Synthesis of a New 2,3-Diaminoconduritol with Conduritol F Structure

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A new 2,3-diaminoconduritol derivative with the conduritol F structure was prepared starting from cyclohexa-1,4-diene. Initially, a lactam, prepared by the cycloaddition of chlorosulfonyl isocyanate (CSI) to cyclohexa-1,4-diene, was converted into an amino acid. The conversion of the acid functionality into an isocyanate resulted in the formation of an imidazolidinone derivative, formed by an intramolecular cyclization. In the second part of this work, the known anhydride, 3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione was successfully converted into the desired bis(carbamate). The bro-

mination of the double bond in the six-membered ring followed by a DBU-induced (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene) HBr elimination furnished the symmetrical diene. The photooxygenation of the diene unit afforded the bicyclic endoperoxide. The reaction of the endoperoxide with thiourea followed by acetylation resulted in the formation of a *syn*-configured diacetate. The deprotection of the urethane and acetate groups gave the new 2,3-diaminoconduritol with the conduritol F structure.

Introduction

Conduritol (1) is a cyclohexenetetrol (see Figure 1). The presence of four stereogenic centers allows it to exist in six different configurations, that is, the two *meso* forms A and D and the four compounds B, C, E, and F, which can exist as enantiomeric pairs.[1] The two isomers conduritol A and conduritol F were found in nature. Conduritol A[1] was first isolated from the bark of the vine *Marsdenia condurango*.[2] The conduritol derivatives have remarkable biological properties,[3] namely, they act as glycosidase inhibitors.[4]
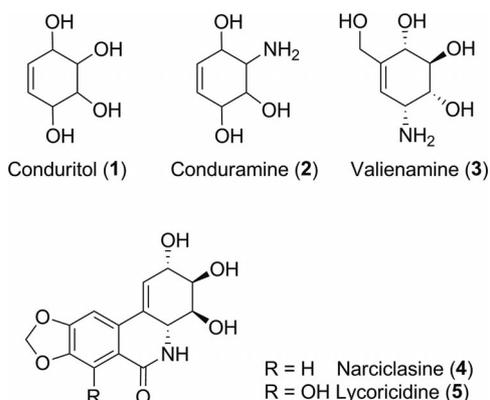
Figure 1. Representative compounds containing conduritol skeleton.

Furthermore, they are potent inhibitors of human immunodeficiency virus (HIV).[5]

Conduramine analogues are aminocyclohexenetriols 2 derived from the conduritols, in which one of the hydroxy groups is replaced by an amino group. One of the most important conduramines is valienamine (3),[6] which was isolated from the microbial degradation of validoxylamine A. Valienamine occurs widely as a building block in several aminoglycoside antibiotics such as narciclasine (4) and lycoricidine (5).[7]

Diaminoconduritols are also derived from the conduritol derivatives, in which two of the hydroxy groups are replaced by amino groups (see Figure 2). There are four constitutional isomers of the diaminoconduritols, namely, 1,2-,[8] 1,3-,[9] 1,4-,[10] 2,3-diaminoconduritols[11] 6–9, and their stereoisomers.
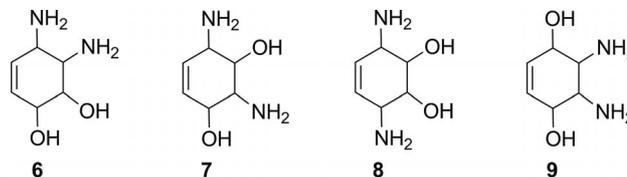
Figure 2. Constitutional isomers of 1,2-, 1,3-, 1,4-, and 2,3-diaminoconduritols 6–9.

The diaminoconduritols also show interesting biological activities such as the inhibition of α- and β-glycosidases.[10a] Furthermore, they are used in the syntheses of diaminoinositol derivatives and some antibiotics[12] as well as cytostatic platinum complexes.[13]

1,2-Diaminoconduritol 6 and 1,3-diaminoconduritol 7 are unknown in free form. However, some derivatives have been reported. In 1984, Kresze et al. synthesized protected

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1,2- and 1,3-diaminoconduritol in five steps starting from benzene oxide.[9] Vogel et al. described the first synthesis of a *meso*-1,4-diaminoconduritol by treating *syn*-benzene dioxide with NaN₃ followed by a reduction.[10c] The application of the same methodology to *anti*-benzene dioxide gave various substituted 1,4-diaminoconduritol derivatives.[10b] Cerè et al. developed an elegant route for the synthesis of 2,3-diaminoconduritol **13**, which has the same configuration as conduritol B, starting with thiepane derivative **10** derived from D-mannitol (Scheme 1).[11a,14] The thiepane derivative **10** was first converted into a diazido derivative, which was then oxidized to **11**, after the protection of the hydroxy groups. The ring contraction and incorporation of the double bond was achieved through the Ramberg–Backlund reaction. The reduction of the azide functions followed by deprotection resulted in the formation of enantiomerically pure 2,3-diaminoconduritol **13**. Savoia et al. synthesized 2,3-diaminoconduritol derivatives through ruthenium-catalyzed ring-closing metathesis starting from the appropriate substrates.[15]
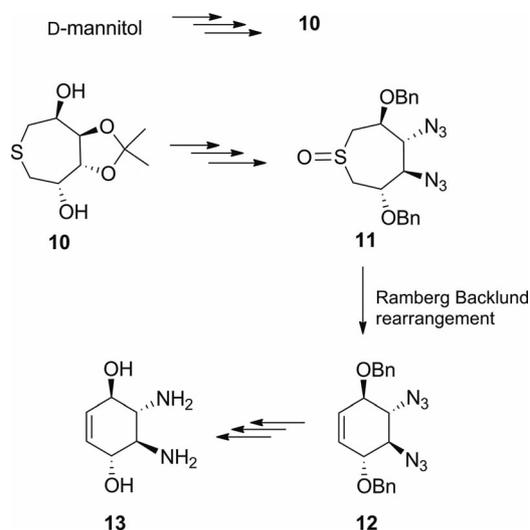
Scheme 1. Synthesis of diaminoconduritol starting from a carbohydrate using the Ramberg–Backlund rearrangement.

In this paper, we describe the synthesis of a new diaminoconduritol, namely, (1*R**,4*S**,5*R**,6*R**)-5,6-diaminocyclohex-2-ene-1,4-diol (**14**).

Results and Discussion

Upon examination of the possible synthetic approaches to the conduritol and various cyclitol derivatives, we decided to adapt a pathway previously used in our laboratory, that is, the photooxygenation of diene systems, to construct a number of conduritol and cyclitol derivatives.[16] According to the retrosynthetic analysis shown in Scheme 2, compound **14** can be obtained by using two concise approaches starting from either 7-azabicyclo[4.2.0]oct-3-en-8-one (**15**) or anhydride **16**.
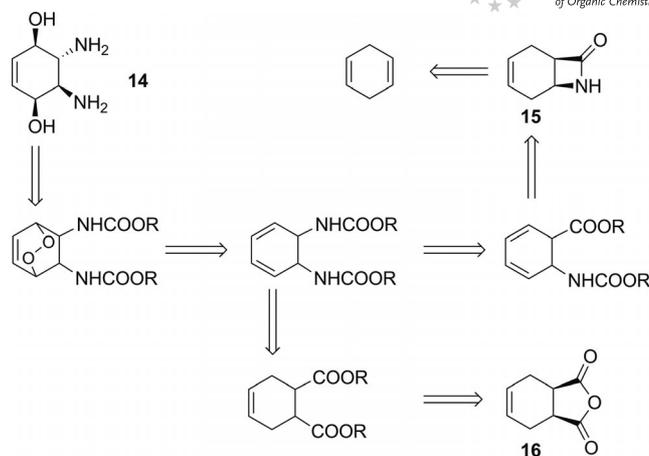
Scheme 2. Retrosynthetic analysis of 2,3-diaminoconduritol **14**.

The cleavage of the azetidin-2-one ring in **15** followed by a Curtius rearrangement of the ester functional group would provide the key intermediate, a derivative of cyclohexa-3,5-diene-1,2-diamine. This intermediate can also be synthesized from anhydride **16**. The photooxygenation of the diene followed by cleavage of the peroxide linkage would provide the desired compound **14**.

Initially, we focused on the synthesis of lactam **15**, which was prepared by the cycloaddition of chlorosulfonyl isocyanate (CSI) to cyclohexa-1,4-diene, as described in the literature.[17] The 1,2-dipolar cycloaddition of CSI took place stereoselectively to form the *cis*-configured lactam **15**. The removal of the sulfonyl chloride group was accomplished by treatment with NaOH. The cleavage of the lactam ring was achieved by treating with concentrated HCl and heating at reflux temperature to form amino acid **17** (Scheme 3).

One of the general and versatile methods for the syntheses of acyl azides involves the reaction of an anhydride with sodium azide. Therefore, the salt of amino acid **17** was first treated with NaOH and then with ethyl chloroformate to give anhydride **18**. The reaction of anhydride **18** with sodium azide in a mixture of acetone and water gave the expected acyl azide **19** in 69 % yield. Upon heating **19** at the reflux temperature of benzene, isocyanate **20** was formed as an intermediate. However, it was not possible to isolate **20**. Instead, the imidazolidinone derivative **21** was formed by an intramolecular attack of the nitrogen atom's lone pair of electrons on the carbonyl carbon of the isocyanate. To prevent this intramolecular cyclization reaction, acyl azide **19** was dissolved in ethanol and heated at reflux temperature. Unfortunately, the cyclization product, imidazolidinone **21**, was formed again as the sole product. At this stage, we decided to change our synthetic strategy and apply the second approach, as described in Scheme 2.

As an alternate method, the previously known diester **22**[18] was synthesized by the addition of maleic anhydride to the in situ generated butadiene to give anhydride **16**.[19] Treatment of **16** with methanol in the presence of a catalytic amount of HCl afforded diester **22**, which was successfully converted into the desired dihydrazide **23** by treatment with
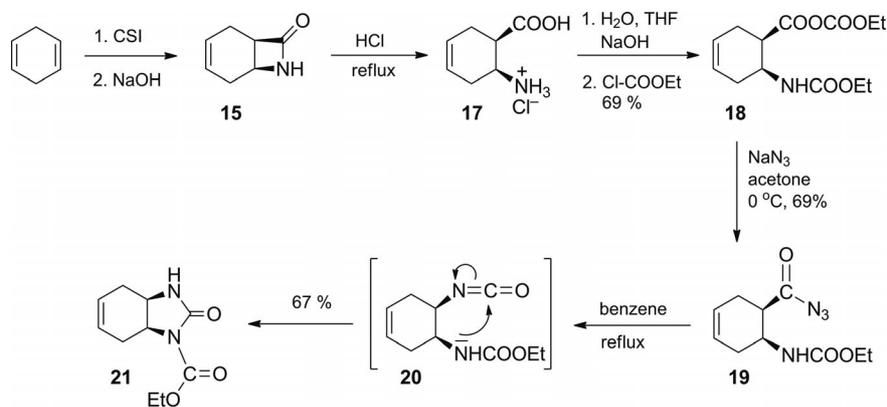
Scheme 3. Synthesis of lactam **15** and its conversion to imidazolidinone derivative **21**.

hydrazine in methanol (Scheme 4). The resulting compound **23** was treated with $NaNO_2$ and HCl at low temperature to give the corresponding diazide **24**.[20] Heating **24** in refluxing benzene gave diisocyanate **25**, which was carried onto the next step. Heating a solution of **25** in ethanol at reflux temperature afforded the two products **26** and **27** in 57% and 40% yields, respectively. The configuration of the substituents in **27** was *trans* and inverted from the *cis* configuration of starting diester **22**. The comparison of the NMR spectroscopic data for **27** with those of **21** clearly indicated that product **27** was a stereoisomer of **21**. We assume that hydrazine can also act as a base during the hydrazination reaction and cause an α-epimerization to occur during the conversion of **22** into **23**. The products **26** and **27** were separated by column chromatography, and their structures were determined unambiguously by NMR spectroscopic data. However, the NMR spectroscopic studies did not reveal the exact configuration of the urethane groups in **26**. To check the effect of temperature on the product distribution, diisocyanate **25** was treated with ethanol at room temperature. Imidazolidinone derivative **27** was formed as the sole product. We assume that the initially formed urethane group blocks the attack of ethanol on the isocyanate group. When the reaction was carried out with methanol at room temperature, again the cyclization product **29** was formed as the sole product. In contrast to ethanol, methanol reacted smoothly with diisocyanate **25** at high temperatures, and the desired addition product **28** was formed as the single product. We assume that the pK_a values of MeOH ($pK_a = 15.5$) and EtOH ($pK_a = 15.9$) are responsible for the product distribution, as MeOH is more reactive than EtOH.

For chemical proof of the configuration, bis(urethane) derivative **28** was treated with *m*-CPBA (*meta*-chloroperoxybenzoic acid) in dichloromethane at room temperature to give **30** as a single isomer with an unsymmetrical structure (Scheme 5). This indicated the isomeric configuration of the urethane substituents. In the case of the substituents in **28** having the *cis* configuration, two isomeric epoxides with symmetrical structures would be formed. The most
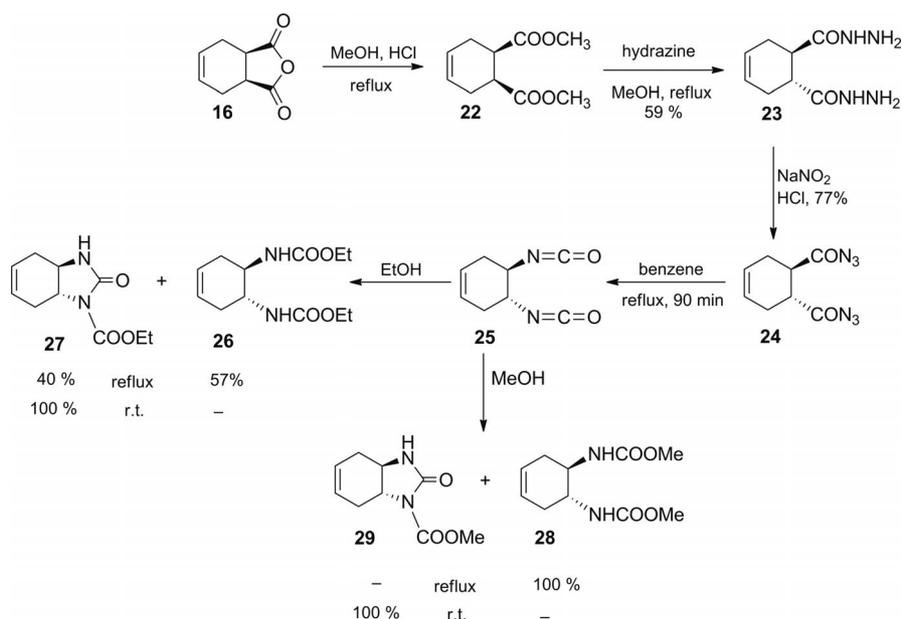
Scheme 4. Syntheses of bis(urethane) derivatives **26** and **28** and imidazolidinones **27** and **29**.

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conspicuous features in the ^{1}H NMR spectrum of **30** are the resonances of the epoxide protons. They appear at $\delta = 3.16$ ppm as a multiplet and 3.08 as a triplet ($J = 4.3$ Hz). The COSY spectrum of **30** shows a strong correlation between the epoxide protons, clearly indicating that these epoxide resonances arise from a single isomer.
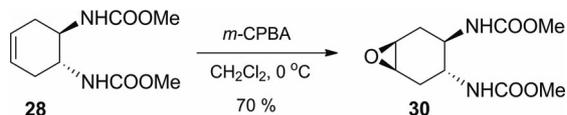
Scheme 5. Epoxidation of bis(urethane) **28**.

After the successful synthesis of bis(carbamate) **28**, the next step was the introduction of hydroxy groups to the C-2 and C-5 positions in **28**. One of the best methods to introduce oxygen functionalities in the *cis* configuration is through a photooxygenation reaction of the appropriate dienes.[22] To synthesize the diene moiety, the double bond in **28** was brominated at 0 °C to give a single isomer **31** (Scheme 6). The symmetrical structure, confirmed by the five-line ^{13}C NMR spectrum, was in agreement with the *trans* addition of bromine to the double bond in **28**. The bromine can approach the double bond from either the top or bottom, and there is no differentiation between those approaches. However, the formed bromonium ion can be opened in two ways. The bromide anion can attack either of the two carbon atoms to give an isomeric mixture consisting of **31** and **34** (see Figure 3).
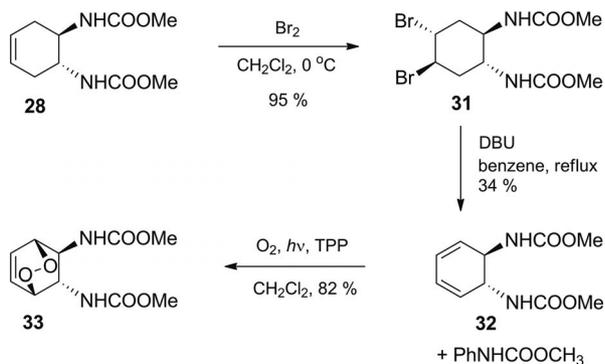
Scheme 6. Synthesis of diene **32** and its photooxygenation reaction.

Figure 3. Possible bromine addition products **31** and **34**.

We assume that the bromide anion attacks the initially formed bromonium ion from the less-hindered side to form **31** as the sole product. A DBU-induced (DBU = 1,8-diaza-bicyclo[5.4.0]undec-7-ene) HBr elimination furnished symmetrical diene **32** in 34% yield. The photooxygenation[22] of **32** in dichloromethane (500 W, projection lamp) at room temperature using tetraphenylporphyrine as the sensitizer

afforded the bicyclic endoperoxide **33** in 82% yield. The diene unit in **32** is symmetric and can be attacked from both sides to form a single isomer. However, the ten-line ^{13}C NMR spectrum as well as the ^{1}H NMR spectrum shows that the formed compound is not symmetric because of the *trans* configuration of the urethane groups.

Unsaturated bicyclic endoperoxides can easily be converted into the corresponding diols upon treatment with thiourea under very mild conditions.[22,23] The reaction of the endoperoxide **33** with thiourea in methanol gave diol **35**. The acetylation of the diol in pyridine with acetic anhydride at room temperature afforded diacetate **36** with the *syn* configuration (Scheme 7). Finally, 2,3-diaminoconduritol **37** with all groups deprotected was obtained by hydrolysis of **36** with NaOH followed by treatment with HCl. The six-line ^{13}C NMR spectrum as well as the ^{1}H NMR spectrum was in agreement with the proposed structure.
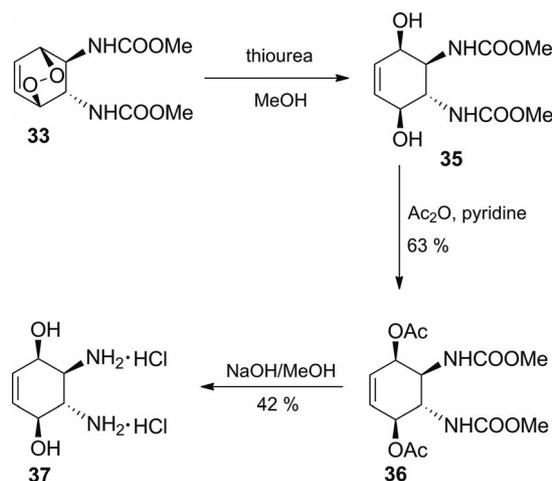
Scheme 7. Synthesis of 2,3-diaminoconduritol **37**.

Conclusions

The synthesis of 2,3-diaminoconduritol **37** with the conduritol F structure was achieved starting from anhydride **16**. The nitrogen functionalities were introduced by the Curtius rearrangement of the corresponding acyl azides, whereas the *cis*-configured oxygen functionalities were attached to C-1 and C-4 by a photooxygenation of the diene unit. The cleavage of the oxygen–oxygen bond followed by hydrolysis of the urethane groups provided 2,3-diaminoconduritol **37**.

Experimental Section

General Methods: Infrared spectra were obtained from solution (CHCl$_3$) in a cell (0.1 mm) or from KBr pellets using a FT-IR Bruker Vertex 70 instrument. The ^{1}H and ^{13}C NMR spectroscopic data were recorded with a Bruker-Biospin (DPX-400) instrument. The apparent splitting is given in all cases. Column chromatography was performed with silica gel (60-mesh, Merck), and TLC was carried out with Merck 0.2 mm silica gel 60 F$_{254}$ analytical aluminum plates.

(1R*,6S*)-7-Azabicyclo[4.2.0]oct-3-en-8-one (15): The lactam derivative **15** was synthesized as described in the literature; m.p. 118–120 °C (CHCl₃, colorless crystals); ref.[17] m.p. 121.5–122.5. ¹H NMR (400 MHz, CDCl₃): δ = 6.44 (br. s, 1 H, NH), 5.82–5.75 (m, 1 H, 4-H), 5.70–5.61 (m, 1 H, 3-H), 3.91 (t, J = 4.8 Hz, 1 H, 6-H), 3.29 (t, J = 4.8 Hz, 1 H, 1-H), 2.42–2.22 (m, 2 H, 5-H), 2.15–2.01 (m, 2 H, 2-H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 170.9, 126.0, 124.3, 47.9, 46.9, 27.1, 21.2 ppm.

(1R*,6S*)-6-Aminocyclohex-3-ene-1-carboxylic Acid·HCl (17): Compound **17** (white solid) was synthesized as described in the literature.[17c] ¹H NMR [400 MHz, DMSO (dimethyl sulfoxide)]: δ = 8.17 (br. s, 3 H, NH₃Cl), 5.70–5.50 (m, 2 H, 3-H and 4-H), 3.58–3.48 (m, 1 H, 6-H), 3.06–2.97 (m, 1 H, 1-H), 2.44–2.22 (m, 4 H, 2-H and 5-H) ppm. ¹³C NMR (100 MHz, DMSO): δ = 173.6, 125.4, 123.0, 45.9, 39.1, 27.5, 24.9 ppm.

Synthesis of {(1R*,6S*)-6-[(Ethoxycarbonyl)amino]cyclohex-3-en-1-yl}carbonyl Ethyl Carbonate (18): To a solution of aminocarboxylic acid **17** (1.16 g, 6.53 mmol) in THF (tetrahydrofuran, 40 mL) and water (2 mL) was added dropwise a cooled solution of NaOH (1.04 g, 26.00 mmol) dissolved in minimum amount of water. After 30 min, a cold (0 °C) solution of ethyl chloroformate (4.24 g, 39.07 mmol) in THF (10 mL) was added dropwise over a period of 10 min, and then the reaction mixture was stirred for 4 h in an ice bath. The reaction mixture was diluted with EtOAc (50 mL), and the resulting solution was washed with a 10% HCl solution (3 × 30 mL). The organic layer was washed with brine (2 × 20 mL), dried with MgSO₄, and concentrated in vacuo. The residue was purified by chromatography on a silica gel column (CH₂Cl₂) to afford anhydride **18** (1.28 g, 4.48 mmol, 69%) as a white solid; m.p. 132–133 °C (EtOAc/hexane, 4:1). ¹H NMR (400 MHz, CDCl₃): δ = 5.63 (apparent t, 2 H, 3-H and 4-H), 5.16 (d, J = 6.3 Hz, 1 H, NH), 4.40–4.14 (m, 4 H, OCH₂), 3.01–2.89 (m, 1 H, 1-H), 2.62–2.13 (m, 4 H, 2-H, and 5-H), 1.32 (t, J = 7.2 Hz, 3 H, CH₃), 1.26 (t, J = 6.5 Hz, 3 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 166.2, 154.9, 147.7, 124.0, 123.2, 64.7, 59.9, 45.2, 41.6, 29.3, 24.3, 13.5, 12.9 ppm. IR [ATR (attenuated total reflectance)]: ṽ = 3340, 3325, 2982, 2934, 1815, 1716, 1514, 1239, 1084, 986 cm⁻¹. C₁₃H₁₉NO₆ (285.29): calcd. C 54.73, H 6.71, N 4.91; found C 54.40, H 7.08, N 4.65.

Ethyl (3aR*,7aS*)-2-Oxo-2,3,3a,4,7,7a-hexahydro-1H-benzimidazole-1-carboxylate (21): To a solution of anhydride **18** (0.32 g, 1.1 mmol) in acetone (30 mL) at 0 °C was added a solution of sodium azide (0.11 g, 1.65 mmol) in water (10 mL). After completion of the addition, the resulting mixture was stirred for 1 h. Ethyl acetate (30 mL) was added, and the organic phase was separated. The organic phase was washed with water (2 × 30 mL) and dried with MgSO₄. After removal of the solvent under reduced pressure, the residue was dissolved in dry benzene (30 mL), and the resulting solution was heated at reflux temperature for 2 h. Evaporation of the solvent yielded imidazolidinone **21** (157 mg, 67%) as a white solid; m.p. 135–136 °C (hexane/dichloromethane, 7:3). ¹H NMR (400 MHz, CDCl₃): δ = 6.83 (s, 1 H, NH), 5.83–5.71 (m, 2 H, 5-H and 6-H), 4.30–4.14 (m, 3 H, 7a-H and OCH₂), 3.93 (q, J = 4.8 Hz, 1 H, 3a-H), 2.36 (dt, A part of AB system, J = 15.6, 5.2 Hz, 1 H, 7-H), 2.28 (dt, B part of AB system, J = 15.6, 5.1 Hz, 1 H, 7'-H), 2.24 (dt, A part of AB system, J = 15.3, 5.0 Hz, 1 H, 4-H), 2.14 (dt, B part of AB system, J = 15.9, 4.4 Hz, 1 H, 4'-H), 1.38 (t, J = 7.0 Hz, 3 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 156.4, 151.9, 127.0, 126.7, 62.2, 54.1, 47.5, 28.5, 26.9, 14.4 ppm. IR (ATR): ṽ = 3307, 3029, 2980, 2909, 1778, 1714, 1318, 1285, 1138, 1099, 778 cm⁻¹. C₁₀H₁₄N₂O₃ (210.23): calcd. C 57.13, H 6.71, N 13.33; found C 57.12, H 6.42, N 13.38.

(1S*,2S*)-Cyclohex-4-ene-1,2-dicarbohydrazide (23): Hydrazine monohydrate (38.22 g, 0.76 mol) was added to a stirred solution of diester **22**[18] (43.22 g, 0.22 mol) in MeOH (75 mL), and the resulting solution was heated at reflux temperature for 12 h. The solvent was removed in vacuo. The residue was filtered and was washed with dichloromethane to give dihydrazide **23** (26.0 g, 59%) as a white solid; m.p. 230–233 °C (THF); ref.[21] m.p. 236–238 °C. ¹H NMR (400 MHz, DMSO): δ = 8.98 (br. s, 2 H, NH), 5.65 (br. s, 2 H, 4-H and 5-H), 3.8–3.2 (br. s, 4 H, NH₂), 2.60–2.44 (m, 2 H, 1-H and 2-H), 2.20–1.95 (m, 4 H, 6-H and 3-H) ppm. ¹³C NMR (100 MHz, DMSO): δ = 174.4, 126.3, 45.5, 29.9 ppm.

(1S*,2S*)-Cyclohex-4-ene-1,2-dicarbonyl Diazide (24): Dihydrazide **23** (6.2 g, 31 mmol) was dissolved in HCl (1 M solution, 100 mL), and the resulting solution was cooled to 0 °C. To this was added dropwise at 0–5 °C a solution of NaNO₂ (4.3 g, 62 mmol) dissolved in water (10 mL). The mixture was stirred at this temperature range for 1 h and then was extracted with diethyl ether (3 × 75 mL). The combined ether layers were washed with saturated NaHCO₃ (2 × 50 mL) and brine (50 mL). The organic layer was dried with MgSO₄, and the solvent was evaporated, keeping the temperature under 30 °C, to give diacyl azide **24** (5.2 g, 24 mmol, 77%) as a light yellow liquid.[21] ¹H NMR (400 MHz, CDCl₃): δ = 5.72–5.64 (m, 2 H, 4-H and 5-H), 2.88–2.78 (m, 2 H, 1-H and 2-H), 2.50–2.38 (br. d, J = 17.9 Hz, 2 H, 3-H and 6-H), 2.20–2.06 (m, 2 H, 3'-H and 6'-H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 181.7, 124.6, 42.9, 27.7 ppm.

(4S*,5S*)-4,5-Diisocyanatocyclohexene (25): Diacyl azide **24** (5.2 g, 24 mmol) was dissolved in dry benzene (75 mL), and the resulting solution was heated to reflux temperature for 90 min. Evaporation of solvent gave the rearranged product, diisocyanate **25**, as light yellow liquid. The compound was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ = 5.64 (m, 2 H, 1-H and 2-H), 3.73–3.66 (m, 2 H, 4-H and 5-H), 2.63–2.52 (br. d, A part of AB system, J = 17.5 Hz, 2 H, 3-H and 6-H), 2.28–2.17 (br. ddd, B part of AB system, J = 17.5, 5.3, and 3.5 Hz, 2 H, 3'-H and 6'-H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 123.7, 55.3, 32.62 ppm.

Reaction of (4S*,5S*)-4,5-Diisocyanatocyclohexene (25) with EtOH at Reflux Temperature: Diisocyanate **25**, obtained from diacyl azide **24** (5.2 g, 23.6 mmol), was dissolved in EtOH (75 mL), and the resulting solution was heated to reflux temperature. After 6 h, the solvent was evaporated. The crude residue was a mixture of **26** and **27**, which were separated by silica gel column chromatography (CH₂Cl₂).

Diethyl [(1S*,6S*)-Cyclohex-3-ene-1,6-diyl]dicarbamate (26): Compound **26** (white powder, 3.43 g, 13.4 mmol, 57%) was isolated in the first fraction; m.p. 126–127 °C (EtOAc); ref.[21] m.p. 135–137 °C. ¹H NMR (400 MHz, CDCl₃): δ = 5.55 (br. s, 2 H, 3-H and 4-H), 5.20 (br. s, 2 H, NH), 4.04 (q, J = 7.0 Hz, 4 H, OCH₂), 3.92 (q, J = 5.8 Hz, 2 H, 1-H and 6-H), 2.47 (br. d, A part of AB system, J = 16.2 Hz, 2 H, 2-H and 5-H), 1.96 (dd, B part of AB system, J = 16.3, 5.6 Hz, 2 H, 2'-H and 5'-H), 1.17 (t, J = 7.0 Hz, 6 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 157.1, 124.9, 60.9, 51.7, 32.6, 14.6 ppm.

Ethyl (3aS*,7aS*)-2-Oxo-2,3,3a,4,7,7a-hexahydro-1H-benzimidazole-1-carboxylate (27): Compound **27** (white solid, 1.99 g, 9.45 mmol, 40%) was isolated in the second fraction; m.p. 136–138 °C (EtOAc). ¹H NMR (400 MHz, CDCl₃): δ = 5.74 (br. s, 1 H, NH), 5.68–5.58 (m, 2 H, 5-H and 6-H), 4.23 (q, J = 7.2 Hz, 2 H, OCH₂), 3.56 (dt, J = 10.8, 4.7 Hz, 7a-H), 3.31 (dt, J = 10.9, 5.0 Hz, 1 H, 3a-H), 2.94–2.82 (m, 1 H), 2.44–2.34 (m, 1 H), 2.22–

2.02 (m, 2 H), 1.28 (t, J = 7.2 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 158.2, 152.9, 125.9, 124.7, 62.7, 59.7, 53.8, 31.3, 30.9, 14.6 ppm. IR (KBr): $\tilde{v}$ = 3298, 3022, 2860, 1771, 1687, 1351, 1321, 1289, 1142, 1152, 1013, 680 cm^{-1}. HRMS (EI): calcd. for C$_{10}$H$_{14}$N$_2$O$_5$ [M + H]$^+$ 211.1077; found 211.1085.

Dimethyl (1S^*,6S^*)-Cyclohex-3-ene-1,6-diyldicarbamate (28): Diisocyanate **25**, obtained from diacyl azide **24** (17.8 g, 81 mmol), was dissolved in MeOH (150 mL), and the resulting solution was heated to reflux temperature for 6 h. After evaporation of solvent, the residue was purified (in small portions) by column chromatography (CH$_2$Cl$_2$) to give bis(urethane) **28** (17.4 g, 87%) as a white solid; m.p. 175–176 °C (CH$_2$Cl$_2$). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.53 (br. s, 2 H, 3-H and 4-H), 4.92 (br. s, 2 H, NH), 3.66–3.55 (m, 2 H, 1-H and 6-H), 3.51 (s, 6 H, CH$_3$), 2.52–2.40 (br. d, A part of AB system, J = 17.3 Hz, 2 H, 2-H and 5-H), 2.03–1.88 (m, B part of AB system, 2 H, 2′-H and 5′-H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 157.5, 124.9, 52.2, 51.8, 32.6 ppm. IR (ATR): $\tilde{v}$ = 3305, 2951, 2921, 2843, 1679, 1540, 1281, 1249, 1085, 1059, 669 cm^{-1}. HRMS (EI): calcd. for C$_{10}$H$_{16}$N$_2$O$_4$ [M + H]$^+$ 229.1183; found 229.1185.

Methyl-(3aS^*,7aS^*)-2-Oxo-2,3,3a,4,7,7a-hexahydro-1H-benzimidazole-1-carboxylate (29): Diisocyanate **25**, obtained from diacyl azide **24** (2.04 g, 9.3 mmol), was dissolved in MeOH (50 mL), and the resulting solution was stirred at room temperature for 6 h. After evaporation of solvent, the residue was purified by chromatography on a silica gel column (CH$_2$Cl$_2$) to give imidazolidinone **29** (1.7 g, 8.6 mmol, 93%) as a white solid; m.p. 172–174 °C (CH$_2$Cl$_2$). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.70–5.58 (m, 2 H, 5-H and 6-H), 5.49 (br. s, 1 H, NH), 3.79 (s, 3 H, OCH$_3$), 3.57 (dt, J = 10.9, 4.9 Hz, 1 H, 7a-H), 3.32 (dt, J = 10.9, 4.9 Hz, 1 H, 3a-H), 2.96–2.86 (m, 1 H, 7-H), 2.43–2.33 (m, 1 H, 7′-H), 2.22–2.05 (m, 2 H, 4-H and 4′-H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 157.9, 153.4, 125.7, 124.4, 59.6, 53.6, 53.4, 30.9, 30.6 ppm. IR (ATR): $\tilde{v}$ = 3329, 3232, 3029, 2913, 2854, 2246, 1740, 1682, 1318, 1289, 1142, 723 cm^{-1}. HRMS: calcd. for C$_9$H$_{12}$N$_2$O$_3$ [M + Na]$^+$ 219.07401; found 219.0769.

Dimethyl [(1R^*,3R^*,4R^*,6S^*)-7-Oxabicyclo[4.1.0]heptane-3,4-diyl]dicarbamate (30): To a stirred solution of **28** (500 mg, 2.19 mmol) in CH$_2$Cl$_2$ (30 mL) was added m-CPBA (60%, 818 mg, 4.38 mmol). The reaction mixture was stirred at room temperature for 12 h. The solid matter was removed by filtration, and the filtrate was washed with saturated NaHCO$_3$ (2 × 50 mL) and water (50 mL) and then dried with MgSO$_4$. Removal of the solvent under reduced pressure gave epoxide **30** (374 mg, 70%) as a white solid; m.p. 192–193 °C (EtOAc/hexane, 2:1). ^{1}H NMR (400 MHz, CCl$_4$): δ = 5.01 (br. s, 1 H, NH), 4.76 (br. s, 1 H, NH) 3.70 (s, 6 H, OCH$_3$), 3.16–3.18 (m, 1-H or 6-H), 3.07 (t, J = 4.3 Hz, 1 H, 1-H or 6-H), 2.54–2.33 (m, 2 H, 5-H), 1.88–1.61 (m, 2 H, 2-H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 157.3 (2 C), 52.7, 52.2, 50.9, 50.7, 48.4, 48.3, 31.5, 30.9 ppm. IR (ATR): $\tilde{v}$ = 3301, 2990, 2951, 1681, 1543, 1465, 1312, 1285, 1248, 1090, 652 cm^{-1}. HRMS: calcd. for C$_{10}$H$_{16}$N$_2$O$_5$ [M + H]$^+$ 215.0914; found 215.0950.

Dimethyl [(1S^*,2R^*,4S^*,5S^*)-4,5-Dibromocyclohexane-1,2-diyl]dicarbamate (31): To a magnetically stirred solution of **28** (19.5 g, 85.5 mmol) in CH$_2$Cl$_2$ (150 mL) at 0 °C was added dropwise a solution of bromine (14.4 g, 90 mmol) in CH$_2$Cl$_2$ (25 mL) over a period of 1 h. The reaction mixture was stirred at room temperature for an additional 2 h. After completion of the reaction, a saturated solution of sodium metabisulfite was slowly added to the homogeneous mixture at 0 °C to reduce the excess amount of bromine. The organic phase was separated, washed with water, and dried with

MgSO$_4$. Removal of the solvent gave the crude product, which was washed with cold EtOAc to give adduct **31** (27.3 g, 81 mmol, 95%) as a white solid; m.p. 197–198 °C (EtOH). ^{1}H NMR (400 MHz, DMSO): δ = 7.18 (br. s, 2 H NH), 4.56 (br. s, 2 H, 4-H and 5-H), 3.80–3.68 (br. s, 2 H, 1-H and 2-H), 3.20 (s, 6 H, OCH$_3$), 2.50–2.44 (m, 2 H), 2.03 (br. d, J = 14.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 155.8, 50.6, 49.6, 49.3, 33.2 ppm. IR (ATR): $\tilde{v}$ = 3333, 2943, 1694, 1533, 1288, 1244, 1049, 777 cm^{-1}. HRMS: calcd. for C$_{10}$H$_{16}$Br$_2$N$_2$O$_4$ [M + Na]$^+$ 408.9369; found 408.9335.

Dimethyl [(1R^*,2R^*)-Cyclohexa-3,5-diene-1,2-diyl]dicarbamate (32): To a solution of dibromide **31** (3.0 g, 7.73 mmol) in dry benzene (100 mL) was added a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (4.73 g, 31.08 mmol) at room temperature. The reaction mixture was heated at reflux for 6 h and then cooled to room temperature. The solid was removed by filtration, and the solvent was evaporated. The residue was dissolved in EtOAc (100 mL), and the resulting solution was extracted with aqueous sodium hydrogen carbonate (2 × 50 mL). The organic phase was dried with MgSO$_4$, and the solvent was evaporated. The residue was separated by silica gel column chromatography (EtOAc/CH$_2$Cl$_2$/hexane, 1:2:0.5). The first fraction was methyl phenylcarbamate[24] (colorless crystals, 109 mg, 9%). The second fraction was identified as diene **32** (colorless crystals, 594 mg, 34%); m.p. 162–163 °C (EtOAc). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.90 (apparent d, A part of AA′BB′ system, J = 8.4 Hz, 2 H, 3-H and 4-H), 5.71 (apparent d, B part of AA′BB′ system, J = 8.7 Hz, 2 H, 2-H and 5-H), 5.00 (br. s, 2 H, NH), 4.40 (br. s, 2 H, 1-H and 6-H), 3.61 (s, 6 H, OCH$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 157.2, 128.7, 125.1, 53.0, 52.3 ppm. IR (ATR): $\tilde{v}$ = 3291, 2991, 1688, 1537, 1263, 1026, 685 cm^{-1}. HRMS: calcd. for C$_{10}$H$_{14}$N$_2$O$_4$ [M + Na]$^+$ 249.0846; found 249.0828.

Dimethyl [(1R^*,4R^*,5R^*,6S^*)-2,3-Dioxabicyclo[2.2.2]oct-7-ene-5,6-diyl]dicarbamate (33): To a stirred solution of **32** (390 mg, 1.72 mmol) in CH$_2$Cl$_2$ (30 mL) was added tetraphenylporphyrine (TPP, 20 mg). The resulting mixture was irradiated with a lamp (500 W), as oxygen was passed through the solution. The reaction mixture was stirred at room temperature for 24 h. After evaporation of solvent (30 °C, 20 Torr), the residue was washed with cold CH$_2$Cl$_2$ to give endoperoxide **33** (364 mg, 82%) as colorless crystals; m.p. 153–155 °C (EtOH). ^{1}H NMR (400 MHz, DMSO): δ = 7.93 (d, J = 6.8 Hz, 1 H, NH), 7.40 (d, J = 6.6 Hz, 1 H, NH), 6.82 (t, J = 6.9 Hz, 1 H, 7-H), 6.64 (t, J = 6.4 Hz, 1 H, 8-H), 4.69 (br. t, J = 4.0 Hz, 1 H, 1-H or 4-H), 4.65 (br. d, J = 6.0 Hz, 1-H or 4-H) 3.96–3.88 (m, 1 H, 5-H), 3.61 (s, 3 H, OCH$_3$), 3.59 (s, 3 H, OCH$_3$), 3.56–3.48 (m, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, DMSO, ppm): δ = 156.6, 156.1, 132.4, 130.7, 74.7, 71.2, 52.7, 51.4 (2 C), 49.0 ppm. IR (ATR): $\tilde{v}$ = 3328, 2955, 1682, 1526, 1291, 1229, 1033, 941 cm^{-1}. HRMS: calcd. for C$_{10}$H$_{14}$N$_2$O$_6$ [M + Na]$^+$ 281.0741; found 281.0803.

(1R^*,4S^*,5S^*,6S^*)-5,6-Bis[(methoxycarbonyl)amino]cyclohex-2-ene-1,4-diyl Diacetate (36): To a solution of endoperoxide **33** (364 mg, 1.41 mmol) in MeOH (50 mL) stirred by a magnetic stir bar was added thiourea (215 mg, 2.82 mmol) at room temperature. The mixture was stirred at room temperature for 3 h, and the solids were removed by filtration. Pyridine (10 mL) and Ac$_2$O (3 mL) were added to the viscous liquid residue followed by stirring at room temperature for 12 h. The residue was then quenched with ice-cold HCl (30 mL), and after stirring for 5 min, the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with a NaHCO$_3$ solution and water and then dried with MgSO$_4$. After evaporation of solvent, the residue was purified by silica gel column chromatography (EtOAc/n-hexane, 2:1) to give diacetate **36** (305 mg, 63%) as colorless crystals; m.p.

180–182 °C (EtOAc/*n*-hexane, 2:1). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.08 (ddd, A part of AB system, *J* = 10.1, 5.0, and 1.7 Hz, 1 H, 2-H), 5.82 (dd, B part of AB system, *J* = 10.1, 2.0 Hz, 1 H, 3-H), 5.43 (br. d, *J* = 9.2 Hz, 1 H, 4-H), 5.32–5.27 (m, 2 H, 1-H and NH), 5.17 (br. d, 1 H, NH), 4.17 (q, *J* = 9.5 Hz, 1 H, 5-H), 3.99 (ddd, *J* = 12.8, 9.5, and 3.7 Hz, 1 H, 6-H), 3.69 (s, 6 H, OCH$_3$), 2.13 (s, 3 H, COCH$_3$), 2.12 (s, 3 H, COCH$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 170.1, 170.0, 158.0, 157.2, 131.6, 126.1, 71.7, 68.4, 52.5, 52.4, 52.3, 52.2, 20.9 (2 C) ppm. IR (ATR): $\tilde{v}$ = 3327, 2950, 1732, 1694, 1532, 1234, 1040, 920 cm^{-1}. HRMS: calcd. for C$_{14}$H$_{20}$N$_2$O$_8$ [M + Na]$^+$ 367.1119; found 367.1177.

(1*R**,4*S**,5*R**,6*R**)-5,6-Diaminocyclohex-2-ene-1,4-diol Dihydrochloride (37): To a solution of compound **36** (148 mg, 0.43 mmol) in MeOH (10 mL) stirred by a magnetic stir bar was added NaOH (2 M solution, 2 mL) at room temperature. The mixture was stirred for 12 h. The solid was removed by filtration, and the pH of the solution was adjusted to pH = 1 by adding HCl (1 M solution). After the addition of water (10 mL), the aqueous phase was extracted with EtOAc (3 × 20 mL). The water phase was evaporated, and the residue was washed with hot ethanol to give compound **37** (39 mg, 42%) as a white solid; m.p. > 210 °C dec (hot EtOH). ^{1}H NMR (400 MHz, D$_2$O): δ = 6.04–5.94 (m, 2 H, 2-H and 3-H), 4.52 (t, *J* = 4.2 Hz, 1 H, 4-H), 4.45–4.39 (br. d, *J* = 8.6 Hz, 1 H, 1-H), 3.87 (dd, *J* = 11.6, 4.2 Hz, 1 H, 5-H), 3.59 (dd, *J* = 11.6, 8.6 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, D$_2$O): δ = 131.5, 126.6, 67.6, 62.9, 52.3, 50.9 ppm. IR (ATR): $\tilde{v}$ = 3339, 2845, 1620, 1556, 1514, 1004, 927 cm^{-1}. HRMS: calcd. for C$_6$H$_{13}$N$_2$O$_2$ [M]$^+$ 145.0972; found 145.1010.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all new compounds.

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