Enantioselective Synthesis of Diamino Dicarboxylic Acids

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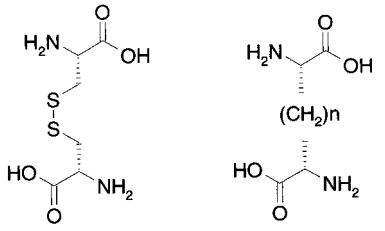
The preparation of alkyl diamino dicarboxylic acids with high optical purity (100% ee, >98.5% de) and high yields based on asymmetric catalytic hydrogenation is described. The required prochiral precursors are prepared from dialdehydes and Z-, Boc-, and acetyl-protected phosphonoglycines. Aqueous solutions of glyoxal, succinic dialdehyde, and glutaric dialdehyde were used to prepare the diunsaturated precursors for 2,5-diaminoadipic acid (DAA), 2,7-diaminosuberic acid (DAS), and 2,8-diaminoazelaic acid (DAZ). Z-Protected dimethyl esters of DAA, DAS, and DAZ were obtained by hydrogenation of the corresponding prochiral starting materials with [(COD)Rh(*S*,*S*)-Et-DuPHOS]OTf.

Introduction

Diamino dicarboxylic acids[1] or bis(amino acids) are characterized by two glycine residues that are connected by a spacer via the α-carbons. They contain two asymmetric carbons, two chemically identical amino and carboxylic groups. Cystine (**1**, proteinogenic amino acid, see Scheme 1) and 2,5-diaminopimelic acid[2] (**2**, DAP, precursor of lysine) are the biologically most important members of this interesting class of compounds.[5−7] In particular, the biological importance of DAP had stimulated the synthesis of DAP isomers and analogues as possible inhibitors of the enzymes involved in the DAP biosynthetic pathway.[8]

The use of diamino dicarboxylic acid derivatives for peptidomimetic drug design is becoming more common place. Recently, members of this class have been used as conformational constraints in order to mimic the secondary structures of peptides, such as β-turns,[9] and to stabilize a helical conformation.[10] Since they contain two amino and two carboxylic groups, they are interesting starting materials for the preparation of chemical libraries using solid-phase chemistry. In addition, alkyne bridged bis(amino acids) have been prepared in order to investigate their nonlinear optical properties.[11]

Scheme 1. Important Members of Diaminodicarboxylic Acids



1 Cystine

2 n = 2 DAA
3 n = 3 DAP
4 n = 4 DAS
5 n = 5 DAZ

Replacement of the chemically and metabolically labile disulfide bridge in cystine **1** by an isosteric ethylene spacer results in the unnatural 2,7-diaminosuberic acid (**4**, DAS). This amino acid has been used successfully as a substitute for cystine to prepare biologically active peptide hormone analogues with improved chemical stability, e.g. oxytocin[12] and somatostatin analogues.[13] Brandenburg and co-workers reported the replacement of cystine even within a protein by incorporating diaminosuberic acid in insulin to give A7,B7-dicarbainsulin.[14]

Recently compound **6**[15] (SK&F 107647, Scheme 2), a nonapeptide with hematoregulatory activity, has demonstrated significant protection in animal models of bacterial, fungal, and viral diseases and bone marrow

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† Topcro Pharma Research GmbH.
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§ Nycomed Austria AG.

(1) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, 1961; Vol. 3, pp 2501−2528.

(2) Diaminopimelic acid is found in bacteria and higher plants. It is the precursor of lysine, which is formed via the diaminopimelic pathway. Since mammals lack this biochemical transformation, inhibitors of the diaminopimelic acid pathway could be potential antimicrobial agents.[3] Clinical studies on FK-565, a peptide containing *meso*-2,6-diaminopimelic acid, revealed that it exhibits strong antiviral activity and remarkable antitumor potency.[4]

(3) Abbott, S. D.; Lane-Bell, P.; Sidhu, K. P. S.; Vederas, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 6513−6520; and references therein.

(4) Hoshi, A.; Castañer, J. *Drugs Fut.* **1994**, *19*, 243−247.

(5) Other naturally occurring sulfur-containing diamino dicarboxylic acids: lanthionine and its 3-methyl homologue. They are found in unusual bioactive polypeptides called "lanthibiotics".[6] Compared to the metabolically labile disulfide bridge of cystine, the monosulfide bridge of lanthionine provides an improvement in the stability toward enzymatic degradation. Therefore lanthionines have been used as peptidomimetic building blocks.[6]

(6) Goodman, M.; Shao, H. *Pure Appl. Chem.* **1996**, *68*, 1303−1308.

(7) For diamino dicarboxylic acids with an aryl ether spacer: Rama Rao, A. V.; Gurjar, M. K.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135−2167.

(8) Gao, Y.; Lane-Bell, P.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2133−2143.

(9) Review: Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789−12854.

(10) Andrews, M. J. I.; Tabor, A. B. *Tetrahedron Lett.* **1997**, *38*, 3063−3066.

(11) Kayser, B.; Altman, J.; Beck, W. *Tetrahedron* **1997**, *53*, 2475−2484.

(12) Keller, O. Doctoral Thesis, No. 5325 E.T.H. Zürich, 1974.

(13) Nutt, R. F.; Veber, D. F.; Saperstein, R. *J. Am. Chem. Soc.* **1980**, *102*, 6539−6545.

(14) Videnov, G.; Büttner, K.; Casaretto, M.; Föhles, J.; Gattner, H.-G.; Stoev, S.; Brandenburg, D. *Biol. Chem. Hoppe-Seyler* **1990**, *371*, 1057−1066.

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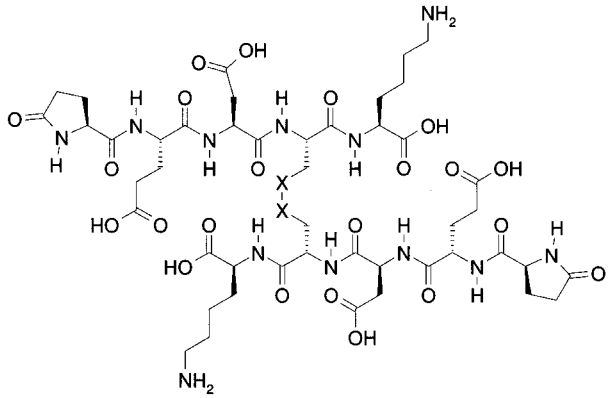
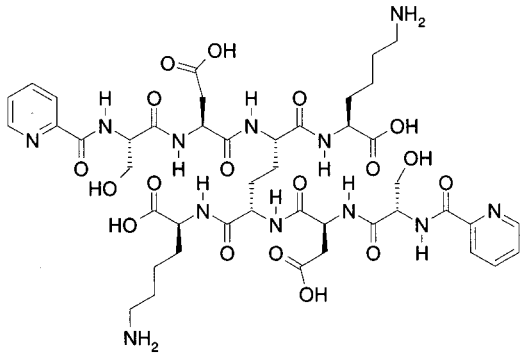
Scheme 2. Hematoregulatory Active Peptides Containing Diaminodicarboxylic Acids



6 X = CH_2, SK&F 107647
7 X = S, Dimer of HP5b

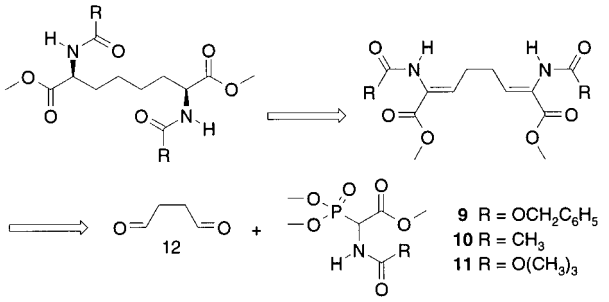


8

transplantation.[16] Compound **6** is the dicarba analogue of the disulfide **7**,[17] which is the dimer of the hemoregulatory peptide, HP5b (Pyr-Glu-Asp-Cys-Lys) isolated by Laerum and Paukovits from mature human leukocytes.[18] The identification of these low molecular weight compounds, **6** and **7**, which display high biological activity, represented a breakthrough in the field of hematopoiesis, which is dominated by proteins, e.g. cytokines.[19]

The 2,7-L,L-diaminosuberic acid used for the structure−activity relationship[15] and toxicological studies of **6** was synthesized by either Kolbe electrolysis[20] or by alkylation of a chiral bislactim ether (Schöllkopf technology).[21] Other synthetic routes published in the literature are based on the alkylation of another chiral glycine template[22] and on the template-promoted ring-closing olefin metathesis.[8,23−25]

Scheme 3. Retrosynthetic Analysis



9 R = $OCH_2C_6H_5$
10 R = CH_3
11 R = $O(CH_3)_3$

The advantage of using the Kolbe electrolysis was that it allowed the preparation of diaminosuberic acid bearing the required protecting groups in just one step from the appropriate *N*-protected α-carboxyl esters of glutamic acid.[20] While useful for the preparation of kilogram quantities of 2,7-diaminosuberic acid, the Kolbe electrolysis had its limitations. The main problems faced in the scale-up process were the heat generated during the electrolysis, which increased the amount of side products, and the high costs for the chiral starting materials.

For further toxicological and clinical evaluation of hematoregulary peptide **6**, a scaleable synthetic route to 2,7-diaminosuberic acid became critical. A method allowing the synthesis of 2,7-diaminosuberic acid with >98% de from achiral starting materials which creates the chiral centers in a catalytic fashion was considered as the most economical approach.

Results and Discussion

Scheme 3 shows our retrosynthetic analysis, which is based on an enantioselective hydrogenation of a prochiral 2,7-diaminosuberic acid derivative. The starting materials **9** and **12** for the prochiral intermediate are commercially available.

The Wittig−Horner reaction of Z-phosphonoglycine methyl ester **9**[26] with anhydrous butanedial[27] in the presence of tetramethylguanidine[28] yielded the desired dimethyl ester **13** (see Table 1) as a mixture of olefin isomers (95:5). The major product could be isolated by a single crystallization, if desired, and was determined to contain the 2*Z*,6*Z* configuration by X-ray analysis.[29] The minor compound **14** (Scheme 4) was determined to be the 2*E*,6*Z* isomer by ^{1}H and ^{13}C NMR. Interestingly, monounsaturated compound **15** was identified as a major side product. It is formed by reaction of butanedial with just 1 equiv of phosphonoglycine **9** and was isolated as the hydrate.

When the Wittig−Horner reaction was carried out with the commercially available aqueous solution of butanedial (40%) in the presence of dichloromethane[30] and DBU,[28] the desired product **13** was isolated in 76% yield. In this case, the ratio between **13** (2*Z*,6*Z*) and **14** (2*E*,6*Z*)

(15) Bhatnagar, P. K.; Agner, E. K.; Alberts, D.; Arbo, B. E.; Callahan, J. F.; Cuthbertson, A. S.; Engelsen, S. J.; Fjerdingstad, H.; Hartmann, M.; Heerding, D.; Hiebl, J.; Huffman, W. F.; Hysben, M.; King, A. G.; Kremminger, P.; Kwon, C.; LoCastro, S.; Løvhaug, D.; Pelus, L. M.; Petteway, S.; Takata, J. S. *J. Med. Chem.* **1996**, *39*, 3814−3819.

(16) Bhatnagar, P. K.; Alberts, D.; Callahan, J. F.; Heerding, D.; Huffman, W. F.; King, A. G.; LoCastro, S.; Pelus, L. M.; Takata, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12862−12863.

(17) Laerum, O. D.; Sletvold, O.; Bjerknes, R.; Eriksen, J. A.; Johansen, J. H.; Schanche, J. S.; Tverteraas, T.; Paukovits, W. R. *Exp. Hematol.* **1988**, *16*, 274−280.

(18) Paukovits, W. R.; Laerum, O. D. *Hoppe-Seylers Z. Physiol. Chem.* **1984**, *365*, 303−311.

(19) Review: Hansen, F. *Acta Oncol.* **1995**, *34*, 453−468.

(20) Hiebl, J.; Blanka, M.; Guttman, A.; Kollmann, H.; Leitner, K.; Mayrhofer, G.; Rovenszky, F.; Winkler, K. *Tetrahedron* **1998**, *54*, 2059−2074.

(21) Kremminger, P.; Undheim, K. *Tetrahedron* **1997**, *53*, 6925−6936.

(22) Williams, R. M.; Yuan, C. *J. Org. Chem.* **1992**, *57*, 6519−6527.

(23) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, *118*, 9606−9614.

(24) O'Leary, D. J.; Miller, S. J.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 1689−1690. We thank Profs. Grubbs and O'Leary for sending a preprint of this work.

(25) Williams, R. M.; Liu, J. *J. Org. Chem.* **1998**, *63*, 2130−2132.

(26) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53−60.

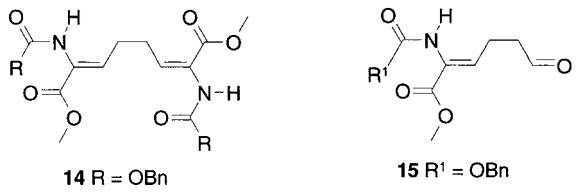
(27) Falkstorp, J.; Raleigh, D.; Schniepp, L. E. *J. Org. Chem.* **1950**, *15*, 869−875.

(28) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487−490.

(29) Klepp, K. O.; Hiebl, J.; Kollmann, H.; Rovenszky, F. *Z. Naturforsch.*, in press.

(30) Ciattini, P. G.; Morera, E.; Ortar, G. *Synthesis* **1988**, 140−142.

Scheme 4. Side Products



14 R = OBn **15** R¹ = OBn

in the crude mixture was also determined to be 95:5. The corresponding Boc- and acetyl-protected derivatives **16** and **17** were available in 60−78% yield from the corresponding *N*-protected glycine derivatives **11** and **10**.[26]

The successful preparation of prochiral precursors **13**, **16**, and **17** for diaminosuberic acid motivated us to investigate the synthesis of diunsaturated analogues of other diamino dicarboxylic acids. These results are summarized in Table 1. High yields were obtained with dialdehydes available as aqueous solutions (with $n = 0$, 2, 3, see entries 1−3), with middle-sized carbon chain dialdehydes ($n = 6$, entry 4), longer carbon chain aldehydes ($n = 10$, entry 5), and aromatic dialdehydes (iso- and *p*-phthalaldehydes, entries 6 and 7). Interestingly, none of the desired product was obtained from the reaction of Z-phosphonoglycine **9** and *o*-phthalaldehyde.[31] Analogues of aromatic compounds **27** and **28** (see Table 1) bearing different protecting groups have been prepared using a Heck reaction as the key step.[32] Interestingly, this method also failed to produce the corresponding *ortho*-substituted derivatives.

The reaction of **15** with acetyl derivative **10** (entry 8, Table 1) in anhydrous CH_2Cl_2 (DBU, molecular sieves) yielded the unsymmetrical protected compound **29**. This result demonstrates the possibility to prepare precursors of orthogonally protected diamino dicarboxylic acids with this new methodology.

Asymmetric Hydrogenation. Having the prochiral precursors **13**, **16**, and **17** in hand, we next identified the best chiral catalyst[33−36] for the transformation into optically pure protected 2,7-diaminosuberic acid. Because the Z-protected 2,7-diaminosuberic acid (di-Z-DAS) **31** was selected as most suitable starting material for the large scale synthesis of hematoregulatory peptide **6**,[37] Z-protected, unsaturated compound **13** was selected for this investigation. The following standard set of parameters was used for the screening: 3.5 g of **13** was dissolved in 200 mL of oxygen-free MeOH. The hydrogenation was carried out with 100 mg of catalyst, 60 psi initial pressure of H_2, at ambient temperature for 18 h.

The results of this screening are shown in Table 2. Et-DuPHOS-Rh catalyst gave the Z-protected 2,7-L,L-diaminosuberic acid **30** in high yield (85%) and high optical purity (100% ee, 99.0% de by HPLC [see legend to Table 2], entry 1, Table 2). The product was identical with material prepared from Z-Glu-OMe by Kolbe electrolysis.[20] None of the D,D-enantiomer **34** of **30** was detectable, but a small amount (0.5%) of the *meso*-compound was formed during the hydrogenation. Me-DuPHOS-Rh and DIPAMP-Rh catalysts gave lower diastereomeric excesses, 97.0% de and 95% de, respectively (entries 3 and 4, Table 2). CHIRAPHOS-Rh catalyst (prepared in situ, entry 5, Table 2) did not hydrogenate the bis-enamide **13** under the standard reaction conditions. Increasing the H_2 pressure to 500 psi at 60 °C was successful, but only 35.8% de was obtained. In addition, a small amount of the D,D-enantiomer was formed under these conditions resulting in 86.5% ee. Ru-BINAP gave only moderate diastereoselectivity (70% de, entry 6, Table 2).

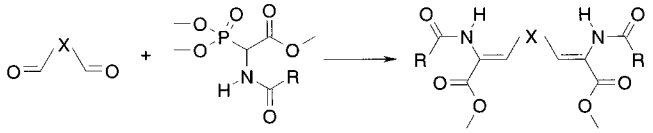
Based on these results, Et-DuPHOS was selected for the large-scale synthesis of 2,7-diaminosuberic acid derivative **30**.[38] In addition, Et-DuPHOS was used successfully for the asymmetric hydrogenation of bis-enamides **18** and **21** (see Table 1) yielding 2,5-diaminoadipic acid **32** (97.2% de, entry 7, Table 2) and 2,8-diaminoazelaic acid **33** (97.0% de, entry 8, Table 2) in 50% and 56% overall yield (two steps) from glyoxal or glutaraldehyde, respectively. In both cases optically pure compounds (100% ee, 100% de by HPLC) could be obtained by a single crystallization. These results were important since derivatives of 2,5-diaminoadipic acid were not available by dialkylation of Schöllkopf's bislactim ether with dibromoethane[39] and the Kolbe electrolysis yielded compound **32** in only 23% yield.[20] Interestingly, an analogue (**8**, see Scheme 2) of hematoregulatory peptide **6** containing 2,5-diaminoadipic acid **2** (DAA, see Scheme 1) instead of 2,7-diaminosuberic acid **4** was found to be more active than **6**.[15]

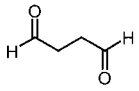
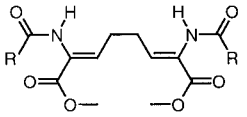
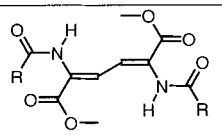
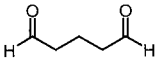
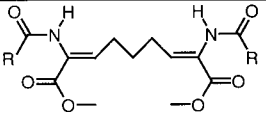
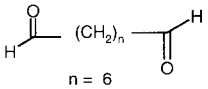
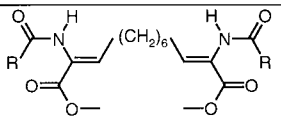
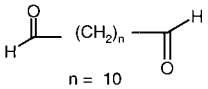
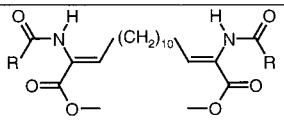
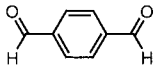
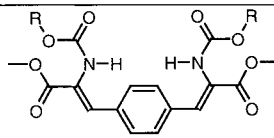
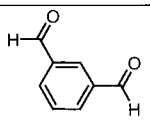
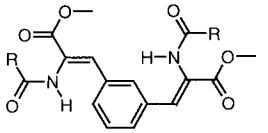
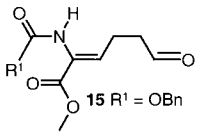
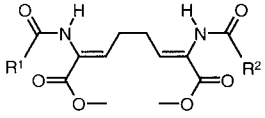
Conclusion. Optically pure (100% ee, ≥ 98.5% de by HPLC) alkyl diamino dicarboxylic acids are prepared in two steps from commercially available starting materials. The key step is the asymmetric catalytic hydrogenation (Et-DuPHOS-Rh) of the bis-enamides which are prepared from the corresponding dialdehydes and N-protected phosphonoglycine methyl esters. Because of the prochiral nature of the precursors, both enantiomers of diamino dicarboxylic acids containing the same configuration at the two chiral centers are available from one starting material.

To use the whole potential of diamino dicarboxylic acids as new building blocks for combinatorial chemistry, or as replacements for cystine in biologically active peptides, orthogonal protected diamino dicarboxylic derivatives are required. Methods to prepare selectively protected bis-(amino acids) have been reported recently.[8,9,22,24,25,39−44] Efforts to extend the methodology described in this paper

(31) Hiebl, J.; Kollmann, H. Unpublished results.
(32) Carlström, A.-S.; Frejd, T. *J. Org. Chem.* **1991**, *56*, 1289−1293.
(33) Et-DuPHOS, Me-DuPHOS: Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125−10138.
(34) DIPAMP: Knowles, W. S.; Sabacky, M. J.: Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567−2568.
(35) CHIRAPHOS: Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262−6267.
(36) BINAP: Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245−1253.
(37) Hiebl, J.; Alberts, D.; Banyard, A. F.; Baumgartner, H.; Bernwieser, I.; Bhatnagar, P. K.; Blanka, M.; Bodenteich, M.; Chen, T.; Esch, P. M.; Kollmann, H.; Lantos, I.; Leitner, K.; Mayrhofer, G.; Patel, R.; Rio, A.; Rovenszky, F.; Stevenson, D.; Tubman, K. D.; Undheim, K.; Weihtrager, H.; Welz, W.; Winkler, K. *J. Peptide Res.*, in press.
(38) Using this new method, optically pure 2,7-diaminosuberic acid derivative **30** was prepared on multikilogram scale in 75% isolated yield with 100% ee and 98.5% de (chiral HPLC) from a technical aqueous solution of succinic dialdehyde **12** (data not shown).
(39) Bold, G.; Allmendinger, T.; Herold, P.; Moesch, L.; Schär, H.-P.; Duthaler, R. O. *Helv. Chim. Acta* **1992**, *75*, 865−882, footnote on page 868.
(40) Hiebl, J.; Kollmann, H.; Rovenszky, F.; Winkler, K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2963−2966.
(41) Nutt, R. F.; Strachan, R.; Veber, D.; Holly, F. J. *J. Org. Chem.* **1980**, *45*, 5, 3078−3080.
(42) Zakhariev, S.; Videnov, G.; Stoev, S.; Golovinsky, E.; Brandenburg, D. Asymmetrical derivatives of diaminosuberic acid useful in peptide synthesis. In *Peptides 1988*; Jung, G., Bayer, E., Eds.; De Gruyter & Co.: Berlin, 1989; pp 307−309.
(43) Holcomb, R. C.; Schow, S.; Ayral-Kaloustian, S.; Powell, D. *Tetrahedron Lett.* **1994**, *35*, 7005−7008.
(44) Jurgens, A. R. *Tetrahedron Lett.* **1992**, *33*, 4727−4730.

Table 1. Prochiral Precursors of Diaminodicarboxylic Acids



Entry	Dialdehyde	Product
1		 **13** R = OBn, 76% **16** R = OtBu, 60% **17** R = CH_3, 78%
2		 **18** R = OBn, 72% **19** R = OtBu, 65% **20** R = CH_3, 73%
3		 **21** R = OBn, 78%
4	 n = 6	 **22** R = OBn, 54% **23** R = OtBu, 65% **24** R = CH_3, 64%
5	 n = 10	 **25** R = CH_3, 51%
6		 **26** R = OBn, 40% **27** R = CH_3, 80%
7		 **28** R = OBn, 55%
8	 **15** R^1 = OBn	 **29** R^1 = OBn R^2 = CH_3

to the preparation of orthogonally protected diamino dicarboxylic acids are ongoing, and the results will be reported in due course.

Experimental Section

General. Common experimental procedures and instrumentation have been described previously.[20] Z-Phosphonoglycine methyl ester **9** was purchased from Fluka. Octanedial and dodecanedial were gifts from DSM Chemie Linz. The Rh-DuPHOS catalysts were obtained from Chiroscience or Strem Chemicals. Rh-DIPAMP catalyst was obtained from NSC-Technologies. The CHIRAPHOS ligand was obtained from Fluka.

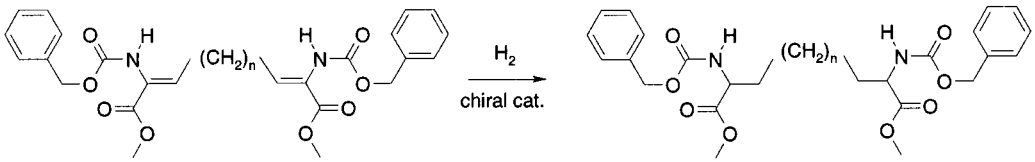
General Method for the Preparation of Protected Dieneamides. The corresponding *N*-protected phosphonoglycine methyl ester **9**, **10**, or **11**[26] (12.075 mmol) was dissolved in dichloromethane (30 mL), DBN (1.45 mL, 12.075 mmol) was added, and the mixture was stirred for 10 min at 10 °C. The dialdehyde (5.84 mmol) was added slowly at a rate to keep the temperature below 10 °C. The reaction was stirred at 5−10 °C for 1 h and allowed to warm to room temperature with stirring overnight.

Workup for Z- or Ac-protected derivatives: The reaction mixture was washed with 1 *N* HCl solution (15.0 mL) and with brine (2 × 10 mL each) until neutral. The organic phase was dried with Na_2SO_4 and filtered, and the filtrate was concentrated in vacuo to yield the crude product, which was purified by crystallization or chromatography as outlined.

Workup for Boc-protected derivatives: The reaction was washed first with a 5% $KHSO_4$ solution and then with brine (2 × 10 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The organic phases were combined, dried with Na_2SO_4, and filtered, and the filtrate was concentrated in vacuo to yield the crude product, which was purified by crystallization or chromatography as outlined.

(2*Z*,6*Z*)-2,7-Bis-(benzyloxycarbonylamino)-octa-2,6-diene-1,8-dioic Acid Dimethyl Ester (13). Compound **13** was prepared from **9** and aqueous butanedial **12**. Crystallization from toluene gave 21.97 g (76.3%) of **13**, mp 130−132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (m, 4 H), 3.75 (s, 6 H), 5.12 (s,

Table 2. Hydrogenation of Unsaturated Precursors Yielding Diaminodicarboxylic Acids[a]



entry	*n*	SM[b]	catalyst	prod[c]	L,L	*meso*	D,D
1	2	**13**	[(COD)Rh(*S*,*S*)-Et-DuPHOS]OTf	**30**	99.5	0.5	–
2	2	**13**	[(COD)Rh(*R*,*R*)-Et-DuPHOS]OTf	**34**	–	0.3	99.7
3	2	**13**	[(COD)Rh(*S*,*S*)-Me-DuPHOS]OTf	**30**	98.5	1.5	–
4	2	**13**	[(COD)Rh(*R*,*R*)-DIPAMP]BF_4	**30**	97.5	2.5	–
5	2	**13**	[(COD)Rh(*R*,*R*)-CHIRAPHOS]OTf[d]	**30**	4.7	30.6	64.7
6	2	**13**	Ru−BINAP·TEA dimer[e]	**30**	85	15	na
7	0	**18**	[(COD)Rh(*S*,*S*)-Et-DuPHOS]OTf	**32**	98.5	1.5	–
8	3	**21**	[(COD)Rh(*S*,*S*)-Et-DuPHOS]OTf	**33**	98.7	1.3	–

[a] All reactions were performed using the following standard set of parameters: 3.5 g of **13**, **18**, or **21** was dissolved in 200 mL oxygen-free MeOH, 100 mg of catalyst, 60 psi initial pressure, ambient temperature, 18 h. The resulting crude material was analyzed by chiral HPLC: Daicel Chiracel OJ-R, 50% 0.5 M $NaClO_4$ buffer pH 6.5 with $HClO_4$; 50% acetonitrile, flow rate: 1.0 mL/min; detection: UV-254 nm. [b] SM = starting material. [c] Prod. = compound number of the major stereoisomer. [d] This catalyst did not hydrogenate at 60 psi: Results shown were obtained using 500 psi and 60 °C, overnight. [e] Because of impurities, the value for the D,D-form was not available (na).

4 H), 6.46 (m, 2 H), 6.51 (m, 2 H), 7.25−7.35 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.25, 52.44, 67.49, 126.50, 128.19, 128.27, 128.54, 134.57, 135.95, 154.10, 164.93. Anal. Calcd for $C_{26}H_{28}N_2O_8$ (MW: 496.52): C, 62.90; H, 5.68; N, 5.64. Found: C, 62.8; H, 5.5; N, 5.7.

(2*E*,6*Z*)-2,7-Bis(benzyloxycarbonylamino)octa-2,6-diene-1,8-dioic Acid Dimethyl Ester (14). Compound **14** containing one *E* configured double bond was isolated as an oil by chromatography (silica gel, eluent: ethyl acetate/petroleum ether = 1/3) of the mother liquor of **13**. The NMR signals are doubled in comparison to **13**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (q, 2 H, J = 7.4 Hz), 2.70 (q, 2 H, J = 7.4 Hz), 3.73 (s, 3 H), 3.77 (s, 3 H), 5.11 (s, 2 H), 5.13 (s, 2 H), 6.40 (br s, 1 H), 6.62 (t, 1 H), 6.71 (m, 1 H), 6.81 (br s, 1 H), 7.26−7.35 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.84, 28.36, 52.30, 67.00, 67.29, 125.35, 126.28, 128.08, 128.16, 128.23, 128.28, 128.48, 128.55, 129.35, 135.99, 136.09, 136.55, 153.76, 154.20, 164.11, 164.96. Anal. Calcd for $C_{26}H_{28}N_2O_8$ (MW: 496.52): C, 62.90; H, 5.68; N, 5.64. Found: C, 62.7; H, 5.4; N, 5.6.

(2*Z*)-2-(Benzyloxycarbonylamino)-1-carboxyhex-2-en-6-al Methyl Ester Hydrate (15). Compound **15** was isolated as an oil by chromatography (silica gel, eluent: ethyl acetate/petroleum ether = 1/3) of the mother liquor of **13**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (m, 1 H), 1.96 (m, 1 H), 1.78 (m, 1 H), 2.10−2.20 (m, 1 H), 2.28−2.40 (m, 1 H), 3.50 (s, 3 H), 5.12 (AB-system, 2 H, J = 12.2 Hz), 6.45−6.58 (m, 3 H), 7.19 (s, 1 H), 7.25−7.38 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.42, 28.06, 51.93, 68.23, 122.96, 128.38, 128.43, 128.56, 129.45, 135.37, 153.45, 165.20. Anal. Calcd for $C_{15}H_{19}NO_6$ (MW: 309.32): C, 58.25; H, 6.19; N, 4.53. Found: C, 58.0; H, 5.9; N, 4.3.

(2*Z*,6*Z*)-2,7-Bis(*tert*-butyloxycarbonylamino)octa-2,6-diene-1,8-dioic Acid Dimethyl Ester (16). Compound **16** was prepared from **11** and aqueous butanedial **12**. Crystallization: toluene/ethyl acetate. Yield: 60%; mp 189−193 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (m, 18 H), 2.34 (m, 4 H), 3.76 (s, 6 H), 6.21 (m, 2 H), 6.45 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.28, 28.22, 52.31, 80.62, 126.52, 133.88, 153.29, 165.26. Anal. Calcd for $C_{20}H_{32}N_2O_8$ (MW:428.48): C, 56.06; H, 7.53; N, 6.54. Found: C, 56.0; H, 7.4; N, 6.6.

2,7-Bis(acetylamino)octa-2,6-diene-1,8-dioic Acid Dimethyl Ester (17). Compound **17** was prepared from **10** and aqueous solution of butanedial **12**. Yield: 78%. Crystallization: MeOH; mp 243−247 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (m, 6 H), 2.20 (m, 4 H), 3.63 (s, 6 H), 6.29 (m, 2 H), 9.20 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.45, 26.06, 51.96, 128.03, 134.36, 164.87, 168.63. Anal. Calcd for $C_{14}H_{20}N_2O_6$ (MW: 312.32): C, 53.84; H, 6.45; N, 8.97. Found: C, 53.8; H, 6.4; N, 8.5.

(2*Z*,4*Z*)-2,5-Bis(benzyloxycarbonylamino)hexa-2,4-diene-1,6-dioic Acid Dimethyl Ester (18). Compound **18** was prepared from aqueous glyoxal and **9**. The resulting crude product was recrystallized from MeOH. Yield: 72%, mp 170−175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 6 H), 5.16 (s, 4 H), 6.66 (s, 2 H), 7.08 (s, 2 H), 7.26−7.40 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.86, 67.87, 123.13, 127.78, 128.37, 128.39, 128.56, 135.67, 153.63, 164.66. Anal. Calcd for $C_{24}H_{24}N_2O_8$ (MW: 468.46): C, 61.53; H, 5.16; N, 5.98. Found: C, 61.1; H, 5.2; N, 5.9.

(2*Z*,4*Z*)-2, 5-Bis(*tert*-butyloxyamino)hexa-2,4-diene-1,6-dioic Acid Dimethyl Ester (19). Compound **19** was prepared from aqueous glyoxal and **11**. Crystallization: MeOH. Yield: 65%. mp: 195−196 °C. ^{1}H NMR(400 MHz, $CDCl_3$) δ 1.40 (s, 18 H), 3.74 (s, 6 H), 6.38 (s, 2 H), 6.98 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.06, 52.67, 81.43, 122.53, 127.83, 152.66, 165.03. Anal. Calcd for $C_{18}H_{28}N_2O_8$(MW: 400.43): C, 53.99; H, 7.05; N, 7.00. Found: C, 53.8; H, 6.9; N, 6.5.

(2*Z*,4*Z*)-2,5-Bis(acetylamino)hexa-2,4-diene-1,6-dioic Acid Dimethyl Ester (20). Compound **20** was prepared from aqueous glyoxal and **10**. During the addition of DBN, a precipitate was formed. After 15 min, TLC ($CHCl_3$/MeOH = 9/1) showed that all starting material was consumed. The resulting precipitated product was filtered, washed on the frit with water (10 mL) and methanol (2 × 5 mL), and dried. Yield: 73%, mp: 274−277 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.98 (s, 6 H), 3.68 (s, 6 H), 6.72 (s, 2 H), 6.87 (s, 2 H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 21.76,51.60, 120.21, 130.38, 164.24, 168.42. Anal. Calcd for $C_{12}H_{16}N_2O_6$ (MW: 284.27): C, 50.70; H, 5.67; N, 9.85. Found: C, 50.6; H, 5.4; N, 9.4.

(2*Z*,7*Z*)-2,8-Bis(benzyloxycarbonylamino)nona-2,7-diene-1,9-dioic Acid Dimethyl Ester (21). Compound **21** was prepared from aqueous glutaraldehyde and **9**. Yield: 78%; mp: 243−247 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (m, 2 H), 2.22 (q, 4 H, J = 7.4 Hz), 3.72 (s, 6 H), 5.11 (s, 4 H), 6.26 (br s, 2 H), 6.58 (t, 2 H, J = 7.4 Hz), 7.25−7.36 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.80, 28.06, 52.36, 67.41, 128.16, 128.26, 128.55, 136.03, 137.10, 154.14, 164.96. Anal. Calcd for $C_{27}H_{30}N_2O_8$ (MW: 510.54): C, 63.52; H, 5.92; N, 5.49. Found: C, 63.2; H, 5.7; N, 5.5.

1,4-Bis[2-(acetylamino)-2-(methoxycarbonyl)ethenyl]-benzene (27). Compound **27** was prepared from *p*-phthalaldehyde and **10**. The crude product was crystallized from toluene to give **2** in 80% yield. mp: 275 °C (decomposition). ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.99 (s, 6 H), 3.70 (s, 6 H), 7.16 (s, 2 H), 7.62 (s, 4 H), 9.51 (s, 2 H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 22.62, 52.48, 127.52, 130.38, 130.86, 134.76, 165.95, 170.08. Anal. Calcd for $C_{18}H_{20}N_2O_6$(MW: 360.37): C, 59.99; H, 5.59; N, 7.73. Found: C, 59.7; H, 5.5; N, 7.5.

1,3-Bis[2-(benzyloxycarbonylamino)-2-(methoxycarbonyl)ethenyl]benzene (28). Compound **28** was prepared from isophthalaldehyde and **9**. The crude product was crystallized from toluene to give **28** in 55% yield. mp: 153−155 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 6 H), 5.05 (s, 4 H), 6.30 (s, 2 H), 7.26−7.30 (m, 10 H), 7.40 (m. 2 H), 7.63 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.66, 67.55, 124.86, 128.25, 128.50, 128.84, 130.41, 130.66, 130.80, 134.13, 135.89, 153.74, 165.50. Anal. Calcd for $C_{30}H_{26}N_2O_8$ (MW: 542.54): C, 66.41; H, 4.83; N, 5.16. Found: C, 66.3; H, 5.2; N, 5.1.

(2Z,6Z)-2-(Acetylamino)-7-(benzyloxycarbonylamino)-hexa-2,6-diene-1,8-dioic Acid Dimethyl Ester (29). Compound **15** (5.09 g, 16.46 mmol) and **10** (3.94 g, 16.46 mmol) were dissolved in dichloromethane (50 mL). Molecular sieves (3 Å, 1 g) were added, and the reaction was stirred for 15 min. Then DBN (1.97 mL, 16.46 mmol) was added via syringe, and the reaction was stirred for 20 h. The reaction was washed with diluted HCl solution (20 mL, 1 N) and water (3 × 50 mL). The organic phase was dried with Na_2SO_4 and filtered, and the filtrate was concentrated to give 5.22 g of crude product. This was crystallized from methanol (35 mL) to yield 3.35 g (50%) of **29**. mp: 141−150 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3 H), 2.31 (m, 4 H), 3.73 and 3.76 (s, 3 H), 5.12 (s, 2 H), 6.45−6.58 (m, 3 H), 7.19 (s, 1 H), 7.25−7.38 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.28, 27.12, 27.51, 52.38, 52.41, 67.40, 126.07, 128.02, 128.08, 128.25, 128.53, 128.56, 135.06, 135.23, 135.89, 154.17, 164.90, 164.97, 168.56. Anal. Calcd for $C_{20}H_{24}N_2O_7$ (MW: 404.42): C, 59.39; H, 5.98; N, 6.93. Found: C, 58.8; H, 6.1; N, 6.8.

(2*S*,7*S*)-2,7-Bis(benzyoxycarbonylamino)octane-1,8-dioic Acid Dimethyl Ester (30). Typical experiment for the catalytic hydrogenation of **13**: **13** (3.5 g, 7.49 mmol) was dissolved in oxygen-free MeOH (200 mL, obtained by refluxing and storing under nitrogen). Rh(COD-*S*,*S*-EtDuPHOS)OTf (100 mg) was added, and the mixture was hydrogenated overnight (18 h) at 4 bar (60 psi) at ambient temperature. The reaction was checked by NMR, indicating that no starting material was detectable. The solution was filtered over silica gel to remove the catalyst. The filtrate was concentrated and degassed to yield crude **30**. This was analyzed by chiral HPLC: 100% ee, 99.0% de. The crude material was crystallized from MeOH to give **30** (100% ee, >99.0% de, $[\alpha]^{20}_D = -14.6$; 5% in $CHCl_3$) in an average yield of 85%. This material was identical with material prepared by Kolbe electrolysis.[20] Optically inactive material was prepared according to ref 20. Retention times: D,D-isomer: 7.11 min; *meso*-isomer: 8.10 min; L,L-isomer: 9.04 min.

(2*S*,5*S*)-2,5-Bis(benzyloxycarbonylamino)hexane-1,6-dioic Acid Dimethyl Ester (32). The hydrogenation was carried out as described for compound **30** using diene **18** and Rh-Et-(*S*,*S*)-DuPHOS as catalyst. Chiral analysis of the crude reaction product by HPLC: 97.0% de (contains 1.5% *meso*-compound), 100% ee (no D,D-compound detectable). Optically inactive material (1:2:1; oil) was prepared using Wilkinson catalyst: retention time of L,L-isomer: 9.94 min; D,D-isomer: 9.24, *meso*-compound: 11.87 min. The crude material (2.02 g) was dissolved in hot MeOH (10 mL) and allowed to crystallize at +4 °C in the refrigerator overnight to give optically pure **32** (100% ee, 100% de by HPLC). Yield: 1.41 g (70%) of colorless crystals. Melting point (111−112 °C) and optical rotation ($[\alpha]^{20}_D = +21.4$; 5% in $CHCl_3$) were identical with material prepared by Kolbe electrolysis.[20]

(2*S*,8*S*)-2,8-Bis(benzyloxycarbonylamino)nonane-1,9-dioic Acid Dimethyl Ester (33). The hydrogenation was carried out as described for **30** using diene **21** as starting material. Chiral analysis of the crude material by HPLC: 97.4% de (contains 1.3% *meso*-compound), 100% ee (no D,D-compound detectable. Optically inactive material (1:2:1; mp 64−67 °C) was prepared using Wikinson catalyst: retention time of L,L-isomer: 15.37 min; *meso*-compound: 13.67; D,D-isomer: 13.18. The crude material (2.34 g) was dissolved in hot MeOH (10 mL) and allowed to crystallize at +4 °C in the refrigerator overnight to give optically pure **33** (100% ee, 100% de by HPLC). Yield: 1.68 g (72.0%) colorless crystals; mp 76−78 °C (MeOH); $[\alpha]^{20}_D = +12.8$ (5% $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (br s, 6 H), 1.61 (br s, 2 H), 1.67 (br s, 2 H), 3.71 (s, 6 H), 4.33 (m, 2 H), 5.09 (s, 4 H), 5.24 (m, 2 H), 7.26−7.35 (m, 10 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 24.92, 28.63, 32.58, 52.31, 53.78, 67.01, 128.10, 128.18, 128.53, 136.29, 155.86, 172.93. Anal. Calcd for $C_{27}H_{34}N_2O_8$ (MW: 514.57): C, 63.02; H, 6.66; N, 5.44. Found: C, 62.9; H, 6.6; N, 5.3.

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Supporting Information Available: Procedures for the synthesis and characterization of compounds **22**−**25**, **26**, and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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