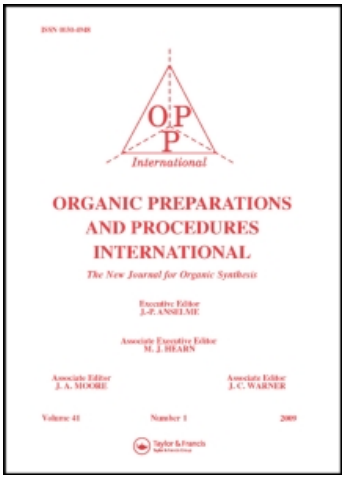

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SYNTHESIS OF AMINOCYCLOBUTANE MONO- AND DICARBOXYLIC ACIDS AND DERIVATIVES THEREOF FROM (PHENYLSULFONYL)BICYCLOBUTANES

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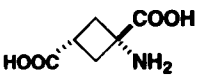
The discovery of the naturally occurring cyclobutane amino acids *cis*-1-aminocyclobutane-1,3-dicarboxylic acid (*cis*-2,4-methanoglutamic acid, **1**), 2,4-methanoproline (**2**),[1] and *cis*-1-amino-3-(hydroxymethyl)cyclobutane-1-carboxylic acid (**3**)[2] has raised a considerable interest in the synthesis of these acids and of the non natural *trans* isomers, *trans*-2,4-methanoglutamic acid (**4**) and *trans*-1-amino-3-(hydroxymethyl)cyclobutane-1-carboxylic acid (**5**).[3-8] Acid **4** was later



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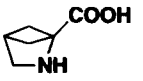

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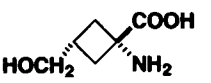

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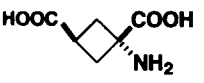

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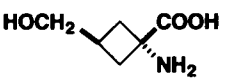
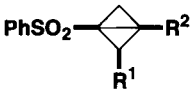


5

found to be a potent neurotransmitter, with selectivity for one subtype of glutamate receptors.[8,9] The synthetic efforts were then extended to a whole range of cyclobutane amino acids of potential biological interest, particularly as antagonists to neurotransmission[8,10] or as substitutes for essential natural amino acids in active peptides.[11]

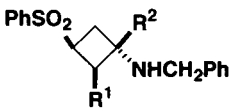
The synthesis of cyclobutane amino acids herein described is based on our general scheme for the preparation of substituted cyclobutanes from 1-(arylsulfonyl)bicyclo[1.1.0]butanes.[12,13] The use of this scheme in the preparation of a number of neuroactive amino acids has been described in detail recently.[10] The present article outlines some further applications of this scheme, either to the synthesis of additional, protected or unprotected, 1-aminocyclobutane-1- or 3- carboxylic acids, or to that of new, geometrically well defined intermediates, useful in the preparation of yet other such acids. Part of this material has appeared in a preliminary form.[5]

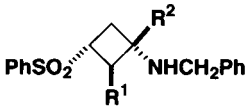
The starting materials for the preparation of the amino acids were the carboxylic acids **6a-c**, derived from the corresponding 1-(phenylsulfonyl)bicyclo-butane,[13] and their esters or amides **6d-j**.



6a: $R^1 = H, R^2 = CO_2H$ **6f**: $R^1 = H, R^2 = CON(CH_2)_5$
6b: $R^1 = CH_3, R^2 = CO_2H$ **6g**: $R^1 = CH_3, R^2 = CO_2Me$
6c: $R^1 = CH(CH_3)_2, R^2 = CO_2H$ **6h**: $R^1 = CH_3, R^2 = CO_2Et$
6d: $R^1 = H, R^2 = CO_2Me$ **6i**: $R^1 = CH_3, R^2 = CON(CH_2)_5$
6e: $R^1 = H, R^2 = CONHCH_2Ph$ **6j**: $R^1 = CH(CH_3)_2, R^2 = CO_2Me$

Benzylamine was used initially as a nitrogen nucleophile for addition to these substrates, but was soon replaced by azidation reagents, such as tetramethylguanidinium azide (TMGA), lithium azide, or, preferably, sodium azide.[5,13] Depending on reagents and conditions, the additions were either stereoselective, or produced a mixture of *trans*- and *cis*-S,N isomers (e. g. **7** and **8**, **11** and **12**). Chromatographic separation of the isomers which could be effected for characterization purposes was not required for carrying out the subsequent steps. Both isomers yield, indeed, the same desulfonylation product, while a similar mixture of isomers is obtained from each of them upon further substitution α to the sulfone.



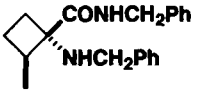


7a: $R^1 = H, R^2 = CO_2Et$ **8a**: $R^1 = H, R^2 = CO_2Et$
7b: $R^1 = H, R^2 = CONHCH_2Ph$ **8b**: $R^1 = H, R^2 = CONHCH_2Ph$
7c: $R^1 = H, R^2 = CON(CH_2)_5$ **8c**: $R^1 = H, R^2 = CON(CH_2)_5$
7d: $R^1 = CH_3, R^2 = CO_2Et$ **8e**: $R^1 = CH_3, R^2 = CONHCH_2Ph$

The addition of benzylamine was effected by warming **6** with an excess of the amine at 140° until completion of the reaction (TLC). The reaction was highly stereoselective, leading to the near exclusive formation of *trans*-S,N products **7**, even in the presence of an *exo* 2-methyl group.[5,13] This results probably from an *endo* delivery of a proton by the attacking amine molecule, which is itself being added from the *endo* side of the bicyclobutane molecule.[14] This selectivity was, however, greatly reduced by a competitive exo delivery of a proton by a 1-carboxamido group, as observed with **6e**, or with **6d** which transiently forms **6e** by reaction with benzylamine. A selective *cis* addition of ammonia and amines to bicyclobutanes had been postulated at an early stage of the study of bicyclobutane chemistry, but no proof could then be supplied.[15]

The benzylamine adducts were not used for the synthesis of unprotected amino acids, mainly because azidation reactions seemed to offer an advantageous approach. However, desulfonylation of **8e** produced **9** as a potential precursor of *rac*-2,4-methanovaline, while methylation of **8e**,

followed by desulfonylation, produced **10** as a direct precursor of *rac*-2,4-methanoisoleucine. Product **10** was obtained as a sole isomer in ca. 65% overall yield from **8e**. An x-ray analysis of **10** corroborated the *trans* relationship of the amine and the 2-methyl group and established the cis relationship of the two methyl groups.[5]



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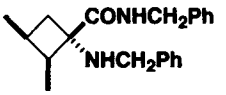

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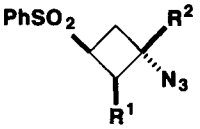
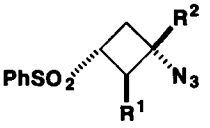
The azidations of compounds **6** was carried out under a variety of conditions, leading usually to a mixture of *trans*- and *cis*-S,N isomers **11** and **12**. However, when azidation of the free acids (**6a-c**) was carried out with sodium azide in DMF in the presence of tetramethylguanidine,[10] the *cis*-S,N isomers **12** (**12a**, **12d** after esterification, and **12f**, respectively) were stereoselectively obtained in over 90% yield. Azidation of **6d** with TMGA in DMF brought about a solvolysis of the ester group, leading to a 3:2 mixture of **11a** and **12a**, separable as **11b** and **12b** after esterification with



11a: $R^1 = H$, $R^2 = CO_2H$
11b: $R^1 = H$, $R^2 = CO_2Me$
11c: $R^1 = H$, $R^2 = CON(CH_2)_5$
11d: $R^1 = CH_3$, $R^2 = CO_2Me$
11e: $R^1 = CH_3$, $R^2 = CON(CH_2)_5$
11g: $R^1 = CH(CH_3)_2$, $R^2 = CO_2Me$
11h: $R^1 = R^2 = H$
11i: $R^1 = CH_3$, $R^2 = H$
11j: $R^1 = CH(CH_3)_2$, $R^2 = H$

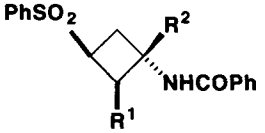


12a: $R^1 = H$, $R^2 = CO_2H$
12b: $R^1 = H$, $R^2 = CO_2Me$
12c: $R^1 = H$, $R^2 = CON(CH_2)_5$
12d: $R^1 = CH_3$, $R^2 = CO_2Me$
12e: $R^1 = CH_3$, $R^2 = CON(CH_2)_5$
12 f: $R^1 = CH(CH_3)_2$, $R^2 = CO_2H$
12g: $R^1 = CH(CH_3)_2$, $R^2 = CO_2Me$
12h: $R^1 = R^2 = H$
12i: $R^1 = CH_3$, $R^2 = H$
12j: $R^1 = CH(CH_3)_2$, $R^2 = H$
12k: $R^1 = H$, $R^2 = CONH_2$

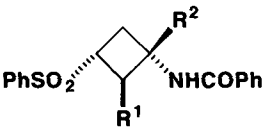
diazomethane. TMGA in DMF was also the reagent of choice for the clean azidation of **6f** and **6g**. The isomeric adducts (**11c** and **12c**, **11e** and **12e**) could be separated by chromatography on silica gel, or else used directly for reduction.

Reductions of the azides were usually carried out by hydrogenation in ethyl acetate over 10% palladium on charcoal catalyst. Stable intermediate triazenes were, however, formed during the reduction and some of them could be isolated as stable compounds and be fully characterized.[16] In the case

of the azido esters, the formation of the triazenes lowered the yield of the amine by intramolecular formation of a triazole.[16] Upon reduction of the azides by catalytic transfer hydrogenation,[17] using 10% palladium on charcoal and ammonium formate in methanol at 50°, no triazenes were detected, and the overall yield of reduced products from the azides was of 60 to 70%. The intermediate amines were usually not isolated as such but were benzoylated to derivatives **13** and **14**. These derivatives, and particularly **14b** and **14j**, are useful intermediates for the preparation of numerous cyclobutane amino acids by substitution α to the sulfone group.[10]



13a: R^1 = H, R^2 = CO_2Me
13b: R^1 = H, R^2 = $CON(CH_2)_5$
13c: R^1 = CH_3, R^2 = CO_2Me
13d: R^1 = CH_3, R^2 = $CON(CH_2)_5$
13f: R^1 = R^2 =H
13g: R^1 = CH_3, R^2 = H



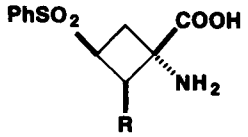
14a: R^1 = H, R^2 = CO_2Me
14b: R^1 = H, R^2 = $CON(CH_2)_5$
14c: R^1 = CH_3, R^2 = CO_2Me
14d: R^1 = CH_3, R^2 = $CON(CH_2)_5$
14e: R^1 = $CH(CH_3)_2$, R^2 = CO_2Me
14f: R^1 = R^2 =H
14g: R^1 = CH_3, R^2 = H
14h: R^1 = $CH(CH_3)_2$, R^2 = H
14i: R^1 = H, R^2 = $CONH_2$
14j: R^1 = H, R^2 = CN

Simple manipulations such as reduction and hydrolysis, of a number of the primary adducts **11** and **12** produce cyclobutane amino acids, either sulfonylated (**15a-c, 16a-c**) or desulfonylated (**17a-c**). While 2-unsubstituted adducts possess a plane of symmetry and are achiral, the 2-alkylated products are chiral, and are obtained here as racemic mixtures.

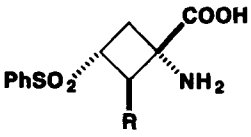
Catalytic hydrogenation of the individual azido acids **11a** and **12a** produced **15a** and **16a**, respectively. Both products precipitated on the catalyst and were extracted from it with boiling water and recovered in over 80% yield. Acids **15b** or **16b** were obtained in 60-65% yields by acid hydrolysis of the amino esters derived from **11d** or **12d**, respectively. Acids **15c** and **16c**, were similarly obtained from **11g** and **12g**, and in similar yields.

The desulfonylated amino acids **17a-c** can be obtained either directly from the azido acid or ester by a one-pot reduction-desulfonylation with sodium amalgam, or stepwise, by first catalytically reducing the azide and then removing the sulfone group, the ester group being usually saponified under these conditions.

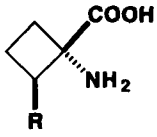
The parent cyclobutane amino acid **17a** [18-20] could thus be readily obtained by desulfonylation with sodium amalgam in THF-methanol either of the total amine from reduction of the azido esters **11b** and **12b**, or, more directly, by reduction-desulfonylation of the azido acids **11a** or **12a**. In



15a: R = H
15b: R = CH_3
15c: R = $CH(CH_3)_2$



16a: R = H
16b: R = CH_3
16c: R = $CH(CH_3)_2$

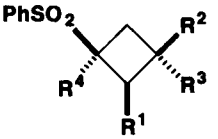


17a: R = H
17b: R = CH_3
17c: R = $CH(CH_3)_2$

particular, **12a** provided **17a** in 75% yield after ion exchange chromatography. Desulfonylation of a mixture of crude amino esters derived from **11d** and **12d** provided **17b** (*rac*-methanovaline) in 66% yield. Amino acid **17c** was similarly obtained from reduced **12g** by treatment with sodium in THF-ethanol. Protected forms of the desulfonylated acids (*e. g.* **20h**) could be readily obtained by desulfonylation of some of compounds **13** or **14** (see below).

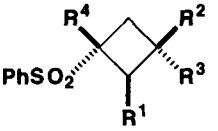
The preparation of compound **10** illustrates the general synthetic scheme for the preparation of 3-substituted cyclobutane amino acids, including compounds **1** to **5**. The first step towards such compounds is a substitution α to the sulfone, leading to compounds **18** and **19**. This is followed then by desulfonylation, before or after modification of group R^4, leading to compounds **20** and **21**.

The most direct route to acids **1** and **4** involved the primary adducts **11a** and **12a** and used no protection of the intermediates.[5] Treatment of the azido acids with two equivalents of BuLi, or with one equivalent of sodium hydride and one of BuLi, in THF at -78°, followed by addition of carbon dioxide, furnished selectively diacid **18a** in up to 55% yield. The moderate yield in this step results, in part, from a retrograde formation of a bicyclobutane by intramolecular displacement the

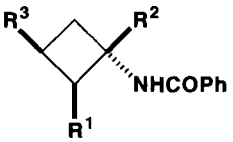


18a: R^1 = H, R^2 = CO_2H, R^3 = N_3, R^4 = CO_2H
18b: R^1 = H, R^2 = CO_2Me, R^3 = N_3, R^4 = CO_2Me
18c: R^1 = H, R^2 = CO_2H, R^3 = NH_2, R^4 = CO_2H
18d: R^1 = H, R^2 = CO_2Me, R^3 = NH_2, R^4 = CO_2Me
18e: R^1 = H, R^2 = CO_2Me, R^3 = NHCOPh, R^4 = CO_2Me
18f: R^1 = H, R^2 = $CON(CH_2)_5$, R^3 = NHCOPh, R^4 = CO_2Me
18g: R^1 = CH_3, R^2 = $CON(CH_2)_5$, R^3 = NHCOPh, R^4 = CO_2H
18h: R^1 = R^2 = H, R^3 = NHCOPh, R^4 = CO_2H
18i: R^1 = R^2 = H, R^3 = NHCOPh, R^4 = CO_2Me
18j: R^1 = CH_3, R^2 = H, R^3 = NHCOPh, R^4 = CO_2H
18l: R^1 = H, R^2 = CN, R^3 = NHCOPh, R^4 = CO_2H

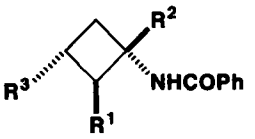
azide. The moderate yield is, however, being compensated for by the small number of steps involved in going from **6a** to acids **1** and **4**, relative to methods which use protection and deprotection of the intermediates (see below). Catalytic hydrogenation of **18a** furnished the *trans*-S,N amino diacid **18c**, the structure of which has been determined by x-ray crystallography.[5] The mixture of acids **1** and **4** obtained from **18c** by desulfonylation was conveniently separated on a Dowex 1 ×8 (acetate form) column by elution with 0.15 M acetic acid. The product first eluted was the major isomer and was found to be acid **4**, its structure being established by x-ray crystallography.[5] The overall yield of the two acids from **6a** was of 25-30%.



19b: $R^1 = H$, $R^2 = CO_2Me$, $R^3 = N_3$, $R^4 = CO_2Me$
19e: $R^1 = H$, $R^2 = CO_2Me$, $R^3 = NHCOPh$, $R^4 = CO_2Me$
19f: $R^1 = H$, $R^2 = CON(CH_2)_5$, $R^3 = NHCOPh$, $R^4 = CO_2Me$
19g: $R^1 = CH_3$, $R^2 = CON(CH_2)_5$, $R^3 = NHCOPh$, $R^4 = CO_2H$
19j: $R^1 = CH_3$, $R^2 = H$, $R^3 = NHCOPh$, $R^4 = CO_2H$
19k: $R^1 = CH(CH_3)_2$, $R^2 = H$, $R^3 = NHCOPh$, $R^4 = CO_2Me$
19l: $R^1 = H$, $R^2 = CN$, $R^3 = NHCOPh$, $R^4 = CO_2H$
19m: $R^1 = CH_3$, $R^2 = CONHCH_2Ph$, $R^3 = NHCH_2Ph$, $R^4 = CH_3$
19n: $R^1 = CH_3$, $R^2 = CONHCH_2Ph$, $R^3 = N(CH_3)CH_2Ph$, $R^4 = CH_3$



20a : $R^1 = H$, $R^2 = CO_2Me$, $R^3 = CO_2Me$
20b : $R^1 = H$, $R^2 = CON(CH_2)_5$, $R^3 = CO_2Me$
20c : $R^1 = CH_3$, $R^2 = CON(CH_2)_5$, $R^3 = CO_2Me$
20d : $R^1 = H$, $R^2 = CN$, $R^3 = CO_2Me$
20e : $R^1 = H$, $R^2 = CON(CH_2)_5$, $R^3 = CH_2OH$
20f : $R^1 = H$, $R^2 = CON(CH_2)_5$, $R^3 = CH_2OSO_2CH_3$
20h : $R^1 = R^3 = H$, $R^2 = CO_2Me$
20i : $R^1 = R^2 = H$, $R^3 = CO_2H$
20j : $R^1 = R^2 = H$, $R^3 = CO_2Me$
20k : $R^1 = CH_3$, $R^2 = H$, $R^3 = CO_2Me$
20l : $R^1 = CH(CH_3)_2$, $R^2 = H$, $R^3 = CO_2Me$



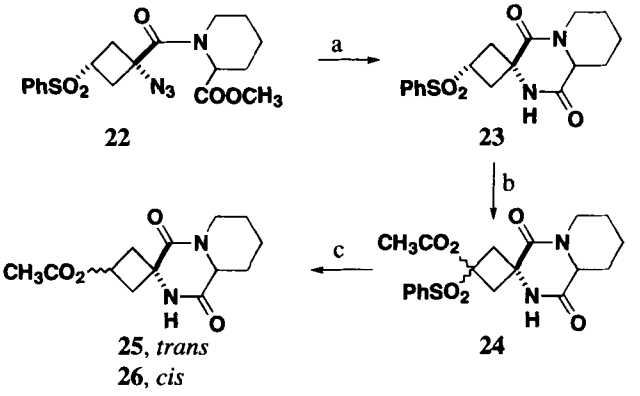
21a : R^1 = H, $R^2 = CO_2Me$, $R^3 = CO_2Me$
21b : R^1 = H, $R^2 = CON(CH_2)_5$, $R^3 = CO_2Me$
21c : $R^1 = CH_3$, $R^2 = CON(CH_2)_5$, $R^3 = CO_2Me$
21d : R^1 = H, R^2 = CN, $R^3 = CO_2Me$
21e : R^1 = H, $R^2 = CON(CH_2)_5$, $R^3 = CH_2OH$
21f : R^1 = H, $R^2 = CON(CH_2)_5$, $R^3 = CH_2OSO_2CH_3$
21g : R^1 = H, $R^2 = CON(CH_2)_5$, $R^3 = CH_2N_3$
21i : $R^1 = R^2$ = H, $R^3 = CO_2H$
21j : $R^1 = R^2$ = H, $R^3 = CO_2Me$
21k : $R^1 = CH_3$, R^2 = H, $R^3 = CO_2Me$
21l : $R^1 = CH(CH_3)_2$, R^2 = H, $R^3 = CO_2Me$

Alternative routes to **1** and **4** and to a large number of other cyclobutane amino acids involved desulfonylation of **18** and **19** and separation of the geometrically well defined intermediates **20** and **21**. These routes require a greater number of steps but enable larger scale separations of direct precursors of the amino acids. One such route to **1** or **4**, involving **13b** and **14b**, has been described in detail recently.[10] Another route involved **20a** and **21a**, obtainable from **18e** and **19e** by desulfonylation and esterification. Compounds **20a** and **21a** were individually hydrolyzed to **4** and **1**, respectively. The overall yield of the two acids from **6a** was of about 35%.

Yet another route to **1** and **4** involved **20d** and **21d**, which were obtained from **13j** and **14j** and which were easier to manipulate than the difficultly soluble **13b** and **14b**. Modifications of the ester side chain of **20d** and **21d** led to neuroactive compounds via a route parallel to that described earlier for **20b** and **21b**[10,21]

In the search for yet other intermediates of type **13** and **14** that would be resistant to BuLi for further manipulation to compounds of type **20** and **21**, pipecolinic acid was used as a protecting group, thus achieving protection of both the carboxyl and the amine functions (Scheme 1). The acid chloride derived from **12a** was reacted with the hydrochloride of pipecolinic acid methyl ester to provide **22** in 89% yield. Catalytic transfer hydrogenation of **22** provided directly **23** in ca. 85% yield (ca. 73% overall yield from **6a**). Carboxylation of **23** was stereotoselective, furnishing after esterification and chromatography one **24** isomer, probably *trans*, in 94% yield. Desulfonylation and repeated esterification provided **25** and **26** in a total 45% yield relative to **23**. The two compounds could be chromatographically separated, but they did not solidify and were characterized only by their ^1H NMR spectra. Hydrolysis of the first eluted isomer **26** furnished acid **1**, while **25** furnished acid **4**.

Scheme 1



a) Catalytic transfer hydrogenation. b) BuLi; CO_2; CH_2N_2.
c) 6% Na-Hg; CH_2N_2

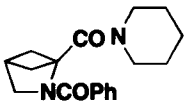
The ^{1}H NMR spectra of compounds **7** through **21** (except **9** and **10**) are grouped in Tables 1 to 6. They typically show, for the 2-unsubstituted compounds, two symmetrical multiplets for the α and β protons of the cyclobutane methylenes and a separate quintuplet, or multiplet, for the tertiary ring proton, besides the side-chain signals. The two methylene multiplets may coalesce in some of the *cis*-S,N derivatives. In the 2-substituted derivatives, the symmetry is perturbed, but the general pattern of the spectra remains unchanged. The ^{1}H NMR of the tricyclic compounds **23-26**, on the other hand, reflect their high dissymmetry relative to most of the monocyclic compounds In particular, the nine protons of the piperidine ring have a wide spread of chemical shifts. The single N-C*H*-CO proton appears at about δ 4.5, the two N-CH_2 protons, being one in the plane of the adjacent carbonyl and one perpendicular to it, appear at δ 3.9 (d) and 2.5 (t), while the six remaining protons appear in four or five separate groups from about δ 1.3 to 2.4.

The scope of the transformations of **20** and **21** to yet other amino acids can be enlarged by modifying the R^4 side chain before hydrolysis.[10] Examples involving the conversion of **20b** and **21b** to amino acids **5** and **3** or to 2,4-methanoornithine are provided below.

Conversion of **20b** and **21b** to acids **5** and **3** involved reduction with sodium borohydride in water-dioxane[10,22] to **20e** and **21e** followed by acid hydrolysis. The two acids were thus obtained in over 80% yield. The natural cis acid **3** had a melting point of 239-240° (decomposition; reported: decomposition at 210° without melting,[2] melting with decomposition at 210°,[6] melting with decomposition at 250-260°[7]). Its 400 MHz ^{1}H NMR in D_2O corresponded to that published,[2,7] with a general downfield shift of 0.1 ppm due probably to the use of a different internal reference. The *trans* isomer **5** had a melting point of 250-255° (dec.); lit.[6] 255° (dec.). The ^{1}H NMR corresponded to that published,[6] but again with a general downfield shift of 0.1 ppm.

Treatment of **21f** with BuLi in THF at room temperature for 20 hrs brought about cyclization to **27**, a precursor of methanoproline **2**, in 71% yield. Acid hydrolysis of an N-benzoyl carboxylic ester derivative related to the carboxylic amide **27** had already provided methanoproline.[7]

Mesylate **21f** was used also for the preparation of *cis*-2,4-methanoornithine (**28**): Treatment of **21f** with TMGA in N-methyl-2-pyrrolidone (NMP) at 85° for 2 hrs provided azide **21g** in 80% yield. Reduction of the azide, followed by acid hydrolysis and by treatment of the hydrochloride with propylene oxide in ethanol, furnished **28** in over 90% yield. Amino acid **28** crystallized from water-ethanol as the monohydrate. It did not melt below 300°.



27

28

The general synthetic scheme outlined above is also potentially useful for the preparation of 3-aminocyclobutane-1-carboxylic acids, and particularly of 2-substituted acids which would be difficult to obtain using the usual malonic synthesis approach.[23] Compounds **20i-l** and **21i-l** are, indeed, direct precursors of such acids. Configurational assignments of these compounds are based on chromatographic behavior, the *cis*-1,3 compounds usually preceding the *trans* ones,[23] and on the chemical shift of a 2-substituent, when present, which is relatively deshielded by a *cis* 1-substituent.

EXPERIMENTAL SECTION

Melting points were taken on a Fisher-Johns apparatus and were not corrected. Proton NMR spectra were measured with a Varian FT-80A spectrometer in $CDCl_3$, unless otherwise indicated. Shifts are given in δ units downfield from internal TMS and *J* values are given in Hertz. High resolution mass spectra (HR-MS) were measured with a Varian MAT 731 instrument. TLC was done on Merck Kieselgel precoated aluminum plates. Silica gel for column chromatography was Merck Kieselgel 60 (70-230 mesh). *The weight ratio of silica gel to product is indicated by x for every chromatography.* Solvent of crystallization is given in parenthesis after the indicated melting point. Elemental analyses were performed at the Microanalytical Laboratory of the Hebrew University, Jerusalem.

2-(2-Methyl)ethyl-3-(phenylsulfonyl)bicyclo[1.1.0]butane-1-carboxylic acid (6c) was prepared as described before for **6a** and **6b**,[13] mp 208-209° (EtOAc), NMR: δ 1.09 and 1.12 (two d, *J*=6.6, two Me), 1.34 (d, *J*=1.5, C4 *endo* -H), 1.58 (d, *J*=10.4, C2 *endo*-H), 2.5 (m, 1), 2.74 (d, *J*=1.4, C4 *exo*-H), 5.1 (br, OH), 7.5-8.0 (5 H).

Anal. Calcd for $C_{14}H_{16}O_4S$: C, 60.00; H, 5.75. Found: C, 59.90; H, 5.65

Methyl 2-(2-methyl)ethyl-3-(phenylsulfonyl)bicyclo[1.1.0]butane-1-carboxylate (6j) was obtained by esterification of **6c** with diazomethane, mp 69-70° (hexane), NMR: δ 1.05 and 1.11 (two d, *J*=6.5, two Me), 1.28 (d, *J*=1.4, 1 H), 1.53 (d, *J*=10.5, 1 H), 2.6 (m, 1 H), 2.73 (d, *J*=1.4, 1 H), 3.78 (s, Me), 7.5-8.0 (5 H).

Anal. ($C_{15}H_{18}O_4S$) HR-MS Found: m/e 262.0667 (M^+ - CH_3OH), 153.0878. Calcd. for $C_{14}H_{14}O_3S$: 262.0664.

Other compounds **6** used have been described earlier.[13]

Addition of Benzylamine to 6. -Compound **6** was warmed under inert atmosphere with benzylamine (2 mL per g of starting material) at 140° for 4 hrs (for **6e**) or 20 hrs (for **6g** or **6h**). Excess amine was evaporated under reduced pressure and the products were purified by chromatography and crystallization. The starting materials, chromatographic conditions (weight ratio of silica gel to crude product, eluting solvent mixture), respective ratio of isomers, and total yield, are indicated in that order for the following adducts.

Methyl *trans*- and *cis*-1-Benzylamino-3-(phenylsulfonyl)cyclobutane-1-carboxylate (7a and **8a**). From ester **6e**; ×20, hexane-ether 1:1; 5 to 1; 83%.

Compound **7a**, mp 76-77° (ether-hexane).

Anal. Calcd for $C_{20}H_{23}NO_4S$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.63; H, 6.25; N, 3.67

Compound **8a**, liquid.

Anal. ($C_{20}H_{23}NO_4S$) HR-MS Found: m/e 232.1443 (M^+ - $PhSO_2$). Calcd. for $C_{14}H_{18}NO_2$: 232.1337.

***trans*- and *cis*-1-Benzylamino-3-(phenylsulfonyl)cyclobutane-1-N-benzylcarboxamide (7b** and **8b**).- From ester **6d** or amide **6f**; ×40, CH_2Cl_2-hexane-EtOAc 4:4:1; approximately 1 to 1; 90%.

Compound **7b**, mp 109-110° (EtOH).

Anal. Calcd for $C_{25}H_{26}N_2O_3S$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.29; H, 5.95; N, 6.38

Compound **8b**, mp 146-147° (EtOH).

Anal. Calcd for $C_{25}H_{26}N_2O_3S$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.35; H, 6.13; N, 6.33

***trans*- and *cis*-1-Benzylamino-3-(phenylsulfonyl)cyclobutane-1-N,N-pentamethylenecarboxamide (7c** and **8c**).- The sole product obtained from amide **6g** was **7c**; ×10, EtOAc-hexane 1:1; 56%. Adduct **8c** was obtained as a recovered, isomerized starting material from experiments involving deprotonation of **7c** α to the sulfone.

Compound **7c**, mp 133-134° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{23}H_{28}N_2O_3S$: C, 66.97; H, 6.84; N, 6.79. Found: C. 66.90; H, 6.86; N, 6.83.

Compound **8c**, mp 108-109° (ether-hexane).

Anal. Calcd for $C_{23}H_{28}N_2O_3S$: C, 66.97; H, 6.84; N, 6.79. Found: C. 67.05; H, 6.92; N, 6.85

Ethyl *r*-1-Benzylamino-*t*-2-methyl-*t*-3-(phenylsulfonyl)cyclobutane-1-carboxylate (7d) and ***r*-1-Benzylamino-*t*-2-methyl-*c*-3-(phenylsulfonyl)-cyclobutane-1-N-benzylcarboxamide (8e)**.- Obtained concurrently from ester **6h**; ×20, hexane-ether 1:1; 49 and 11%, respectively. Only **8e** was obtained from **6g**.

Compound **7d**, mp 95-96° (ether-hexane).

Anal. Calcd for $C_{21}H_{25}NO_4S$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.18; H, 6.57; N, 3.47

Compound **8e**, mp 113-114° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{26}H_{28}N_2O_3S$: C, 69.63; H, 6.29; N, 6.25. Found: C, 69.71; H, 6.41; N, 6.23

Table 1. ^{1}H NMR Spectra of Compounds **7** and **8**.[a]

Cmpd	Ring CH_2's and CH	2-Methyl	R^2-Substituent	N*H*-	NHCH_2Ph
7a	2.0-2.3, 2.7-3.0 (4); 3.99 (1)		1.3 (t, 3), 4.21 (q, 2)	1.87	3.55 (s, 2)
7b	2.02-2.33, 2.87-3.15 (4); 3.91 (1)		4.43 (d, 2)[b]	1.89	3.52 (s, 2)
7c	2.1-2.45, 2.9-3.2 (4); 3.85 (1)		1.6 (6), 3.45 (4)[c]	1.6	3.57 (s, 2)
7d	1.85-2.2, 2.5-2.85, 3.20 (3); 3.97 (1)	1.43 (d)	1.33 (t, 3), 4.25 (q, 2)	1.9	3.49 (s,2)
8a	2.67 (d, 4); 3.77 (1)		1.27 (t, 3), 4.19 (q, 2)	1.87	3.67 (s, 2)
8b	2.35-2.95 (4); 3.93 (1)		4.38 (d, 2)[b]	1.9	3.54 (s, 2)
8c	2.3-2.55, 2.8-3.2 (4); 3.5 (1)		1.55 (6), 3.5 (4)	1.85	3.57 (s, 2)
8e	2.34, 2.6-3.05 (3); 3.5 (1)	0.92 (d)	4.40 (d, 2)[b]	1.8	3.5 (s, 2)

a) The aromatic protons appear in the region of ca. δ 7.3-8.0 and are not reported. Amide protons are also not reported. b) Singlet after addition of D_2O. c) The piperidine ring protons appear in two distinct regions of the spectrum in groups of four (CH_2NCH_2) and six protons.

***trans*-2-Methyl-1-(benzylamino)cyclobutane-1-N-benzylcarboxamide (9).-** Desulfonylation of **8e** (252 mg, 0.56 mmol) was carried out in MeOH-THF (6:1, 7 mL), by stirring with 6% sodium amalgam (Na-Hg; 1 g) at room temperature for 1 hr, in the presence of Na_2HPO4 (320 mg, 1.8 mmol). Extractive work up with ethyl acetate and water, followed by chromatography on silica gel (5 g, hexane-ether 7:3) provided **9** (125 mg, 72% yield), mp 55-56° (pentane). NMR: δ 0.99 (d, *J*=6.5, Me), 1.56 (br, amine NH, rapidly exchanged with D_2O), 1.6-2.4 (m, 4 H), 2.5-2.8 (m, 1 H), 3.37 and 3.71 (ABq, *J*=12.5, NHCH_2Ph), 4.47 (d, *J*=5.9, CONHCH_2Ph), 7.3 (10 H), 7.5 (br, amide NH, exchanged after 24 hrs with D_2O, the 4.47 d becoming a singlet).

Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.81; H, 7.58; N, 9.02

***r*-1-Benzylamino-*t*-2-methyl-*t*-3-methylcyclobutane-1-N-benzylcarboxamide (10).-** Methylation of **8e** was carried out in THF at -78°, using two equivalents of BuLi and excess methyl iodide. The major product, obtained by chromatographic separation on silica gel (elution with hexane-ether 1:1), was **19m** (66-74% yield relative to unrecovered starting material). This was usually accompanied by the N-methylated product **19n** (ca. 15% relative to unrecovered starting material) and by 10-15% of starting material. Product **19m** did not solidify. It was characterized by its ^{1}H NMR and used directly for desulfonylation. NMR: δ 0.86 (d, *J*=7.4, Me), 1.41 (s, Me), 1.95 (N*H*), 2.82 (s, ring CH_2), 3.10 (q, *J*=7.3, ring C*H*), 3.30 and 3.76 (ABq, *J*=12.1, amine side chain CH_2) 4.41 (d, *J*=5.8, amide side chain CH_2), 6.92 (amide N*H*), 7.2-7.9 (15 H). Product **19n**, mp 109-110° (*tert*-butyl methyl ether (TBME)-

hexane), NMR: δ 0.80 (d, *J*=6.4, Me), 2.20 (s, N-Me), 2.53 (d, *J*=8.0, ring C*H*$_2$), 3.45 (s and m, 4 H), 4.44 (d, amide C*H*$_2$), 7.2-8.0 (15 H).

Anal. Calcd for $C_{27}H_{30}N_2O_3S$: C, 70.11; H, 6.54; N, 6.06. Found: C, 70.15; H, 6.44; N, 6.12

Desulfonylation of **19m** (0.4 g, 0.87 mmol) was carried out as described above for **8e.** Chromatography of the crude product on silica gel (10 g; hexane-ether 2:1) provided **10** (256 mg, 92% yield), mp 113-114° (hexane), NMR: δ 0.93 (d, *J*=6.8, Me), 1.05 (d, *J*=6.0, Me), 1.59 (N*H*), 2.0-2.6 (m, 4), 3.31 and 3.72 (ABq, *J*=12.4, amine C*H*$_2$), 4.44 (d, *J*=5.8, amide C*H*$_2$; s after 24 hrs with D_2O), 7.28 (10 H), 7.5 (br, amide N*H*).

Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.07; H, 7.79; N, 8.49

The x-ray analysis of **10** has been described earlier.[5]

Azidation of Acids 6a-c.- The acid (10 mmol) was warmed in a mixture of DMF (20 mL) and tetramethylguanidine (2 mL) with either lithium azide or sodium azide (15 mmol) at 90° until all starting material had been consumed (**6a**, 6 hrs; **6b**, 20 hrs; **6c**, 20 hrs and additional 4 hrs at 115°). The cooled down solution was diluted with water, extracted twice with ether to remove non-acidic material, and then acidified and extracted for the acid product.

Acid **12a**: See ref 10.

Acid **11a** was obtained alongside with **12a** by azidation of **6d** (see below).

Methyl *r*-1-Azido-*t*-2-methyl-*c*-2-(phenylsulfonyl)cyclobutane-1-carboxylate (12d) was obtained from **6b** as a liquid acid product. It was esterified with diazomethane in ether, providing **12d**, free of **11d**, in 93% yield, mp 77-78°.

Anal. Calcd for $C_{13}H_{15}N_3O_4S$: C, 50.49; H, 4.89; N, 13.59. Found: C, 50.62; H, 4.80; N, 13.45

***r*-1-Azido-*t*-2-(2-methyl)ethyl-*c*-3-(phenylsulfonyl)cyclobutane-1-carboxylic acid (12f).**- Extraction of the acid product with EtOAc and trituration of the crude product with ether-hexane furnished solid acid **12f** in 75% yield, mp 114-115° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{14}H_{17}N_3O_4S$: C, 52.01; H, 5.30; N. 13.00. Found: C, 52.21; H, 5.26; N, 13.05.

Esterification of the mother liquors provided **12g** (described below) in 19% yield.

Azidation of Bicyclic Esters 6d, 6g, and 6j.- Azidation was carried out by warming the ester (1 equiv) in DMF or NMP (1 mL per mmol of starting material) at 85° with TMGA (1.5 equiv). Concurrent solvolylsis of the esters furnished the azido acids as reaction products. The duration of the reaction was determined by TLC of a worked up and esterified aliquote. Work up of the reaction followed the procedure outlined above. The total acid mixture was usually esterified with diazomethane and used for reduction to the amine, or else chromtographed for separation of the isomers, which were usually obtained in about equal amounts. In the case of acids **11a** and **12a**, a partial separation of the acids could be achieved by fractional precipitation from the total mixture.

***trans*-1-Azido-3-(phenylsulfonyl)cyclobutane-1-carboxylic acid (11a).**- The total acid mixture obtained from **6d** (94% yield) solidified partly. It was taken in ether and filtered after 20 hrs, providing **11a** in about one third of the total amount of product material; mp 160-161° (decomposition; benzene).

Anal. Calcd for $C_{11}H_{11}N_3O_4S$: C, 46.98; H, 3.94; N, 14.94. Found: C, 46.88; H, 3.80; N, 14.85

Methyl *trans*- and *cis*-1-Azido-3-(phenylsulfonyl)cyclobutane-1-carboxylate (11b and 12b).- Esterification of the above mixture and chromatography (silica gel ×40; hexane-ether, 1:1) separated partly the two isomers, **11b** being eluted first.

When the azidation of **6d** was carried out with TMGA in ethanol-free chloroform and NMP (20:3) at 85° for 20 hrs, practically no solvolysis occured and the mixture of **11b** and **12b** was obtained directly.

Compound **11b**, mp 58-59° (ether-hexane).

Anal. Calcd for $C_{12}H_{13}N_3O_4S$: C, 48.82; H, 4.44; N, 14.23. Found: C, 48.65; H, 4.60; N, 14.05

Compound **12b**, liquid.

Anal. ($C_{12}H_{13}N_3O_4S$) HR-MS Found: 126.0547 ($M^+ - N_2 - PhSO_2$). Calcd for $C_6H_8NO_2$: 126.0539.

Methyl *r*-1-azido-*t*-2-methyl-*t*-3-(phenylsulfonyl)cyclobutane-1-carboxylate (11d) and **Methyl *r*-1-azido-*t*-2-methyl-*c*-3-(phenylsulfonyl)cyclobutane-1-carboxylate (12d)** were obtained from **6g** in a total 95% yield and separated as described for **11b** and **12b**

Compound **11d**, liquid.

Anal. ($C_{13}H_{15}N_3O_4S$) HR-MS Found: m/e 222.0523 ($M^+ - N_2 - CO_2CH_3$). Calcd for $C_{11}H_{12}NO_2S$: 222.0475.

Compound **12d**, mp 77-78° (ether-hexane).

Anal. Calcd for $C_{13}H_{15}N_3O_4S$: C, 50.49; H, 4.89; N, 13.59. Found: C, 50.62; H, 4.80; N, 13.45

Methyl *r*-1-azido-*t*-2-(2-methyl)ethyl-*t*-3-(phenylsulfonyl)cyclobutane-1-carboxylate (11g) and **Methyl *r*-1-azido-*t*-2-(2-methl)ethyl-*c*-3-(phenylsulfonyl)cyclobutane-1-carboxylate (12g)** were obtained from **6j** in a total 89% yield (eluted with hexane-ether 2:1).

Compound **11g**, mp 101-102° (hexane).

Anal. Calcd for $C_{15}H_{19}N_3O_4S$: C, 53.41; H, 5.68; N, 12.46. Found: C, 53.30; H, 5.51; N, 12.31

Compound **12g**, mp 86-87° (hexane).

Anal. Calcd for $C_{15}H_{19}N_3O_4S$: C, 53.41; H, 5.68; N, 12.46. Found: C, 53.22; H, 5.70; N, 12.44

Azidation of the Bicyclic Piperidine Amides 6f and 6i.- The solid, crude amides, prepared from the corresponding acid chlorides, were treated with TMGA (1.2 equiv) in NMP (6 mL per g of amide) at 90° for 3 hrs (**6f**) or 20 hrs (**6i**). The cooled reaction mixture was added with water, slightly acidified, and extracted with ethyl acetate. The organic extract was washed with water, dried, and concentrated at reduced pressure to yield mixtures of isomeric products. These were usually filtered on a relatively small amount of silica gel (×5, hexane-CH_2Cl_2-EtOAc 5:5:2) and used for reduction to the amine without separation of the isomers. The yields relative to the bicyclic acids were of 78-82%.

***trans*- and *cis*-1-Azido-3-(phenylsulfonyl)cyclobutane-1-N,N-pentamethylenecarboxamide (11c and 12c).**- The two isomers were obtained from **6f** in approximately 1:1 ratio. Partial separation was achieved by using higher proportion of silica gel (×30 by weight). A more convenient preparation of pure **12c** starts from **12a**.[10]

Compound **11c**, mp 98-99° (CH_2Cl_2-hexane).

Anal. Calcd. for $C_{16}H_{20}N_4O_3S$: C, 55.17; H, 5.79; N, 16.08. Found: C, 55.47; H, 6.01; N, 16.11
Compound **12c**, see ref 10.

***r*-1-Azido-*t*-2-methyl-*t*-3-(phenylsulfonyl)cyclobutane-1-N,N-pentamethylenecarboxamide (11e)** and ***r*-1-Azido-*t*-2-methyl-*c*-3-(phenylsulfonyl)cyclobutane 1-N,N-pentamethylenecarboxamide (12e)** were obtained from **6i** in a ratio of about 2:1, respectively. Separation was achieved by treatment of the crude reaction mixture with ether, whereby **11e** could be collected by filtration and be purified by crystallization. Filtration of the residual material on silica gel and repeating the trituration with ether separated yet some more of **11e**, while **12e** could be obtained by crystallization of the residual material.
Compound **11e**, mp 155-156° (EtOAc-hexane).

Table 2. ^{1}H NMR Spectra of Compounds **11** and **12**.[a]

Cmpd	Ring CH_2's and CH	2-Me or 2-*i*Pr	R^2 protons
11a[b]	2.3-2.5, 2.9-3.2 (4); 4.03 (1)		
11b	2.2-2.5, 3.0-3.3; 3.8-4.1 (1)		3.84 (s, Me)
11c	2.2-2.5, 3.0-3.6 (4,4); 3.87 (1)		1.6 (6)
11d	1.9-2.2, 2.9-3.5 (3); 3.8-4.1 (1)	1.51 (d, Me)	3.86 (s, Me)
11e	2.0-2.3 (1), 2.6-4.1 (7)	1.44 (d, Me)	1.64 (6)
11g	2.6-2.8, 2.91 (3); 3.8 (1)	1.01 (d, Me), 1.11 (d, Me), 2.17 (1)	3.91 (s, Me)
11j	1.9-2.7 (m, 4), 3.75 (br t,1), 4.23 (q,1)	0.96 (d, two Me)	
12a	2.83 (d, 4); 3.86 (1)		8.51 (O*H*)
12b	2.8 (d, 4); 3.6-4.0 (1)		3.82 (s, Me)
12c	2.8-3.0 (4); 3.3-3.6 (5)		1.6 (6)
12d	2.35-2.85, 3.1-3.6 (4)	0.96 (d, Me)	3.83 (s, Me)
12e	2.5 (2), 3.2 (4), 3.5-4.1 (2)	1.04 (d, Me)	1.6 (6)
12f	2.46 (2), 2.93 (1); 3.68 (1)	0.91 (d, Me), 0.95 (d, Me) 1.5-2.0 (1)	
12g	2.3-3.0 (3); 3.58 (1)	0.89 (d, Me), 0.96 (d, Me)	3.81 (s, Me)
12j	2.30 (2), 2.65 (1), 3.08-3.55 (2)	0.91 (d, two Me), 1.63 (1)	

(a) See footnote a, Table 1. (b) In $CDCl_3$ + DMSO-d_6.

Anal. Calcd for $C_{17}H_{22}N_4O_3S$: C, 56.35; H, 6.12; N, 15.46. Found: C, 56.30; H, 6.05; N, 15.55
Compound **12e**, mp 82-83° (EtOAc-hexane).
Anal. Calcd for $C_{17}H_{22}N_4O_3S$: C, 56.35; H, 6.12; N, 15.46. Found: C, 56.47; H, 6.14; N, 15.30

***r*-1-Azido-*t*-2-(2-methyl)ethyl-*t*-3-(phenylsulfonyl)cyclobutane (11j)** and ***r*-1-Azido-*t*-2-(2-methyl)ethyl-*c*-3-(phenylsulfonyl)cyclobutane (12j)** were prepared as described for **11h** and **11i** and their *cis* isomers.[13] Chromatography on silica gel (× 40; hexane-ether 7:3) separated **11j** from **12j** in a total 89% yield (ratio ca. 1:2, respectively).

Compound **11j**, mp 78-79° (pentane).

Anal. Calcd for $C_{13}H_{17}N_3O_2S$: C, 55.91; H, 6.10. Found: C, 55.85; H, 6.10

Compound **12j** did not solidify and was used directly for reduction.

***cis*-1-Azido-3-(phenylsulfonyl)cyclobutane-1-carboxamide (12k).** See ref 16.

Catalytic Hydrogenation of the Azides and Benzoylation of the Amines: Products 13 and 14.- The hydrogenations were carried out in ethyl acetate (30 mL per g of total azides) over 10% Pd/C (10% by weight of azides) at room temperature and under atmospheric pressure and for 20 to 24 hrs. The reaction mixture was then refluxed under air atmosphere until disappearence of the TLC triazene spot, observable during hydrogenation between that of the starting azide and that of the amine product.[16] Filtration of the catalyst and concentration under reduced pressure provided the amine or amine mixture which was usually directly benzoylated with benzoyl chloride in dichloromethane-pyridine according to standard procedures.

Methyl *trans*- and *cis*-1-benzoylamino-3-(phenylsulfonyl)cyclobutane-1-carboxylates (13a and 14a) were obtained as a solid mixture in 88% yield from a mixture of **11b** and **12b**. The individual isomers were separately prepared from the pure azides **11b** or **12b**.

Compound **13a**, mp 152-153° (benzene-hexane).

Anal. Calcd for $C_{19}H_{19}NO_5S$: C, 61.12; H, 5.13; N, 3.75. Found: C, 61.32; H, 5.27; N, 3.84

Compound **14a**, mp 139-140° (benzene-hexane).

Anal. Calcd for $C_{19}H_{19}NO_5S$: C, 61.12; H, 5.13; N, 3.75. Found: C, 61.25; H, 5.20; N, 3.82

Methyl *r*-1-benzoylamino-*t*-2-methyl-*t*-3-(phenylsulfonyl)cyclobutane-1-carboxylate (13c) and **Methyl *r*-1-benzoylamino-*t*-2-methyl-*c*-3-(phenylsulfonyl)cyclobutane-1-carboxylate (14c)** were obtained separately either from azides **11d** or **12d**, or by chromatographic separation of a benzoylated amine mixture, **14c** being eluted first in this case (×30, hexane-CH_2H_2-EtOAc 3:3:1). A mixture of **13c** and **14c** was obtained in an overall 68% yield from **6a** by azidation, esterification, reduction, and benzoylation, followed by trituration of the crude product with CH_2Cl_2-hexane.

Compound **13c**, mp 150-151° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{20}H_{21}NO_5S$: C, 62.01; H, 5.46; N, 3.62. Found: 61.75; H, 5.21; N, 3.69

Compound **14c**, mp 149-150° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{20}H_{21}NO_5S$: C, 62.01; H, 5.46; N, 3.62. Found: 62.15; H, 5.40; N, 3.65

Methyl *r*-1-Benzoylamino-*t*-2-(2-methyl)ethyl-*c*-3-(phenylsulfonyl)cyclobutane-1-carboxylate (14e).- Only the major isomer **11g** was reduced and benzoylated, producing **14e** in 82% yield. mp 177-178° (EtOAc-hexane).

Anal. Calcd for $C_{22}H_{25}NO_5S$: C, 63.61; H, 6.07; N, 3.37. Found: C, 63.55; H, 6.02; N, 3.30

Catalytic Transfer Hydrogenation of Azido Amides 11c, 12c, 11e and 12e.- The azides were stirred in methanol (10 mL per g) with ammonium formate (1 g per g of azides) and 5% Pd/C (0.08 g per g of azides) at 50°, adding fresh catalyst (one half of the initial amount) when gas evolution slowed down (about 40 min). The total reaction time was of 4 to 5 hrs (TLC monitoring). The cooled down reaction mixture was filtered and the methanol was evaporated at reduced pressure. The residue

was added with a saturated NaCl solution and extracted with ethyl acetate. The crude amine product, obtained from the ethyl acetate extract after drying and evaporating the solvent, was benzoylated in dichloromethane-pyridine, in the usual way.

***trans*- and *cis*-1-Benzoylamino-3-(phenylsulfonyl)cyclobutane-1-N,N-pentamethylenecarboxamide (13b and 14b).**- The worked up dichloromethane solution of the benzoylated product (acid and water washings then drying) was concentrated under reduced pressure to give a gummy foam which solidified upon trituration with ethanol. The filtered solid mixture was obtained in 60-70% yield relative to the azides. The individual isomers **13b** and **14b** were obtained by separate reduction and benzoylation of azides **11c** and **12c**.[10]

Compound **13b**, mp 232-233° (EtOH).

Anal. Calcd for $C_{23}H_{26}NO_4S$: C, 64.78; H, 6.15; N, 6.57. Found: C, 64.47; H, 6.08; N, 6.62

Compound **14b**: see ref 10.

***r*-1-Benzoylamino-*t*-2-methyl-*t*-3-(phenylsulfonyl)cyclobutane-1-N,N-pentamethylenecarboxamide (13d) and *r*-1-Benzoylamino-*t*-2-methyl-*c*-3-(phenyl-sulfonyl)cyclobutane-1-N,N-pentamethylenecarboxamide (14d).**- The crude solid amine mixture from reduction of **11e** and **12e** gave upon benzoylation a difficultly soluble product which precipitated from the reaction mixture. This was worked up by addition of dichloromethane, water, and acid, and filtration of the precipitate. The latter was washed with water and air dried, providing almost pure **14d** in 64% yield. The dichloromethane solution furnished more product which crystallized in ethanol, providing 5% of **13d** (TLC in CH_2Cl_2-EtOAc-ether 2:1:1). Additional crystallizations furnished pure **13d** and **14d**.

Compound **13d**, mp 295-296° (CH_2Cl_2-MeOH).

Anal. Calcd for $C_{24}H_{28}N_2O_4S$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.41; H, 6.37; N, 6.35

Compound **14d**, mp 276-277° (EtOH-THF).

Anal. Calcd for $C_{24}H_{28}N_2O_4S$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.60; H, 6.39; N, 6.42

Reduction and benzoylation of a mixture of **11h** and **12h** gave an inseparable mixture of *trans*- and *cis*-1-benzoylamino-3-(phenylsulfonyl)cyclobutane, **13f** and **14f**; it could be recrystallizes from CH_2Cl_2-hexane, mp 145-170° and be used as such for carboxylation.

Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.66; H, 5.25; N, 4.56

***r*-1-Benzoylamino-*t*-2-methyl-*t*-3-(phenylsulfonyl)cyclobutane (13g) and *r*-1-Benzoylamino-*t*-2-methyl-*c*-3-(phenylsulfonyl)cyclobutane (14g)** were obtained by reduction and benzoylation of the individual isomers **11i** and **12i**.[13]

Compound **13g**, mp 194-195° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.66; H, 5.86; N, 4.35

Compound **14g**, mp 167-168° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.55; H, 5.79; N, 4.20

***r*-1-Benzoylamino-*t*-2-(2-methyl)ethyl-*c*-3-(phenylsulfonyl)cyclobutane (14h)** was obtained by reduction and benzoylation of **12j** in 82% yield; **14h**, mp 157-158° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.01; H, 6.41; N, 3.85

Table 3. ^{1}H NMR Spectra of Compounds **13** and **14**[a]

Cmpd	Ring CH_2's and CH	2-Me or 2-*i*Pr	R^2 protons
13a	2.45-2.75, 3.1-3.4 (4); 4.15 (1)		3.78 (s, Me)
13b	2.6-2.9 (2), 3.2-3.8 (7)		1.53 (6)
13c	2.3-2.6, 3.0-3.3, 3.4-3.65 (3); 3.9-4.2 (1)	1.52 (d, Me)	3.80 (s, Me)
13d	2.25 (1), 3.0-4.0 (7)	1.47 (d, Me)	1.52 (6)
13+14f	2.3-3.1 (4), 3.4-4.0 (1), 4.4-4.8 (1)		
13g	2.1-3.2 (m,3), 3.78 (1), 4.65 (1),	1.50 (d, Me)	
14a	2.9 (d, 4); 3.9 (1)		3.72 (s, Me)
14b	2.6-3.4 (4); 4.15 (1)		1.6 (6), 3.5 (4)
14c	2.4-2.7 (1), 3.0-3.7 (3)	1.08 (d, Me)	3.72 (s, Me)
14d	2.2 (1), 3.0-4.0 (7)	1.16 (d, Me)	1.55 (6)
14e	2.4 (1), 2.8-3.2 (2), 3.75 (1)	1.01 (d, Me), 1.05 (d, Me),1.4-1.8 (1)	3.75 (s, Me
14g	2.2-3.4 (4), 4.27 (1)	1.08 (d, Me),	
14h	2.1-2.8 (m,3), 3.33 (1), 4.46 (1)	0.84 (d, Me), 0.92 (d, Me) 1.7 (1)	
14i[b]	2.92-2.98, 3.10-3.16 (4), 4.01 (1)		
14j	2.96-3.02, 3.11-3.17 (4), 3.99 (1)		

a) See footnote a, Table 1. (b) In $CDCl_3$ + TFA.

***cis*-1-Benzoylamino-3-(phenylsulfonyl)cyclobutane-1-carboxamide (14i).-** Azide **12k** (5.6 g) was reduced in ethyl acetate (150 mL), as described for the reduction of **12c**. *cis*-1-Amino-3-(phenylsulfonyl)cyclobutane-1-carboxamide was obtained as a solid (4.96 g, 98%), mp 130-131° (CH_2Cl_2-hexane). NMR: δ 1.8 (NH_2) 2.40-2.46 and 2.83-2.89 (two m, 4 H), 3.84 (quint, 1 H), 5.43 and 7.09 (1 and 1 H, $CONH_2$), 7.5-7.9 (5 H).

Anal. Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.97; H, 5.55; N, 11.02. Found: C, 52.08; H, 5.31; N, 11.05

Benzoylation provided **14i** in a total 93% yield from **12k**; **14i**, mp 223-224° (EtOH).

Anal. Calcd for $C_{18}H_{18}N_2O_4S$: C, 60.33; H, 5.06. Found: C, 60.35; H, 5.07

***cis*-1-Benzoylamino-3-(phenylsulfonyl)cyclobutane-1-carbonitrile (14j).-** Trifluoroacetic anhydride (5.4 mL) was added to a solution of **14i** (6.27 g) in dioxane (120 mL) and pyridine (5.6 mL) and the resultant mixture was kept at 80° for 3 hrs. Water (20 mL) was added and most of the dioxane was evaporated at reduced pressure. The residual water layer was slightly acidified and extracted with ethyl acetate. The combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated. The residual solid was taken in ether and filtered to provide pure **14j** (4.0 g). The residue from the ether layer was chromatographed (30 g of silica gel, CH_2Cl_2-EtOAc-hexane 6:1:3) to provide an additional amount of **14j** (0.8 g; total, 4.8 g, 81% yield).

Compound **14j**, mp 217-218° (EtOAc-hexane).

Anal. Calcd for $C_{18}H_{16}N_2O_3S$: C, 63.53; H, 4.74. Found: C, 63.83; H, 4.82

***trans*- and *cis*-1-Amino-3-(phenylsulfonyl)cyclobutane-1-carboxylic acid (15a and 16a).**- Acid **11a** (600 mg) was hydrogenated in ethyl acetate (25 mL) over 5% Pd/C (204 mg) at room temperature and under atmospheric pressure for 4 hrs. The solid was filtered, washed with ether and air dried (774 mg total weight). It was then extracted by boiling in water (50 mL) and filtering. This operation was repeated twice more (50 and 30 mL of water). The combined water filtrates were concentrated to about one third of the volume and the deposited amino acid was collected as a monohydrate by filtration (450 mg, and a second crop of 30 mg by further concentration, 88% yield).

Similar treatment of **12a** provided **16a**, again as a monohydrate, in a similar yield.

Acid **15a**, mp: decomposition above 250°, no melting.

Anal. Calcd for $C_{11}H_{13}NO_4S.H_2O$: C, 48.35; H, 5.53; N, 5.13. Found: C, 48.13; H, 5.28; N, 5.31

Acid **16a**, mp: same behavior as **15a**.

Anal. Calcd for $C_{11}H_{13}NO_4S.H_2O$: C, 48.35; H, 5.53; N, 5.13. Found: C,48.01; H, 5.40; N, 5.43

1-Aminocyclobutane-1-carboxylic acid (17a).- A solution of **12a** (0.86 g) in methanol-THF (20 mL, 3:1) was stirred at room temperature with Na-Hg (5 g) for 1 hr and then with additional Na-Hg (6.5 g) for 40 hrs. The solution obtained after filtration on Celite was evaporated and the residue was taken in water. The water solution was brought to about pH 8 with HCl, extracted with TBME, and applied on a column of Dowex 1 ×8 (OH form, 100-200 mesh, 60 cm). The column was washed with water until Cl—free and then with 1 N AcOH to displace **17a** (0.27 g, 75% yield). Recrystallization from ethanol-water gave **17a** as prismatic needles, subliming above 250° and more rapidly above 280°, not melting below 300° (reported: 290°[18]; 290-296°[19]; >300°[20]).

Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.61; H, 7.98; N, 12.30

***r*-1-Amino-*t*-2-methyl-*t*-3-(phenylsulfonyl)cyclobutane-1-carboxylic Acid (15b) and *r*-1-Amino-*t*-2-methyl-*c*-3-(phenylsulfonyl)cyclobutane-1-carboxylic Acid (16b).**- The total amine from reduction of a mixture of **11d** and **12d** (520 mg) was warmed in 3 M HCl (15 mL) at 90° for 4 hrs. Water (30 mL) was added to the cooled reaction mixture which was then extracted twice with TBME to remove water-insoluble material. The water was evaporated to dryness and this operation was repeated twice more after addition of fresh water. The residual hydrochlorides were dissolved in ethanol (20 mL) and added with propylene oxide (3 mL). Precipitation of the free amino acids occured after a while. When this was complete, the acids were filtered, providing a mixture of **15b** and **16b** (395 mg, 80% yield). A sample of this mixture (about 100 mg) was separated on a column of Dowex 1 ×8 (acetate form; 200-400 mesh; 50 cm) by elution with 0.2 M acetic acid, the major isomer **16b** being eluted first. Analytical samples were obtained by crystallization from water.

Acid **15b**, mp: melting with decomposition in the range of 275-280°.

Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.42; H, 5.55; N, 5.15

Acid **16b**, mp: same behavior as **15b.**

Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.28; H, 5.59; N, 5.29

***trans*-1-Amino-2-methylcyclobutane-1-carboxylic Acid (17b).**- The crude amine from reduction of

1.2 g of **11d** and **12d** was stirred in methanol (50 mL) with 7 g of Na-Hg for 15 hrs. The solution obtained after filtration on Celite was evaporated at reduced pressure and the residue was taken in 1 M acetic acid until slightly acidic and applied onto a column of Dowex 50 ×8 (60 cm). The column was washed with water (300 mL) and the acid was then displaced with 1 M ammonium hydroxide, yielding 0.46 g of **17b**. Recrystallization from ethanol-water provided the pure product (0.32 g, 64%); mp: sublimation above 250°.

Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.34; H, 8.47; N, 10.50

Table 4. ^{1}H NMR Spectra of Compounds **15-17**[a,b]

Cmpd	Ring CH_2's and CH	2-Me or 2-*i*Pr
15a	2.6-2.9, 3.2-3.5 (4), 4.46 (1)	
15b	2.3-2.7 (1), 3.3-3.7 (2), 4.3-4.7 (1)	1.47 (d, Me)
15c	2.2-2.8 (5)	0.84 (d, Me), 1.11 (d, Me)
16a	3.01 (d, 4), 4.37 (1)	
16b	2.8-2.9 (2), 3.0-3.5 (1), 3.8-4.2 (1)	0.97 (d, Me)
16c	2.5-2.75 (2), 2.95-3.2(1), 4.19 (1)	0.73 (d, Me), 0.91 (d, Me), 1.6-2.2 (1)
17a	1.93-2.78	
17b	1.8-3.0 (5)	1.11 (d, Me)
17c	1.7-2.7 (6)	0.89 (d, Me), 0.95 (d, Me)

a) See footnote a, Table 1. b) Compounds **15** and **16** were measured in D_2O+TFA, compounds **17** were measured in D_2O; the sodium salt of 3-trimethylsilylpropionic acid-*d*4 was used as an internal standard.

***r*-1-Amino-*t*-2-(2-methyl)ethyl-*t*-3-(phenylsulfonyl)cyclobutane-1-carboxylic Acid (15c)** and ***r*-1-Amino-*t*-2-(2-methyl)ethyl-*c*-3-(phenylsulfonyl)cyclobutane-1-carboxylic Acid (16c).**- Acid **15c** was obtained in 44% yield from **11g** by hydrogenation and hydrolysis, as described for **15b** and **16b**. Acid **16c** was obtained from **11f** in 79% yield as described above for **16a**.

Acid **15c**, mp 278-279° (decomposition; H_2O).

Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.65; H, 6.40; N, 4.86

Acid **16c**, mp 279-280° (decomposition; H_2O).

Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.69; H, 6.42; N, 4.95

***trans*-1-Amino-2-(2-methyl)ethylcyclobutane-1-carboxylic Acid (17c).**- The crude amine from reduction of 0.36 g of **12g** was treated in solution in THF (10 mL)-abs. ethanol (2 mL) with small pieces of freshly cut sodium (0.22 g; room temperature, 4 hrs). The solvent was evaporated at reduced pressure and the residue was taken in 1 M AcOH and extracted twice with TBME. The aqueous layer was applied on a column of Dowex 50 ×8 (15 cm). Washing with water and displacement with 0.5 M ammonium hydroxide provided 0.15 g of **17c** (72%). An analytical sample was obtained by crystallization from ethanol, mp: sublimation above 250°.

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.88; H, 9.41; N, 8.89

Introduction of a Third Group onto the Cyclobutane Ring. Compounds 18 and 19.- Most preparations involved addition of electrophiles to the α-sulfonyl carbanion generated from **11** and **12** or, mainly, from **13** and **14**. When the electrophile was carbon dioxide, the acid pruducts could be esterified for characterization purposes, but were usually used as such for desulfonylation to **20** and **21**.

***trans*- and *cis*-1-Azido-3-(phenylsulfonyl)cyclobutane-1,3-dicarboxylic Acid (18a and 19a) and dimethyl *trans*- and *cis*-1-azido-3-(phenylsulfonyl)cyclobutane-1,3-dicarboxylate (18b and 19b).**

(a) By carboxylation of 12a.[5]- To a solution of recrystallized **12a** (from benzene; 1.0 g, 3.6 mmol) in THF (50 mL) were added at -78° 2.2 equiv of BuLi. After stirring at that tempertature for 15 min, the reaction flask was removed from the cold bath, and pieces of dry ice were added to it. Stirring was continued until the flask reached room temperature. Some water was added and most of the THF was evaporated at reduced pressure. The residue was taken with water and extracted with ether before being acidified with 3 M HCl. The acidic products were then extracted three times with ether (total volume: 100mL) to yield, after drying and evaporating, 1.1 g of total product. Esterification of an aliquote from this material and ^1H NMR examination showed it to be constituted in major part of diesters **18b** and **19b**, in a ratio of ca 10 to 1. The major diacid **18a** precipitated cleanly when the total product was dissolved in ca. 5 mL of chloroform and a few drops of hexane, a total of 685 mg being collected in two crops (59% yield). The yield of **18a** could vary in this procedure between 48 and 59%, using as starting material either **12a** or a mixture of **11a** and **12a**.

A variation of this procedure which gave similar results consisted of adding 1.2 equiv of NaH to the THF solution of the starting material at room temperature and then, after the reaction with the free acid had subsided, cooling to -78° and proceeding as above, using 1.1 equiv of BuLi.

Esterification of the residual material obtained after filtration of **18a**, followed by chromatography on silica gel (hexane-ether 1:1), showed it to be constituted of diester **18b**, monoester **11b**, bicyclic ester **6d** (formed probably by intramolecular displacement of the azide by the α-sulfonyl anion), and diester **19b**, in varying proportions.

(b) By Carboxymethylation of 11b and 12b.- The reaction of **11b** and **12b** with LDA and dimethyl carbonate produced almost equal amounts of **18b** and **19b**, albeit in only 40-45% yield. The reaction was carried out by preparing 1.2 equiv of LDA in THF at 0° (0.19 mL of diisopropylamine and 0.77 mL of 1.6 M BuLi in 5 mL THF per mmol of staring material), cooling to -78°, adding 1 equiv of **11b** and **12b** followed after 10 min by excess dimethyl carbonate and stirring for 20 hrs, while letting warm to room temperature. Extractive work up with ether involved first extraction of the basic solution followed by acidification and extraction of acidic material and esterification. The two extracts contained about equal amounts of material. They were combined and chromatographed on silica gel (×60; hexane-ether 1:1) for the separation of **18b** and **19b.**

Compound **18a**, mp 171-173° (decomposition; H_2O).

Anal. Calcd for $C_{12}H_{11}N_3O_6S$: C, 44.32; H, 3.41; N, 12.92. Found: C, 44.31; H, 3.29; N, 12.68

Compound **18b**, liquid.

Anal. ($C_{14}H_{15}N_3O_6S$) HR-MS Found: m/e 152.0328 ($M^+ - N_2$ - $PhSO_2$ - CH_3OH). Calcd for $C_7H_6NO_3$: 152.0308.

Compound **19b**, mp 74-75° (ether-hexane).

Anal. Calcd for $C_{14}H_{15}N_3O_6S$: C, 47.60;H, 4.28; N, 11.89. Found: C, 47.71; H, 4.22; N, 11.95

***trans*-1-Amino-3-(phenylsulfonyl)cyclobutane-1,3-dicarboxylic Acid (18c).**- Compound **18a** (1.47 g) was reduced in ethanol (40 mL) over 10% Pd/C at room temperature and under atmospheric pressure for 20 hrs. Most of the product precipitated on the catalyst and was extracted from the filtered and dried precipitate with boiling water (60 mL). By concentration of the filtered water solution (to about 40 mL) and cooling it down, **18c** precipitated and was collected by filtration (940 mg). By evaporating the alcoholic hydrogenation solution, more of **18c** (160 mg) could be recovered (total yield 81%).

Table 5. ^1H NMR Spectra of Compounds **18** and **19**[a]

Cmpd	Ring protons	R^2 and R^4 protons
18a	2.87 and 3.62[b]	
18b	2.75 and 3.51[b]	3.71 (s,Me), 3.88 (s,Me)
18c[c]	2.80 and 3.55[b]	
18d	2.46 and 3.37[b]	3.67 (s, Me), 3.78 (s,Me)
18e	2.97 and 3.67[b]	3.62 (s, Me), 3.83 (s, Me)
18h[d]	2.9-3.6 (4), 4.60 (1)	
18i	2.67-3.03 (2), 3.13-3.50 (2), 4.68 (1)	3.65 (s, Me)
19b	3.20 (s, 4)	3.67 (s,Me), 3.77 (s, Me)
19e	3.28 and 3.36[b]	3.66 (s, Me), 3.70 (s,Me)
19k	2.6-3.2 (3), 4.68 (1)	0.86 (d, Me), 0.91 (d,Me), 1.7 (1)[e]

a) See footnote a, Table 1. (b) AB-like spectrum of the 4 ring protons, with a secondary long-range coupling. (c) In D_2O + TFA. (d) In $CDCl_3$ + TFA. (e) *iso*-Propyl protons.

Product **18c**, mp about 230° (decomposition; H_2O-EtOH).

Anal. Calcd for $C_{12}H_{13}NO_6S.2H_2O$: C, 42.99; H, 5.11; N, 4.18. Found: C, 42.90; H, 4.78; N, 4.23

The molecular structure of **18c** has been determined by x-ray analysis.[5]

Dimethyl *trans*-1-Amino-3-(phenylsulfonyl)cyclobutane-1,3-dicarboxylate (18d) was obtained by catalytic reduction (5% Pd/C in EtOAc) of **18b** in 82% yield, mp 130-131° (EtOAc-hexane).

Anal. Calcd for $C_{14}H_{17}NO_6S$: C, 51.38; H, 5.24; N, 4.28. Found: C, 51.51; H, 5.36; N, 4.30

Dimethyl *trans*- and *cis*-1-Benzoylamino-3-(phenylsulfonyl)cyclobutane-1,3-dicarboxylate (18e and 19e).- LDA (2.5 equivalents: 0.39 mL of diisopropylamine and 1.6 mL of 1.6 M BuLi in 10 mL of THF per mmol of **13a** and **14a**) was prepared at 0° and then cooled to -78°. The solid, powdered mixture of **13a** and **14a** was added to the flask which was then let warm gradually until dissolution occured at ca. -40°. The dark solution was cooled back to -78° and added with pieces of solid CO_2. The flask was then removed from the cold bath and let warm to room temperature. Work up

proceeded as described above for the carboxylation of **11a** and **12a**, the extractions of the non-acidic and acidic material being carried out with ethyl acetate. The acid product was obtained in 80-85% yield. Esterification showed it to be constituted by a mixture of **18e** and **19e** in a ratio of approximately 1 to 10. Chromatography on silica gel (×40; hexane-CH_2Cl_2-EtOAc 2:2:1) separated the two isomers. The non-acidic extract contained some unreacted starting material which was usually not recovered.

Compound **18e**, mp 208-209° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{21}H_{21}NO_7S$: C, 58.47; H, 4.91; N, 3.25. Found: C, 58.72; H, 5.10; N, 3.37

Compound **19e**, mp 165-166° (benzene).

Anal. Calcd for $C_{21}H_{21}NO_7S$: C, 58.47; H, 4.91; N, 3.25. Found: C, 58.58; H, 5.06; N, 3.29

Compounds **18f** and **19f**: see ref 10.

Compounds **18g** and **19g** were obtained as a mixture from **13d** and **14d**, as has been described for **14b**,[10] in 81% yield relative to unrecovered starting material (15%) and were used directly for desulfonylation.

***trans*-3-Benzoylamino-1-(phenylsulfonyl)cyclobutane-1-carboxylic Acid (18i).**- A mixture of **13f** and **14f** (1.39 g) was carboxylated at -78°, using 2.2 equiv of BuLi and solid CO_2. Work up was carried out as described above, by first extracting the total aqueous solution for non acidic material and then acidifying. Upon acidification the acidic product precipitated. It was filtered and air dried to give one product isomer, **18h** (1.41 g, 89% yield), which produced only **18i** upon esterification. A very small proportion of the *cis*-S,N isomer could be observed by NMR by extraction of the acidic water layer with ethyl acetate and esterifiction, but no pure product was secured. On the basis of this NMR the *trans* configuration could be safely assigned to the main reaction product.

Acid **18h**, mp 239-240° (ethanol).

Anal. Calcd for $C_{18}H_{17}NO_5S$: C, 60.17; H, 4.77; N, 3.90. Found: C, 60.15; H, 4.75; N, 3.84

Ester **18i**, mp 166-167° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{19}H_{19}NO_5S$: C, 61.12; H, 5.13; N, 3.75. Found: C, 60.88; H, 5.03; N, 3.68.

Carboxylation of a mixture of **13g** and **14g** provided the acid product **18j** and **19j** as a solid foam in a practically quantitative yield (1.21 g). Esterification of a sample (0.17 g) showed it to be composed of a mixture of two esters in a ratio of ca. 4:1 (by integration of the methyl doublets signals). The crude acid product was used directly for desulfonylation.

Carboxylation of **14h** gave similar results to those obtained with **13g** and **14g**. The majority of the acid product was used for desulfonylation. Esterification of a sample and chromatographic separation (silica gel ×100, CH_2Cl_2-hexane-EtOAc 4:4:1) provided the pure major ester isomer **19k** but the *trans*-S,N isomer was not obtained free of **19k**.

Methyl *r*-3-benzoylamino-*t*-2-(2-methyl)ethyl-*c*-1-(phenylsulfonyl)cyclobutane-1-carboxylate (19k), mp 164-165° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{22}H_{25}NO_5S$: C, 63.61; H, 6.07; N, 3.37. Found: C, 63.55; H, 6.02; N, 3.41

Carboxylation of **14j** gave in 92% yield a mixture of **18l** and **19l** which was used as such for desulfonylation.

Desulfonylated Products 20 and 21. Desulfonylations of products **18** and **19** were usually carried out by the use of excess 6% sodium amalgam in methanol-THF 4:1 as described previously.[10] The geometry at the sulfone site is usually lost, and a mixture of isomeric products is obtained. Esterification of the primary products and chromatographic separation provided the individual **20** and **21** isomers.

Dimethyl *trans*- and *cis*-1-(Benzoylamino)cyclobutane-1,3-dicarboxylate (20a and 21a).- From **18e** and **19e**; ×40, CH_2Cl_2-hexane-EtOAc 3:3:1; ca. 1:1; 87%).

Compound **20a**, mp 118-119° (benzene-hexane).

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.76; H, 5.95; N, 4.89

Compound **21a**, mp 120-121° (benzene-hexane).

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.66; H, 6.03; N, 4.71

Compounds **20b** and **21b**: see ref 10.

Methyl *r*-1-Benzoylamino-*t*-2-methyl-1-(N,N-pentamethylenecarbamoyl)cyclobutane-*t*-3-carboxylate (20c) and **Methyl *r*-1-benzoylamino-*t*-2-methyl-1-(N,N-pentamethylenecarbamoyl)-cyclobutane-*c*-3-carboxylate (21c).**- From **18g** and **19g**; ×40, CH_2Cl_2-ether-EtOAc 4:2:1; ca. 1:1; 74% from **14d**.

Compound **20c**, mp 225-226° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.12; H, 7.35; N, 7.95

Compound **21c**, mp 196-197° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.15; H. 7.22; N, 7.91

Methyl *trans*- and *cis*-1-Benzoylamino-1-cyano-3-carboxylate (20d and 21d).- From **18l** and **19l**; ×40, CH_2Cl_2-hexane-EtOAc 6:2:1; ca. 1:1; 67% from **14j**.

Compound **20d**, mp 129-130° (EtOAc-hexane).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46. Found: C, 65.36; H, 5.43

Compound **21d**, mp 104-105° (EtOAc-hexane),

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46. Found: C, 65.35; H, 5.64

Compounds **20e and 21e**: see ref 10.

***trans*- and *cis*-1-Benzoylamino-3-(methanesulfonyloxy)methylcyclobutane-1-N,N-pentamethylenecarboxamide (20f and 21f).**- The mesylates were prepared in 75% yield by mesylation of **20d** and **21d**, respectively, with mesyl chloride in dichloromethane and triethylamine.

Compound **20f**, mp 193-194° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{19}H_{26}N_2O_5S$: C, 57.86; H, 6.64; N, 7.10. Found: C, 57.81; H, 6.42; N, 7.19

Compound **21f**, mp 183-184° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{19}H_{26}N_2O_5S$: C, 57.86; H, 6.64; N, 7.10. Found: C, 57.72; H, 6.37; N, 7.28

***cis*-1-Benzoylamino-3-(azidomethyl)cyclobutane-1-N,N-pentamethylenecarboxamide (21g).**- The crude mesylate **21f** obtained from **21e** (1.25 g, 4 mmol) was warmed in NMP (12 mL) with TMGA (0.6 g, 4 mmol) at 85° for 3 hrs. Water (50 mL) was added to the cooled reaction mixture which was then extracted several times with dichloromethane. The organic layer was washed three times with

water, dried, and evaporated. The solid residue was taken in ether and filtered to yield pure **21g** (0.86 g, 63% relative to **21e**).

Table 6. ^{1}H NMR Spectra of Compounds **20** and **21**.[a]

Cmpd	Ring protons	R^1 protons	R^2 protons	R^3 protons
20a	2.6-3.5 (5)		3.73 (s, Me)	3.77 (s, Me)
20c	2.44 (1), 2.8-3.7 (7)[b]	1.10 (d, Me)	1.52 (6)	3.67 (s, Me)
20d	2.76-2.82, 3.07-3.12 (4), 3.73 (1)			3.73 (s, Me)
20f	2.6-2.8 (5)		1.56 (6), 3.5 (4)	4.22 (d, 2), 3.01 (s, Me)
20h	2.0-2.8 (6)		3.78 (s, Me)	
20i	2.1-2.5 (2), 2.6-3.2 (3), 4.65 (1)			
20j	1.9-2.9 (5), 4.61 (1)			3.68 (s, Me)
20k	1.9-2.2 (1), 2.6 (3), 4.45 (1)	1.14 (d, Me)		3.73 (s, Me)
20l	1.6-2.8 (4), 3.1 (1), 4.75 (1)	0.84 (d, Me), 0.88 (d, Me),		3.72 (s, Me)
21a	2.57-2.32 (5)		3.71 (s, Me)	3.79 (s, Me)
21c	2.0-3.8 (8)	1.22 (d, Me)	1.5 (6),	3.69 (s, Me)
21d	2.68-2.73, 3.11-3.17 (4), 3.36 (1)			3.70 (s, Me)
21f	2.3-2.6 (3), 2.9-3.2 (2)		1.53 (6), 3.5 (4)	4.32 (d, 2), 2.99 (s, Me)
21g	2.41 (3), 3.05 (2)		1.55 (6), 3.51 (4)	3.44 (d, 2)
21i	2.2-3.0 (4), 3.2 (1), 4.79 (1)			
21j	2.1-3.2 (5), 4.75 (1)			3.72 (s, Me)
21k	1.9-2.7 (4), 4.19 (1)	1.26 (d, Me)		3.69 (s, Me)
21l	1.6-2.7 (5), 4.38 (1)	0.87 (d, Me), 0.91 (d, Me)		3.69 (s, Me)

a) See footnote a, Table 1. b) Four protons of piperidine-ring are also included.

Compound **21g**, mp 194-195° (decomposition; CH_2Cl_2-hexane).

Anal. Calcd for $C_{18}H_{23}N_5O_2$: C, 63.32; H, 6.79. Found: C, 63.07; H, 6.81

Methyl 1-(Benzoylamino)cyclobutane-1-carboxylate (20h).- From **13a**; ×10, hexane-ether 7:3; 71%. mp 139-140° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.25; H, 6.21; N, 5.88

***trans*- and *cis*-3-(Benzoylamino)cyclobutane-1-carboxylic acid (20i and 21i) and Methyl *trans*- and *cis*-3-(benzoylamino)cyclobutane-1-carboxylate (20j and 21j).**- Acid **18h** (723 mg, 2 mmol) was stirred in methanol (20 mL) with Na-Hg (4g, ca. 11 mmol of Na) for 20 hrs. After filtration on Celite, acidic resin AG 50 was added portionwise to the solution until acidic. The resin was filtered and the solution was concentrated to a small volume, whereby acid **20i** precipitated. Water was added

to the mixture and acid **20i** was filtered, washed with water and air dried (243 mg). Upon concentration and cooling of the solution some more acid precipitated which was found by esterification to be **21i** (56 mg; total yield 68%). The residue from the mother liquors was esterified and was shown to contain esters **20j** and **21j**, but these were difficult to separate by chromatography. They were obtained by esterification of the purified acid isomers.

Acid **20i**, mp 187-188° (TBME).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.21; H, 5.71; N, 6.45

Acid **21i**, mp 135-136° (TBME).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.60; H, 5.80; N, 6.69

Ester **20j**, mp 121-122° (ether-hexane).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00%. Found: C, 66.85; H, 6.45; N, 5.92

Ester **21j**, mp 103-104° (ether-hexane).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.80; H, 6.55; N, 5.88

Methyl *r*-3-Benzoylamino-*t*-2-methylcyclobutane-*t*-1-carboxylate (20k) and Methyl *r*-3-benzoylamino-*t*-2-methylcyclobutane-*c*-1-carboxylate (21k).- From **18j** and **19j**; × 40, CH_2Cl_2-hexane-EtOAc 5:4:1; ca. 1:3; 87%).

Compound **20k**, mp 124-125° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.14; H, 6.87; N, 5.60

Compound **21k**, mp 76-77° (CH_2Cl_2-hexane).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.91; H, 6.95; N, 5.73

Methyl *r*-3-Benzoylamino-*t*-2-(2-methyl)ethylcyclobutane-*t*-1-carboxylate (20l) and Methyl *r*-3-benzoylamino-*t*-2-(2-methyl)ethylcyclobutane-*c*-1-carboxylate (21l).- From **19k**; × 40, CH_2Cl_2-hexane-EtOAc 5:4:1; ca. 1:3; 86%.

Compound **20l**, mp 179-180° (ether-hexane).

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.86; H, 7.73; N, 5.21

Compound **21l**, mp 124-125° (ether-hexane).

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.51; H, 7.62; N, 5.00

Amino Acids 1 and 4. (a) By Desulfonylation of 18c.- Compound **18c** (940 mg, 2.8 mmol of dihydrate) was stirred for 20 hrs with Na-Hg (10 g, 27 mmol of Na). After filtration on Celite and evaporation of the solvent, the residue was taken in some water and neutralized with 3 M HCl. Chromatographic separation on a column of 60 cm Dowex 1 ×8 (200–400 mesh; acetate form) was achieved by washing the column first with water until the fractions were Cl—free, and then eluting with 0.15 M AcOH. Were thus obtained by order of elution 218 mg of **4**, 65 mg in mixed fractions, and 115 mg of **1** (80% yield).

(b). By Desulfonylation-reduction of 18a.- To compound **18a** (1 g, 3 mmol) in THF (80 mL) and ethanol (8 mL) was added a total of 1 g of sodium in small pieces. A thick mixture formed which became thinner with continued stirring. Another 0.5 g of sodium was added and the mixture was stirred overnight. Water was carefully added and most of the THF was rotevaporated. The residue was

acidified with HCl and extracted twice with EtOAc for non-acidic material. The aqueous solution was chromatographed on a column of 50 cm Dowex 50, washing first with water and displacing then the amino acids **1** and **4** with 1 M NH_4OH (460 mg, 84%). The two isomers could then be separated on Dowex 1, as described above.

(c) By Desulfonylation of 18d.- The reaction was carried out as described for **18c** above, with similar results.

(d) By Acid Hydrolysis.- Acids **4** and **1** were preferably prepared by acid hydrolysis of **20b** and **21b**[10] and, similarly, of **20a** and **21a**, or **20d** and **21d**.

Amino acids 3 and 5.- Compound **21e** was warmed in excess 6 M HCl at 120° for 20 hrs. Work up as described for **15b** and **16b** furnished crude **3** in almost quantitative yield. Recrystallization from water-ethanol provided pure **3**, mp 239-240° (decomposition); NMR (D_2O; 400 MHz): δ 2.09-2.14 (m, 2 H), 2.58-2.71 (m, 3 H), 3.62 (d, J = 5.8, 2 H).

Amino acid **5** was similarly obtained from **20e**: mp 250-255° (decomposition); NMR (D_2O; 400 MHz): δ 2.33-2.39 (m, 2 H), 2.43-2.49 (m, 2 H), 2.76 (pentuplet, 1 H), 3.70 (d, J = 7.3, 2 H).

2*H*-Pyrido[1,2-*a*]pyrazine-1,4-dione-3-spiro[*cis*-3'-(phenylsulfonyl)cyclobutane] (23).- The acid chloride obtained from **12a**[10] (1.5 g, 5.3 mmol) was dissolved in CH_2Cl_2 (30 mL) and stirred with the hydrochloride of pipecolinic acid methyl ester (1.04 g, 5.8 mmol) and ethyldiisopropylamine (2.2 mL) at room temperature for 1 hr. The solution was then washed with dilute HCl and with water, dried, and evaporated to yield crude **22** in quantitative yield. Azide **22** did not solidify and was used directly in the reduction step.

To the total crude **22** from 7.5 g of **12a** (ca. 12 g) dissolved in methanol (100 mL) was added a mixture of ammonium formate (10 g), 10% Pd/C (1 g), and methanol (20 mL) and the total was warmed at 60° for 2 hrs. After filtration, the solvent was evaporated and the residue was taken with water and extracted with CH_2Cl_2. The crude product was triturated with ether and filtered to yield **23** which was further purified by taking in warm benzene, cooling down and filtering.(7.9 g, 85%).

Compound **23**, mp 166-167° (EtOAc-hexane). NMR (400 MHz): δ 1.37-1.44 (m, 2 H), 1.56-1.60 (m, 1 H), 1.97 (d, J=12.9, 1 H), 2.37 (d, J=13.4, 1 H; 5 H of piperidine ring), 2.51 (dt, J_1=13.0, J_2=2.7, 1 H, NC*H*H), 2.70-2.75 and 2.95-3.10 (m, 4 H), 3.82 (dd, J_1=13.1, J_2=2.8, 1 H, NCH*H*), 3.97 (pentuplet, 1 H), 4.63 (d, J=13.2, 1 H, NC*H*CO), 7.17 (s, 1 H, N*H*), 7.5-7.9 (5 H).

Anal. Calcd for $C_{17}H_{20}N_2O_4S$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.49; H, 5.82; N, 7.82

2*H*-Pyrido[1,2-*a*]pyrazine-1,4-dione-3-spiro[3'-methoxycarbonyl-3'-(phenylsulfonyl)cyclobutane] (24).- Sulfone **23** (0.41 g, 1.2 mmol) was carboxylated at -75° using 2.2 equivalents of BuLi, stirring for 20 min, then adding CO_2 and letting warm to rt. Extractive work up of the acidic product followed by esterification with diazomethane provided the crude ester **24** that was purified by chromatography on silica gel (10 g; CH_2Cl_2-ether-EtOAc 3:3:2).

Compound **24** (0.45 g, 94% yield), mp 182-183° (EtOAc-hexane). NMR (400 MHz; compare with **23**): δ 1.3-1.6 (m, 2 H), 1.74 (d, J=13.7, 1 H), 1.98 (d, J=12.8, 1 H), 2.28 (d, J=13.0, 1 H), 2.54 (dt, J_1=12.9, J_2=2.7, 1 H), 2.65-2.70 (m, 2 H), 3.75 (s, Me), 3.76-3.87 (m, 2 H), 4.02 (d, J=12.7, 1 H),

4.68 (d, *J*=13.2, 1 H), 7.19 (s, N*H*), 7.5-7.9 (5 H).

Anal. Calcd for $C_{19}H_{22}N_2O_6S$: C, 56.16; H, 5.46; N, 6.89. Found: C, 56.45; H, 5.60; N, 6.77

Desulfonylation of 24: Esters 25 and 26.- The total crude acidic product (1.2 g) from carboxylation of **23** (1.2 g) was desulfonylated in the usual way and the crude acid (quite soluble in water, needs thorough extraction) was esterified and chromatographed. Total separation of the liquid product isomers **25** and **26** was not achieved (ratio of isomers ca. 1:1, 416 mg, 45% yield relative to **23**).

Compound **25**: NMR (400 MHz): δ 1.36-1.63 (m, 2 H), 1.72 (d, *J*=13.0, 1 H), 1.99 (d, *J*=12.7, 1 H), 2.32 (d, *J*=13.1, 1 H), 2.40-2.46 (m, 2 H), 2.51 (dt, J_1=12.9, J_2=2.9, 1 H), 3.14-3.17 (m, 1 H), 3.23-3.37 (m, 2 H), 3.75 (s, Me), 3.82 (dd, J_1=12.1, J_2=2.9, 1 H), 4.67 (d, *J*=13.3, 1 H), 7.6-7.9 (5 H), 8.70 (s, N*H*).

Compound **26**: NMR (400 MHz): δ 1.37-1.63 (m, 2 H), 1.74 (d, *J*=13.0, 1 H), 1.99 (d, *J*=13.9, 1 H), 2.34 (d, *J*=12.9, 1 H), 2.41-2.49 (m, 2 H), 2.52 (dt, J_1=12.9, J_2=2.9, 1 H), 2.95-3.08 (m, 2 H), 3.32 (pentuplet, 1 H), 3.71 (s, Me), 3.83 (dd, J_1=12.1, J_2=2.9, 1 H), 4.69 (d, *J*=13.2, 1 H), 7.57 (s, N*H*), 7.6-7.9 (5 H).

N-Benzoyl-1-azabicyclo[2.1.1]hexane-1-N,N-pentamethylenecarboxamide (27).- To mesylate **21f** (570 mg, 1.45 mmol) in THF (25 mL; incompletely soluble) was added at 0° BuLi (1.5 mmol). Solubilization occured after about 5 min. The solution was stirred for 20 hrs, while letting it warm to rt. Extractive work up and chromatography on silica gel (10 g; CH_2Cl_2-ether-EtOAc 2:1:1) furnished **27** (366 mg, 85% yield).

Compound **27**, mp 144-145° (CH_2Cl_2-hexane). NMR (270 MHz): δ 1.55 (br, 6 H), 1.88-1.94 (m, 2 H), 2.20-2.30 (m, 2 H), 2.78 (s, 1 H), 3.5 (br, 4 H), 3.73 (br, 2 H), 7.4-7.7 (5 H).

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.18; H, 7.50; N, 9.29

***cis*-1-Amino-3-(aminomethyl)cyclobutane-1-carboxylic Acid (28)**,- Azide **21g** (840 mg, 2.5 mmol) was reduced in ethanol (40 mL) over prereduced 10% Pd/C catalyst (150 mg) at rt and under normal pressure until no azide could be detected by TLC (ca. 6 hrs). After filtration of the catalyst and evaporation of the solvent, 6 M HCl (15 mL) was added to the residue and the resultant solution was warmed at 120° for 20 hrs. Work up with propylene oxide, as described above for **15b** and **16b**, gave a gummy precipitate which solidified slowly under ethanol (305 mg, 85%). Recrystallization from water ethanol provided pure **28**, mp: no melting up to 300°.

Anal. Calcd for $C_6H_{12}N_2O_2.H_2O$: C, 37.11; H, 7.27; N, 14.43. Found: C, 36.88; H, 7.35; N, 13.97

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