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Synthesis of 3-(*trans*-2'-Nitrocyclopropyl)alanine: An Unusual Natural Amino Acid[1]

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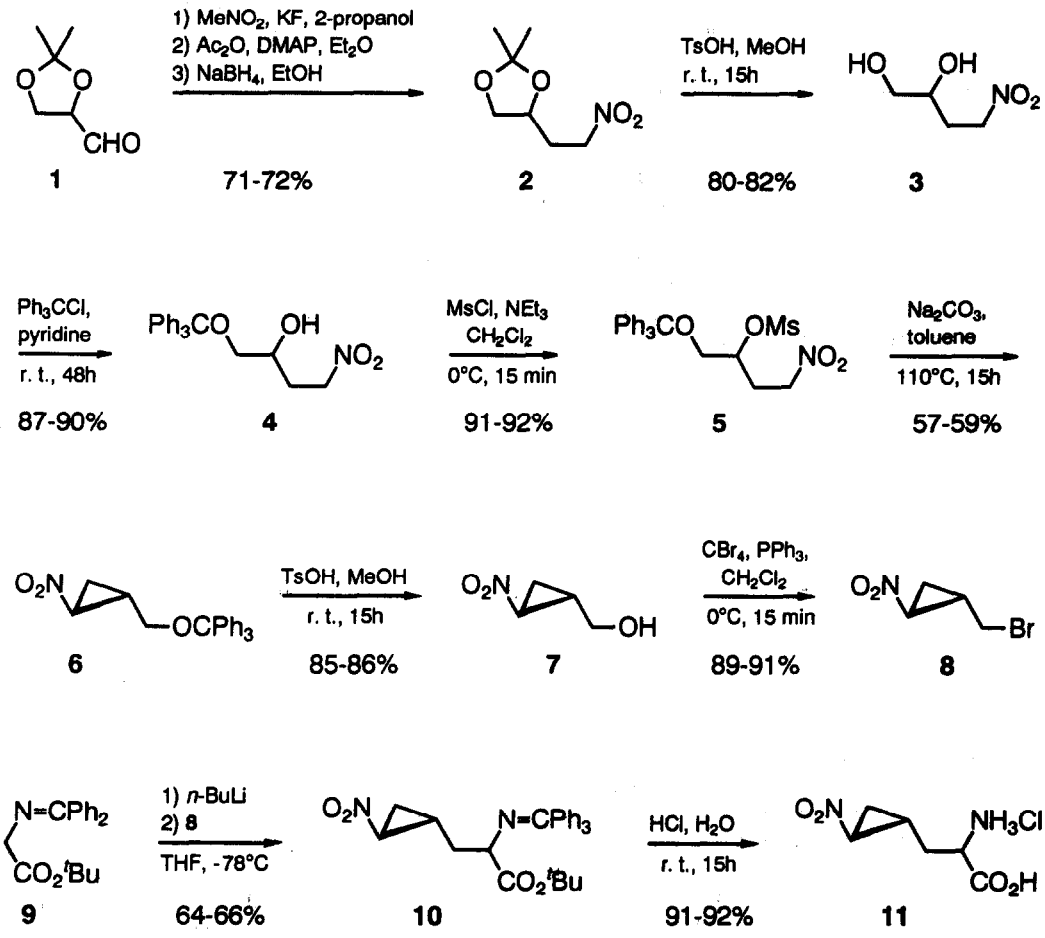
Abstract: Racemic (*trans*-2'-nitrocyclopropyl)methanol *rac*-7 is prepared in three steps from *t*-butyl acrylate, while enantiopure (1'*S*,2'*S*)-7 and (1'*R*,2'*R*)-7 is obtained in six steps from (*R*)- and (*S*)-2,3-O-isopropylideneglyceraldehyde, respectively. The alcohol 7 can be transformed to the bromide 8 and this in turn coupled with the glycine equivalent 2-(diphenylmethylenamino)acetate 9 to yield 3-(*trans*-2'-nitrocyclopropyl)alanine (Ala(3-Ncp)) 11, after deprotection. The natural material, part of the peptide-lactone hormaomycin, has (1'*R*,2'*R*)-configuration, as determined by comparison with the synthesized authentic compounds.

The peptide-lactone hormaomycin[2] produced by *Streptomyces griseoflavus* shows a selective antibiotic effect against some gram-positive bacteria. This intercellular signal substance has an influence on the formation of air mycel as well as the production of secondary metabolites in streptomyces. The structure includes two molecules of 3-(*trans*-2'-nitrocyclopropyl)-alanine 11 with a *trans* orientated nitro group and both possible configurations at C-2. As the absolute configuration at the three stereogenic centers can best be determined by comparison of the natural 3-(*trans*-2'-nitrocyclopropyl)alanines 11 with authentic synthetic products, we have embarked to synthesize all four stereoisomers of 11 as part of our continuing interest[3] in natural and non-natural amino acids containing a cyclopropyl group.[4]

Our synthetic strategy towards 11 called for an enantioselective construction of 4-nitrobutane-1,2-diol 3, its transformation into a derivative with a protected primary hydroxy group as well as a reasonable secondary leaving group and ring closure by γ-elimination under S_N2 conditions with inversion of configuration to give a (*trans*-2-nitrocyclopropyl)methyl derivative to be combined with a suitable glycine equivalent.

This sequence was realized with the readily available starting materials (*R*)- und (*S*)-2,3-O-isopropylideneglyceraldehyde 1,[5] which can be transformed to the protected 4-nitrobutane-1,2-diol 2 by one-pot reductive nitromethylation following the protocol of Kozikowski et al.[6] (Scheme 1 and Table 1). The acetal in 2 is cleaved with *p*-toluenesulfonic acid and the primary hydroxy group in diol 3 selectively protected with triphenylmethyl chloride in pyridine. The secondary hydroxy group in the ether 4 is transformed into a leaving group with methanesulfonyl chloride/triethylamine, and the methanesulfonate 5 is treated with sodium carbonate in toluene at 110°C. The γ-elimination occurs with complete inversion of configuration at C-2 to give only the *trans*-configurated (2-nitrocyclopropyl)methyl ether 6. After cleavage of the ether with *p*-toluenesulfonic acid, the primary alcohol 7 can be converted to the bromide 8 by treatment with tetrabromomethane/triphenylphosphine[7] in dichloromethane at 0°C, and the bromide can be substituted with the lithium enolate of the glycine equivalent *t*-butyl (diphenylmethylenamino)acetate 9[8] in tetrahydrofuran at -78°C. The protected amino acid 10 is deprotected with 1N hydrochloric acid to give the hydrochloride of 3-(*trans*-2'-nitrocyclopropyl)alanine 11 (Scheme 1).

All these steps went well and with good to excellent yields in both sequences starting with (*R*)-1 and with (*S*)-1 (Table 1), except for the cyclization of 5 (59 and 57%) and the substitution on 8 to give 10 (64 and 66%). The two diastereomers obtained in each sequence were not easily separated (e. g. by simple column chromatography), but are clearly distinguished by ^{13}C NMR spectroscopy.[9] Both sets of diastereomers were transformed to the corresponding N-trifluoroacetyl methyl esters and compared with the same derivatives obtained from the hydrolysate of hormaomycin,[2] by coinjection on a gas chromatographic column with a chiral phase.[10] The derivatized natural material coeluted with the two peaks of (1'*R*,2'*R*)-configurated synthetic 3-(*trans*-2'-nitrocyclopropyl)-N-(trifluoroacetyl)alanine methyl ester but not with those of the (1'*S*,2'*S*)-diastereomers. It remains to be clarified, which of the two (1'*R*,2'*R*)-diastereomers is in the peptide-lactone ring and which is in the side chain of hormaomycin.[2]



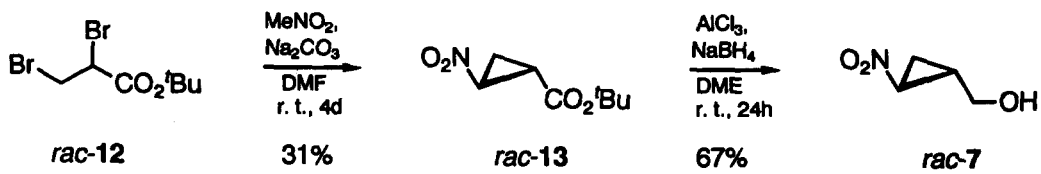
Scheme 1. (Details see Table 1.)

Table 1. Synthesis of Enantiopure (*trans*-2'-Nitrocyclopropyl)methanols (1'*S*,2'*S*)-7 and (1'*R*,2'*R*)-7 and Reaction with the Glycine Equivalent 9 to give 3-(*trans*-2'-Nitrocyclopropyl)alanines (2*RS*,1'*S*,2'*S*)-11 and (2*RS*,1'*R*,2'*R*)-11 (Scheme 1).[9]

Starting Material	Product	Yield [%]	$[\alpha]_D^{20}$ [°]	Starting Material	Product	Yield [%]	$[\alpha]_D^{20}$ [°]
(2*R*)-1	(2*S*)-2	72	-19.3 (c=1.0)[a]	(2*S*)-1	(2*R*)-2	71	+21.5 (c=1.0)[a]
(2*S*)-2	(2*S*)-3	80	-40.5 (c=1.1)[b]	(2*R*)-2	(2*R*)-3	82	+39.2 (c=1.1)[b]
(2*S*)-3	(2*S*)-4	87	-5.5 (c=1.0)[a]	(2*R*)-3	(2*R*)-4	90	+6.2 (c=1.0)[a]
(2*S*)-4	(2*S*)-5	92		(2*R*)-4	(2*R*)-5	91	
(2*S*)-5	(1'*S*,2'*S*)-6	59	+66.2 (c=1.0)[a]	(2*R*)-5	(1'*R*,2'*R*)-6	57	-64.0 (c=1.0)[a]
(1'*S*,2'*S*)-6	(1'*S*,2'*S*)-7	86	+97.8 (c=1.6)[a]	(1'*R*,2'*R*)-6	(1'*R*,2'*R*)-7	85	-95.1 (c=1.1)[a]
(1'*S*,2'*S*)-7	(1'*S*,2'*S*)-8	91	+52.6 (c=0.9)[a]	(1'*R*,2'*R*)-7	(1'*R*,2'*R*)-8	89	-50.4 (c=0.8)[a]
(1'*S*,2'*S*)-8	(2*RS*,1'*S*,2'*S*)-10	64		(1'*R*,2'*R*)-8	(2*RS*,1'*R*,2'*R*)-10	66	
(2*RS*,1'*S*,2'*S*)-10	(2*RS*,1'*S*,2'*S*)-11	91	+55.0 (c=0.3)[c]	(2*RS*,1'*R*,2'*R*)-10	(2*RS*,1'*R*,2'*R*)-11	92	-57.2 (c=0.3)[c]

[a]Solvent $CHCl_3$. - [b]Solvent CH_3OH. - [c]Solvent H_2O.

The precursor to totally racemic 3-(*trans*-2'-nitrocyclopropyl)alanine 11, *rac*-(*trans*-2'-nitrocyclopropyl)methanol *rac*-7 can easily be prepared in multigram quantities in only three steps from the bromine adduct of *t*-butyl acrylate 12. *t*-Butyl-2,3-dibromopropionate *rac*-12 is transformed into *t*-butyl (*trans*-2'-nitrocyclopropyl)carboxylate *rac*-13 by simple treatment with nitromethane and sodium carbonate in dimethylformamide; the sequence of dehydrobromination, Michael addition of nitromethane nitronate and 1,3-elimination[11] gives 13 in 31% yield. Selective reduction of the ester group with sodium borohydride in the presence of anhydrous aluminium chloride in dimethoxyethane leads to *rac*-7 (Scheme 2).



rac-12 31% *rac*-13 67% *rac*-7

Scheme 2

(*trans*-2'-Nitrocyclopropyl)methanol 7 is not only a precursor to 11, but also to an interesting aminoalcohol as well as the yet unknown 2-aminocyclopropanecarboxylic acid.[12]

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(9) All new compounds were fully characterized by spectroscopic techniques (^{1}H NMR, ^{13}C NMR, IR, MS) and their molecular formulas in general established by microanalysis or high resolution mass spectrometry. ^{1}H NMR (250 MHz, $CDCl_3$) and ^{13}C NMR (50.3 MHz, $CDCl_3$) data of representative products are as follows: 4: 1.96 - 2.22 (m, 2 H), 2.31 (d, 1 H, J = 4.4 Hz), 3.10 (dd, 1 H, J = 6.9, J = 9.5 Hz), 3.24 (dd, 1 H, J = 3.7, J = 9.5 Hz), 3.81 - 3.92 (m, 1 H), 4.41 - 4.60 (m, 2 H), 7.23 - 7.46 (m, 15 H); 30.81 (-), 67.12 (-), 67.76 (+), 72.13 (-), 86.89 (-), 127.25 (+), 127.95 (+), 128.54 (+), 143.51 (-). - 6: 1.30 (ddd, 1 H, J = 6.0, J = 7.4, J = 7.4 Hz), 1.82 (ddd, 1 H, J = 3.7, J = 6.0, J = 10.5 Hz), 2.14 - 2.31 (m, 1 H), 3.06 (dd, 1 H, J = 5.7, J = 10.4 Hz), 3.30 (dd, 1 H, J = 4.5, J = 10.4 Hz), 4.23 (ddd, 1 H, J = 3.7, J = 3.7, J = 7.4 Hz), 7.20 - 7.42 (m, 15 H); 15.51 (-), 25.37 (+), 57.71 (+), 61.66 (-), 86.80 (-), 127.23 (+), 127.94 (+), 128.49 (+), 143.49 (-). - 7: 1.29 (ddd, 1 H, J = 5.9, J = 7.2, J = 7.2 Hz), 1.84 (ddd, 1 H, J = 3.6, J = 5.9, J = 9.5 Hz), 2.09 (s br., 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, J = 3.6, J = 7.2 Hz); 15.15 (-), 27.05 (+), 57.63 (+), 60.93 (-). - 10 (both isomers): 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); (1st isomer): 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 (-); (2nd 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 (-). - 11 (in D_2O): (both isomers): 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, J = 3.6, J = 7.2 Hz); (1st isomer): 18.19 (-), 22.15 (+), 31.00 (-), 52.25 (+), 59.43 (+), 171.46 (-); (2nd isomer): 18.12 (-), 21.71 (+), 30.81 (-), 52.28 (+), 59.34 (+), 171.40 (-).

(10) (a) 25m Fused silica capillary column with octakis(3-O-butyryl-2,6-di-O-pentyl)-γ-cyclodextrin (Lipodex E®), commercially available from Macherey-Nagel, D-5160 Düren, Germany. - (b) W. A. König, R. Krebber, P. Mischnick, *J. High Res. Chromatogr.* 1989, *12*, 732.

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