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Stereoselective Synthesis of Cyclopropane-1,2-*bis*(Glycine) Derivatives.

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Abstract: Conformationally constrained *bis*(glycines) as *trans* derivatives of cyclopropane have been prepared in stereoselective syntheses. (*S*)-4-Benzyl-2-oxazolidinone was used as a chiral auxiliary, trisyl azide was the electrophilic source of amine nitrogen. Four stereogenic centers were created. A related *cis*-cyclopropane derivative suffered ring closure with formation of a *bicyclo*[3.1.0]hex-3-one derivative. X-ray data for the latter and for (1*S*,2*S*)-1,2-*bis*{(1*S*)-azido-2-oxo-2[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]-ethyl}cyclopropane are presented. © 1997 Elsevier Science Ltd.

Introduction

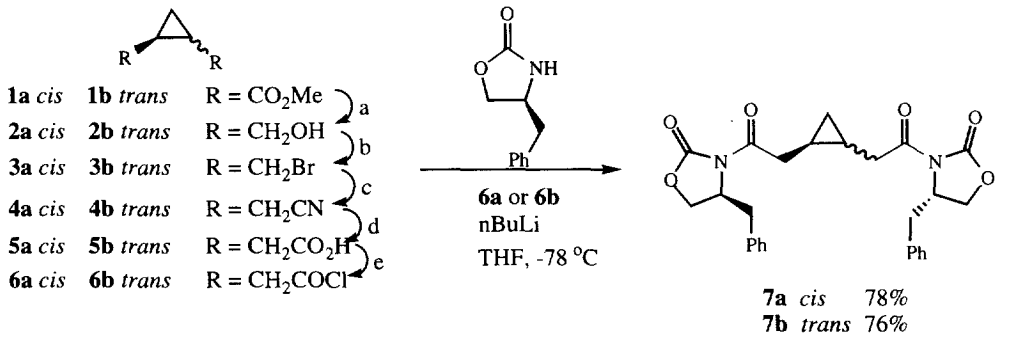
Incorporation of rigidified amino acids into small and medium-sized peptides and peptidomimetics will lead to conformationally constrained molecules. These modifications have significant effects on bioactivities, with concomitant medical implications.[1] In our effort to construct rigidified analogs of the physiological amino acid cystine we have replaced the four-atom -CH_2SSCH_2- bridge in cystine with various C_4-bridges between the α- and α´-positions in the two glycine residues in cystine. Unsaturation in the bridge between the two central carbons gives a *cis*- or a *trans*-olefin bridge that corresponds to a β,β´-interconnection of two alanine residues through the double bond.[2] When the C_4-bridge is part of the benzene ring between the 1- and 4-positions, the bridge corresponds to connecting two glycine units.[3] When the amino acid units have a 1,2-relationship in a carbo- or heteroaromatic ring, the interconnection is between two alanine residues at the β- and β´-carbons.[4] The aim in this work was to construct rigidified C_2-bridges between the α- and α´-positions in two glycine residues in a stereoselective manner. A natural choice might be a 1,2-disubstituted ethene bridge. But because the double bond in such a molecule was expected to undergo ready migration into an α-position in one of the glycine residues, we chose to concentrate on the preparation of methano analogs, *i.e.* two glycine units are connected through cyclopropane. In the rigid cyclopropane system the distance between the glycine residues in the *trans*-configuration may well correlate with significantly populated cystine conformations. This report describes a successful, stereoselective synthesis of the two *trans*-isomers.

Results and Discussion

We have previously used the Evans chiral carboximide approach for amino acid synthesis, where the nitrogen is introduced as an electrophile on a chiral phenylacetamide derivative for the preparation of *bis*(glycines).[4,5] The same methodology was adapted for creating the two new stereogenic centers at the glycine carbons in the C_2-bridged *bis*(glycines). The target molecules **12** and **13** are shown in Scheme 3. The substrate for the amination reaction was to be cyclopropane-1,2-diacetic acid. Both the *cis*- and *trans*-isomers were to be included (Scheme 1).

In the synthesis of propane-1,2-diacetic acid the *trans*-isomers were obtained as a racemate. No attempt was made to resolve the racemate because we wanted to convert both stereoisomers into *bis*(glycines). This

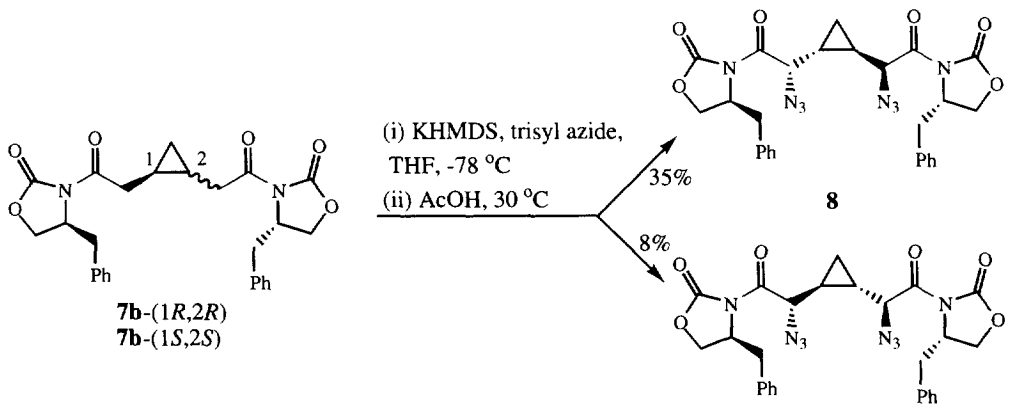
was to be effected at a later stage in the synthesis when the cyclopropane isomers would be present as diastereomers suitable for separation.



(a) LAH, Et_2O, rfx; 74%
(b) Br_2PPh_3, MeCN, 20 °C; 88%
(c) KCN, H_2O/EtOH, rfx; 73%/67%
(d) NaOH, rfx; 82/66%
(e) $(COCl)_2$, CH_2Cl_2, DMF, 0 °C; 92%/97%

Scheme 1

The synthesis of propane-1,2-diacetic acid starts with the preparation of cyclopropane-1,2-dicarboxylic acid methyl esters **1a** and **1b** by reacting methyl acrylate with methyl chloroacetate and sodium hydride in toluene.[6] The ratio of *cis* to *trans* products is temperature dependent; we found a *cis*:*trans* ratio of 7:1 at 35 °C, and 3:2 at 105 °C. The mixture could be separated into the *cis*- and *trans*-isomers by careful fractional distillation (Fischer Spaltrohr column). In the present case, however, it was more convenient to reduce the mixture of isomers with lithium aluminum hydride (LAH) to form the diols **2**, which were readily separated by flash chromatography. The subsequent reactions were carried out on the pure stereoisomers. The diols were converted into the respective bromides **3a** and **3b** by reaction with the bromine complex of triphenylphosphine in acetonitrile. Subsequent treatment with potassium cyanide in aqueous ethanol yielded

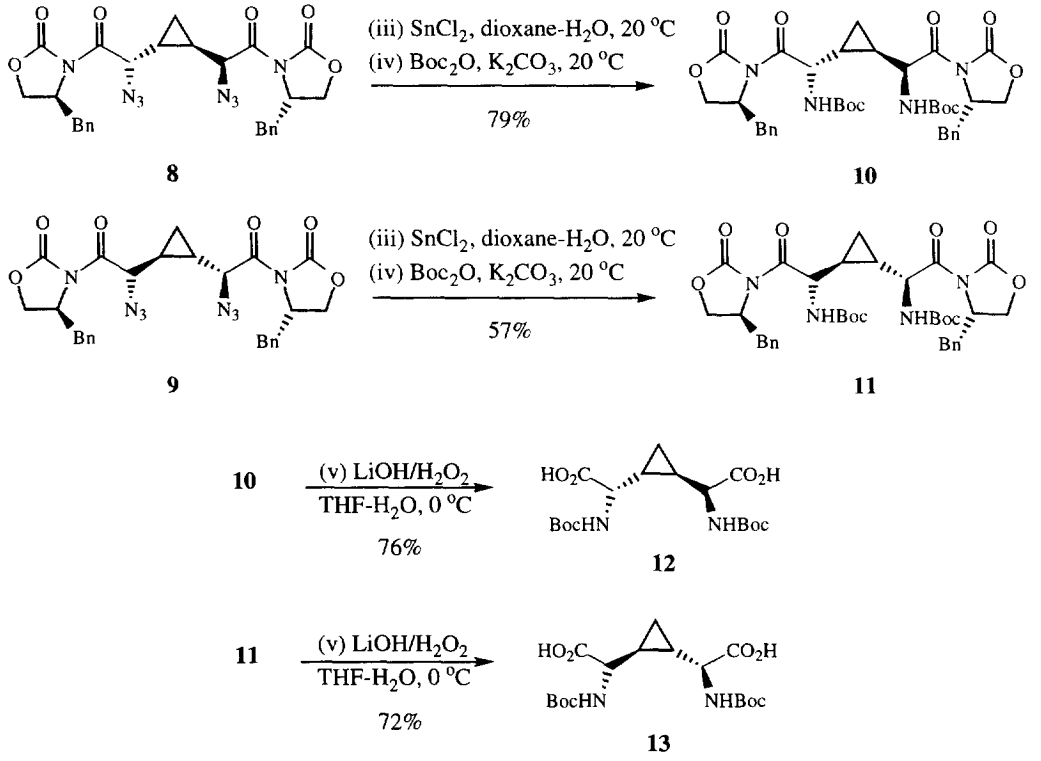


Scheme 2

the *bis* nitriles **4a** and **4b**. Hydrolysis with sodium hydroxide furnished the cyclopropane-1,2-diacetic acids **5a** and **5b**. Oxalyl chloride at 0 °C was used to effect formation of the acid chlorides **6a** and **6b**. The *N*-acylation of lithiated (*S*)-4-benzyl-2-oxazolidinone was run at -78 °C; the products were the *cis*- and *trans*-diacetamides **7a** and **7b**.

The NMR spectra of the *cis*-structure **7a** at 300 and 500 MHz showed a complex splitting pattern in the range 2.5-3.5 ppm, and the ^{13}C NMR spectrum showed doublets of almost every peak, in agreement with the stereochemistry of **7a**.

For the introduction of electrophilic nitrogen in the form of 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide)[13] at the α-carbons in the *trans*-isomer **7b**, the latter was enolized by addition of 2.1 mole equivalents of potassium hexamethyldisilazide (KHMDS) at -78 °C; enolization was effected at both α-carbons. The triazenes initially formed in the substitution were converted to the corresponding azides by addition of acetic acid.[5b] The product was purified by flash chromatography with separation of the diastereomers **8** and **9** which were isolated pure in 35 and 8% yield, respectively, after repeated chromatographic separations. The minor isomer crystallized from ethyl acetate:hexane. Its structure was determined by single-crystal X-ray analysis as (1*S*,2*S*)-1,2-bis{(1*S*)-azido-2-oxo-2[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]ethyl}cyclopropane (**9**) (*vide infra*); the major *trans*-isomer therefore has been assigned the structure (1*R*,2*R*)-1,2-bis{(1*S*)-azido-2-oxo-2[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]ethyl}cyclopropane (**8**).

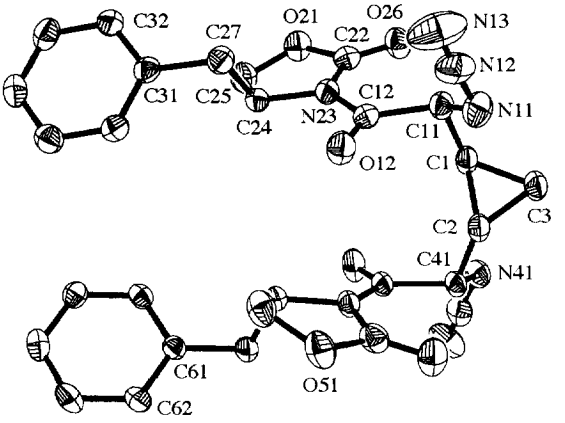


Scheme 3

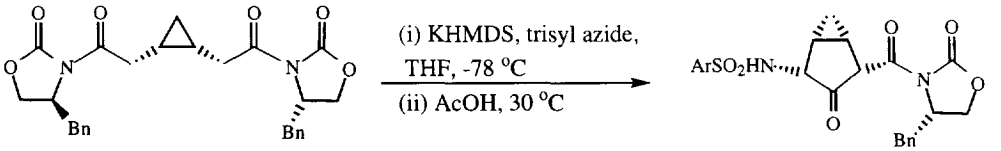
The azido group in these derivatives was reduced to amino groups with tin(II) chloride in aqueous dioxane. The (1*S*,2*S*)-isomer **9** was reduced at a significantly lower rate than its (1*R*,2*R*)-stereoisomer **8**. The amino compounds were isolated and purified as the *N*-Boc derivatives **10** and **11** after treatment of the crude

amination product with *t*-butyloxycarbonyl anhydride; overall yields in the one-pot reactions were 79 and 57%, respectively. Treatment of the *N*-Boc derivatives **10** and **11** with two equivalents of lithium peroxide, from lithium hydroxide in hydrogen peroxide, in aqueous THF at ambient temperature cleaved off the chiral auxiliary functions to furnish the *N*-Boc-protected cyclopropane-1,2-*bis*(glycines) **12** and **13**; yields 76 and 72%. With lithium hydroxide alone, extensive endocyclic cleavage of the oxazolidinone ring was observed in accordance with previous observations in work with this methodology.[5b]

Fig 1. Thermal-ellipsoid plot of the X-ray structure of the *trans* compound **9.**



In the thermal-ellipsoidal plot of the X-ray structure of the *trans*-compound **9**, ellipsoids are shown at 50% probability. H-atoms have been omitted in order to avoid clutter. Where appropriate, the final digit in each atom label corresponds to the numbering used in the text. Label numbers in the bottom half of the drawing are obtained by adding 30 to the corresponding number in the upper half. The absolute configuration shown was established from the known chirality of (*S*)-4-benzyl-2-oxazolidinone. The molecule has approximate two-fold symmetry, but some deviations are quite large. The angles C1-C2-C41 and C2-C1-C11 are about 120° The torsion angles C3, C2, C1, C11 and C3, C1, C2, C41 are close to 112° only slightly larger than corresponding angles in **14**. The distances in the azido group (1.232(2) and 1.131(2) Å) as well as the N-N-N angle of 172.8(3)° are consistent with $-\bar{N}-\overset{+}{N}\equiv N$ and $-N=\bar{N}=\bar{N}$ as the major contributors to the structure. Other geometric features are generally unremarkable.



7a **14**

Scheme 4

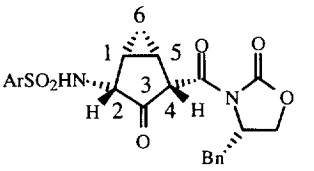
Ar = 2,4,6-$iPr_3C_6H_2$

The metallation of the *cis*-isomer with KHMDS at -78 °C, followed by addition of the sulfonyl azide reagent, did not take the same course as with the *trans*-isomers (*vide supra*). The chiral auxiliary (*S*)-4-benzyl-2-oxazolidinone was found in the reaction mixture. A complementary product with structure **14** was isolated

from the mixture after the reaction. ^{1}H and ^{13}C NMR suggested a bicyclic fused structure for this product, which was thought to be a 2-trisyltriazene derivative of bicyclo[3,1,0]hex-3-one, presumably a precursor of the 2-sulfonamide **14** (Table 1). Single-crystal X-ray analysis, however, showed that a molecule of nitrogen had been lost, and that the compound was the sulfonamide **14**. The crystal habits of the sulfonamide **14** were dependent on the solvent used for recrystallization. In *t*-butyl methyl ether edge-truncated tetrahedra were formed, whereas in mixtures of ethyl acetate and hexane stout needles were precipitated; the unit cells were also quite different.

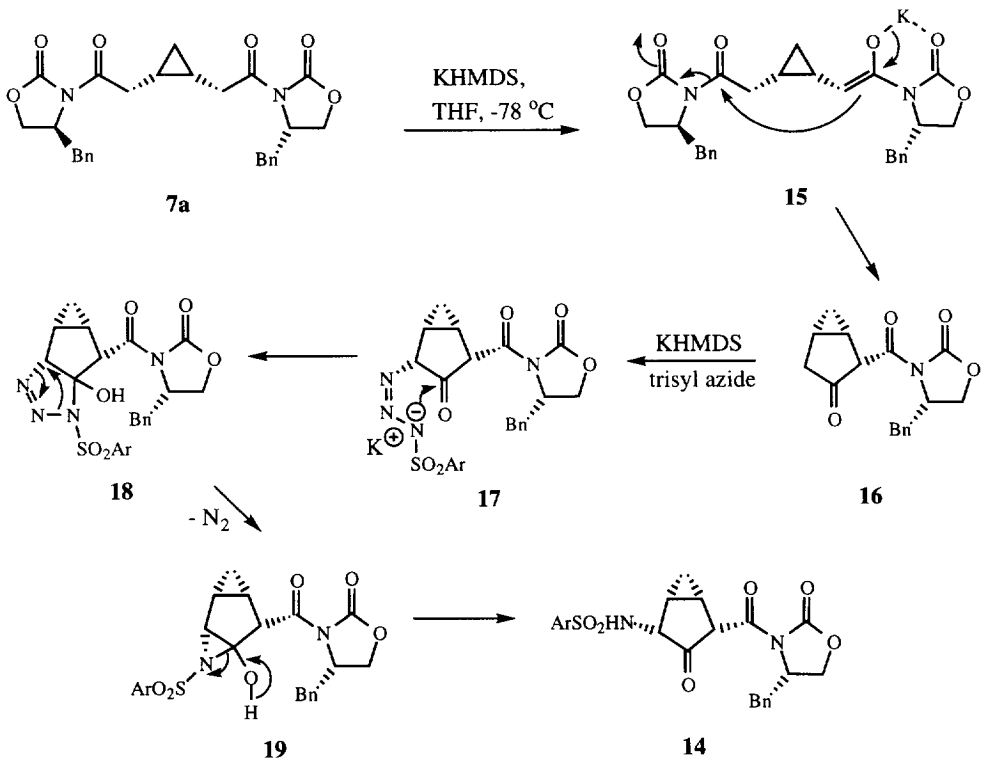
Table 1. Selected Correlations from the Gradient Selected HMBC Spectrum of Compound **14**.

	C-1	C-2	C-3	C-4	C-5	C(O)N
N-H	X		X			
H-1			X			
H-2						
H-4			X		X	X
H-5			X			
$H\text{-}6_A$	X	X		X	X	
$H\text{-}6_B$		X		X		



14

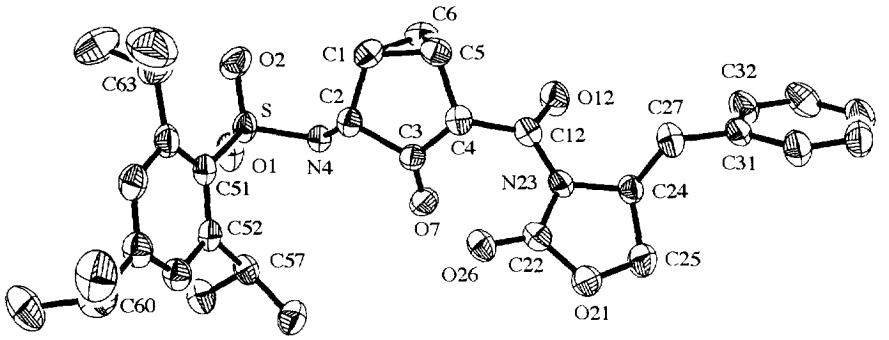
Ar = 2,4,6-$iPr_3C_6H_2$



Scheme 5

A possible rationalization for the formation of **14** is shown in Scheme 5. After initial lithiation the *cis* carbonyl group in the vicinal cyclopropane position is ideally spaced for five-membered ring formation by nucleophilic attack from the lithiated substituent. The resulting bicyclic pentanone **16** is subsequently metallated and reacts with the azide to form a triazene **17** which as a nucleophile may add to the carbonyl carbon, with subsequent loss of nitrogen to form the observed sulfonamide **14**. No further study of this reaction has been carried out.

Fig. 2. Thermal-ellipsoid plot of the X-ray structure of the *cis*-compound **14**



In the thermal-ellipsoid plot of the X-ray structure of the *cis*-compound **14**, crystal form 2, ellipsoids are shown at 50% probability. H-atoms have been omitted in order to avoid clutter. Disorder at C63 is also not shown. Where appropriate, the final digit in each atom label corresponds to the numbering used in the text. The absolute configuration shown was established from X-ray data for each crystal form of **14**; it agrees with the known chirality of (*S*)-4-benzyl-2-oxazolidinone. The central, fused ring system is boat shaped. C1, C2, C4 and C5 are coplanar, as expected from fusion with cyclopropane. The cyclopropane ring makes an angle of 69.4° with the central plane, and the C2, C3, C4 plane makes an angle of 31° with the same plane. N4 carries a hydrogen atom in a pyramidal configuration. C2, C3, C4 and O7 are coplanar.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded at 200 MHz with a Varian Gemini 200 if nothing else is noted, at 300 MHz with a Bruker Avance DPX 300 or at 500 MHz with a Bruker Avance DRX 500 instrument. The ^{13}C NMR spectra were recorded at 50, 75 or 125 MHz using the above instruments. Molecules **7a** and **14** were investigated by gradient selected (z gradient) $^{1}H\{^{13}C\}$ HMBC (optimized for 10 Hz coupling constants) and gradient selected $^{1}H\{^{13}C\}$ HMQC spectra, recorded with the Bruker Avance DRX 500 spectrometer equipped with either a 5 mm triple resonance (^{1}H, ^{13}C, ^{15}N) inverse detection probe (TXI) or with a 2.5 mm broad-band inverse probe (BBI) equipped with actively shielded z-gradient coils. The following Bruker experiments were used; cosygsmf (gradient selected multiple quantum filtered correlated spectroscopy), inv4gslplrnd (GS-HMBC) and inv4gs (GS-HMQC).

The mass spectra under electron impact conditions were recorded at 70 eV (EI). The chemical ionization mass spectra were recorded either with methane (CI-CH_4) or ammonia (CI-NH_3) as ionization gas. Under direct chemical ionization conditions methane was used as the ionization gas (DCI-CH_4). The spectra are presented as *m/z* (% rel. int.).

X-ray data were measured with Siemens diffractometers, a P4/RA with a rotating-anode (Cu) generator for one modification of **14**, and an R3/V with sealed-tube (Mo) generator for **9**, and for a second modification of **14** (*vide infra*). The crystals were kept at 120(1) K during data collection. The low-temperature equipment was locally modified versions of commercial equipment (Siemens and Enraf-Nonius). The structures were

solved by direct methods with program shelxs-93,[7] and refined with a beta version of shelxl-96,[8] both running on a Macintosh Performa® computer. Graphics is from the XP program of SHELXTL,[9] running on a DEC VAX 3200®, Observational data and results of structure refinements have been deposited with the Cambridge Data Centre.

Materials. Potassium *bis*(trimethylsilyl)amide (KHMDS) was purchased from Aldrich Chemical Co. as a 0.5 M solution in toluene and titrated prior to use.[5b] The solid KHMDS (95%) was purchased from Aldrich Chemical Company and was used as received.

Dimethyl *cis-/trans*-cyclopropane-1,2-dicarboxylate (**1**). A mixture of the *cis*- and *trans*-isomers were obtained as described.[6] The mixture could be separated by Spaltrohr distillation but the isomer mixture was normally used directly in the subsequent reaction. *cis-Isomer* (**1a**): ^{1}H NMR ($CDCl_3$): δ 1.16-1.27 (1H, m), 1.60-1.69 (1H, m), 2.00-2.07 (2H, m), 3.66 (6H, s). ^{13}C NMR ($CDCl_3$): δ 11.7, 21.3, 52.0, 170.3. *trans -Isomer* (**1b**): ^{1}H NMR ($CDCl_3$): δ 1.35-1.42 (2H, m), 2.08-2.16 (2H, m), 3.65 (6H, s). ^{13}C NMR ($CDCl_3$): δ 15.3, 22.1, 52.1, 172.1.

cis-(**2a**) and *trans*-(**2b**) 1,2-bis(hydroxymethyl)cyclopropane. LAH reduction of the *cis/trans* mixture of the diester **1** gave the alcohols **2** as described.[10] The mixture of *cis*- and *trans*-diol was separated by flash chromatography using hexane:EtOAc (1:9), EtOAc and EtOAc + 5% MeOH. *cis*-Isomer (**2a**): ^{1}H NMR ($CDCl_3$): δ 0.19 (1H, dd, *J* 5.3, 10.5 Hz), 0.72-0.83 (1H, m), 1.19-1.37 (2H, m), 3.12 (2H, s, OH), 3.16-3.27 (2H, m), 4.03-4.12 (2H, m). ^{13}C NMR ($CDCl_3$): δ 8.5, 17.4, 62.9. *trans*-Isomer (**2b**): ^{1}H NMR ($CDCl_3$): δ 0.40 (2H, dd, *J* 6.6, 7.1 Hz), 0.92-1.05 (2H, m), 3.00 (2H, dd, *J* 8.8, 11.4 Hz), 3.82 (2H, dd, *J* 8.8, 11.4 Hz), 4.07 (2H, s, OH). ^{13}C NMR ($CDCl_3$): δ 7.2, 20.0, 66.1.

cis-1,2-Bis(bromomethyl)cyclopropane (**3a**). Bromine (7.89 g, 2.54 mL, 49.35 mmol) was added dropwise with stirring to a suspension of triphenylphosphine (13.34 g, 49.35 mmol) in acetonitrile (70 mL) at 0 °C. The cooling bath was subsequently removed and a solution of the *cis*-alcohol **2a** (2.40 g, 23.50 mmol) in acetonitrile (7 mL) was added dropwise. This mixture was stirred at ambient temperature for 1 h, the precipitate filtered off and the filtrate concentrated at reduced pressure. The residue was dissolved in diethyl ether, filtered, concentrated and distilled, bp. 100 °C/10 mm Hg [lit.[10b] bp. 86-88 °C/7 mm Hg]. The isomer **3a** was obtained in 87% yield (4.647 g). ^{1}H NMR ($CDCl_3$): δ 0.41 (1H, dd, *J* 5.7, 11.4 Hz), 1.09-1.21 (1H, m), 1.57-1.70 (2H, m), 3.39-3.55 (4H, m). ^{13}C NMR ($CDCl_3$): δ 16.7, 22.7, 33.5.

trans-1,2-Bis(bromomethyl)cyclopropane (**3b**); yield 89% . ^{1}H NMR ($CDCl_3$): δ 0.83 (2H, dd, *J* 6.8, 7.2 Hz), 1.25-1.35 (2H, m), 3.23-3.39 (4H, m). ^{13}C NMR ($CDCl_3$): δ 17.9, 24.9, 37.2.

cis-1,2-Bis(cyanomethyl)cyclopropane (**4a**). A solution of potassium cyanide (4.08 g, 62.65 mmol) in water (10 mL) was poured into a solution of the bromide **3a** (3.57 g, 15.66 mmol) in ethanol (23 mL, 96 %) at 60-70 °C.[11] The mixture was heated under reflux for 15 h, the brown reaction mixture cooled, the solvents removed under reduced pressure and enough water added to dissolve the inorganic salts. The resulting mixture was extracted with diethyl ether several times, and the combined organic phases washed with brine and dried ($MgSO_4$). Evaporation of the solution gave a yellow oil which was distilled, bp. 130-150 °C/0.25-0.3 mm Hg, yield 73% (1.367 g), colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.35 (1H, dd, *J* 5.7, 11.6 Hz), 0.99-1.10 (1H, m), 1.19-1.37 (2H, m), 2.42-2.52 (4H, m). ^{13}C NMR ($CDCl_3$): δ 11.3, 11.8, 16.7, 118.3.

trans-1,2-Bis(cyanomethyl)cyclopropane (**4b**) was obtained as above in 67% yield. ^{1}H NMR ($CDCl_3$): δ 0.74 (2H, dd, *J* 6.6, 7.2 Hz), 1.03-1.14 (2H, m), 2.47 (2H, d, *J* 5.7 Hz). ^{13}C NMR ($CDCl_3$): δ 11.1, 13.5, 20.6, 117.6.

cis-Cyclopropane-1,2-diacetic acid (**5a**).[11b] The cyanide isomer **4a** (0.563 g, 4.686 mmol) was heated under reflux with sodium hydroxide (1.874 g, 46.86 mmol) in water (10 mL) for 2.5 h, the cold mixture extracted with diethyl ether (x3), the water phase acidified with 30% H_2SO_4 to pH 3, extracted several times with diethyl ether and dried ($MgSO_4$). Evaporation of the combined ether solution yielded a solid which was recrystallized from ethyl acetate, m.p.129-130 °C [lit.[11b] 130.5-132 °C]; yield 82% (0.609 g). ^{1}H NMR ($CDCl_3$): δ 0.01 (1H, dd, *J* 5.5, 11.1 Hz), 0.81-0.92 (1H, m), 1.21-1.37 (2H, m), 1.88-2.03 (2H, m, C<u>H</u>HC=O), 2.86-2.97 (2H, dd, *J* 4.2, 16.8 Hz, CH<u>H</u>C=O), 12.25 (br s, OH). ^{13}C NMR ($CDCl_3$): δ 11.2, 19.8, 34.2, 180.7.

trans-Cyclopropane-1,2-diacetic acid (**5b**) was prepared as above in 66% yield. Mp. 114.5-115.5 °C (EtOAc) [lit.[12] 116 °C]. $[\alpha]_D^{20}$ -3.2° (c = 0.5, MeOH). IR (neat): ν 1714 (O=C-alkyl). ^{1}H NMR ($CDCl_3$): δ 0.49 (2H, dd, *J* 6.7, 7.0 Hz, CH_2), 0.92-1.09 (2H, m, C<u>H</u>C<u>H</u>), 1.57 (2H, dd, *J* 11.0, 14.9 Hz, C<u>H</u>HC=O), 2.87 (2H, dd, *J* 3.1, 14.9 Hz, CH<u>H</u>C=O), 12.3 (br s, OH). ^{13}C NMR ($CDCl_3$): δ 10.9, 14.4, 38.5, 180.1.

cis-Cyclopropane-1,2-diacetyl dichloride (**6a**). Oxalyl chloride (0.602 g, 4.742 mmol) in dry dichloromethane (3 mL) was added dropwise at 0 °C to a solution of the acid **5a** (0.250 g, 1.581 mmol) in dry dichloromethane (7 mL) and DMF (2 drops), the solution stirred at 0 °C for 2.5 h, and at ambient temperature for 2 h before the solvent was evaporated. The residual oil was triturated with hexane before distillation; bp. 75-85 °C/0.3 mm Hg of a colorless oil; yield 92% (0.282 g). ^{1}H NMR ($CDCl_3$): δ 0.16-0.26 (1H, m), 1.00-1.11 (1H, m), 1.27-1.48 (2H, m), 2.77-3.00 (4H, m). ^{13}C NMR ($CDCl_3$): δ 11.0, 11.7, 46.6, 173.0.

trans-Cyclopropane-1,2-diacetyl dichloride (**6b**) was prepared as above from *trans*-cyclopropane-1,2-diacetic acid (1.169 g, 7.39 mmol), oxalyl chloride (2.815 g, 22.18 mmol), DMF (3 drops) in dichloromethane (45 mL) in 97% yield (1.398 g); bp. 90-100 °C/0.23 mm Hg. IR (neat): ν 1802 (C=O acid chloride). ^{1}H NMR ($CDCl_3$): δ 0.64 (2H, dd, *J* 6.6, 7.0 Hz, CH_2), 0.98-1.13 (2H, m, C<u>H</u>C<u>H</u>, 2H), 2.72-2.98 (4H, m, CH_2C=O). ^{13}C NMR ($CDCl_3$): δ 11.5, 14.2, 50.5, 172.8.

(1*R*,2*S*)-1,2-Bis{2-oxo-2[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]ethyl}cyclopropane (**7a**). A solution of *n*BuLi (2.5 M in hexane) was added dropwise with stirring to a solution of (*S*)-4-benzyl-2-oxazolidinone (6.212 g, 35.06 mmol) and triphenylmethane (indicator) in dry THF (58 mL) under argon, at -78 °C until an orange color persisted. The solution was kept between -78 °C and -65 °C during the addition. The solution was stirred at -78 °C for 30 min, and then treated with the acid chloride **6a** (3.624 g, 18.58 mmol) dissolved in dry THF (6 mL). The temperature was kept below -65 °C during the addition. The resulting solution was stirred under argon at -78 °C for 4 h, then poured into saturated aqueous ammonium chloride solution, diluted with water and extracted with dichloromethane (x3). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography using hexane:EtOAc (3:2) to provide a white solid/glassy foam; yield 6.479 g (78%), mp. 100-102 °C. IR (neat): ν 1785, 1705 cm^{-1}. Found: C, 68.43; H, 5.88. Calc. for $C_{27}H_{28}N_2O_6$: C, 68.05; H, 5.92. $[\alpha]_D^{20}$ +95.2° (c = 0.588, EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.17 (1H, dd, *J* 5.5, 10.9 Hz, C<u>H</u>H in cyclopropane), 0.95 (1H, td, *J* 5.1, 8.5, 8.6 Hz, CH<u>H</u> in cyclopropane), 1.36-1.42 (2H, m, C<u>H</u>C<u>H</u> in cyclopropane), 2.78 (1H, dd, *J*7.0, 13.4 Hz, H-6_A), 2.80 (1H, dd, *J* 6.9, 13.4 Hz, H-6_B), 2.88 (1H, dd, *J* 7.5, 17.3 Hz, H-α_A), 2.97-3.06 (2H, m, H-α_B and H-α'_B), 3.18 (1H, dd, *J* 6.1, 17.4 Hz, H-α'_A), 3.32 (1H, dd, *J* 3.2, 13.4 Hz, H-$6'_A$), 3.37 (1H, dd, *J* 3.2, 13.4 Hz, H-$6'_B$), 4.15-4.31 (4H, m, OCH_2), 4.64-4.69 (2H, m, NCH), 7.17-7.37 (10H, m, aromatics). ^{13}C NMR (500 MHz, $CDCl_3$): δ 10.2 (CH_2), 10.8 (<u>C</u>HCH), 11.0 (CH<u>C</u>H), 35.1 (C-α), 35.3 (C-α'), 37.8 (C-6), 37.9 (C-6'), 55.2 (C-4), 55.3 (C-4'), 66.18 (C-5), 66.21 (C-5'), 127.3, 128.89, 128.92, 129.4 (aromatics), 135.3 (C in Ph), 135.4 (C' in Ph), 153.48 (C-ß), 153.49 (C-ß'), 172.7 (C-2), 172.8 (C-2'). MS (CI-CH_4): 477 (*M* + 1, 10), 476 (54), 475 (1), 177 (100).

(1*R*,2*R*)- and (1*S*,2*S*)-1,2-Bis{2-oxo-2[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]ethyl}cyclopropane (**7b**) was isolated in 76% yield (0.637 g) from the reaction between (*S*)-4-benzyl-2-oxazolidinone (0.619 g, 3.50 mmol) and **6b** (0.409 g, 2.10 mmol) in THF (7 mL) using the reaction conditions described for **7a**. IR (neat): ν 1788, 1709 cm^{-1}. Found: C, 68.07; H, 6.00. Calc. for $C_{27}H_{28}N_2O_6$: C, 68.05; H, 5.92. $[\alpha]_D^{20}$ +101.4° (c = 0.576, EtOAc). Mp. 104-105 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 0.55-0.61 (2H, m), 1.04-1.13 (2H, m), 2.78 (2H, dd, *J* 9.7, 13.4 Hz, PhCHH), 2.76-3.09 (4H, m, $CH_2C{=}O$), 3.34 (2H, dd, *J* 3.0, 13.4 Hz, PhCHH), 4.14-4.26 (4H, m, OCH_2), 4.68-4.69 (2H, m, NCH), 7.18-7.34 (10H, m, aromatics). ^{13}C NMR ($CDCl_3$): δ 11.8, 14.4, 38.3, 40.1, 55.5, 66.3, 126.7, 128.3, 128.7, 134.6 (aromatics), 152.6, 171.4. MS (CI-CH_4): 477 (*M*+1, 1), 476 (3), 177 (100).

(1*R*,2*R*)-1,2-Bis{(1*S*)-azido-2-oxo-2-[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]ethyl}cyclopropane (**8**) and (1*S*,2*S*)-1,2-Bis{(1*S*)-azido-2-oxo-2[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]ethyl}cyclopropane (**9**). A precooled (-78 °C) solution of **7b** (0.415 g, 0.87 mmol) in dry THF (7 mL) was added via a teflon cannula to a precooled (-78 °C) solution of potassium bis(trimethylsilyl)amide (0.5 M in toluene, 3.66 mL, 1.83 mmol) diluted with dry THF (6 mL) under argon. The solution of the resulting potassium enolate was kept at this low temperature for 30 min before a precooled (-78 °C) solution of 2,4,6-triisopropylbenzenesulfonyl azide[13] (0.593 g, 1.916 mmol) in dry THF (5.2 mL) was added via a teflon cannula. The reaction was quenched by addition of acetic acid (0.46 mL, 8.01 mmol, 9.2 equiv.) after stirring the solution for 12-15 min. at -78 °C. The slurry was warmed at once to 30 °C in a water bath and stirred at this temperature for 2 h. Ethyl acetate and brine were added and the layers were separated. The aqueous phase was washed with ethyl acetate (x3), the combined organic extracts washed with dilute sodium bicarbonate, dried (Na_2SO_4), and concentrated *in vacuo*. The products were isolated from the residual material by flash chromatography using hexane:EtOAc (5:2). Isomer **8** was first eluated; glassy foam, 0.294 g. Further eluation gave the second isomer **9**; 0.096 g. Both isomers were rechromatographed separately by flash chromatography. Pure **8** was obtained using CH_2Cl_2; yield 0.171 g (35%) of a glassy foam. Pure **9** was obtained using CH_2Cl_2 and CH_2Cl_2 with 1% EtOAc; yield 0.040 g (8%).

(1*R*,2*R*)-1,2-Bis{(1*S*)-azido-2-oxo-2[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]ethyl}cyclopropane (**8**). IR (neat): ν 2100 cm^{-1} (—$N{=}N^+{=}N^-$). R_f (silica plates) in hexane:EtOAc (1:1) 0.51. Found: C, 57.75; H, 4.73. Calc. for $C_{27}H_{26}N_8O_6$: C, 58.06; H, 4.69. $[\alpha]_D^{20}$ +94.6° (c = 0.52, EtOAc). ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (2H, dd, *J* 6.9, 7.1 Hz), 1.52-1.61 (2H, m), 2.85 (2H, dd, *J* 9.4, 13.5 Hz, PhCHH), 3.30 (2H, dd, *J* 3.3, 13.5 Hz, PhCHH), 4.23-4.27 (2H, dd, *J* 2.9, 9.0 Hz, OCHH), 4.36-4.42 (2H, br dd, OCHH), 4.64-4.72 (4H, m, NCH + CHN_3), 7.18-7.38 (10H, m, aromatics). ^{13}C NMR (300 MHz, $CDCl_3$): δ 9.9, 17.0, 37.7, 55.5, 61.8, 66.7, 127.6, 129.1, 129.3, 134.7, 153.1, 169.8. MS (CI-CH_4): 530 (*M*-N_2, 16), 516 (*M*-N_3, 29). MS (DCI-CH_4): 575 (*M*+CH_5^+, 2.8), 558 (*M*, 1.1), 177 (100).

(1*S*,2*S*)-1,2-Bis{(1*S*)-azido-2-oxo-2[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]ethyl}cyclopropane (**9**). This compound could be recrystallized from EtOAc:hexane; the colorless crystals were subjected to X-ray analysis as described below. IR (neat): ν 2105 cm^{-1} (—$N{=}N^+{=}N^-$); R_f (silica plates) in hexane:EtOAc (1:1) 0.40. Found: C, 57.91; H, 4.38. Calc. for $C_{27}H_{26}N_8O_6$: C, 58.06; H, 4.69. $[\alpha]_D^{20}$ +107.1° (c = 0.45, EtOAc). ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (2H, dd, *J* 7.2, 7.3 Hz), 1.47-1.56 (2H, m), 2.77 (2H, dd, *J* 9.4, 13.5 Hz, PhCHH), 3.24 (2H, dd, *J* 3.2, 13.5 Hz, PhCHH), 4.15 (2H, dd, *J* 2.9, 9.0 Hz, OCHH), 4.24 (2H, dd, *J* 7.8, 9.0 Hz, OCHH), 4.61-4.69 (2H, m, NCH), 4.95 (2H, d, *J* 6.3, CHN_3), 7.11-7.27 (10H, m, aromatics). ^{13}C NMR (300 MHz, $CDCl_3$): δ 7.2, 16.6 ($\underline{C}HCH_2$), 37.6 (Ph$\underline{C}H_2$), 55.5 (NCH), 60.7 (CHN_3), 66.8 (OCH_2), 127.5, 129.1, 129.4, 134.7, 153.1, 169.3. MS (CI-NH_3): 576 (*M*+NH_4^+, 0.6), 195 (100).

X-ray data for **9**: Orthorhombic, space group $P2_12_12_1$, a = 9.283(7), b = 9.293(7), c = 30.434(20) Å, V = 2625.4(33) $Å^3$ at 120(1) K, λ (Mo $K\alpha$) = 0.71073 Å, Z = 4, measured 12025 reflections in 2θ range 0-55°, ω scans, 5990 independent, R_{int} = 0.032, 5638 with $I_o > 2\sigma(I_o)$, 372 parameters refined against F^2, R = 0.034

for $I_o > 2\sigma(I_o)$ and 0.037 for all data. The crystals were twinned to mimic tetragonal symmetry, presumably related to the similarity in length of *a* and *b*. Note: The statistical uncertainties for *a* and *b* may be unrealistic because of this. Although the structure could be solved to give a recognizable molecule without taking the twinning into account, it could not be refined to below $R = 0.18$. When twinning was invoked refinement proceeded smoothly. The twin ratio was refined to 0.795:0.295(1). Corresponding bond lengths in the two halves of the molecule were restrained to be similar.

(1*R*,2*R*)-1,2-Bis{(1*S*)-*t*-butyloxycarbonylamino-2-oxo-2[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]ethyl}-cyclopropane (**10**). (1*R*,2*R*-1,2-Bis{(1*S*)-azido-2-oxo-2[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]ethyl}cyclopropane (95% pure, 0.105 g, 0.179 mmol) in dioxane (1.5 mL) was added dropwise at 0 °C to a solution of $SnCl_2$ (97% pure, 0.209 g, 1.069 mmol) in dioxane (1 mL) and water (2 mL). The white solution was stirred at ambient temperature for 4.5 h before Boc-anhydride (0.410 g, 1.88 mmol) and sodium bicarbonate (0.158 g, 1.88 mmol) were added. The resultant suspension was stirred overnight at ambient temperature and acidified with an aqueous solution of potassium bisulfate (1 M). The solution was extracted with ethyl acetate (x3). The combined organic phases were washed with an aqueous solution of sodium bicarbonate, brine, dried (Na_2SO_4), and evaporated. The product was purified by flash chromatography using hexane:EtOAc (2:1). The title compound was obtained as a glassy foam; yield 0.095 g (75%), mp. 96 °C (dec.). Found: C, 63.09; H, 6.53. Calc. for $C_{37}H_{46}N_4O_{10}$: C, 62.88; H, 6.56. $[\alpha]_D^{20}$ +36.8° (c = 0.468; EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.73 (2H, br dd, 1.32-1.39 (2H, m), 1.46 (18H, s, Boc-Me), 2.77 (2H, dd, *J* 9.8, 13.3 Hz, PhCHH), 3.32 (2H, br dd, PhCHH), 4.16 (2H, dd, *J* 2.2, 8.8 Hz, OCHH), 4.31-4.49 (2H, br dd, OCHH), 4.62-4.71 (2H, m, NCH), 5.26 (2H, br s), 5.31 (2H, br s), 7.18-7.38 (10H, m, aromatics). ^{13}C NMR ($CDCl_3$): δ 7.2, 18.1, 28.3, 37.6, 53.0, 55.8, 66.5, 80.1, 127.3, 129.0, 129.4, 135.3, 153.1, 155.1, 172.4.

(1*S*,2*S*)-1,2-Bis{(1*S*)-*t*-butyloxycarbonylamino-2-oxo-2-[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]ethyl}-cyclopropane (**11**) was obtained in 57% yield when the reduction of the azido group in (1*S*,2*S*)-1,2-bis{(1*S*)-azido-2-oxo-2[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]ethyl}cyclopropane was carried out as above with $SnCl_2$. Reduction of this isomer proceeded more slowly, and Boc-anhydride and sodium bicarbonate was added to the reaction mixture after 6 h. Found: C, 62.35; H, 6.46. Calc. for $C_{37}H_{46}N_4O_{10}$: C, 62.88; H 6.56. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.73 (2H, br dd), 1.25-1.29 (2H, m), 1.46 (18H, s, Boc-Me), 2.77 (2H, dd, *J* 9.9, 13.1 Hz, PhCHH), 3.3 (2H, br dd, PhCHH), 4.15-4.19 (2H, m, OCHH), 4.32 (2H, br dd, OCHH), 4.63-4.69 (2H, m, NCH), 5.32 (2H, br s), 5.49 (2H, br s), 7.20-7.37 (10H, m, aromatics). ^{13}C NMR ($CDCl_3$): δ 5.5, 16.9, 28.2, 37.5, 52.6, 55.6, 66.6, 80.0, 127.3, 129.0, 129.3, 135.1, 152.9, 155.1, 171.6.

(1*R*,2*R*)-1,2-Bis[(2*S*)-*t*-butyloxycarbonylamino]cyclopropanediacetic acid (**12**). (1*R*,2*R*)-1,2-Bis{(1*S*)-*t*-butyloxycarbonylamino-2-oxo-2[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]ethyl}cyclopropane (161 mg, 0.228 mmol) was dissolved in THF:H_2O (3:1; 4.56 mL), 30% H_2O_2 (0.186 mL, 1.82 mmol; 8 mole equivalents) added at 0 °C followed by LiOH (LiOH·H_2O, 38.2 mg, 0.911 mmol; 4.0 mole equiv.). The mixture was stirred for 30 min. at 0 °C and quenched by addition of 1.5 M aq. Na_2SO_3 (10% excess, 8.8 mole equivalents). Most of the THF was distilled off and the oxazolidinone chiral auxiliary (67 mg) was recovered by CH_2Cl_2 extraction. The aqueous phase was acidified (pH 1-2) at 0 °C and the carboxylic acid was isolated by EtOAc extraction. The ^{1}H NMR spectrum showed only small impurities. Further purification was effected by trituration with hexane:EtOAc (1:1) using vigorous stirring for 30 min; yield 68 mg (76%) of a white powder; mp. >242 °C (decomp.). Found: C, 52.58; H, 7.21. Calc. for $C_{17}H_{28}N_2O_8$: C, 52.57; H 7.27: $[\alpha]_D^{20}$ +15.0° (c = 0.494, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (2H, br s, CH_2), 1.29 (2H, br s, CHCH), 1.40 (18H, s, CH_3), 3.51 (2H, br d, *J* 9.0 Hz, CHC=O), 5.49 (1.6H, br s, NH), 6.31 (0.4H, br s, NH), 10.66 (2H, br s, OH). ^{13}C NMR (300 MHz, $CDCl_3$): δ 11.8, 19.6, 28.2 (CH_3), 56.9 (CHC=O), 80.3 (C), 155.5 (C=O), 176.8 (C=O).

(1*S*,2*S*)-1,2-Bis[(2*S*)-*t*-butyloxycarbonylamino]cyclopropanediacetic acid (**13**). (1*S*,2*S*)-1,2-bis{(1*S*)-*t*-butyloxycarbonylamino-2-oxo-2[(4*S*)-benzyl-2-oxo-3-oxazolidinyl]ethyl}cyclopropane (61 mg, $8.63 \cdot 10^{-5}$ mol) was dissolved in THF:H_2O (3:1; 1.65 mL), 30% H_2O_2 (0. 078 mL, $6.90 \cdot 10^{-4}$ mol; 8 mole equival.) added at 0 °C followed by LiOH (LiOH·H_2O, 14.5 mg, $3.45 \cdot 10^{-4}$ mol; 4.0 mole equiv.). The mixture was stirred for 30 min. at 0 °C and quenched by addition of 1.5 M aq. Na_2SO_3 (10% excess, 8.8 mole equivalents). pH 11 was registered in the solution. Most of the THF was distilled off and the oxazolidinone chiral auxiliary (67 mg) was recovered by CH_2Cl_2 extraction. The aqueous phase was acidified (pH 1-2) at 0 °C and the carboxylic acid was isolated by EtOAc extraction. The ^{1}H NMR spectrum showed only small impurities. Further purification was effected by trituration with hexane:EtOAc (1:1) using vigorous stirring for 30 min; yield 24 mg (72%) of a white powder, recrystallized from hexane:EtOAc; mp. >103 °C (decomp.). ^{1}H NMR (300 MHz, Acetone-d_6): δ 0.83-0.88 (2H, m, CH_2), 1.27-1.34 (2H, m, CHCH), 1.43 (18H, s, CH_3), 3.59 (2H, br d, *J* 6.2 Hz, CHC=O), 6.03 (1H, br s, NH). ^{13}C NMR (300 MHz, Acetone-d_6): δ 8.3, 19.9, 28.1 (CH_3), 56.6 (CHC=O), 79.0 (C), 155.8 (C=O), 172.6 (C=O).

(1*R*,2*R*,4*S*,5*S*)-4-[(4*S*)-Benzyl-2-oxo-3-oxazolidinyl)carbamoyl]-2-(2,4,6-triisopropylbenzenesulfonylamino)bicyclo[3.1.0]hex-3-one (**14**). A precooled (-78 °C) solution of **7a** (0.200 g, 0.42 mmol) in dry THF (3 mL) was added via a teflon cannula to a precooled (-78 °C) solution of potassium bis(trimethylsilylamide (0.5 M in toluene, 1.76 mL, 0.88 mmol) diluted with dry THF (3 mL) under argon. The solution of the potassium enolate was stirred at this temperature for 30 min, before a precooled (-78 °C) solution of 2,4,6-triisopropylbenzenesulfonyl azide[13] (0.286 g, 0.924 mmol) in dry THF (2.5 mL) was added via a teflon cannula. The solution was stirred for 30 min. at -78 °C and the reaction quenched by addition of acetic acid (0.22 mL, 3.86 mmol, 9.2 equiv). The slurry was quickly warmed to 30 °C on a water bath and stirred at this temperature for 20 h. Ethyl acetate and brine were added and the layers were separated. The aqueous phase was washed with ethyl acetate (x3), the combined organic extracts washed with aq. sodium bicarbonate, dried (Na_2SO_4), and the solvents removed at reduced pressure. The crude product was purified by flash chromatography using hexane:EtOAc 2:1 and hexane:EtOAc 3:2; yield 0.133 g of impure cyclic sulfonamide **14** as a yellow-white, glassy foam. The product was further purified by recrystallization from hexane:EtOAc which gave long, stout needles (Form 1), whereas crystals from *t*-butyl methyl ether were truncated tetrahedra (Form 2). The crystallographic cell dimensions were completely different, but X-ray analysis established that the crystals were of identical composition. Found: C, 66.14; H, 6.85. Calc. for $C_{32}H_{40}N_2O_6S$: C, 66.18; H 6.94: $[\alpha]_D^{20}$ +35.3° (c = 0.252, EtOAc). ^{1}H NMR (500 MHz $CDCl_3$): δ 0.39-0.42 (1H, m, CHH), 0.84-0.88 (1H, m, CHH), 1.15-1.22 (18H, m, CH_3-isopropyl), 1.85-1.93 (2H, m, CHCH), 2.73 (1H, dd, *J* 9.6, 13.4 Hz, PhCHH), 2.77-2.86 (1H, m, CH-isopropyl), 3.21 (1H, dd, *J* 3.1, 13.4 Hz, PhCHH), 4.06-4.13 (3H, m, OCHH + 2 CH-isopropyl), 4.18 (1H, br dd, OCHH), 4.30-4.32 (1H, m, H-2), 4.57-4.62 (1H, m, H-4'), 4.79 (1H, d, *J* 2.6 Hz, NH), 5.18 (1H, d, *J* 4.6 Hz, H-4), 7.11-7.26 (7H, m, aromatics). ^{13}C NMR (500 MHz, $CDCl_3$): δ 7.9 (CH_2), 13.7 (CHCH), 15.6 (CHCH), 23.50, 23.55, 24.8, 25.0, 29.8, 34.2, 37.8 (benzylic), 53.2 (C-2), 55.6 (C-4'), 61.3 (C-4), 66.5 (C-5), 123.9 (trisyl), 127.5, 129.0, 129.4, 131.8 (trisyl), 134.9, 150.5 (trisyl), 153.1 (trisyl), 153.4 (C-2'), 167.3 (carbamoyl C=O), 202.6 (C-3).

X-ray data for **14**: Form 1, monoclinic, space group $P2_1$, a = 21.572(7), b = 6.147(2), c = 23.159(9)Å, β = 92.32(3)°, V = 3068.2(13) Å^3 at 120(1) K), λ (Cu $K\alpha$) = 1.54178 Å, Z = 4, colorless prism 0.20×0.24×0.41 mm, cut from larger needle, measured 7836 reflections in 2θ range 0-112° with θ-2θ scans, 7719 independent, R_{int} = 0.052, 7125 with $I_o > 2\sigma(I_o)$, 329 parameters refined, R = 0.061 for $I_o > 2\sigma(I_o)$ and 0.066 for all data.

Form 2, monoclinic, space group $P2_1$, a = 15.944(7), b = 6.132(2), c = 15.961(7)Å, β = 94.94(4)°, V = 1554.7(11) Å^3 at 120(1) K), λ (Mo $K\alpha$) = 0.71073 Å, Z = 2, colorless, tetrahedron with all six edges truncated, approximate cross section 0.8 mm, measured 4013 reflections in 2θ range 0-55°, ω scans, 3896

independent, R_{int} = 0.020, 3275 with $I_o > 2\sigma(I_o)$, no absorption correction, min, max transmission factors 0.87, 0.91, 384 parameters refined, R = 0.045 for $I_o > 2\sigma(I_o)$ and 0.056 for all data. Disorder of end atoms of one isopropyl group (occupancy ratio 0.77:0.23) complicated refinement.

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