Articles

Synthesis of 3-(*trans*-2′-Nitrocyclopropyl)alanine, a Constituent of the Natural Peptide–Lactone Hormaomycin†

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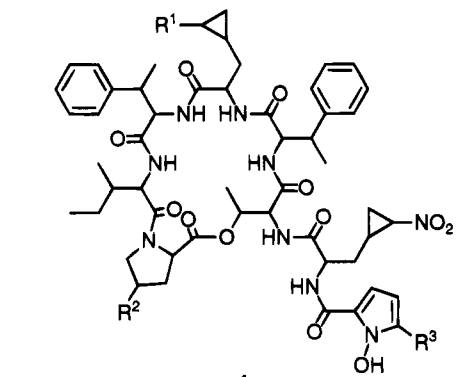
The peptide–lactone hormaomycin **1a** produced by *Streptomyces griseoflavus* contains two molecules of 3-(*trans*-2′-nitrocyclopropyl)alanine [Ala(3-Ncp)] (**6**). In order to determine the unknown absolute configurations of these unusual natural amino acid molecules, which supposedly are essential for the biological activity of **1a**, enantiopure alcohols (*trans*-2-nitrocyclopropyl)methanol [(1*S*,2*S*)-**13** and (1*R*,2*R*)-**13**] have been prepared in six steps from (*R*)- and (*S*)-2,3-*O*-isopropylideneglyceraldehyde (**17**). The alcohols **13** were transformed to the bromides **23**, and these in turn were coupled with suitable glycine equivalents like 2-[(diphenylmethylene)amino]acetates (**24**) to yield (2*R*/*S*,1′*S*,2′*S*)- and (2*R*/*S*,1′*R*,2′*R*)-3-(*trans*-2′-nitrocyclopropyl)alanines (**6**), after deprotection. The natural compound **1a** contains one molecule each with (2*R*,1′*R*,2′*R*)- and (2*S*,1′*R*,2′*R*)-configuration, as established by comparison of the hydrolysate from natural **1a** with the synthesized samples of (2*R*/*S*,1′*R*,2′*R*)-**6** and (2*R*/*S*,1′*S*,2′*S*)-**6**.

Introduction

The peptide–lactone hormaomycin **1a**, produced by *Streptomyces griseoflavus*, is a novel signal metabolite.[1] Its molecules consist of D-*allo*-threonine (D-*allo*-Thr) (**2**), L-isoleucine (L-Ile) (**3**), the unusual amino acids L-*threo*-(3-methylphenyl)alanine [L-*threo*-Phe(3-Me)] (**4**), 4-[(*Z*)-prop-1-enyl]proline [Pro(4-Pe)] (**5**), 3-(*trans*-2′-nitrocyclopropyl)alanine [Ala(3-Ncp)] (**6**), and 5-chloro-*N*-hydroxypyrrole-2-carboxylic acid (Chpca) (**7**). Recently, Zeeck *et al.* have prepared the modified peptide–lactone **1b** with a 3-[(*trans*-2′-(hydroxylamino)cyclopropyl]alanine moiety in the ring by selective partial hydrogenolysis of hormaomycin **1a** (Figure 1).[2] The absolute configurations of the two molecules of **6** in **1a**, one in the ring and one in the side chain, remained unknown. In order to help establish these configurations, to enable a planned total synthesis of **1a**, and to elucidate the biosynthetic route to **1a**, we have developed synthetic methods leading to three diastereomerically pure 3-(*trans*-2′-nitrocyclopropyl)alanines (**6**). A short route to racemic **6** was also developed to provide material for biological testing, as the biological activity of **1a** is believed to rely on the presence of the previously unknown amino acid **6**.

Our strategy toward (2*R*/*S*,1′*S*,2′*S*)- and (2*R*/*S*,1′*R*,2′*R*)-3-(*trans*-2′-nitrocyclopropyl)alanine (**6**) called for both enantiopure (*trans*-2-nitrocyclopropyl)methyl derivatives with a suitable leaving group to be combined with appropriate glycine equivalents.[3] Several methods for the preparation of (*trans*-2-nitrocyclopropyl)methyl de-



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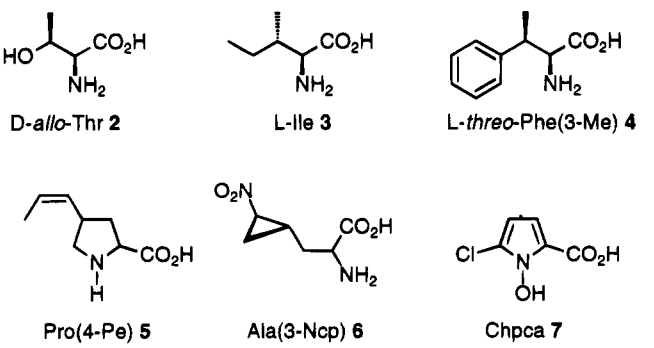
	R^1	R^2	R^3
a	NO_2	(*Z*)-propenyl	Cl
b	NHOH	*n*-propyl	H



D-*allo*-Thr **2** L-Ile **3** L-*threo*-Phe(3-Me) **4**

Pro(4-Pe) **5** Ala(3-Ncp) **6** Chpca **7**

Figure 1. Structure of hormaomycin **1a** and amino acids contained therein.

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† Dedicated to Professor Jürgen Bestmann on the occasion of his 70th birthday.

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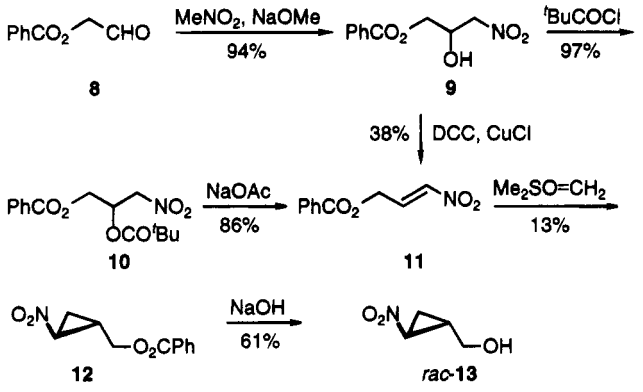
Scheme 1

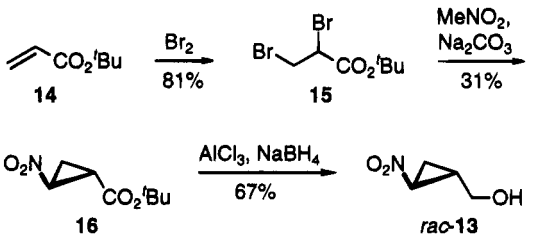


rivatives have been reported: 1,3-dehydrohalogenation of γ-nitrohaloalkanes,[4] 1,3-dehydrosulfonylation of (γ-nitroalkyl)methanesulfonates,[5] intramolecular Mitsunobu reaction of γ-nitro alcohols,[6] Michael addition of methyl nitronate to α-halogenated Michael acceptors[7] or to vinyl selenones,[8] cyclopropanation of nitroalkenes with dimethylsulfoxonium methylide[5,9] or diazomethane[10] and of alkenes with nitrodiazomethane in the presence of dirhodium(II) tetraacetate.[11] Two of these possibilities were tried out, and eventually, one was adopted for the synthesis of both enantiopure (*trans*-2-nitrocyclopropyl)-methanols [(1*S*,2*S*)-**13** and (1*R*,2*R*)-**13**].

Results and Discussion

Synthesis of Racemic (*trans*-2-Nitrocyclopropyl)-methanol (*rac*-13). Nitro aldol addition of sodium methyl nitronate in diethyl ether to the readily available benzoyl-protected glycol aldehyde **8**[12] gave the secondary alcohol **9** in nearly quantitative yield even after crystallization. Acylation of **9** with pivaloyl chloride[13] and β-elimination of the pivalate **10** with sodium acetate in diethyl ether gave the nitroalkene **11**[14] in 83% yield over two steps. Direct dehydration of **9** with dicyclohexylcarbodiimide (DCC) and copper(I) chloride in tetrahydrofuran according to Seebach et al.[15] gave nitroalkene **11** in 38% yield. The cyclopropanation[5,9] of **11** with dimethylsulfoxonium methylide[16] in dimethyl sulfoxide produced the expected ester **12**, but only in 13% yield, and **12** could be cleaved with sodium hydroxide to give *rac*-**13** (Scheme 1).

Scheme 2



On the other hand, *rac*-**13** can easily be prepared in multigram quantities in only three steps from *tert*-butyl acrylate (**14**) (17% overall yield). Addition of bromine[17] to **14** in chloroform gave *tert*-butyl 2,3-dibromopropanoate (**15**), which was transformed to *tert*-butyl (*trans*-2-nitrocyclopropyl)carboxylate (**16**) by simple treatment with nitromethane and sodium carbonate in dimethylformamide. This sequence[7] of 1,2-dehydrobromination, Michael addition of methyl nitronate, and 1,3-dehydrobromination gave **16** in 31% yield. After selective reduction of the *tert*-butoxycarbonyl group with sodium borohydride in the presence of anhydrous aluminum chloride[18] in dimethoxyethane, alcohol *rac*-**13** was isolated in 17% overall yield (Scheme 2).

Synthesis of Enantiopure Alcohols (1*S*,2*S*)-13 and (1*R*,2*R*)-13. A sequence to both enantiopure alcohols (1*S*,2*S*)-**13** and (1*R*,2*R*)-**13** was established with the readily available starting materials (*R*)- and (*S*)-2,3-*O*-isopropylideneglyceraldehyde [(*R*)-**17** and (*S*)-**17**],[19] which can be transformed to the protected 4-nitrobutane-1,2-diols [(*S*)-**18** and (*R*)-**18**],[20] respectively, by one-pot reductive nitromethylation following the procedure of Wollenberg et al.[21] (Scheme 3 and Table 1). The acetals **18** were cleaved with *p*-toluenesulfonic acid in methanol, and the primary hydroxy groups in diols **19** were selectively protected with triphenylmethyl chloride in pyridine[22] in very good yields (80–82 and 87–90%, respectively). The secondary hydroxy groups in the ethers **20** were transformed into a leaving group with methanesulfonyl chloride/triethylamine in dichloromethane, and the methanesulfonates **21** were treated with sodium carbonate in toluene at 110 °C. The 1,3-displacements in **21** occur with complete inversion of configuration at C-2 to give only the *trans*-configurated (2-nitrocyclopropyl)methyl triphenylmethyl ethers (**22**) in 57–59% yield. The enantiopure alcohols (1*S*,2*S*)-**13** and (1*R*,2*R*)-**13** were obtained by cleavage of the ethers **22** with *p*-toluenesulfonic acid in methanol. The ethers (1*S*,2*S*)-**22** and (1*R*,2*R*)-**22** both had enantiomeric purities of >95%, as determined from their ^{1}H NMR spectra measured in the presence of the chiral europium(III) shift reagent [Eu(TFC)$_3$][23] (Scheme 3 and Table 1).

Synthesis of [Ala(3-Ncp)] (6). The primary alcohols **13** were transformed into the bromides **23** by treatment with tetrabromomethane/triphenylphosphane in dichlo-

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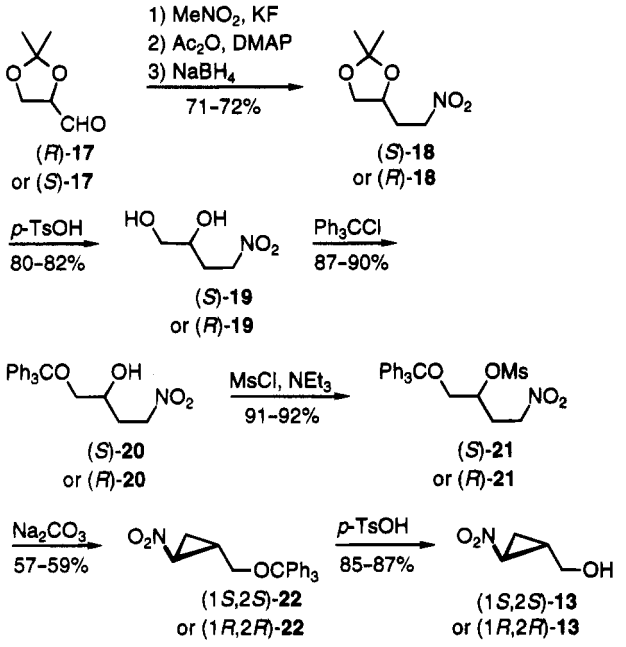
Scheme 3



romethane[24] at 0 °C in excellent yield (89–91%). The bromides **23** were substituted with the lithium enolates of the O'Donnell glycine equivalent **24a**[25] or its Oppolzer sultam-modified chiral analogue **24b**[26] in tetrahydrofuran at −78 °C to give (2*R*/*S*,1′*S*,2′*S*)-**25a**, (2*R*/*S*,1′*R*,2′*R*)-**25a**, and (2′*S*,1″*R*/*S*,2″*R*/*S*)-**25b** in 61–66% yield. The two diastereomers each of these protected amino acids obtained in each sequence could not be easily separated but were clearly distinguished in their ^{13}C NMR spectra. They were easily deprotected by treatment with 1 N hydrochloric acid and 0.5 N hydrochloric acid, respectively. Subsequent hydrolysis with lithium hydroxide, followed by acidification with hydrochloric acid, afforded the hydrochlorides of 3-(*trans*-2′-nitrocyclopropyl)alanines [(2*R*/*S*,1′*S*,2′*S*)-**6**, (2*R*/*S*,1′*R*,2′*R*)-**6**, and (2*S*,1′*R*/*S*,2′*R*/*S*)-**6**[27]] (Scheme 4 and Table 1).

Comparison of Synthetic 6 with Natural Material. The two sets of diastereomers (2*R*/*S*,1′*S*,2′*S*)-**6** and (2*R*/*S*,1′*R*,2′*R*)-**6** were transformed to the corresponding *N*-trifluoroacetyl methyl esters **26** and compared with the same derivatives obtained from the hydrolysate of hormaomycin **1a** by coinjection on a gas chromatographic column with a chiral phase.[28] The derivatized natural material coeluted with the two peaks of (2*R*/*S*,1′*R*,2′*R*)-**26** but not with those of (2*R*/*S*,1′*S*,2′*S*)-**26** (Scheme 5). Therefore, the two molecules of 3-(*trans*-2′-nitrocyclopropyl)alanine (**6**) in hormaomycin **1a** have (2*R*,1′*R*,2′*R*)- and (2*S*,1′*R*,2′*R*)-configuration.

To clarify the absolute configuration at C-2 of the 3-(*trans*-2′-nitrocyclopropyl)alanine moiety in the side chain of hormaomycin **1a**, the hydrolysate of the modified peptide–lactone **1b** with a single such fragment would have to be derivatized and coinjected with (2*S*,1′*R*/*S*,2′*R*/*S*)-**26**. However, at the time when the syntheses of all three diastereomeric compounds **6** had been completed, the previously prepared sample of **1b** had deteriorated and no more natural material was available on short notice.[29]

Conclusion

Three diastereopure 3-(*trans*-2′-nitrocyclopropyl)alanines (2*R*/*S*,1′*S*,2′*S*)-**6**, (2*R*/*S*,1′*R*,2′*R*)-**6**, and (2*S*,1′*R*/*S*,2′*R*/*S*)-**6** have been synthesized for comparison with natural material from the hydrolysate of the peptide–lactone hormaomycin. Using this established methodology, the correct enantiopure diastereomers for the ring and the side chain of **1a** can now be prepared and used for the synthesis of simple di- and tripeptides as contained in **1a** and eventually for the first total synthesis of hormaomycin.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD, and D_2O. The attached proton test (APT) technique indicated (+) for CH and CH_3 and (−) for C and CH_2. Melting points are uncorrected. All solvents and reagents were purified and dried by standard techniques; reactions with organometallic reagents were performed in anhydrous solvents under dry nitrogen.

(±)-2-Hydroxy-3-nitroprop-1-yl Benzoate (9). To a stirred solution of nitromethane (10.7 mL, 150 mmol) and sodium methanolate (1.1 g, 20 mmol) in Et_2O (150 mL) was added a solution of 1-oxoeth-1-yl benzoate (**8**)[12] (16.4 g, 100 mmol) in Et_2O (20 mL) dropwise at 0 °C. The mixture was stirred for 15 h at rt and then poured into H_2O (300 mL). The aqueous solution was extracted three times with Et_2O (50 mL each), and the combined organic extracts were dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude product was crystallized from Et_2O/petroleum ether to give 21.2 g (94%) of **9**: mp 95 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 3.17 (d, 1 H, J = 5.7 Hz), 4.46–4.79 (m, 5 H), 7.43–7.63 and 8.01–8.06 (m, 5 H); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT) δ 65.30 (−), 67.16 (+), 77.72 (−), 128.61 (+), 128.90 (−), 129.76 (+), 133.70 (+), 166.50 (−). Anal. Calcd for $C_{10}H_{11}NO_5$: C, 53.34; H, 4.92. Found: C, 53.36; H, 4.94.

(±)-3-Nitro-2-(pivaloyloxy)prop-1-yl Benzoate (10). A suspension of ester **9** (11.3 g, 50 mmol) in dry dichloromethane (50 mL) was treated with pivaloyl chloride (18.5 mL, 150 mmol). After the mixture was stirred for 15 h under reflux, it was poured into dichloromethane (150 mL). The solution was washed three times with aqueous 2 N sodium chloride (50 mL) and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The crude product was crystallized from Et_2O/petroleum ether to give 15.1 g (97%) of **10**: mp 52 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.17 (s, 9 H), 4.49 (dd, 1 H, J = 4.7 and 12.1 Hz), 4.65 (dd, 1 H, J = 4.7 and 12.1 Hz), 4.73 (d, 1 H, J = 4.7 Hz), 4.74 (d, 1 H, J = 7.1 Hz), 5.77 (dddd, 1 H, J = 4.7, 4.7, 4.7, and 7.1 Hz), 7.44–7.64 and 7.99–8.04 (m, 5 H); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT) δ 26.87 (+), 38.82 (−), 62.53 (−), 67.57 (+), 74.97 (−), 128.59 (+), 129.10 (−), 129.66 (+), 133.56 (+), 165.73 (−), 177.05 (−). Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19. Found: C, 58.26; H, 6.13.

(*E*)-3-Nitro-2-propen-1-yl Benzoate (11). A solution of ester **10** (12.4 g, 40 mmol) in dry Et_2O (80 mL) was treated with dry sodium acetate (6.6 g, 80 mmol). After the mixture was stirred for 24 h at rt, it was filtered and the solvent was evaporated under reduced pressure. The residue was crystallized from methanol to give 7.13 g (86%) of **11**: mp 97 °C (lit.[14]

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(27) For comparison of its possible biological activity, the lower homologue of **6**, 2-(*trans*-2′-nitrocyclopropyl)glycine, has also been synthesized: Zindel, J.; de Meijere, A. *Synthesis* **1994**, 190.
(28) (a) A 25 m fused silica capillary column with octakis(3-*O*-butyryl-2,6-di-*O*-pentyl)-γ-cyclodextrin (Lipodex E), commercially available from Macherey-Nagel, D-52313 Düren, Germany. (b) König, W. A. Unpublished results.
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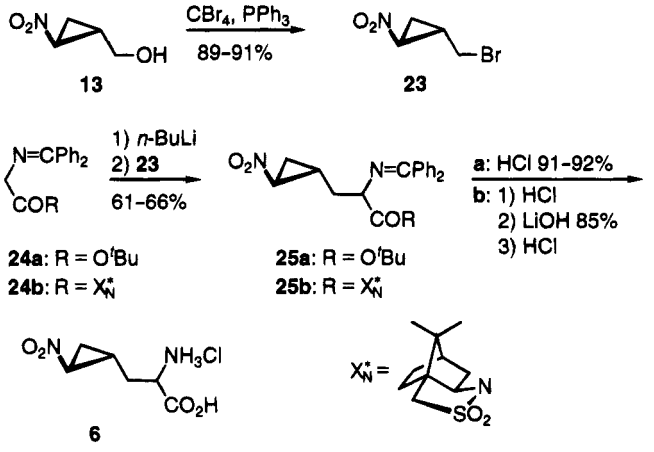
Table 1. Synthesis of Enantiopure (2-Nitrocyclopropyl)methanols 13 and 3-(*trans*-2′-Nitrocyclopropyl)alanine Hydrochlorides 6 (Schemes 3 and 4)

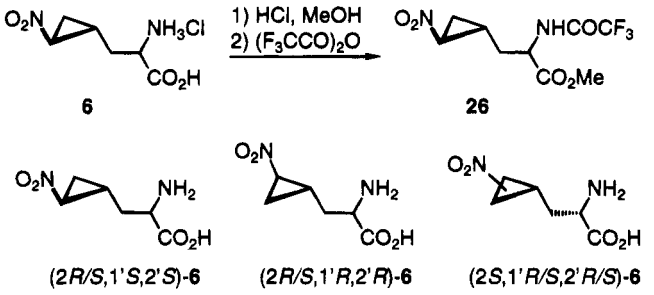
starting material	product	yield (%)	$[\alpha]_D^{20}$ (deg)	starting material	product	yield (%)	$[\alpha]_D^{20}$ (deg)
(2*R*)-**17**	(2*S*)-**18**	72	−19.3(c = 1.0)[a]	(2*S*)-**17**	(2*R*)-**18**	71	+21.5(c = 1.0)[a]
(2*S*)-**18**	(2*S*)-**19**	80	−40.5(c = 1.1)[b]	(2*R*)-**18**	(2*R*)-**19**	82	+39.2(c = 1.1)[b]
(2*S*)-**19**	(2*S*)-**20**	87	−5.5(c = 1.0)[a]	(2*R*)-**19**	(2*R*)-**20**	90	+6.2(c = 1.0)[a]
(2*S*)-**20**	(2*S*)-**21**	92		(2*R*)-**20**	(2*R*)-**21**	91	
(2*S*)-**21**	(1*S*,2*S*)-**22**	59	+66.2(c = 1.0)[a]	(2*R*)-**21**	(1*R*,2*R*)-**22**	57	−64.0(c = 1.0)[a]
(1*S*,2*S*)-**22**	(1*S*,2*S*)-**13**	87	+97.8(c = 1.6)[a]	(1*R*,2*R*)-**22**	(1*R*,2*R*)-**13**	85	−95.1(c = 1.1)[a]
(1*S*,2*S*)-**13**	(1*S*,2*S*)-**23**	91	+52.6(c = 0.9)[a]	(1*R*,2*R*)-**13**	(1*R*,2*R*)-**23**	89	−50.4(c = 0.8)[a]
(1*S*,2*S*)-**23**	(2*R*/*S*,1′*S*,2′*S*)-**25a**	64		(2*R*/*S*,1′*S*,2′*S*)-**25a**	(2*R*/*S*,1′*S*,2′*S*)-**6**	91	+55.0(c = 0.3)[c]
(1*R*,2*R*)-**23**	(2*R*/*S*,1′*R*,2′*R*)-**25a**	66		(2*R*/*S*,1′*R*,2′*R*)-**25a**	(2*R*/*S*,1′*R*,2′*R*)-**6**	92	−57.2(c = 0.3)[c]
rac-**23**	(2′*S*,1″*R*/*S*,2″*R*/*S*)-**25b**	61		(2′*S*,1″*R*/*S*,2″*R*/*S*)-**25b**	(2*S*,1′*R*/*S*,2′*R*/*S*)-**6**	85	+29.5(c = 0.3)[c]

[a] Solvent = chloroform. [b] Solvent = methanol. [c] Solvent = water.

Scheme 4



Scheme 5



mp 96 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.85 (dd, 2 H, J = 2.0 and 3.5 Hz), 7.35−7.70 and 8.00−8.20 (m, 7 H); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT) δ 59.74 (−), 128.51 (+), 128.74 (−), 129.59 (+), 133.60 (+), 135.62 (+), 139.99 (+), 165.32 (−).

(*E*)-3-Nitro-2-propen-1-yl Benzoate (11). A solution of ester **9** (9.01 g, 40 mmol) and dicyclohexylcarbodiimide (10.3 g, 50 mmol) in dry tetrahydrofuran (40 mL) was treated with copper(I) chloride (0.20 g, 2 mmol). After the mixture was stirred for 2 d at rt, it was filtered and then poured into H_2O (150 mL). The aqueous solution was extracted three times with Et_2O (50 mL each), and the combined organic layers were dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the residue was crystallized from methanol to give 3.15 g (38%) of **11**.

(±)-(*trans*-2-Nitrocyclopropyl)methyl Benzoate (12). A mixture of trimethylsulfoxonium iodide (2.42 g, 11 mmol) and dimethyl sulfoxide (20 mL) was treated with sodium hydride (0.26 g, 11 mmol). After the mixture was stirred for 1 h at rt, a solution of the ester **11** (2.07 g, 10 mmol) in dimethyl sulfoxide (10 mL) was added dropwise at 10 °C. The mixture was stirred for 2 h at rt and then poured into H_2O (150 mL). The aqueous solution was extracted three times with Et_2O (50 mL each), and the combined organic extracts were washed two times with H_2O (100 mL each) and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography over 50 g of silica gel, eluting with Et_2O/petroleum ether (1:1), to give 0.29 g (13%) of **12**: R_f = 0.31; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36 (ddd, 1 H, J = 6.4, 7.2, and 7.2 Hz), 1.94 (ddd, 1 H, J = 3.8, 6.4, and 10.1 Hz), 2.39−2.56 (m, 1 H), 4.19 (dd, 1 H, J = 7.3 and 12.2 Hz), 4.31−4.41 (m, 1 H), 4.42 (dd, 1 H, J = 5.9 and 12.2 Hz), 7.41−7.62 and 7.97−8.04 (m, 5 H); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT) δ 15.70 (−), 23.76 (+), 58.00 (+), 63.28 (−), 128.51 (+), 129.42 (−), 129.66 (+), 133.40 (+), 166.12 (−). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01. Found: C, 59.55; H, 4.96.

(±)-(*trans*-2-Nitrocyclopropyl)methanol (13). To a solution of the ester **12** (1.10 g, 5 mmol) in methanol (40 mL) was added sodium hydroxide (400 mg, 10 mmol). After the mixture was stirred for 15 h at rt, it was poured into concd sodium chloride solution (150 mL). The aqueous solution was extracted three times with Et_2O (50 mL each), and the combined organic layers were dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography over 50 g of silica gel, eluting with Et_2O/petroleum ether (1:1), to give 0.36 g (61%) of *rac*-**13**: R_f = 0.13; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.29 (ddd, 1 H, J = 5.9, 7.2, and 7.2 Hz), 1.84 (ddd, 1 H, J = 3.6, 5.9, and 9.5 Hz), 2.09 (br s, 1 H), 2.19−2.32 (m, 1 H), 3.46−3.62 (m, 1 H), 3.72−3.88 (m, 1 H), 4.26 (ddd, 1 H, J = 3.6, 3.6, and 7.2 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT) δ 15.15 (−), 27.05 (+), 57.63 (+), 60.93 (−). Anal. Calcd for $C_4H_7NO_3$: C, 41.03; H, 6.03. Found: C, 40.99; H, 6.01.

(±)-*tert*-Butyl 2,3-Dibromopropanoate (15). To a stirred solution of *tert*-butyl acrylate (**14**) (72.6 mL, 0.5 mol) in chloroform (200 mL) was added a solution of bromine (25.6 mL, 0.5 mol) in chloroform (100 mL) dropwise at rt. The mixture was stirred for 15 h at rt and then washed with H_2O (100 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure. The crude product was distilled to give 116.6 g (81%) of **15**: bp 60 °C/0.5 Torr; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 (s, 9 H), 3.62 (dd, 1 H, J = 4.0 and 8.1 Hz), 3.86 (dd, 1 H, J = 8.1 and 9.2 Hz), 4.31 (dd, 1 H, J = 4.0 and 9.2 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT) δ 27.64 (+), 30.02 (−), 42.66 (+), 83.36 (−), 166.34 (−).

(±)-*tert*-Butyl (*trans*-2-Nitrocyclopropyl)carboxylate (16). A solution of the ester **15** (28.8 g, 100 mmol) and nitromethane (10.7 mL, 200 mmol) in dimethylformamide (150 mL) was treated with sodium carbonate (31.8 g, 300 mmol). After the mixture was stirred for 4 d at rt, it was poured into H_2O (700 mL). The aqueous solution was extracted three times with Et_2O (100 mL each), and the combined organic extracts were washed two times with H_2O (200 mL each) and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography over 200 g of silica gel, eluting with Et_2O/petroleum ether (1:20), to give 5.8 g (31%) of **16**: R_f = 0.35; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.46 (s, 9 H), 1.67 (ddd, 1 H, J = 6.0, 7.5, and 7.5 Hz), 2.00 (ddd, 1 H, J = 4.5, 6.0, and 10.5 Hz), 2.64 (ddd, 1 H, J = 3.0, 7.5, and 10.5 Hz), 4.53 (ddd, 1 H, J = 3.0, 4.5, and 7.5 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT) δ 17.06 (−), 26.07 (+), 27.93 (+), 59.14 (+), 82.64 (−),

167.88 (−). Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00. Found: C, 51.45; H, 6.96.

(±)-(*trans*-2-Nitrocyclopropyl)methanol (13). A stirred solution of the ester **16** (3.74 g, 20 mmol) in dimethoxyethane (100 mL) was treated with anhydrous aluminum chloride (2.27 g, 17 mmol), and sodium borohydride (1.89 g, 50 mmol) was added in small portions (0.19 g each). After the mixture was stirred for 24 h at rt, aqueous 2 N sodium chloride (300 mL) was added carefully and the pH was adjusted to 6 with 1 N hydrochloric acid. The aqueous solution was extracted three times with Et_2O (50 mL each), and the combined organic extracts were washed two times with aqueous 2 N sodium chloride (150 mL each) and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography over 100 g of silica gel, eluting with Et_2O/petroleum ether (1:1), to give 1.57 g (67%) of *rac*-**13**: $R_f = 0.13$.

(2*R*)- and (2*S*)-(Isopropylidenedioxy)-4-nitrobutane (18). Compound (2*S*)-**18** has been prepared from the aldehyde (2*R*)-**17** as previously described.[20] When the reported procedure was followed, (2*R*)-**17** and (2*S*)-**17** were converted to (2*S*)-**18** and (2*R*)-**18** in 72 and 71% yield, respectively. The spectroscopic data were identical with the reported ones.[21]

(2*R*)- and (2*S*)-4-Nitrobutane-1,2-diol (19). To a solution of the acetal (2*R*)-**18** or (2*S*)-**18**[20] (4.38 g, 25 mmol) in methanol (40 mL) was added *p*-toluenesulfonic acid (190 mg, 1.1 mmol). The mixture was stirred for 15 h at rt, and then sodium carbonate (106 mg, 1 mmol) was added. The solvent was evaporated under reduced pressure, and the crude product was purified by flash chromatography over 100 g of silica gel, eluting with Et_2O/petroleum ether (10:1), to give 2.77 g (82%) of (2*R*)-**19** or 2.70 g (80%) of (2*S*)-**19**: $R_f = 0.21$; ^1H NMR (250 MHz, CD_3OD) δ 1.74−2.25 (m, 2 H), 3.19−3.56 (m, 3 H), 4.51−4.74 (m, 4 H); ^{13}C NMR (50.3 MHz, CD_3OD, APT) δ 31.94 (−), 66.92 (−), 69.97 (+), 73.39 (−). Anal. Calcd for $C_4H_9NO_4$: C, 35.56; H, 6.71. Found: C, 35.69; H, 6.80.

(2*R*)- and (2*S*)-4-Nitro-1-[(triphenylmethyl)oxy]butan-2-ol (20). To a solution of the alcohol (2*R*)-**19** or (2*S*)-**19** (2.03 g, 15.0 mmol) in dry pyridine was added triphenylmethyl chloride (4.60 g, 16.5 mmol). After the mixture was stirred for 48 h at rt, methanol (1 mL) was added, and the mixture was stirred for an additional 1 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane (50 mL). The organic layer was washed with aqueous 2 N ammonium chloride (100 mL) and H_2O (100 mL) and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography over 100 g of silica gel, eluting with Et_2O/petroleum ether (1:3), to give 5.10 g (90%) of (2*R*)-**20** or 4.93 g (87%) of (2*S*)-**20**: $R_f = 0.18$; mp 92 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.96−2.22 (m, 2 H), 2.31 (d, 1 H, $J = 4.4$ Hz), 3.10 (dd, 1 H, $J = 6.9$ and 9.5 Hz), 3.24 (dd, 1 H, $J = 3.7$ and 9.5 Hz), 3.81−3.92 (m, 1 H), 4.41−4.60 (m, 2 H), 7.23−7.46 (m, 15 H); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT) δ 30.81 (−), 67.12 (−), 67.76 (+), 72.13 (−), 86.89 (−), 127.25 (+), 127.95 (+), 128.54 (+), 143.51 (−). Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14. Found: C, 73.24; H, 6.15.

(2*R*)- and (2*S*)-4-Nitro-1-[(triphenylmethyl)oxy]but-2-yl Methanesulfonate (21). To a stirred solution of the alcohol (2*R*)-**20** or (2*S*)-**20** (3.77 g, 10 mmol) in dry dichloromethane (80 mL) were added triethylamine (1.53 mL, 11 mmol) and methanesulfonyl chloride (0.80 mL, 10 mmol) dropwise at −10 °C. After the mixture was stirred for 15 min at 0 °C, the organic layer was washed with H_2O (100 mL), aqueous 2 N sodium hydrogencarbonate (100 mL), and aqueous 2 N sodium chloride (100 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure to give 4.15 g (91%) of (2*R*)-**21** or 4.16 g (92%) of (2*S*)-**21**: ^1H NMR (250 MHz, $CDCl_3$) δ 2.32−2.41 (m, 2 H), 2.98 (s, 3 H), 3.33 (dd, 1 H, $J = 5.5$ and 10.8 Hz), 3.43 (dd, 1 H, $J = 4.0$ and 10.8 Hz), 4.39−4.53 (m, 2 H), 4.77−4.85 (m, 1 H), 7.24−7.47 (m, 15 H); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT) δ 29.25 (−), 38.54 (+), 64.74 (−), 70.92 (−), 77.84 (+), 87.51 (−), 127.47 (+), 128.08 (+), 128.49 (+), 143.00 (−).

(1*R*,2*R*)- and (1*S*,2*S*)-[Triphenylmethyl)oxy]-(*trans*-2-nitrocyclopropyl)methane (22). A stirred solution of methanesulfonate (2*R*)-**21** or (2*S*)-**21** (4.56 g, 10 mmol) in dry toluene (30 mL) was treated with sodium carbonate (2.12 g, 20 mmol). After the mixture was stirred for 15 h under reflux, it was washed two times with H_2O (20 mL each). The aqueous solution was extracted with toluene (10 mL), and the combined organic layers were dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography over 100 g of silica gel, eluting with Et_2O/petroleum ether (1:10), to give 2.05 g (57%) of (1*R*,2*R*)-**22** or 2.12 g (59%) of (1*S*,2*S*)-**22**: $R_f = 0.29$; mp 105 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (ddd, 1 H, $J =$ 6.0, 7.4, and 7.4 Hz), 1.82 (ddd, 1 H, $J = 3.7$, 6.0, and 10.5 Hz), 2.14−2.31 (m, 1 H), 3.06 (dd, 1 H, $J = 5.7$ and 10.4 Hz), 3.30 (dd, 1 H, $J = 4.5$ and 10.4 Hz), 4.23 (ddd, 1 H, $J = 3.7$, 3.7, and 7.4 Hz), 7.20−7.42 (m, 15 H); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT) δ 15.51 (−), 25.37 (+), 57.71 (+), 61.66 (−), 86.80 (−), 127.23 (+), 127.94 (+), 128.49 (+), 143.49 (−). Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89. Found: C, 76.98; H, 6.02.

(1*R*,2*R*)- and (1*S*,2*S*)-(*trans*-2-Nitrocyclopropyl)methanol (13). To a solution of the ester (1*R*,2*R*)-**22** or (1*S*,2*S*)-**22** (1.80 g, 5.0 mmol) in methanol (40 mL) was added *p*-toluenesulfonic acid (95 mg, 0.6 mmol). The mixture was stirred for 15 h at rt and then poured into concd sodium chloride solution (150 mL). The aqueous solution was extracted three times with Et_2O (50 mL each), and the combined organic layers were dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography over 50 g of silica gel, eluting with Et_2O/petroleum ether (1:1), to give 0.50 g (85%) of (1*R*,2*R*)-**13** or 0.51 g (87%) of (1*S*,2*S*)-**13**: $R_f = 0.13$.

(1*R*,2*R*)-, (1*S*,2*S*)-, and (±)-1-Bromo(*trans*-2-nitrocyclopropyl)methane (23). To a stirred solution of the alcohol (1*R*,2*R*)-**13**, (1*S*,2*S*)-**13**, or *rac*-**13** (468 mg, 4.0 mmol) and tetrabromomethane (1.66 g, 5.0 mmol) in dry dichloromethane (10 mL) was added triphenylphosphane (1.57 g, 6.0 mmol) in small portions (0.32 g each) at 0 °C. After the mixture was stirred for 15 min, half of the solvent was evaporated under reduced pressure, and the mixture was treated with Et_2O (20 mL) and filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by flash chromatography over 50 g of silica gel, eluting with Et_2O/petroleum ether (1:10), to give 641 mg (89%) of (1*R*,2*R*)-**23**, 655 mg (91%) of (1*S*,2*S*)-**23**, or 650 mg (90%) of *rac*-**23**: $R_f = 0.66$; ^1H NMR (250 MHz, $CDCl_3$) δ 1.34 (ddd, 1 H, $J = 6.4$, 7.2, and 7.2 Hz), 2.02 (ddd, 1 H, $J = 4.0$, 6.4, and 10.4 Hz), 2.39−2.53 (m, 1 H), 3.32 (dd, 1 H, $J = 7.3$ and 10.9 Hz), 3.41 (dd, 1 H, $J = 6.9$ and 10.9 Hz), 4.25 (ddd, 1 H, $J = 3.2$, 4.0, and 7.2 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT) δ 19.33 (−), 26.72 (+), 31.19 (−), 60.49 (+). Anal. Calcd for $C_4H_6BrNO_2$: C, 26.69; H, 3.36. Found: C, 26.88; H, 3.35.

(2*R*/*S*,1′*R*,2′*R*)-, (2*R*/*S*,1′*S*,2′*S*)-, and (±)-*tert*-Butyl 3-(*trans*-2′-Nitrocyclopropyl)-2-[(diphenylmethylene)amino]propanoate (25a). To a stirred solution of *tert*-butyl 2-[(diphenylmethylene)amino]ethanoate (**24a**)[25] (1.09 g, 3.7 mmol) in tetrahydrofuran (100 mL) was added a solution of *n*-butyllithium in hexane (2.36 N, 1.69 mL, 4.0 mmol) dropwise at −78 °C. After the mixture was stirred for 1 h at −78 °C, a solution of the bromide (1*R*,2*R*)-**23**, (1*S*,2*S*)-**23**, or *rac*-**23** (630 mg, 3.5 mmol) in tetrahydrofuran (5 mL) was added dropwise. The mixture was stirred for 10 h at −78 °C, the solvent was removed in vacuo at rt, and H_2O (150 mL) was added to the residue. The mixture was extracted three times with Et_2O (100 mL each), and the combined organic layers were dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography over 50 g of silica gel, eluting with Et_2O/petroleum ether (1:5) containing triethylamine (1%), to give 911 mg (66%) of (2*R*/*S*,1′*R*,2′*R*)-**25a**, 884 mg (64%) of (2*R*/*S*,1′*S*,2′*S*)-**25a**, or 895 mg (65%) of *rac*-**25a**: $R_f = 0.18$; ^1H NMR (250 MHz, $CDCl_3$) (both isomers) δ 1.02−1.11 (m, 1 H), 1.43 (s, 9 H), 1.68−1.85 (m, 1 H), 1.90−2.07 (m, 3 H), 3.98−4.16 (m, 2 H), 7.12−7.19 and 7.29−7.67 (m 10 H); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT) (first isomer) δ 17.82 (−), 23.27 (+), 27.98 (+), 34.65 (−), 59.95 (+), 65.21 (+), 81.57 (−), 127.66 (+), 128.05 (+), 128.55 (+), 128.70 (+), 128.75 (+), 130.48 (+), 136.32 (−), 139.14 (−), 170.16 (−), 171.13 (−); ^{13}C NMR (50.3

MHz, $CDCl_3$, APT) (second isomer) 18.73 (−), 23.31 (+), 27.98 (+), 34.80 (−), 59.40 (+), 65.21 (+), 81.57 (−), 127.39 (+), 128.08 (+), 128.25 (+), 128.70 (+), 128.75 (+), 130.02 (+), 136.26 (−), 139.14 (−), 170.23 (−), 171.09 (−). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64. Found: C, 70.11; H, 6.47.

(2*R*/*S*,1′*R*,2′*R*)-, (2*R*/*S*,1′*S*,2′*S*)-, and (±)-3-(*trans*-2′-Nitrocyclopropyl)alanine Hydrochloride (6). The protected amino acid (2*R*/*S*,1′*R*,2′*R*)-**25a**, (2*R*/*S*,1′*S*,2′*S*)-**25a**, or *rac*-**25a** (789 mg, 2.0 mol) was treated with aqueous 1 N hydrochloric acid (80 mL). After the mixture was stirred for 15 h at rt, the aqueous layer was extracted two times with Et_2O (80 mL each). Evaporation of the aqueous solvent under reduced pressure gave 388 mg (92%) of (2*R*/*S*,1′*R*,2′*R*)-**6**, 383 mg (91%) of (2*R*/*S*,1′*S*,2′*S*)-**6**, or 385 mg (91%) of *rac*-**6**: ^{1}H NMR (250 MHz, D_2O) (both isomers) δ 1.12−1.23 (m, 1 H), 1.71−1.82 (m, 1 H), 1.87−2.08 (m, 3 H), 3.98−4.06 (m, 1 H), 4.23 (ddd, 1 H, J = 3.6, 3.6, and 7.2 Hz); ^{13}C NMR (50.3 MHz, D_2O, APT) (first isomer) δ 18.19 (−), 22.15 (+), 31.00 (−), 52.25 (+), 59.43 (+), 171.46 (−); ^{13}C NMR (50.3 MHz, D_2O, APT) (second isomer): 18.12 (−), 21.71 (+), 30.81 (−), 52.28 (+), 59.34 (+), 171.40 (−). Anal. Calcd for $C_6H_{11}ClN_2O_4$: C, 34.22; H, 5.26. Found: C, 34.05; H, 5.30.

(2′*S*,1″*R*/*S*,2″*R*/*S*)-4-[3′-(*trans*-2″-Nitrocyclopropyl)-2′-[(diphenylmethylene)amino]-1′-oxo-1′-propyl]-(7*R*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0^{3,7}]decane 5,5-Dioxide (25b). To a stirred solution of 4-[2′-[(diphenylmethylene)amino]acetyl]-(7*R*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0^{3,7}]decane 5,5-dioxide (**24b**)[26] (109 mg, 0.25 mmol) in tetrahydrofuran (30 mL) was added a solution of *n*-butyllithium in hexane (2.36 N, 0.12 mL, 0.28 mmol) dropwise at −78 °C. After the mixture was stirred for 30 min at −78 °C, a solution of the bromide *rac*-**23** (45 mg, 0.25 mmol) in tetrahydrofuran (5 mL) and HMPA (1 mL) was added dropwise. The mixture was stirred for 15 h at −78 °C and then poured into H_2O (100 mL). The mixture was extracted three times with dichloromethane (50 mL each), and the combined organic layers were washed two times with H_2O (50 mL each) and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude product was crystallized from Et_2O/petroleum ether to give 81 mg (61%) of (2′*S*,1″*R*/*S*,2″*R*/*S*)-**25b**: mp 110 °C; ^{1}H NMR (250 MHz, $CDCl_3$) (both isomers) δ 0.97 (s, 3 H), 1.06 (s, 3 H), 1.00−1.15 (m, 1 H), 1.31−1.45 (m, 2 H), 1.58−1.69 (m, 1 H), 1.85−2.19 (m, 8 H), 3.36 (s, 2 H), 3.88 (br t, 1 H, J = 7.0 Hz), 3.96 and 4.12 (ddd, 1 H, J = 3.5, 3.5, and 7.0 Hz), 4.72−4.87 (m, 1 H), 7.05−7.17, 7.28−7.50, and 7.62−7.72 (m, 10 H); ^{13}C NMR (125.7 MHz, $CDCl_3$, APT) (first isomer) δ 17.67 (−), 19.72 (+), 20.54 (+), 23.09 (+), 26.35 (−), 32.61 (−), 36.29 (−), 38.24 (−), 44.34 (+), 47.71 (−), 48.47 (−), 52.85 (−), 59.93 (+), 64.77 (+), 65.14 (+), 127.72 (+), 127.97 (+), 128.60 (+), 128.74 (+), 128.84 (+), 130.54 (+), 135.76 (−), 139.03 (−), 171.37 (−) 171.78 (−); ^{13}C NMR (125.7 MHz, $CDCl_3$, APT) (second isomer) 18.79 (−), 19.74 (+), 20.51 (+), 23.13 (+), 26.35 (−), 32.56 (−), 36.47 (−), 38.21 (−), 44.32 (+), 47.71 (−), 48.49 (−), 52.85 (−), 58.75 (+), 64.94 (+), 65.09 (+), 127.35 (+), 127.97 (+), 128.21 (+), 128.69 (+), 128.84 (+), 129.98 (+), 135.68 (−), 139.03 (−), 171.26 (−), 171.88 (−).

(2*S*,1′*R*/*S*,2′*R*/*S*)-3-(*trans*-2′-Nitrocyclopropyl)alanine Hydrochloride (6). To a solution of the sultam (2′*S*,1″*R*/*S*,2″*R*/*S*)-**25b** (80 mg, 0.15 mmol) in tetrahydrofuran (2 mL) was added 0.5 N hydrochloric acid (2 mL). After the mixture was stirred for 48 h at rt, it was extracted three times with Et_2O (3 mL each). The aqueous solvent was evaporated under reduced pressure, the residue was dissolved in H_2O (2 mL) and tetrahydrofuran (2 mL), and the solution was treated with lithium hydroxide (15 mg, 0.60 mmol). After the mixture was stirred for 48 h at rt, H_2O (3 mL) was added, and the solution was extracted three times with dichloromethane (2 mL each). The aqueous layer was adjusted to pH 5 with 1 N hydrochloric acid, and the solvent was evaporated under reduced pressure to give 27 mg (85%) of (2*S*,1′*R*/*S*,2′*R*/*S*)-**6**.

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