,5S)-**8**

(i) According to a known procedure[29] a solution of (2*S*,3*S*)-**7a** (0.2 g, 1.42 mmol), 85 mg of Pd/C, 0.8 mL of water and *p*-toluenesulfonic acid ($TsOH \cdot H_2O$) (43 mg, 0.23 mmol) in 7 mL of methanol was heated to 60°C for 19 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was taken up in 150 mL of diethyl ether, dried (Na_2SO_4), concentrated, and reacted without further purification.

(ii) The crude diol obtained was taken up in 10 mL of 2,2-dimethoxypropane, and TsOH (33 mg, 0.2 mmol) was added. After being stirred for 24 h at room temperature, pyridine (2 equiv. referred to TsOH) was added. The precipitate was filtered off, and the filtrate was concentrated. The residue was taken up in toluene (2×50 mL) which was immediately removed. Chromatography

on silica gel with petroleum ether:ethyl acetate (7:1) afforded 142 mg (71%) of (4*S*,5*S*)-**8**; bp 62°C/10 torr; $[\alpha]_D^{20} = +15.8$ (*c* 1.0, $CHCl_3$), 91% *de*. ^{1}H NMR (500 MHz): δ 1.43 (d, $J = 5.9$ Hz, 3H), 1.47, 1.49 (2 s, 6H), 4.18 (d, $J = 7.0$ Hz, 1H), 4.48 (dq, 1H). CIMS (*m*/*z*,%): 142.1 (MH^+, 20), 126.1 (M–CH_3, 100), 115.1 (M–CN, 50), 43 (22). HRMS calcd for $C_7H_{12}NO_2$ (MH^+): 142.0868. Found: 142.0863.

3.7. Silylation of (2S,3S)-7a,b to (2S,3S)-9a,b: general procedure

According to Effenberger et al.[15a] trimethylchlorosilane was added dropwise over 10 min to a solution of **7** and pyridine in dry diethyl ether at 0°C, and the reaction mixture was stirred at room temperature for 10 h. The precipitate was filtered off, and the filtrate was concentrated. The residue was taken up in diethyl ether (50 mL), and again the precipitate was filtered off. The filtrate was concentrated, and the residue distilled under vacuum.

3.7.1. 3-Allyloxy-2-trimethylsilyloxybutanenitrile (2S,3S)-9a

Yield: 66%; bp 53°C/0.02 torr; $[\alpha]_D^{20} = +15.2$ (*c* 1.35, $CHCl_3$), 91% *de*. ^{1}H NMR (500 MHz): δ 0.22 (s, 9H), 1.31 (d, $J = 6.3$ Hz, 3H), 3.57–3.62 (m, 1H), 4.04–4.15 (m, 2H), 4.43 (d, $J = 5.3$ Hz, 1H), 5.27–5.33 (m, 2H), 5.86–5.94 (m, 1H). Anal. calcd for $C_{10}H_{19}NO_2Si$ (213.3): C, 56.30; H, 8.98; N, 6.57. Found: C, 56.10; H, 9.13; N, 6.64.

3.7.2. 3-Allyloxy-5-methyl-2-trimethylsilyloxyhexanenitrile (2S,3S)-9b

Yield: 64%; bp 58°C/0.002 torr; $[\alpha]_D^{20} = -12.0$ (*c* 1.0, $CHCl_3$), 87% *de*. ^{1}H NMR (500 MHz): δ 0.23 (s, 9H), 0.93, 0.97 (2 d, $J = 6.6$ Hz, 6H), 1.23–1.36 (m, 2H), 1.56–1.65 (m, 1H), 3.24–3.28 (m, 1H), 3.84–3.99 (m, 2H), 4.21 (d, $J = 5.6$ Hz, 1H), 4.97–5.08 (m, 2H), 5.64–5.72 (m, 1H). Anal. calcd for $C_{13}H_{25}NO_2Si$ (255.4): C, 61.13; H, 9.87; N, 5.48. Found: C, 61.10; H, 9.83; N, 5.43.

3.8. Preparation of (4S,5S,6S)-11a,b, and 12a: general procedure

(i) To a sonified solution of allyl Grignard reagent in diethyl ether [prepared by slow addition of allyl bromide (3.2 mmol for **9a**, 23.6 mmol for **9b**, 10.8 mmol for **8**) to equimolar amounts of Mg in diethyl ether] a solution of **9a** (1.6 mmol), **9b** (5.9 mmol) or **8** (6.7 mmol) in diethyl ether (30 mL for **9a**, **8**, 200 mL for **9b**) was added dropwise over 25 min. After sonification for 1–5 h (TLC control), the reaction mixture was cooled to −78°C. Methanol (5–40 mL) was added followed by $NaBH_4$ (ca. 2 equiv. referred to **8** and **9**) in three portions. The reaction mixture was allowed to warm to room temperature (12 h), and hydrolyzed with water (50 mL). Workup for allyl protected amino diols: the aqueous phase was adjusted to pH 2 with 1 M HCl and separated. The organic phase was extracted with dilute HCl (pH 2, 2×20 mL). The combined aqueous phases were adjusted to pH 10 with NaOH, and extracted with ethyl acetate (3×150 mL). The combined extracts were dried (Na_2SO_4), concentrated, and acetylated without further purification. Workup for isopropylidene protected amino diol: the organic phase was separated, and the aqueous phase extracted with diethyl ether (3×150 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and acetylated.

(ii) To a solution of the respective amino diol (1.3–3.8 mmol) and dimethylaminopyridine (DMAP, 0.15 equiv. referred to amino diol) in pyridine (4.5 or 10 mL) at 0°C acetic anhydride (ca. 3.4–5 equiv. referred to amino diol) was added over 0.5 h. After being stirred for 14 h at room temperature, dichloromethane (50 mL) and ice (50 g) was added, and the organic phase was

washed to neutralize with dilute HCl (pH 2). Concentration and chromatography on silica gel with petroleum ether:ethyl acetate (3:1) (**11a**), (2:1) (**12a**) or dichloromethane:methanol (30:1) and bulb-to-bulb distillation (**11b**) gave the products.

*3.8.1. 4-Acetamido-4-(1-acetoxy-2-allyloxypropyl)-1,6-heptadiene **10a***

Characterized as diastereomeric mixture: bp 125/0.007 torr. ^{1}H NMR (500 MHz): δ 1.09, 1.14 (2 d, $J=6.3$ Hz, 3H), 1.89, 1.92 (2 s, 3H), 2.10 (s, 3H), 2.39–3.02 (m, 4H), 3.84–4.17 (m, 3H), 4.97–5.35 (m, 7H), 5.75–5.98 (m, 3H), 6.51, 6.94 (2 br s, 1H). Anal. calcd for $C_{17}H_{27}NO_4$ (309.4): C, 65.99; H, 8.80; N, 4.53. Found: C, 66.04; H, 8.92; N, 4.56.

*3.8.2. 4-Acetamido-(2,2,5-trimethyl-1,3-dioxolan-4-yl)-1,6-heptadiene **10c***

$[\alpha]_D^{20}=-5.6$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz): δ 1.33 (d, $J=6.0$ Hz, 3H), 1.38, 1.40 (2 s, 6H), 1.95 (s, 3H), 2.44–2.51 (m, 4H), 3.98 (d, $J=7.8$ Hz, 1H), 4.18 (dq, 1H), 5.12–5.16 (m, 4H), 5.44 (s, 1H), 5.80–5.91 (m, 2H). Anal. calcd for $C_{15}H_{25}NO_3$ (267.4): C, 67.38; H, 9.43; N, 5.24. Found: C, 66.98; H, 9.39; N, 4.85.

*3.8.3. 4-Acetamido-5-acetoxy-6-allyloxy-1-heptene (4S,5S,6S)-**11a***

Yield: 67%; $[\alpha]_D^{20}=+6.38$ (*c* 0.8, $CHCl_3$), *dr* = 95:4:1 (4th diastereomer could not be detected; assignment only of main diastereomer). ^{1}H NMR (500 MHz): δ 1.16 (d, $J=6.3$ Hz, 3H), 1.95 (s, 3H), 2.11 (s, 3H), 2.10–2.30 (m, 2H), 3.84–4.19 (m, 3H), 4.35–4.41 (m, 1H), 4.85–4.90 (m, 1H), 5.06–5.34 (m, 4H), 5.74–5.99 (m, 2H), 6.43 (d, $J=7.9$ Hz, 1H). Anal. calcd for $C_{14}H_{23}NO_4$ (269.3): C, 62.43; H, 8.61; N, 5.20. Found: C, 62.61; H, 8.89; N, 5.01.

*3.8.4. 4-Acetamido-5-acetoxy-6-allyloxy-8-methyl-1-nonene (4S,5S,6S)-**11b***

Yield: 60%; bp 140°C/0.01 torr; $[\alpha]_D^{20}=-4.4$ (*c* 1.1, $CHCl_3$), *dr* = 92:4:2:2 (assignment only of main diastereomer). ^{1}H NMR (500 MHz): δ 0.89 (d, $J=6.7$ Hz, 3H), 0.89 (d, $J=6.4$ Hz, 3H), 1.33–1.49 (m, 2H), 1.55–1.62 (m, 1H), 1.95 (s, 3H), 2.10 (s, 3H), 2.23–2.36 (m, 2H), 3.73 (dt, $J_1=3.0$, $J_2=7.3$ Hz, 1H), 3.98–4.19 (m, 2H), 4.35–4.40 (m, 1H), 4.92 (dd, $J=5.5$ Hz, 1H), 5.07–5.35 (m, 4H), 5.75–6.00 (m, 2H), 6.47 (d, $J=8.5$ Hz, 1H). Anal. calcd for $C_{17}H_{29}NO_4$ (311.4): C, 65.57; H, 9.39; N, 4.50. Found: C, 65.37; H, 9.47; N, 4.43.

*3.8.5. 4-Acetamido-5,6-isopropylidenedioxy-1-heptene **12a***

(4*S*,5*S*,6*S*)-**12a**: yield: 34%; mp 94–96°C; $[\alpha]_D^{20}=-10.0$ (*c* 0.6, $CHCl_3$). ^{1}H NMR (500 MHz): δ 1.28 (d, $J=6.1$ Hz, 3H), 1.39, 1.40 (2 s, 6H), 1.98 (s, 3H), 2.25–2.53 (m, 2H), 3.52 (dd, $J_1=5.8$, $J_2=8.1$ Hz, 1H), 4.00–4.04 (m, 1H), 4.13–4.18 (m, 1H), 5.09–5.13 (m, 2H), 5.54 (d, $J=7.3$ Hz, 1H), 5.76–5.84 (m, 1H). Anal. calcd for $C_{12}H_{21}NO_3$ (227.3): C, 63.41; H, 9.31; N, 6.16. Found: C, 63.06; H, 9.39; N, 6.12.

(4*R*,5*S*,6*S*)-**12a**: yield: 29%; mp 89–91°C; $[\alpha]_D^{20}=+13.4$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz): δ 1.27 (d, $J=5.9$ Hz, 3H), 1.38, 1.40 (2 s, 6H), 2.00 (s, 3H), 2.34 (dd, $J=7.2$ Hz, 2H), 3.59 (dd, 1H), 3.76 (dq, $J=8.4$ Hz, 1H), 4.07–4.12 (m, 1H), 5.07–5.13 (m, 2H), 5.70 (d, $J=9.2$ Hz, 1H), 5.70–5.82 (m, 1H). Anal. calcd for $C_{12}H_{21}NO_3$ (227.3): C, 63.41; H, 9.31; N, 6.16. Found: C, 63.23; H, 9.38; N, 6.06.

*3.9. Preparation of (4S,5S,6S)-**12a,b** from (4S,5S,6S)-**11a,b**: general procedure*

(i) The allyl protecting group was removed from **11a** (0.74 mmol) or **11b** (0.64 mmol) according to a known procedure[29] as described above for **8**.

(ii) The obtained crude product was taken up in 7 mL of methanol, and a 0.5 M solution of sodium methanolate (0.3 mL for **12a**, 1 mL for **12b**) was added. After being stirred for 14–16 h, the reaction mixture was neutralized with acidic ion exchanger DOWEX-H^+ (pH control). The ion exchanger was filtered off, and the filtrate was concentrated and reacted without further purification.

(iii) As described above for (4*S*,5*S*)-**8**, the crude product was taken up in 10 mL of 2,2-dimethoxypropane, and TsOH (ca. 0.18 equiv. referred to **11**) was added. After being stirred for 10 min (**12a**) or 1 h (**12b**), pyridine was added. The precipitate was filtered off, and the filtrate was concentrated. The residue was taken up in toluene (2×50 mL), which was immediately removed. Chromatography on silica gel with petroleum ether:ethyl acetate (1:1 for **12a**, 1:2 for **12b**) afforded products **12**.

*3.9.1. 4-Acetamido-5,6-isopropylidenedioxy-1-heptene (4*S*,5*S*,6*S*)-**12a***

Total yield: 65%; $[\alpha]_D^{20} = -9.0$ (*c* 1.84, $CHCl_3$), *dr* = 95:4:1 (4^{th} diastereomer could not be detected). ^1H NMR see above.

*3.9.2. 4-Acetamido-5,6-isopropylidenedioxy-8-methyl-1-nonene (4*S*,5*S*,6*S*)-**12b***

Total yield: 19%; mp 111°C (pentane); $[\alpha]_D^{20} = -42.6$ (*c* 1.2, $CHCl_3$), *dr* = 95:5 (assignment only of main diastereomer). ^1H NMR (500 MHz, acetone): δ 0.88, 0.91 (2 d, $J = 6.8$ Hz, 6H), 1.32, 1.34 (2 s, 6H), 1.36–1.48 (m, 2H), 1.74–1.80 (m, 1H), 1.87 (s, 3H), 2.14–2.53 (m, 2H), 3.46 (dd, $J = 7.7$ Hz, 1H), 4.00–4.11 (m, 2H), 4.99–5.09 (m, 2H), 5.76–5.84 (m, 1H), 6.96 (d, $J = 8.3$ Hz, 1H). Anal. calcd for $C_{15}H_{27}NO_3$ (269.4): C, 66.88; H, 10.10; N, 5.20. Found: C, 66.78; H, 10.11; N, 5.11.

*3.10. Ozonolysis of (4*S*,5*S*,6*S*)-**12a**,**b** to (3*S*,4*S*,5*S*)-**13a**,**b**: general procedure*

Ozone (40 L/h) was passed through a solution of **12a** (0.44 mmol) or **12b** (0.41 mmol) in methanol (8 mL) at −78°C over 10 min, and subsequently O_2 was passed through for 5 min to remove excess O_3. Then dimethylsulfide (6.8 mmol for **13a**, 4.1 mmol for **13b**) was added, and the reaction mixture was allowed to warm to room temperature (12 h). The reaction mixture was concentrated, and the residue was chromatographed on silica gel with petroleum ether:ethyl acetate (1:2 to 1:20).

*3.10.1. 3-Acetamido-4,5-isopropylidenedioxyhexanal (3*S*,4*S*,5*S*)-**13a***

Yield: 85%; mp 84°C; $[\alpha]_D^{20} = +8.4$ (*c* 0.8, $CHCl_3$), *dr* could not be determined by GC and NMR spectroscopy. ^1H NMR (500 MHz): δ 1.30 (d, $J = 5.9$ Hz, 3H), 1.34, 1.38 (2 s, 6H), 1.99 (s, 3H), 2.70–2.89 (m, 2H), 3.64 (dd, $J_1 = 6.8$, $J_2 = 7.9$ Hz, 1H), 3.93 (dq, $J_1 = 5.9$, $J_2 = 7.9$ Hz, 1H), 4.42–4.48 (m, 1H), 6.19 (d, $J = 8.8$ Hz, 1H), 9.78 (d, $J = 1.9$ Hz, 1H). CIMS (*m*/*z*,%): 230.1 (MH^+, 100). HRMS calcd for $C_{11}H_{20}NO_4$ (MH^+): 230.1392. Found: 230.1398.

*3.10.2. 3-Acetamido-4,5-isopropylidenedioxy-7-methyloctanal (3*S*,4*S*,5*S*)-**13b***

Yield: 79%; mp 105°C; $[\alpha]_D^{20} = -24.8$ (*c* 1.1, $CHCl_3$), *dr* could not be determined by GC and NMR spectroscopy; ^1H NMR (500 MHz): δ 0.84 (d, $J = 6.6$ Hz, 3H), 0.87 (d, $J = 6.7$ Hz, 3H), 1.18–1.49 (m, 2H), 1.30 (s, 6H), 1.72–1.74 (m, 1H), 1.91 (s, 3H), 2.61–2.81 (m, 2H), 3.62 (dd, $J = 6.5$ Hz, 1H), 3.78–3.82 (m, 1H), 4.37–4.41 (m, 1H), 6.05 (d, $J = 9.0$ Hz, 1H), 9.71 (d, $J = 1.9$ Hz, 1H). FAB-MS (*m*/*z*,%): 272.2 (MH^+, 100). HRMS-FAB calcd for $C_{14}H_{26}NO_4$ (MH^+): 272.1862. Found: 272.1860.

3.11. Cyclization of (3S,4S,5S)-13a,b to aminodeoxy sugars (2S,3S,4S)-14a,b: general procedure

To a solution of **13a** (0.33 mmol) or **13b** (0.28 mmol) in THF/water (10 mL/3 mL) DOWEX-H^+ (250 mg) was added. After being stirred for 5.5 h (**14a**) or 10 h (**14b**) (TLC control), the ion exchanger was filtered off, and the filtrate was concentrated to give products **14**.

3.11.1. N-Acetyl-L-daunosamine (2S,3S,4S)-14a

Yield: 95%; α:β = 1:1.6; *dr* could not be determined. α-anomer: ^{1}H NMR (500 MHz, D_2O): δ 1.18 (d, J = 6.6 Hz, 3H), 1.70 (dd, J_1 = 4.7, J_2 = 13.5 Hz, 1H), 1.86–1.91 (m, 2H), 2.00 (s, 6H), 3.67 (d, J = 6.9 Hz, 1H), 4.20 (q, 1H), 4.22–4.24 (m, 1H), 5.33 (d, 1H).

β-anomer: ^{1}H NMR (500 MHz, D_2O): δ 1.23 (d, J = 6.4 Hz, 3H), 1.56–1.63 (m, 1H), 1.86–1.91 (m, 2H), 2.00 (s, 6H), 3.56 (d, 1H), 3.75 (dq, J = 0.8 Hz, 1H), 3.99 (dt, J_1 = 3.7, J_2 = 12.3 Hz, 1H), 4.89 (dd, J_1 = 2.1, J_2 = 9.9 Hz, 1H). For comparison see published data.[8] Anal. calcd for $C_8H_{15}NO_4$ (189.2): C, 50.78; H, 7.99; N, 7.40. Found: C, 50.82; H, 8.03; N, 7.41.

3.11.2. 4-Acetamido-2-isobutyl-3,6-dihydroxytetrahydropyran (2S,3S,4S)-14b

Yield: 89%; mp 56°C (decomp.); α:β = 1:1.2. α-anomer: ^{1}H NMR (500 MHz, D_2O): δ 0.90 (d, 12H), 1.31 (ddd, J_1 = 5.0, J_2 = 8.0, J_3 = 13.4 Hz, 1H), 1.47–1.73 (m, 6H), 1.86–1.91 (m, 2H), 2.00 (s, 6H), 3.69 (d, 1H), 4.08–4.12 (m, 1H), 4.20 (ddd, J_1 = 2.8, J_2 = 4.9, J_3 = 13.2 Hz, 1H), 5.32 (d, J = 3.3 Hz, 1H).

β-anomer: ^{1}H NMR (500 MHz, D_2O): δ 0.90 (d, 12H), 1.39 (ddd, J_1 = 5.8, J_2 = 7.7, J_3 = 13.5 Hz, 1H), 1.47–1.73 (m, 6H), 1.86–1.91 (m, 2H), 2.00 (s, 6H), 3.61 (d, 1H), 3.64–3.67 (m, 1H), 3.99 (ddd, J_1 = 2.9, J_2 = 4.7, J_3 = 12.9 Hz, 1H), 4.86 (dd, J_1 = 2.0, J_2 = 9.8 Hz, 1H). Anal. calcd for $C_{11}H_{21}NO_4$ (231.3): C, 57.12; H, 9.15; N, 6.06. Found: C, 57.27; H, 9.30; N, 6.23.

3.12. Determination of enantiomeric and diastereomeric excesses

(i) A solution of compounds **4** or **7** (10 mg), acetic anhydride (50 μL) and pyridine (10 μL) in dichloromethane (300 μL) was heated to 60°C in a sealed tube for 5 h. The reaction mixture was then filtered through a silica gel column (3×0.5 cm) with dichloromethane as eluent. The enantiomeric and diastereomeric excess was determined directly from the filtrate by gas chromatography.

(ii) The *ee*- and *de*-values of compounds **5**, **9**, **11**, and **12** could be determined by gas chromatography directly without derivatization.

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References

1. Enzyme catalyzed reactions, Part 38. Part 37: Roos, J.; Effenberger, F. *Tetrahedron: Asymmetry* **1999**, *10*, 2817–2828.
2. (a) Arcamone, F.; Franceschi, G.; Orezzi, P.; Cassinelli, G.; Barbieri, W.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5334–5335. (b) Arcamone, F.; Cassinelli, G.; Orezzi, P.; Franceschi, G.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5335–5336.

3. Arcamone, F.; Franceschi, G.; Penco, S.; Selva, A. *Tetrahedron Lett*. **1969**, 1007–1010.
4. (a) Horton, D.; Weckerle, W. *Carbohydr. Res*. **1975**, *44*, 227–240. (b) Grethe, G.; Mitt, T.; Williams, T. H.; Uskokovic, M. R. *J. Org. Chem*. **1983**, *48*, 5309–5315. (c) Naguma, S.; Umezawa, I.; Akiyama, J.; Akita, H. *Chem. Pharm. Bull*. **1995**, *43*, 171–173.
5. (a) Arcamone, F.; Penco, S.; Vigevani, A.; Redaelli, S.; Franchi, G.; Di Marco, A.; Casazza, A. M.; Dasdia, T.; Formelli, F.; Necco, A.; Soranzo, C. *J. Med. Chem*. **1975**, *18*, 703–707. (b) Hamada, Y.; Kawai, A.; Shioiri, T. *Tetrahedron Lett*. **1984**, *25*, 5409–5412. (c) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem*. **1986**, *51*, 4245–4249. (d) Kita, Y.; Itoh, F.; Tamura, O.; Ke, Y. Y.; Miki, T.; Tamura, Y. *Chem. Pharm. Bull*. **1989**, *37*, 1446–1451.
6. Hauser, F. M.; Ellenberger, S. R. *Chem. Rev*. **1986**, *86*, 35–67.
7. (a) Marsh, J. P.; Mosher, C. W.; Acton, E. M.; Goodman, L. *Chem. Commun*. **1967**, 973–975. (b) Pauls, H. W.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun*. **1983**, 1031–1032. (c) Brimacombe, J. S.; Hanna, R.; Tucker, L. C. N. *Carbohydr. Res*. **1985**, *136*, 419–425.
8. Herczegh, P.; Zsély, M.; Kovács, I.; Batta, G.; Sztaricskai, F. J. *Tetrahedron Lett*. **1990**, *31*, 1195–1198.
9. Kimura, Y.; Matsumoto, T.; Suzuki, M.; Terashima, S. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 663–664.
10. (a) Medgyes, G.; Kuszmann, J. *Carbohydr. Res*. **1981**, *92*, 225–237. (b) Gurjar, M. K.; Pawar, S. M. *Tetrahedron Lett*. **1987**, *28*, 1327–1328.
11. Mukaiyama, T.; Goto, Y.; Shoda, S. *Chem. Lett*. **1983**, 671–674.
12. (a) Hiyama, T.; Kobayashi, K. (Sagami Chemical Research Center) PCT Int. Appl. WO 84 00,755, 01 Mar 1984; *Chem. Abstr*. **1984**, *101*, 131034r. (b) Hirama, M.; Nishizaki, I.; Shigemoto, T.; Ito, S. *J. Chem. Soc., Chem. Commun*. **1986**, 393–394. (c) Hiyama, T.; Kobayashi, K.; Nishide, K. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 2127–2137.
13. (a) Warm, A.; Vogel, P. *Tetrahedron Lett*. **1985**, *26*, 5127–5128. (b) Warm, A.; Vogel, P. *J. Org. Chem*. **1986**, *51*, 5348–5353.
14. Fronza, G.; Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun*. **1980**, 442–444.
15. (a) Effenberger, F.; Gutterer, B.; Ziegler, T. *Liebigs Ann. Chem*. **1991**, 269–273. (b) Jackson, W. R.; Jacobs, H. A.; Matthews, B. R.; Jayatilake, G. S.; Watson, K. G. *Tetrahedron Lett*. **1990**, *31*, 1447–1450. (c) Brussee, J.; Dofferhoff, F.; Kruse, C. G.; van der Gen, A. *Tetrahedron* **1990**, *46*, 1653–1658.
16. Aurich, H. G.; Biesemeier, F.; Boutahar, M. *Chem. Ber*. **1991**, *124*, 2329–2334.
17. Förster, S.; Roos, J.; Effenberger, F.; Wajant, H.; Sprauer, A. *Angew. Chem*. **1996**, *108*, 493–494; *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 437–439.
18. (a) Pinner, A. *Ber. Dtsch. Chem. Ges*. **1883**, *16*, 1643–1655. (b) Warmerdam, E. G. J. C.; van den Nieuwendijk, A. M. C. H.; Kruse, C. G.; Brussee, J.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 20–24.
19. (a) Effenberger, F.; Gaupp, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1765–1775. (b) Zandbergen, P.; van der Linden, J.; Brussee, J.; van der Gen, A. *Synth. Commun*. **1991**, *21*, 1387–1391.
20. Effenberger, F.; Stelzer, U. *Chem. Ber*. **1993**, *126*, 779–786.
21. Schmeichel, M.; Redlich, H. *Synthesis* **1996**, 1002–1006.
22. (a) Pirrung, M. C.; Hwu, J. R. *Tetrahedron Lett*. **1983**, *24*, 565–568. (b) Duhamel, L.; Tombret, F. *J. Org. Chem*. **1981**, *46*, 3741–3742.
23. Benkeser, R. A. *Synthesis* **1971**, 347–358.
24. (a) Allen, B. B.; Henze, H. R. *J. Am. Chem. Soc*. **1939**, *61*, 1790–1794. (b) Henze, H. R.; Thompson, T. R. *J. Am. Chem. Soc*. **1943**, *65*, 1422–1425. (c) Henze, H. R.; Allen, B. B.; Leslie, W. B. *J. Am. Chem. Soc*. **1943**, *65*, 87–89. (d) Horowitz, R. M.; Geissman, T. A. *J. Am. Chem. Soc*. **1950**, *72*, 1518–1522. (e) Henze, H. R.; Sutherland, G. L.; Edwards, G. D. *J. Am. Chem. Soc*. **1951**, *73*, 4915–4918. (f) Gauthier, R.; Axiotis, G. P.; Chastrette, M. *J. Organomet. Chem*. **1977**, *140*, 245–255.
25. (a) MOPAC, method AM1; program Insight II (MSI/Biosym). (b) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc*. **1985**, *107*, 3902–3909.
26. Roos, J. Dissertation, Universität Stuttgart, 1999.
27. Zemplén, G.; Pacsu, E. *Ber. Dtsch. Chem. Ges*. **1929**, *62*, 1613–1614.
28. Cable, K. M.; Herbert, R. B.; Knaggs, A. R.; Mann, J. *J. Chem. Soc., Perkin Trans 1* **1991**, 595–599.
29. Boss, R.; Scheffold, R. *Angew. Chem*. **1976**, *88*, 578–579; *Angew. Chem., Int. Ed. Engl*. **1976**, *15*, 558–559.