192. An Unusual Rearrangement of a Lithiated *N*-Acyl-tetrahydroisoquinoline to an Amino-indan Skeleton and Structural Comparison of 3-Amino-2-methylindan- and -tetrahydronaphthalene-2-carboxylic Acids as Possible Building Blocks for Peptide-Turn Mimics

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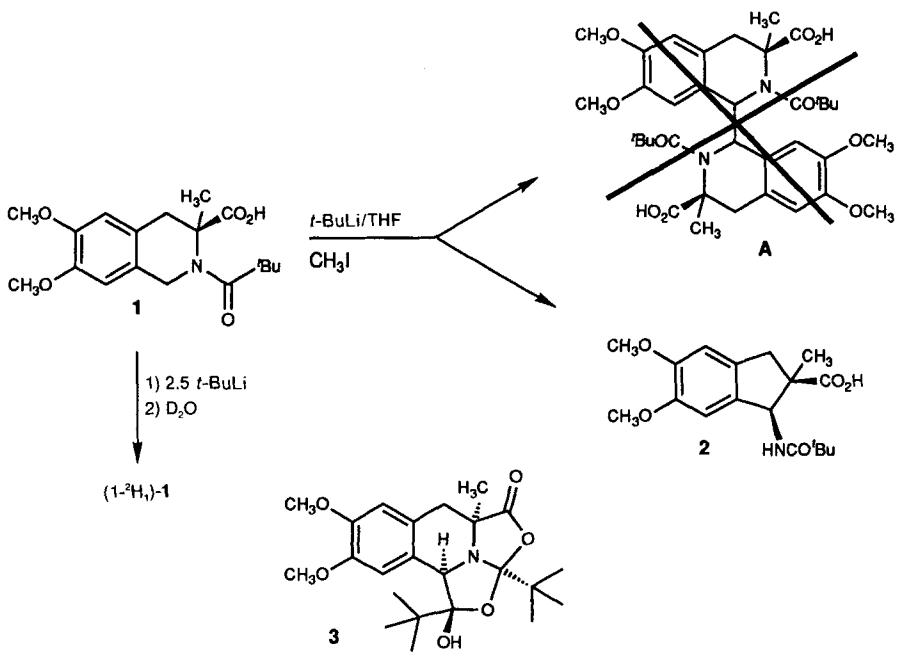
Lithium 1-lithio-6,7-dimethoxy-3-methyl-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate rearranges to the dilithio derivative of 5,6-dimethoxy-2-methyl-1-(pivaloylamino)indan-2-carboxylic acid (**2**, [1,2]-sigmatropic shift with retention of configuration) by 1,2-migration resembling the *Wittig* rearrangement of deprotonated ethers (*Scheme 2*). The structure, including absolute configuration of the rearrangement product, was determined by X-ray diffraction. Structural conditions for the rearrangement to occur are tested by subjecting various other tetrahydroisoquinoline derivatives (**6**, **7**, **10**, **15**) to the metalating conditions. Only one other compound was found to undergo the same rearrangement (**15** → **16**). Possible mechanisms of the rearrangement are discussed (**B**–**G**). Due to the presence of a tetrasubstituted C-atom, the indan-type β-amino-acid derivative **2** has a conformationally locked structure (N–C–C–CO_2R dihedral angle 44°). For comparison, the corresponding tetralin-type β-amino-acid derivatives **19**–**22** were prepared, and it was shown by X-ray analysis (of the ester **21**) that these have larger dihedral angles (*ca.* 60°). It is proposed that β-amino acids of the type described here could be incorporated into peptides, providing bents of known angles along the peptide backbone.

1. Discovery of a New Type of Rearrangement. – In a previous paper dealing with the synthesis of 1,2,3,4-tetrahydroisoquinoline (THIQ) alkaloids *via* lithiated *N*-acyl-THIQ derivatives, we have reported that sequential treatment of the carboxylic acid **1** with excess *t*-BuLi and MeI in THF did not lead to the expected product of methylation at C(1) of the heterocycle but resulted in dimerization to the bis-THIQ **A** [1] (*Scheme 1*). Since the THIQ derivative **1** was obtained from (*S*)-α-methyl-DOPA, and was thus enantiomerically pure, we thought that the dimer[2]) could serve as starting material for the preparation of novel chelating ligands which might be useful in asymmetric synthesis [5]. We set out to make larger amounts of **A**, an endeavour which turned out to become an ordeal of many months. Neither could we isolate a compound of structure **A** nor could we reproduce the spectra obtained in the previous work [1] [6]. The only electrophile which gave rise to a product derived from a 1-lithio-THIQ-3-carboxylate was D_2O (→(1-$^2H_1$)-**1**, 92% yield, > 95% ^2H incorporation). All the conventional, but also exotic oxidants were

[1]) Part of the Dissertation of *Th. G.*, ETH Zürich, No. 9948 (1992).

[2]) Simple bis-THIQ derivatives are known since the beginning of the century. They have been prepared by reductive coupling of the corresponding iminium salts [2], by *Bischler-Napieralsky* ring closure of the appropriate oxalic-acid diamides [3], or by oxidative coupling of 1-lithio-2-acyl- or -2-phosphoryl-THIQs [4] (*cf.* **1** → **A**!).

Scheme 1



employed[3]) to cause the lithiated THIQ to dimerize, without success. Careful analysis of the reaction mixture, obtained with various oxidants, and chromatographic separation of its numerous components revealed the presence of a main product **X** the spectra of which were not compatible with the dimeric structure. Ironically, compound **X** was also formed, simply by letting a solution of lithiated **1** stand long enough at dry-ice temperature or by allowing it to warm up to room temperature overnight. The best conditions for preparing compound **X** gave reproducibly 30–35% yields of chromatographically separated and recrystallized material, with 40–50% of starting material **1** being recovered. Mass spectra, osmometric molecular-weight determination, and elemental analysis proved that the new compound was an isomer of the original THIQ derivative **1**. Compound **X** was still enantiomerically pure, with a specific rotation of $[\alpha]_D = -30$ which did not change after repeated recrystallizations. The crystals were suitable for X-ray structure analysis; the surprising result is shown in *Fig. 1*. A rearrangement had occurred, with ring contraction of the THIQ skeleton **1** to an amino-indan system **2**, having *cis*-configuration of the CO_2H and NHCO(*t*-Bu) substituents!

The absolute configuration of **2** was determined by crystal structure analysis of the ammonium salt obtained with (*R*)-1-(*p*-nitrophenyl)ethylamine [7] (see *Fig. 2*). This establishes that the ring contraction has taken place with retention of configuration. The only other product we could isolate, besides **2**, from a crystallization experiment was the

[3]) Cu^I, and Cu^{II} salts, Br_2, I_2, $K_3[Fe(CN)_6]$, $NiCl_2$, $CoCl_2$, $HgCl_2$, AgOAc, $PtCl_2$, $PdCl_2$ were used. The parent *N*-pivaloyl-THIQ could be dimerized by sequential treatment with *t*-BuLi and $NiCl_2$ in 70% yield. Previously, we used I_2 or $Ti(OCHMe_2)_3Cl$ for dimerizing simple THIQ derivatives [4].

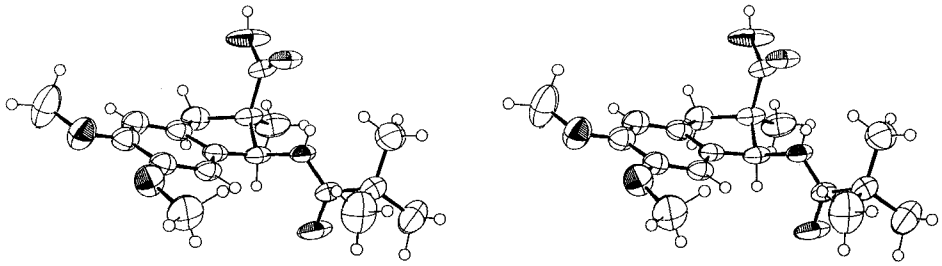


Fig. 1. *ORTEP Stereoplot of the crystal structure of the rearrangement product* **2** (50% probability ellipsoids)

tetracyclic amide acetal **3** of which only very tiny amounts could have been formed. The structure was again determined by X-ray diffraction and is shown in *Fig. 3*. It arises from a pivaloylation at C(1) of **1**, followed by double ring closure[4]).

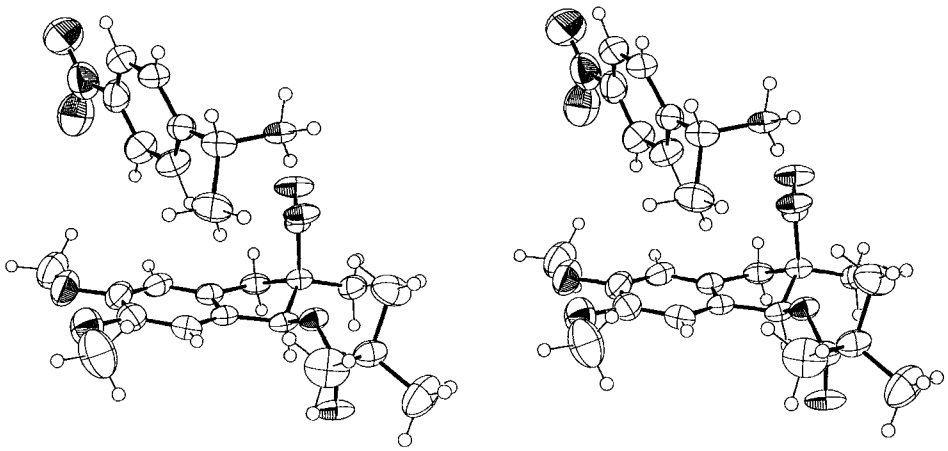


Fig. 2. *ORTEP Stereoplot of one of the two independent moieties in the asymmetric unit of the (+)-(R)-1-(p-nitrophenyl)ethylammonium salt of* **2** (50% probability ellipsoids)

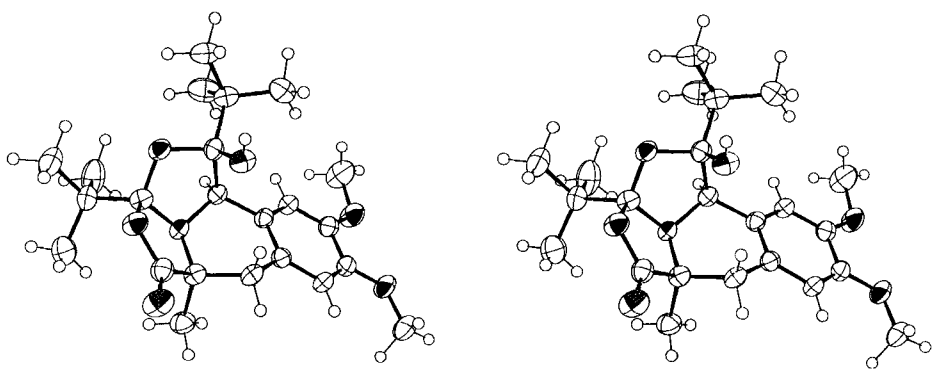
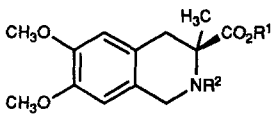


Fig. 3. *ORTEP Stereoplot of the THIQ derivative* **3**. The absolute configuration must be as shown, since the original (*S*)-THIQ moiety of the starting material is still present. The 50% probability ellipsoids are shown.

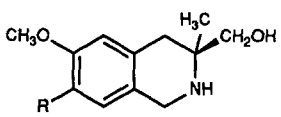
[4]) The Li 1-Li-THIQ-3-carboxylate derived from **1** probably reacts with its monolithiated precursor (the Li-carboxylate of **1**), by nucleophilic additon to the pivaloyl C=O bond, during the metallation step. Cyclization to compound **3** could be formed in the reaction mixture or during workup and isolation procedures.

In view of the fact that numerous metallated amides, especially THIQ-derived ones, have been described [4] [8], it is astonishing that the type of rearrangement leading from **1** to **2** has not been discovered before. A unique structural feature of THIQ **1** seems to be the COO group on a quaternary center at C(3) of the heterocyclic ring[5]). To test whether other compounds containing such a center will also undergo the rearrangement, we have prepared analogs of **1**.

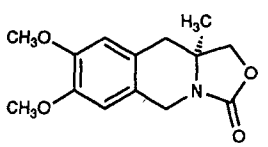
2. Preparation of Starting Materials and a Second Example of the Rearrangement. – The precursor of the rearrangement product was prepared from the known THIQ derivative **4** (*Pictet-Spengler* cyclization of (*S*)-*O*,*O*-dimethyl-2-methyl-DOPA [11]) by esterification ($SOCl_2$/MeOH, → **5**), pivaloylation (*t*-BuCOCl, → **6**), and saponification (KOH/MeOH/H_2O, → **1**), with rather drastic conditions being required for the last step. The corresponding *N*-benzoyl derivative **7** was obtained by a modified *Kricheldorf* procedure[6]) [1] [6] [12], *i.e.* treatment of amino acid **4** with Et_2NSiMe_3 and then PhCOCl/Et_3N. $LiAlH_4$ reduction of **4** gave the *β*-amino-alcohol **8** which was cyclized to the urethane **10**. The racemic monomethoxy-2-methylphenylalanine ester **11** [13] was employed for the synthesis of '7-demethoxy-**1**': *N*-formylation ($CH_3COOCHO$, → **12**), *Bischler-Napieralsky* ring closure ($POCl_3$/toluene), hydrogenation of the resulting dihydroisoquinoline (H_2/PtO_2 in EtOH, → **13**; surprisingly, excess $NaBH_4$ in MeOH/0° reduced the ester group as well, → **9**), pivaloylation (→ **14**), and ester hydrolysis (90% H_2SO_4/0°) gave the THIQ-3-carboxylic acid **15** (*ca.* 20% overall yield).



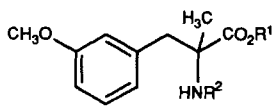
4 $R^1 = R^2 = H$
5 $R^1 = CH_3$, $R^2 = H$
6 $R^1 = CH_3$, $R^2 = CO^tBu$
7 $R^1 = H$, $R^2 = COPh$



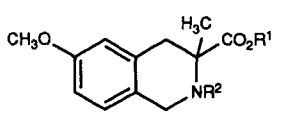
8 $R = OCH_3$
9 $R = H$



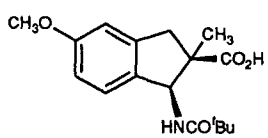
10



11 $R^1 = CH_3$, $R^2 = H$
12 $R^1 = CH_3$, $R^2 = CHO$



13 $R^1 = CH_3$, $R^2 = H$
14 $R^1 = CH_3$, $R^2 = CO^tBu$
15 $R^1 = H$, $R^2 = CO^tBu$



16 (*rac*)

The *N*-acyl-THIQ derivatives **6**, **7**, **10**, and **15** were all subjected to treatment with excess *t*-BuLi in THF at −75°. Except with **15**, no formation of a Li derivative could be detected by deuterolysis and NMR analysis, and no rearrangement products could be

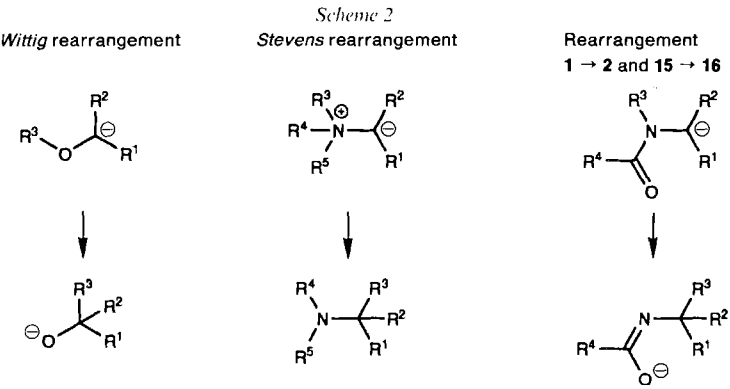
[5]) Neither 3-unsubstituted nor simple THIQ-3-carboxylate-derived *N*-acyl derivatives were found to undergo this rearrangement upon lithiation [1] [4] [6] [10]. A recently reported [9] ring contraction of an *N*-Boc-3,6-dihydro-1,2-oxazine to a 2,5-dihydro-2-furylamine, upon treatment with $LiN(CHMe_2)_2$, is phenomenologically similar, but has a much bigger driving force ($C^{\ominus} \rightarrow O^{\ominus}$).

[6]) For **1**, the overall yield using this one-step procedure is lower than with the three-step sequence applied herein.

isolated. With the monomethoxy analogue of **1**, *i.e.* the THIQ-3-carboxylic acid **15**, however, a product was formed in *ca.* 30% yield, isomeric with **15**, to which we assign structure **16**, mainly due to the fact that its ^{1}H- and ^{13}C-NMR spectra are very similar to those of **2**. Thus, the rearrangement is still observed after the minor structural change of leaving out the 7-MeO group in **1**. Intriguingly, the corresponding compound lacking the 6-MeO group, *i.e.* the THIQ of type **1** prepared from 2-methylphenylalanine itself, does *not* rearrange, according to hitherto unpublished work by *Soo Ko*[7]). It is hard to see how the additional electron-donating effect of the *p*-MeO group onto the lithiated benzylic C-atom could play such a decisive role in causing the rearrangement to occur (see the disucssion in the next section).

3. Mechanistic Considerations. – Formally, the THIQ-to-indan rearrangement observed here is the N-analog of the well known *Wittig* rearrangement (see *Scheme 2*). In both cases, an anionic charge is transferred from the C-atom to a more electronegative atom, with concomitant 1,2-shift of a C-atom. In both cases, the rearrangement must be exothermic: the pK_a values of the CH acids from which the carbanions are derived are above 30, the acidity of an alcohol (product of *Wittig* rearrangement) is *ca.* 16, and that of an amide (product[8]) of rearrangement leading to **2** and **16**) *ca.* 19. Both rearrangements

Scheme 2

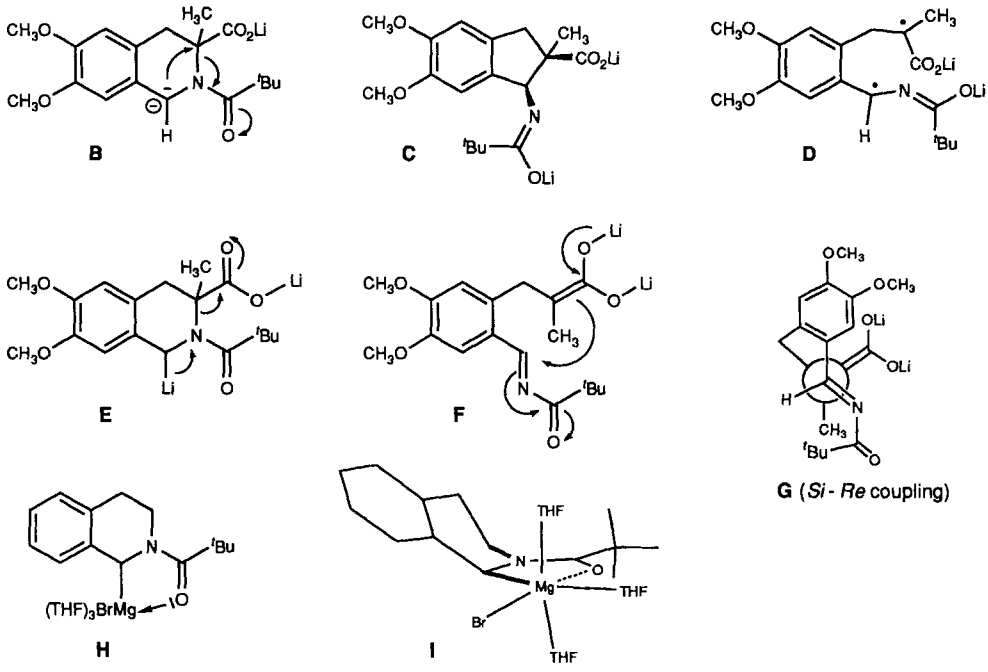


are formally forbidden by the *Woodward-Hoffmann* rules for pericyclic reactions (four electrons, suprafacial), and, indeed, the *Wittig* rearrangement of simple metallated ethers, a [1,2]-sigmatropic shift, has been shown to involve radicals, and at least partial loss of configurational integrity is usually observed [15] (*cf.* also the *Stevens* rearrangement with a migrating stereogenic center [16]). The THIQ-to-indan rearrangement **B** → **C** is totally stereoselective, and the stereogenic center migrates with retention of configuration. A radical dissociation can be depicted as shown in **D**. With the particular structure of the two rearranging THIQ derivatives, the process can also be viewed as a fragmenting elimination (**E** → **F**) followed by a nucleophilic addition to an *N*-acyl-imine (**F** → **C**). As with a homolytic pathway, an achiral intermediate (**D** or **F**) would be formed. The observed steric course of the rearrangement, if occurring through an imine-enolate **F**,

[7]) We thank Dr. *S. Ko* and the *Sandoz Pharma AG* (Basel), Preclinical Research Division, for allowing us to communicate these hitherto unpublished results herein.

[8]) We draw the lithiated amide in *Scheme 2* (and in the formulae **C** and **D** below) as *O*-lithiated aza-enolates or imino carboxylates, in accordance with known crystal structures of such species [14].

would require collaps of the trigonal centers to occur faster than rotation around C–C bonds; for a possible coupling mode, see **G**[9]). The crystal structure of the 1-magnesio-2-pivaloyl-THIQ **H** [17] may be taken to support the elimination pathway: the C(1)–Mg and the N(2)–C(3) bonds are approximately antiperiplanar (see **I**); if we assume that the Li_2-derivative **E** has an analogous structure, the condition for cleavage of the C–Li and the C–N bonds with maximum conservation of bonding would be fulfilled; this would, however, lead to an *N*-acyl-imine with a linear geometry on nitrogen (transition state of N-inversion!). With the experimental results at hand, it is of course not possible to make a choice between the different mechanistic possibilities.



4. A Tetralone Analog 22 of the Amino-indancarboxylic-Acid Derivatives 2 and 16. – When looking at the crystal structures shown in *Figs. 1* and *2*, it occurred to us that the 1-aminoindan-2-carboxylic acid, which probably has a rigid conformation due to the *geminal* disubstitution at C(2), might be interesting for the construction of peptide mimics (see the *Newman* projection **J**). It would provide a building block for constructing a bent of known geometry into a peptide backbone, with a lipophilic flap, the aromatic ring, attached to it. Of course, the route to such indan-type β-amino acids could not possibly be our rearrangement reaction (low overall yields, many steps, structural restrictions!)[10]).

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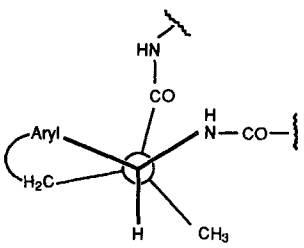
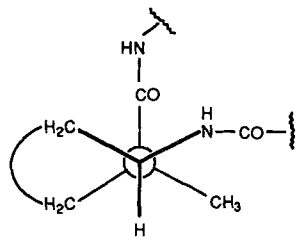
[9]) The neighborhood between the LiO and the *p*-MeO groups in **G** suggests that a complexation between the two might be the cause for the necessity of having the 6-MeO substituent in the starting THIQ for the rearrangement to occur!?

[10]) Indeed, *Soo Ko*[7]) has converted the amide **2** to the corresponding free amino acid using the following steps: esterification, thiocarbonylation of the amide with *Lawesson* reagent, *S*-methylation with *Meerwein* salt, and hydrolysis with 6N HCl.

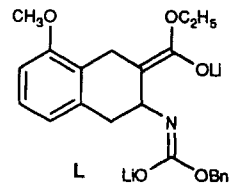
More direct synthetic approaches can easily be deviced, and some 1-aminoindan-2-carboxylic-acid derivatives have actually been described [18]. On the other hand, we had access to large amounts of the corresponding racemic 3-aminotetralin-2-carboxylic acids, such as **17**, and we thought that it may be rewarding to compare corresponding amino-indan- and amino-tetralin-carboxylic acids. The amino ester **17** (*ca.* 4:1 *cis*/*trans*-mixture) is readily available by reductive amination of the corresponding ethyl 3-oxotetralin-2-



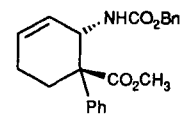
J (*Newman* projection from crystal structure of **2**)



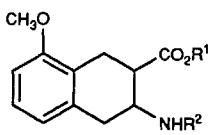
K (*Newman* projection from crystal structure of **21**)



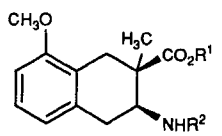
L



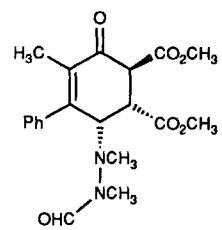
M
(*CSD* code: BECHCB)



17 $R^1 = C_2H_5$, $R^2 = H$
18 $R^1 = C_2H_5$, $R^2 = CO_2Bn$



19 $R^1 = C_2H_5$, $R^2 = CO_2Bn$
20 $R^1 = C_2H_5$, $R^2 = H$
21 $R^1 = C_2H_5$, $R^2 = CO^tBu$
22 $R^1 = H$, $R^2 = CO^tBu$
(only one enantiomer shown)



N
(*CSD* code: CEYJIZ)

carboxylate[11]). Reaction with benzyl chlorocarbonate, double deprotonation of the resulting Z-protected amino ester **18** (→ **L**)[12]), and alkylation with MeI gave the *cis*-amino-tetralin-carboxylic-acid derivative **19** (81% yield, no second diastereoisomer detectable in the 300-MHz ^{1}H-NMR spectrum of the crude product). Deprotection of the amino group (→ **20**), *N*-pivaloylation (→ **21**), and saponification furnishes a six-ring analog **22** of the amino-indancarboxylic acids **2**, **16**. All analytical and spectroscopic data were compatible with the constitution and configuration of **22** as shown; NOE measurements indicated the *cis*-disposition of CH_3–C(2) and H–C(3). To unambiguously confirm the structure and to determine the exact value for the dihedral angle CO–C(CH_3)–CH–N, we ob-

[11]) For the preparation of such β-keto esters, by carboxyalkylation of tetralones, see [19] and ref. cit. therein. The keto esters can be reduced enantio- and diastereoselectively with baker's yeast [19]. The amino ester **17** was prepared by the *Kilo-Labor* of the *Sandoz Pharma AG*, Basel (we thank Dr. *H. Braunschweiger* for a generous gift). For literature procedures leading to analogous compounds, see [20].

[12]) This is a general method for the diastereoselective, synthesis of α-branched β-amino acids [21]. For another route to this type of amino acids developed in our group, see [22]. Preparation of enantiomerically pure α,β-diamino-acid derivatives [23].

tained an X-ray crystal structure of the ester **21** (see *Fig. 4*). Not surprisingly, the synclinal angle between the ester and the amide group of **21** is somewhat larger (61°, see **K**) than in the aminoindan-carboxyclic acid **2** (44°, see **J**). Thus, the two β-amino acids would provide residues for incorporation into peptides with *ca.* 45 and 60° angles of the attached peptide chains. A search in the *Cambridge Structural Data Base* (*CSD*) as of August 1992 gave only two further examples of β-amino-acid structures in which the NR_2 and the COX group are substituents on a ring (both cyclohexanes; see **M** and **N**); in one of them the N–C–C–CO dihedral angle is 47°, in the other one 65°.

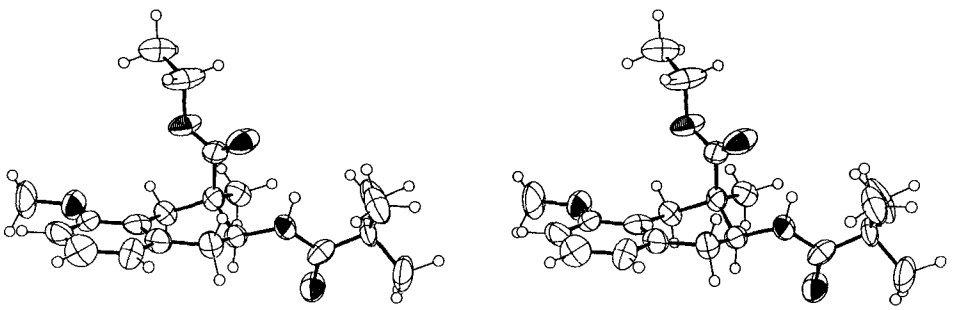


Fig. 4. *ORTEP Stereoplot of the β-amino-ester derivative* **21**

Boehringer Mannheim (Dr. *G. Lettenbauer*) generously supplied samples of (*S*)-*O*,*O*-dimethyl-2-methyl-DOPA for the preparation of **1**. *EMS Dottikon AG* (Dr. *U. Brändli*) provided us with (*R*)-1-(4-nitrophenyl)ethylamine used for preparing the ammonium salt of **2** (*Fig. 2*). Continuing support of our work by the *Sandoz AG* (Basel) is gratefully acknowledged. *Th. G.* thanks the *Stipendienfonds der Basler Chemischen Industrie* for a stipend in 1988/89.

Experimental Part

General. THF was purified by distillation from Na wire under Ar. All other solvents were distilled from P_2O_5. Commercial starting materials were generally used as supplied. The DOPA derivative **11** was a gift from *Boehringer Mannheim*. The amino ester **17** was supplied by *Sandoz*[10]). BuLi and *t*-BuLi (*Chemetall Gesellschaft*, 15% in hexane, 15% in pentane, resp.) were titrated according to the procedure of *Watson* and *Eastham* [24] using 1,10-phenanthroline as indicator. $(i\text{-}Pr)_2NH$ was distilled from CaH_2 prior to use. Flash chromatography was performed on *Fluka* silica gel *60*. M.p.: *Büchi-510* apparatus, uncorrected. Optical rotations: 10-cm, 1-ml cell, *Perkin Elmer 241* polarimeter at r.t. (*ca.* 22°). IR: *Perkin Elmer 983* or *PE FT-IR 1600* spectrometers. ^1H- and ^{13}C-NMR: *Bruker WM-300*, *Bruker WM-400*, *or Varian XL-300*. MS: *Hitachi-Perkin-Elmer RMU-6M* spectrometer; fragment ions in *m/z* with relative intensities (%) in parantheses.

(3S)-6,7-Dimethoxy-3-methyl-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (**1**). As described in [25], 11.0 g (31 mmol) of **6** were suspended in a soln. of 15.0 g (0.27 mol) of KOH and 60 ml of $MeOH/H_2O$ 1:1 and heated under reflux for 20 h or until a clear soln. was formed. The mixture was acidified to pH 1–2 with 2N HCl. Extraction (CH_2Cl_2), drying ($MgSO_4$), and evaporation gave the crude product which was purified by recrystallization from AcOEt leading to 7.0 g (67%) of **1** as a colorless solid (anal. data as published in [1]).

(1S,2R)-5,6-Dimethoxy-2-methyl-1-(pivaloylamino)indan-2-carboxylic Acid (**2**). To a soln. of 0.5 g (1.5 mmol) of **1** in 20 ml THF at −76°, 3.0 ml (3.8 mmol) of *t*-BuLi were added, and the deep orange soln. was kept at this temp. for 10 h. The mixture was poured into 50 ml of 2N HCl. Extraction of the aq. phase with CH_2Cl_2, drying ($MgSO_4$), and evaporation gave the crude product which was purified by FC (Et_2O/pentane/AcOH 4:1:0.1) and crystallized from Et_2O/pentane to give 0.16 g (32%) **2** as a white solid. M.p. 193.2–193.6°. $[\alpha]_D = -30.3$ ($c = 0.95$, CH_2Cl_2). IR (KBr): 3400*m*, 2960*s*, 2940*s*, 2880*m*, 2840*m*, 1730*s*, 1710*s*, 1620*s*, 1510*s*, 1470*s*, 1460*s*, 1415*m*, 1370*m*, 1310*s*, 1260*s*, 1210*s*, 1170*s*, 1100*s*, 1000*m*, 895*m*, 860*m*, 760*m*, 665*w*, 530*w*. ^1H-NMR (400 MHz, $CDCl_3$): 6.70 (*s*, 1 arom. H); 6.64 (*s*, 1 arom. H); 6.62 (*s*, NH); 5.42 (*d*, $J = 9.5$, PhC*H*N); 3.85 (*s*, MeO); 3.82 (*s*, MeO); 3.49, 2.78 (*AB*, $J = 15.8$, PhCH_2); 1.51 (*s*, Me–C(3)); 1.20 (*s*, *t*-Bu). ^{13}C-NMR (100 MHz, $CDCl_3$): 180.6 (C); 178.9 (C); 149.5 (C); 148.9 (C); 133.2 (C); 132.0 (C); 107.7 (CH); 106.7 (CH); 61.6 (CH); 56.1 (2 Me); 55.6 (C); 42.5 (CH_2); 38.9 (C); 27.5

(Me); 22.9 (Me). MS: 335 (26, M^+), 289 (18), 250 (42), 234 (100), 219 (16), 204 (18), 188 (31), 175 (15), 102 (27), 91 (4), 77 (5), 57 (69), 41 (24), 28 (84), 18 (13). Anal. calc. for $C_{18}H_{25}NO_5$ (335.39): C 64.46, H 7.51, N 4.18; found: C 64.37, H 7.40, N 4.13.

(R)-1-(4-Nitrophenyl)ethylammonium Salt of **2** (see crystal structure in *Fig. 2*). A soln. of **2** and the amine (see [7] and acknowledgment) in boiling AcOEt was allowed to cool to r.t., the resulting solid was filtered, dried, and dissolved in AcOEt at r.t. (sat. soln.). Crystallization was induced by putting the soln. in a vial stoppered with a serum cap through which a fine needle was pinched so that the solvent did evaporate very slowly.

(3S)-6,7-Dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Hydrochloride (**4**). A suspension of 50.0 g (0.21 mol) of (2*S*)-3-(3,4-dimethoxyphenyl)-2-methylalanine, 400 ml of 6N HCl and 170 ml of formalin soln. (30–40%) was kept at 100° for 35 min. After *ca.* 5 min, a dark brown soln. was formed. The solvent was evaporated and the crude product recrystallized from i-PrOH, yielding 40.0 g (67%) of **4** as a white solid (anal. data as reported in [11]).

Methyl (3S)-6,7-Dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**5**). Slow addition of 35.0 g (0.3 mol) of freshly destilled $SOCl_2$ to 12.0 g (42 mmol) of **4** gave, after stirring for *ca.* 20 min, a brownish oil, to which 300 ml of MeOH were added carefully. The mixture was heated at reflux for 8 h, cooled to r.t., basified to pH 8–10 with 2N NaOH. Extraction (CH_2Cl_2) and drying ($MgSO_4$) gave the crude product. Recrystallization of the residue from AcOEt/Et_2O gave 10.0 g (90%) of **5** as a slight yellow solid. M.p. 71–72°. $[\alpha]_D = +108.1$ ($c = 1.00$, CH_2Cl_2). IR ($CHCl_3$): 3000*m*, 2960*m*, 2940*m*, 2900*w*, 2840*w*, 1725*s*, 1615*w*, 1515*s*, 1460*s*, 1450*m*, 1440*m*, 1360*w*, 1335*m*, 1320*m*, 1280*m*, 1250*s*, 1180*m*, 1140*m*, 1110*s*, 1100*s*, 1070*w*, 1000*m*, 855*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.57 (*s*, 1 arom. H); 6.49 (*s*, 1 arom. H); 4.07, 3.94 (*AB*, $J = 15.7$, PhCH_2N); 3.85 (*s*, MeO); 3.82 (*s*, MeO); 3.68 (*s*, CO_2Me); 3.19, 2.72 (*AB*, $J = 15.9$, PhCH_2C); 2.12 (br. *s*, NH); 1.43 (*s*, Me–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.4 (C); 147.5 (C); 125.3 (C); 124.8 (C); 111.5 (CH); 108.9 (CH); 58.0 (C); 55.8 (2 CH_3); 52.2 (CH_3); 44.6 (CH_2); 37.1 (CH_2); 26.2 (CH_3). MS: 265 (12, M^+), 206 (100), 190 (12), 164 (18), 121 (6), 103 (8), 91 (4), 77 (6), 42 (10), 15 (9). Anal. calc. for $C_{14}H_{19}NO_4$ (265.31): C 63.38, H 7.22, N 5.28; found: C 63.16, H 7.32, N 5.22.

Methyl (3S)-6,7-Dimethoxy-3-methyl-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**6**). To 10.0 g (38 mmol) of **5**, 6.2 ml (44 mmol) of Et_3N, 4.7 ml (38 mmol) of pivaloyl chloride in 80 ml of CH_2Cl_2, 100 mg of DMAP were added, and the mixture was stirred at r.t. for 20 h. The soln. was acidified with 100 ml 2N HCl, extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated. The crude product was purified by recrystallization from AcOEt yielding 11.1 g (84%) of **6** as a colorless solid. M.p. 157.5–158.5°. $[\alpha]_D = -37.7$ ($c = 0.93$, CH_2Cl_2). IR ($CHCl_3$): 3000*s*, 2960*m*, 2940*m*, 2920*w*, 2840*w*, 1735*s*, 1620*s*, 1515*s*, 1465*s*, 1445*m*, 1435*m*, 1410*s*, 1375*s*, 1365*s*, 1340*s*, 1320*m*, 1295*m*, 1240*s*, 1170*s*, 1150*m*, 1110*s*, 1085*w*, 1000*m*, 855*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.73 (*s*, 2 arom. H); 4.71, 4.59 (*AB*, $J = 14.4$, PhCH_2N); 3.90 (*s*, MeO); 3.89 (*s*, MeO); 3.69 (*s*, CO_2Me); 3.14, 2.72 (*AB*, $J = 14.8$, PhCH_2C); 1.36 (*s*, Me–C(3)); 1.33 (*s*, *t*-Bu). ^{13}C-NMR (100 MHz, $CDCl_3$): 176.3 (C); 174.7 (C); 148.7 (C); 147.8 (C); 127.1 (C); 126.4 (C); 111.4 (CH); 109.0 (CH); 62.1 (C); 56.2 (Me); 56.1 (Me); 52.1 (Me); 47.2 (CH_2); 39.5 (CH_2); 38.8 (C); 28.1 (Me); 21.5 (Me). MS: 349 (6, M^+), 290 (6), 264 (38), 248 (22), 232 (5), 206 (19), 189 (7), 164 (19), 121 (8), 91 (5), 77 (6), 57 (100), 41 (18), 29 (11). Anal. calc. for $C_{19}H_{27}NO_5$ (349.43): C 65.31, H 7.79, N 4.01; found: C 65.29, H 7.84, N 3.90.

(3S)-2-Benzoyl-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (**7**). By the addition of 4.9 ml (26 mmol) of *N,N*-dimethyl(trimethylsilyl)amine to a suspension of 5.76 g (20 mmol) of **4** in 20 ml of CH_2Cl_2, a clear soln. resulted, which was heated at reflux for 1 h. After cooling to –15° and combining with 5.1 ml (44 mmol) of benzoyl chloride, 3.1 ml (22 mmol) of Et_3N were slowly added and stirring continued for 24 h at r.t. The soln. was washed with 2N HCl and H_2O, dried ($MgSO_4$), and evaporated. The residue was purified by FC (hexane/AcOEt/AcOH 1:1:0.1) yielding 2.8 g (39%) of **7** as a colorless solid. M.p. 176.5–178.0°. $[\alpha]_D = -39.7$ ($c = 0.95$, CH_2Cl_2). IR ($CHCl_3$): 3000*m*, 2960*w*, 2940*w*, 2840*w*, 1740*m*, 1715*s*, 1630*s*, 1600*m*, 1515*s*, 1465*s*, 1450*m*, 1410*s*, 1375*w*, 1345*m*, 1320*w*, 1280*m*, 1190*m*, 1135*m*, 1115*s*, 1080*w*, 1000*m*, 855*w*, 700*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.60–7.54 (br. *s*, CO_2H); 7.50–7.41 (*m*, 5 arom. H); 6.76 (*s*, 1 arom. H); 6.52 (*s*, 1 arom. H); 4.47, 4.35 (*AB*, $J = 14.6$, PhCH_2N); 3.87 (*s*, MeO); 3.81 (*s*, MeO); 3.29, 2.86 (*AB*, $J = 14.8$, PhCH_2C); 1.57 (*s*, Me–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 177.0 (C); 171.0 (C); 149.2 (C); 148.4 (C); 136.7 (C); 129.8 (CH); 128.5 (CH); 127.0 (CH); 126.4 (C); 112.4 (CH); 110.0 (CH); 61.8 (C); 56.4 (2 Me); 49.1 (CH_2); 39.9 (CH_2); 21.7 (Me). MS: 355 (12, M^+), 250 (14), 234 (30), 204 (23), 190 (32), 164 (43), 122 (25), 105 (100), 91 (9), 77 (64), 51 (20), 28 (6). Anal. calc. for $C_{20}H_{21}NO_5$ (355.39): C 67.59, H 5.96, N 3.94; found: C 67.37, H 5.82, N 3.91.

(3S)-6,7-Dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-methanol (**8**). Following the procedure described in [26], 15.0 g (52 mmol) of **1**, 2.3 g (104 mmol) of $LiBH_4$, and 26.4 ml (208 mmol) of Me_3SiCl in 150 ml of THF reacted to give 10.0 g (81%) of **8** (recrystallized from $CHCl_3$). M.p. 156.8–157.3°. $[\alpha]_D = -14.5$ ($c = 0.92$, CH_2Cl_2). IR (KBr): 3320*m*, 3160*s* (br.), 3000*m*, 2970*s*, 2940*s*, 2900*s*, 2840*s*, 1610*m*, 1515*s*, 1460*s*, 1440*m*, 1425*m*, 1375*m*, 1335*s*, 1250*s*, 1225*s*, 1190*m*, 1175*m*, 1115*s*, 1085*s*, 1060*s*, 1020*m*, 1000*m*, 975*m*, 910*m*, 880*s*, 860*s*, 830*m*, 750*m*, 720*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.56 (*s*, 1 arom. H); 6.53 (*s*, 1 arom. H); 3.95, 3.89 (*AB*, $J = 17.0$,

PhCH_2N); 3.85 (*s*, MeO); 3.84 (*s*, MeO); 3.52, 3.41 (*AB*, *J* = 10.7, CH_2O); 2.69, 2.44 (*AB*, *J* = 16.3, PhCH_2C); 2.30–1.75 (br., 2 H, exchangeable, OH, NH); 1.14 (*s*, Me–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 147.7 (C); 147.4 (C); 126.5 (C); 125.5 (C); 112.4 (CH); 108.7 (CH); 68.8 (CH_2); 56.0 (2 Me); 52.4 (C); 43.6 (CH_2); 35.8 (CH_2); 22.4 (Me). MS: 237 (2, M^+), 206 (100), 190 (20), 174 (16), 164 (26), 149 (9), 121 (10), 103 (14), 91 (8), 77 (9), 42 (10), 28 (14). Anal. calc. for $C_{13}H_{19}NO_3$ (237.30): C 65.80, H 8.07, N 5.90; found: C 65.60, H 8.22, N 5.75.

rac-*6-Methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-methanol* (**9**). A soln. of 5.0 g (20 mmol) of **12** in 300 ml of toluene was heated to 90° and 7.3 ml (80 mmol) of $POCl_3$ were added in one portion. The mixture was kept at this temp. for 3.5 h and, after cooling to r.t., evaporated to dryness. The residue was dissolved in 150 ml of MeOH, the soln. cooled to 0°, 1.5 g (40 mmol) of $NaBH_4$ were added, and the mixture was stirred at this temp. overnight. Addition of 100 ml of 1N HCl, extraction (CH_2Cl_2), drying ($MgSO_4$), evaporation of the solvent, and FC (Et_2O) led to 2.0 g (48%) of **9** as a colorless solid. M.p. 110.2–110.6°. IR (KBr): 3290*s*, 3170*s* (br.), 3000*s*, 2920*s*, 2860*s*, 2830*s*, 1610*s*, 1580*m*, 1510*s*, 1460*s*, 1440*s*, 1350*s*, 1260*s*, 1150*s*, 1120*s*, 1060*s*, 1040*s*, 1000*s*, 980*w*, 920*m*, 860*s*, 810*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.95 (*d*, *J* = 8.4, 1 arom. H); 6.71 (*dd*, J_{ortho} = 8.4, J_{meta} = 2.6, 1 arom. H); 6.61 (*d*, J_{meta} = 2.6, 1 arom. H); 3.96, 3.89 (*AB*, *J* = 16.5, PhCH_2N); 3.77 (*s*, MeO); 3.51, 3.40 (*AB*, *J* = 10.6, CH_2O); 2.74, 2.49 (*AB*, *J* = 16.4, PhCH_2C); 2.40–1.60 (br., OH, NH); 1.12 (*s*, Me–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.1 (C); 135.1 (C); 127.0 (C); 126.6 (CH); 114.3 (CH); 112.1 (CH); 68.8 (CH_2); 55.2 (Me); 52.3 (C); 43.3 (CH_2); 36.6 (CH_2); 22.5 (Me). MS: 206 (1.4, $[M-1]^+$), 176 (100), 160 (10), 91 (9), 77 (5), 28 (43). Anal. calc. for $C_{12}H_{17}NO_2$ (207.27): C 69.54, H 8.27, N 6.76; found: C 69.45, H 8.46, N 6.57.

*(10a*S*)-7,8-Dimethoxy-10a-methyl-10,10a-dihydro-1*H,*5*H-*[1,3]oxazolo[3,4-*b*]isoquinolin-3-one* (**10**). The soln. of 0.50 g (2.0 mmol) of **8** and 0.52 g (4.6 mmol) of *t*-BuOK in 15 ml of THF was cooled to 0°. To the mixture 0.18 ml (2.3 mmol) of methyl chlorocarbonate were added and stirred at r.t. for 6 h. The resulting suspension was treated with sat. NH_4Cl soln., extracted with CH_2Cl_2, the org. layer dried ($MgSO_4$), and evaporated. After recrystallization of the crude product from hexane/AcOEt, 0.33 mg (60%) of **10** resulted. M.p. 184.2–184.8°. $[\alpha]_D = -150.3$ (*c* = 0.94, CH_2Cl_2). IR (KBr): 3010*w*, 2990*w*, 2950*m*, 2940*m*, 2900*m*, 2860*m*, 2840*m*, 1740*s*, 1610*m*, 1520*s*, 1460*s*, 1445*s*, 1415*s*, 1375*s*, 1365*m*, 1340*s*, 1315*m*, 1275*s*, 1255*s*, 1225*s*, 1200*s*, 1170*m*, 1110*s*, 1070*s*, 1020*s*, 1000*m*, 960*m*, 850*s*, 765*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.60 (*s*, 1 arom. H); 6.56 (*s*, 1 arom. H); 4.79, 4.23 (*AB*, *J* = 16.8, CH_2O); 4.22, 4.17 (*AB*, *J* = 8.5, PhCH_2N); 3.87 (*s*, MeO); 3.86 (*s*, MeO); 3.02, 2.60 (*AB*, *J* = 15.2, PhCH_2C); 1.32 (*s*, Me–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 157.1 (C); 148.3 (C); 148.1 (C); 123.4 (C); 122.4 (C); 112.4 (CH); 108.9 (CH); 74.7 (CH_2); 56.0 (Me); 55.9 (C); 40.8 (CH_2); 38.2 (CH_2); 21.9 (Me). MS: 263 (42, M^+), 202 (51), 190 (19), 164 (100), 149 (21), 121 (33), 91 (19), 77 (21), 41 (11), 28 (13). Anal. calc. for $C_{14}H_{17}NO_4$ (263.29): C 63.87, H 6.51, N 5.32; found: C 64.06, H 6.50, N 5.32.

rac-N-*Formyl-3-(3-methoxyphenyl)-2-methylalanine Methyl Ester* (**12**). A soln. of 7.0 g (31 mmol) of **11** in 70 ml of HCOOH (98%) was cooled to 2°, and, within 30 min, 40 ml (0.42 mol) of Ac_2O were added. The mixture was stirred for 3 h, evaporated to dryness, and the residue distilled to give 7.6 g (97%) of **12** as a colorless oil. B.p. 130°/0.1 Torr. IR (film): 3340*m* (br.), 3000*w*, 2950*m*, 1740*s*, 1680*s*, 1600*s*, 1580*s*, 1490*s*, 1450*s*, 1380*m*, 1325*m*, 1260*s*, 1210*s*, 1155*s*, 1120*s*, 1050*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.14 (*d*, *J* = 1.7, CHO); 7.17 (*t*, *J* = 7.0, 1 arom. H); 6.80–6.76 (*m*, 1 arom. H); 6.66–6.61 (*m*, 2 arom. H); 6.29 (br. *s*, NH); 3.81 (*s*, MeO); 3.76 (*s*, CO_2Me); 3.57, 3.17 (*AB*, *J* = 13.4, PhCH_2); 1.75 (*s*, Me–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.9 (C); 160.4 (C); 159.5 (CH); 137.5 (C); 129.3 (CH); 122.1 (CH); 115.6 (CH); 112.4 (CH); 61.5 (C); 55.1 (Me); 52.8 (Me); 41.5 (CH_2); 23.6 (CH_3). MS: 251 (15, M^+), 206 (100), 192 (10), 146 (20), 121 (42), 102 (65), 91 (21), 77 (13), 42 (51).

rac-*Methyl 6-Methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate* (**13**). A soln. of 3.7 g (15 mmol) of **12** in 200 ml of toluene was heated to 90°, and 5.4 ml (59 mmol) of $POCl_3$ were added in one portion. The mixture was kept at this temp. for 3.5 h and, after cooling to r.t., evaporated to dryness. The residue was dissolved in 50 ml of EtOH, 20 mg of PtO_2 were added, and a H_2 atmosphere was applied for 18 h. After filtration of the mixture over *Celite*, the solvent was evaporated and the residue purified by FC (Et_2O) to give 1.9 g (55%) of **13** as a colorless oil. IR (film): 3340*w*, 3000*w*, 2950*m*, 2900*m*, 2840*m*, 1730*s*, 1610*s*, 1590*w*, 1510*s*, 1460*s*, 1450*s*, 1370*w*, 1320*m*, 1270*s*, 1250*s*, 1195*s*, 1110*s*, 1040*s*, 980*w*, 810*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.92 (*d*, *J* = 8.4, 1 arom. H); 6.70 (*dd*, J_{ortho} = 8.4, J_{meta} = 2.6, 1 arom. H); 6.62 (*d*, J_{meta} = 2.6, 1 arom. H); 4.06, 3.96 (*AB*, *J* = 15.6, PhCH_2N); 3.77 (*s*, MeO); 3.67 (*s*, CO_2Me); 3.24, 2.77 (*AB*, *J* = 16.1, PhCH_2C); 2.33–1.98 (br. *s*, NH); 1.43 (*s*, Me–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.4 (C); 157.9 (C); 134.2 (C); 127.1 (CH); 125.8 (C); 113.4 (CH); 112.5 (CH); 57.9 (C); 55.2 (Me); 52.2 (Me); 44.4 (CH_2); 37.9 (CH_2); 26.2 (Me). MS: 235 (9, M^+), 220 (6), 176 (100), 134 (6), 91 (4), 77 (2).

rac-*Methyl 6-Methoxy-3-methyl-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate* (**14**). To 50 ml of CH_2Cl_2, 1.5 g (6.0 mmol) of **13**, 1.3 ml (9.0 mmol) of Et_3N, a catalytic amount of 4-(dimethylamino)pyridine, and 0.74 ml (6.0 mmol) of pivaloyl chloride were added, and the mixture was kept at r.t. for 72 h, before addition of 50 ml of 2N HCl, extraction (CH_2Cl_2), drying ($MgSO_4$), and evaporation of the solvent. The crude product was purified by FC (Et_2O/pentane 1:2) to give 1.1 g (57%) of **14** as a colorless solid. M.p. 114.2–114.4°. IR ($CHCl_3$):

3020*m*, 3000*s*, 2980*s*, 2960*s*, 1730*s*, 1620*s*, 1500*s*, 1460*m*, 1400*s*, 1380*m*, 1360*m*, 1320*m*, 1150*s*, 1110*s*, 1035*m*, 990*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.11 (*d*, *J* = 7.8, 1 arom. H); 6.79–6.76 (*m*, 2 arom. H); 4.74, 4.58 (*AB*, *J* = 14.4, PhCH_2N); 3.81 (*s*, MeO); 3.68 (*s*, CO_2Me); 3.15, 2.76 (*AB*, *J* = 14.7, PhCH_2C); 1.35 (*s*, Me–C(3)); 1.32 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.2 (C); 174.7 (C); 159.5 (C); 136.4 (C); 126.9 (C); 126.1 (CH); 113.8 (CH); 111.9 (CH); 62.1 (C); 55.4 (Me); 52.1 (Me); 46.9 (CH_2); 40.4 (CH_2); 38.7 (C); 28.0 (Me); 21.6 (Me). MS: 319 (3, M^+), 260 (15), 234 (100), 176 (31), 134 (15), 85 (11), 57 (60). Anal. calc. for $C_{18}H_{25}NO_4$ (319.40): C 67.69, H 7.89, N 4.39; found: C 67.53, H 8.03, N 4.31.

rac-*6-Methoxy-3-methyl-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid* (**15**). A soln. of 16.6 g of H_2SO_4 (95–97%) and 1.0 g of H_2O was cooled to 0°, and 0.25 g (0.80 mmol) of powdered **14** was added in one portion. The mixture was stirred until a clear soln. was formed, which was poured on ice, extracted (CH_2Cl_2), dried ($MgSO_4$), and evaporated. The crude product was triturated with Et_2O at 4° overnight. After filtration 0.150 g (63%) of **15** were collected as a colorless solid. M.p. 186.8–187.2°. IR (KBr): 3060*m*, 2980*m*, 2960*m*, 1750*s*, 1620*m*, 1590*s*, 1505*m*, 1465*m*, 1410*s*, 1350*m*, 1290*m*, 1265*s*, 1180*s*, 1155*m*, 1125*m*, 1080*w*, 1025*m*, 800*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.13–7.10 (*m*, 1 arom. H); 6.79–6.76 (*m*, 2 arom. H); 4.77, 4.58 (*AB*, *J* = 14.5, PhCH_2N); 3.82 (*s*, MeO); 3.25, 2.82 (*AB*, *J* = 14.7, PhCH_2C); 1.35 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.9 (C); 159.6 (C); 136.3 (C); 126.6 (C); 126.1 (CH); 113.8 (CH); 112.0 (CH); 62.0 (C); 55.4 (Me); 46.9 (CH_2); 40.3 (CH_2); 38.8 (C); 27.9 (Me); 21.4 (Me). MS: 305 (13, M^+), 260 (22), 220 (69), 176 (99), 160 (38), 134 (28), 91 (11), 77 (5), 57 (100), 41 (17). Anal. calc. for $C_{17}H_{23}NO_4$ (305.37): C 66.86, H 7.59, N 4.59; found: C 66.61, H 7.64, N 4.56.

rac-*5-Methoxy-2-methyl-1-(pivaloylamino)indan-2-carboxylic Acid* (**16**). In 30 ml of THF, 0.100 g (0.30 mmol) of **15** were dissolved, cooled to −76°, and 0.53 ml (0.75 mmol) of *t*-BuLi were added. The deep orange soln. was allowed to warm to r.t. overnight, 20 ml of 2N HCl were added. Extraction (CH_2Cl_2), drying ($MgSO_4$), and evaporation of the solvent gave the crude product which was purified by FC (Et_2O/pentane/AcOH 1:1:0.1) to yield 30 mg (30%) of **16** as a colorless solid. M.p. > 210°. IR (KBr): 3400*m*, 3000*m*, 2960*s*, 2900*m*, 2870*m*, 1710*s*, 1620*s*, 1515*s*, 1490*s*, 1460*m*, 1370*m*, 1300*m*, 1270*s*, 1230*m*, 1170*s*, 1090*m*, 1030*m*, 890*m*, 860*m*, 805*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.03 (*d*, *J* = 8.1, 1 arom. H); 6.76–6.73 (*m*, arom. H); 6.50 (*d*, *J* = 9.4, NH); 5.40 (*d*, *J* = 9.4, PhC*H*); 3.78 (*s*, MeO); 3.51, 2.82 (*AB*, *J* = 16.2, PhCH_2); 1.51 (*s*, Me–C(3)); 1.19 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 179.6 (C); 178.9 (C); 160.1 (C); 142.0 (C); 133.6 (C); 124.5 (CH); 113.3 (CH); 110.1 (CH); 61.0 (CH); 55.8 (C); 55.5 (Me); 42.7 (CH_2); 38.8 (C); 27.6 (Me); 23.0 (Me). MS: 305 (22, M^+), 259 (40), 220 (100), 204 (31), 174 (29), 158 (46), 145 (14), 91 (7), 57 (85). Anal. calc. for $C_{17}H_{23}NO_4$ (305.37): C 66.86, H 7.59, N 4.59; found: C 66.77, H 7.65, N 4.49.

rac-*Ethyl 3-[(Benzyloxycarbonyl)amino]-8-methoxy-1,2,3,4-tetrahydronaphthaline-2-carboxylate* (**18**). A soln. of 15.0 g (60 mmol) of freshly distilled rac-*ethyl 3-amino-8-methoxy-1,2,3,4-tetrahydronaphthaline-2-carboxylate* (**17**) in 250 ml CH_2Cl_2, 9.2 ml (66 mmol) of Et_3N, and a catalytic amount of 4-(dimethylamino)pyridine, was cooled to 0°, and 9.4 ml (66 mmol) of benzyl chlorocarbonate were added in such a way that the temp. of the soln. did not rise above 4°. The mixture was stirred at r.t. overnight, 200 ml sat. NH_4Cl soln. were added. Extraction (CH_2Cl_2), drying ($MgSO_4$), and evaporation of the solvent gave the crude product. After purification by FC (Et_2O/pentane 3:1), 22.5 g (98%) of **18** were obtained as a slightly yellow solid, which can be recrystallized from hexane/AcOEt. M.p. 121.4–121.8°. IR (KBr): 3340*s*, 3060*w*, 3040*w*, 3000*w*, 2830*m*, 2925*w*, 1730*s*, 1715*s*, 1585*m*, 1540*s*, 1470*s*, 1455*m*, 1440*m*, 1380*w*, 1330*m*, 1310*m*, 1270*s*, 1250*s*, 1190*s*, 1090*s*, 1035*m*, 1025*m*, 770*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.27 (*m*, 5 arom. H); 7.10 (*t*, *J* = 7.9, 1 arom. H); 6.69–6.65 (*m*, 2 arom. H); 5.09 (*s*, PhCH_2O); 4.92–4.90 (br. *m*, NH); 4.31–4.20 (*m*, H–C(3)); 4.14 (*q*, *J* = 7.1, CH_3CH_2O); 3.81 (*s*, MeO); 3.22–3.15 (*m*, H–C(2)); 3.11–3.01 (*m*, 2 H–C(4) or 2 H–C(1)); 2.88–2.68 (*m*, 2 H, 2 H–C(1) or 2 H–C(4)); 1.23 (*t*, *J* = 7.1, 3 H, CH_3CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.3 (C); 157.1 (C); 155.5 (C); 136.4 (C); 134.5 (C); 128.5 (CH); 128.1 (CH); 126.8 (CH); 122.5 (C); 121.1 (CH); 107.6 (CH); 66.7 (CH_2); 60.9 (CH_2); 55.3 (Me); 48.3 (CH); 45.0 (CH); 35.0 (CH_2); 24.7 (CH_2); 14.2 (Me). MS: 383 (1, M^+), 275 (9), 232 (44), 203 (13), 174 (14), 159 (100), 144 (32), 115 (20), 104 (10), 91 (79), 77 (22), 65 (14), 51 (13), 28 (82), 18 (30). Anal. calc. for $C_{22}H_{25}NO_5$ (383.44): C 68.91, H 6.57, N 3.65; found: C 69.11, H 6.64, N 3.72.

rac-cis-*Ethyl-3-[(Benzyloxycarbonyl)amino]-8-methoxy-2-methyl-1,2,3,4-tetrahydronaphthaline-2-carboxylate* (**19**). To a soln. of 17.5 ml (26.8 mmol) of BuLi, 3.8 ml (26.8 mmol) of $(i\text{-}Pr)_2NH$ in 70 ml THF and 2.13 g (50 mmol) of anh. LiCl at −76°, a soln. of 5.0 g (13 mmol) of **18** dissolved in 30 ml of THF was added in such a way that the temp. did not rise above −70°. The deep yellow soln. was stirred for 45 min, 3.3 ml (52 mmol) of MeI were added and the soln. allowed to warm to r.t. overnight. To the mixture, 100 ml of sat. NH_4Cl soln. were added. Extraction (CH_2Cl_2), drying ($MgSO_4$), and evaporation of the org. solvent led to the crude product, which was purified by FC (Et_2O/pentane 1:2) and distillation to give 4.2 g (81%) of **19** as a colorless oil. B.p. 150°/$1 \cdot 10^{-4}$ mbar. IR ($CHCl_3$): 3430*w*, 3020*w*, 3005*m*, 2975*w*, 2940*w*, 1720*s*, 1590*m*, 1510*s*, 1470*s*, 1440*m*, 1360*m*, 1340*m*, 1300*m*, 1260*s*, 1140*m*, 1095*s*, 1080*s*. ^{1}H-NMR (300 MHz, CDC_3): 7.37–7.29 (*m*, 5 arom. H); 7.07 (*t*, *J* = 7.9, 1 arom. H); 6.64 (*d*, *J* = 8.0,

2 arom. H); 5.71 (*d*, *J* = 10.1, NH); 5.11 (*s*, OCH_2Ph); 4.1–4.00 (*m*, CO_2CH_2, H–C(3)); 3.81 (*s*, MeO); 3.48, 2.51 (*AB*, *J* = 17.7, 2 H–C(1)); 3.09, 2.86 (*AB* of *ABX*, J_{AX} = 5.5, J_{BX} = 9.6, J_{AB} = 17.1, 2 H–C(4)); 1.37 (*s*, Me–C(2)); 1.11 (*t*, *J* = 7.1, CH_3CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 175.9 (C); 157.1 (C); 156.3 (C); 136.7 (C); 135.2 (C); 128.5 (CH); 128.0 (CH); 126.6 (CH); 123.0 (C); 121.0 (CH); 107.3 (CH); 66.7 (CH_2); 60.7 (CH_2); 55.3 (Me); 52.8 (CH); 45.1 (C); 33.8 (CH_2); 32.8 (CH_2); 23.7 (Me); 14.0 (Me). MS: 397 (1, M^+), 306 (9), 262 (12), 246 (73), 232 (29), 216 (18), 188 (33), 173 (100), 158 (30), 134 (19), 91 (83), 77 (15), 28 (40), 18 (54). Anal. calc. for $C_{23}H_{27}NO_5$ (397.47): C 69.50, H 6.85, N 3.52; found: C 69.19, H 7.03, N 3.50.

rac-cis-*Ethyl 3-Amino-8-methoxy-2-methyl-1,2,3,4-tetrahydronaphthaline-2-carboxylate* (**20**). To a soln. of 10.4 g (26 mmol) of **19** in 150 ml AcOEt, 1 g of 10% Pd on charcoal was added and the reaction put under H_2 atmosphere for 36 h, filtered over *Celite* and evaporated. Purification of the crude product by distillation gave 5.0 g (73%) of **20** as a colorless liquid. B.p. 150°/0.02 Torr. IR (film): 3390*w*, 2990*s*, 2930*s*, 2830*m*, 1725*s*, 1590*s*, 1470*s*, 1380*m*, 1340*m*, 1260*s*, 1230*s*, 1115*s*, 1080*s*, 1030*m*, 870*m*, 770*s*, 710*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.10 (*t*, *J* = 7.9, 1 arom. H); 6.69 (*t*, *J* = 8.9, 2 arom. H); 4.17 (*q*, *J* = 7.1, CH_2O); 3.82 (*s*, MeO); 3.30–3.07 (*m*, 3 H); 2.75–2.66 (*m*, 2 H); 1.45 (br. *s*, NH_2); 1.25 (*s*, Me–C(2)); 1.24 (*t*, *J* = 7.1, CH_3CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.7 (C); 157.5 (C); 134.5 (C); 126.4 (CH); 123.0 (C); 121.5 (CH); 107.2 (CH); 60.4 (CH_2); 55.2 (Me); 52.1 (CH); 45.9 (C); 35.2 (CH_2); 28.9 (CH_2); 23.0 (Me); 14.2 (Me). MS: 263 (57, M^+), 246 (19), 217 (45), 190 (33), 173 (100), 162 (50), 147 (18), 134 (97), 115 (24), 104 (59), 91 (25), 77 (13), 44 (13), 30 (25), 28 (19). Anal. calc. for $C_{15}H_{21}NO_3$ (263.34): C 68.42, H 8.04, N 5.32; found: C 68.27, H 8.19, N 5.07.

rac-cis-*Ethyl 8-Methoxy-2-methyl-3-pivaloylamino-1,2,3,4-tetrahydronaphthaline-2-carboxylate* (**21**). In 50 ml of CH_2Cl_2, 2.0 g (7.6 mmol) of **20** were dissolved, cooled to 0°, and 1.3 ml (9.1 mmol) of Et_3N and 0.94 ml (7.6 mmol) of pivaloyl chloride were added, and the soln. was stirred at r.t. overnight. Addition of 2N HCl, extraction (CH_2Cl_2), drying ($MgSO_4$), and evaporation of the solvent led to the crude product, which was purified by FC (Et_2O/pentane 1:2), to yield 2.4 g (91%) of **21**, which was recrystallized from hexane. M.p. 105.2–105.8°. IR (KBr): 3440*s*, 2980*m*, 2940*m*, 2870*w*, 1705*s*, 1665*s*, 1590*s*, 1510*s*, 1470*s*, 1445*m*, 1360*m*, 1340*m*, 1300*m*, 1260*s*, 1215*s*, 1200*s*, 1140*s*, 1110*m*, 1095*s*, 1070*s*, 1030*m*, 770*m*, 610*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.07 (*t*, *J* = 7.9, 1 arom. H); 6.91 (br. *d*, *J* = 9.3, NH); 6.66–6.62 (*m*, 2 arom. H); 4.39–4.30 (*m*, H–C(3)); 4.09 (*q*, *J* = 7.1, CH_2O); 3.82 (*s*, MeO); 3.56, 2.46 (*AB*, *J* = 17.6, 2 H–C(1)); 3.03, 2.75 (*AB* of *ABX*, J_{AB} = 17.0, J_{AX} = 5.9, J_{BX} = 10.5, 2 H–C(4)); 1.36 (*s*, Me–C(2)); 1.24 (*s*, *t*-Bu); 1.13 (*t*, *J* = 7.1, 3 H, CH_3CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.1 (C); 176.5 (C); 157.0 (C); 135.6 (C); 126.5 (CH); 123.3 (C); 120.8 (CH); 107.3 (CH); 60.8 (CH_2); 55.3 (Me); 50.5 (CH); 45.2 (C); 38.8 (C); 33.7 (CH_2); 33.4 (CH_2); 27.6 (Me); 23.8 (Me); 14.0 (Me). MS: 347 (7, M^+), 302 (6), 246 (39), 173 (100), 158 (18), 102 (15), 57 (22), 41 (11), 28 (44), 18 (52). Anal. calc. for $C_{20}H_{29}NO_4$ (347.45): C 69.14, H 8.41, N 4.03; found: C 69.31, H 8.50, N 3.95.

rac-cis-*8-Methoxy-2-methyl-3-pivaloylamino-1,2,3,4-tetrahydronaphthaline-2-carboxylic Acid* (**22**). To a soln. of 2.0 g (5.8 mmol) of **21** in 50 ml anh. EtOH, 2.0 g (31 mmol) of finely powdered KOH were added, and the soln. was heated at reflux for 1.5 h. Acidification of the mixture (2N HCl) to pH 1–2, addition of 50 ml of H_2O, extraction (CH_2Cl_2), drying ($MgSO_4$), and evaporation of the org. solvent gave the crude product, which was stirred in CH_2Cl_2 overnight for further purification, leading to 1.63 g (88%) of **22** as a slighly yellow solid. M.p. > 210°. IR (KBr): 3420*m*, 2960*s*, 2910*m*, 2840*w*, 1710*s*, 1620*s*, 1590*m*, 1520*s*, 1470*s*, 1440*m*, 1400*w*, 1365*w*, 1295*w*, 1265*s*, 1225*m*, 1210*m*, 1195*s*, 1140*m*, 1100*m*, 1070*w*, 905*w*, 780*s*, 650*w*. ^{1}H-NMR (300 MHz, CD_3OD): 7.44 (br. *d*, *J* = 8.7, NH); 7.06 (*t*, *J* = 7.9, 1 arom. H); 6.71 (*d*, *J* = 8.0, 1 arom. H); 6.63 (*d*, *J* = 8.2, 1 arom. H); 4.23–4.14 (*m*, H–C(3)); 3.81 (*s*, MeO); 3.56, 2.39 (*AB*, *J* = 17.5, 2 H–C(1)); 2.88 (*AB* of *ABX*, J_{AB} = 17.1, J_{AX} = 6.2, J_{BX} = 11.0, 2 H–C(4)); 1.35 (*s*, Me–C(2)); 1.23 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, CD_3OD): 180.7 (C); 179.8 (C); 158.5 (C); 136.6 (C); 127.8 (CH); 124.4 (C); 121.8 (CH); 108.5 (CH); 55.8 (Me); 52.3 (CH); 46.0 (C); 39.9 (C); 34.9 (CH_2); 34.6 (CH_2); 27.8 (Me); 24.7 (Me). MS: 319 (8, M^+), 218 (26), 173 (100), 159 (18), 102 (60), 91 (6), 57 (21), 41 (15), 28 (84), 18 (52). Anal. calc. for $C_{18}H_{25}NO_4$ (319.40): C 67.69, H 7.89, N 4.39; found: C 67.59, H 7.84, N 4.23.

Crystal Structure Analysis. Intensities of suitable crystals for compounds **2**, **2a** (ammonium salt of **2**), **3**, and **21** were measured at r.t. with an *Enraf Nonius CAD4* diffractometer equipped with a graphite monochromator (MoK_α, λ = 0.7107 Å). The structures were solved by direct methods with SHELXS86 [27] and refined by full-matrix least-squares analysis [28]. Non-H-atoms were refined anisotropically. The positions of the H-atoms were calculated and partly refined isotropically in the final least-squares cycles. The weighting scheme used was $\sigma(F^2)^{-2} \cdot \exp(2\sin^2(\theta/\lambda))$. Experimental details and final agreement factors of the refinement are given in the *Table*. Atomic positional and anisotropic displacement parameters for the non-H-atoms are deposited with the *Cambridge Crystallographic Data Centre*, Cambridge, England.

In compound **2**, an intramolecular H-bond is formed between the N-atom of the amide group and the carbonyl O-atom of the acid group (N(H)···O: 2.722(4) Å). The acid proton is involved in an intermolecular H-bond to the carbonyl O-atom of the amide (O(H)···O: 2.540(4) Å).

Table. *Experimental Details of X-Ray Crystal-Structure Analyses and Final Agreement Factors of the Refinement for the Compounds* **2**, **2a**, **3**, *and* **21**

Compound	**2**	**2a**	**3**	**21**
Crystal system	orthorhombic	monoclinic	orthorhombic	triclinic
Space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P1$
a [Å]	8.411	11.018	9.060	9.921
b [Å]	10.523	19.930	9.445	9.920
c [Å]	21.580	13.641	26.096	12.883
α [°]				109.34
β [°]		94.79		93.40
γ [°]				119.48
Z	4	4	4	2
θ_{max} [°]	27.5	25	25	25
$F^2(tot)/F^2 > 3\sigma(F^2)$/parameters	2498/1491/308	5391/3929/773	2253/1828/403	3519/1568/508 > $2\sigma(F^2)$
R_w	0.037	0.044	0.029	0.053

The structure of **2a** (the ammonium salt of **2**) contains two molecule complexes in the asymmetric unit and one solvent molecule of AcOEt. The two symmetry-indepentent molecules differ mainly in the conformation of the MeO substituents. The MeO groups of the molecule shown in *Fig. 2* hardly deviate from the plane of the Ph ring as in the structures of **2**, **3**, and **21**, whereas the CH_3–O bond of one MeO group in the second molecule **2a** is almost perpendicular to the ring plane. The same kind of intramolecular H-bond as in **2** is formed in both molecules **2a** (N(H)···O: 2.647(5)/2.615(5) Å) *ca.* 0.1 Å shorter probably caused by the deprotonation of the acid group. The O-atom is involved in an intermolecular H-bond with the protonated N-atom of the 1-(4-nitrophenyl)ethylamine (O···(H)N: 2.752(4)/2.724(5) Å). The N-atom again has a short contact to the carbonyl O-atom of the amide group from a type-**2a** molecule (N(H)···O: 2.825(5)/2.798(5) Å).

Compound **3** shows only a short intermolecular contact from the OH group to the carbonyl O-atom of the lactone (2.911(3) Å).

REFERENCES

[1] I. M. P. Huber, D. Seebach, *Helv. Chim. Acta* **1987,** *70,* 1944.

[2] M. Freud, O. Kupfer, *Liebigs Ann. Chem.* **1911,** *384,* 1.

[3] A. S. Dreiding, M.-A. Siegfried, H. Hilpert, M. Rey, *Helv. Chim. Acta* **1980,** *63,* 938.

[4] D. Seebach, J.-J. Lohmann, M.-A. Syfrig, M. Yoshifuji, *Tetrahedron* **1983,** *39,* 1963; J.-J. Lohmann, D. Seebach, M.-A. Syfrig, M. Yoshifuji, *Angew. Chem.* **1981,** *93,* 125; *ibid. Int. Ed.* **1981,** *20,* 128; D. Seebach, M. Yoshifuji, *Helv. Chim. Acta* **1981,** *64,* 643; W. Wykypiel, J.-J. Lohmann, D. Seebach, *ibid.* **1981,** *64,* 1337.

[5] H. Brunner, *Top. Stereochem.* **1988,** *18,* 129; H.-U. Blaser, *Chem. Rev.* **1992,** *92,* 935.

[6] I. M. P. Huber, ETH-Disseration, Nr. 8397, Zürich, 1987.

[7] C. W. Perry, A. Brossi, K. H. Deitcher, W. Tautz, S. Teitel, *Synthesis* **1977,** 492.

[8] P. Beak, W. J. Zajdel, D. B. Reitz, *Chem. Rev.* **1984,** *84,* 471; P. Beak, D. B. Reitz, *ibid.* **1978,** *78,* 275; P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986,** *19,* 356; A. I. Meyers, *Aldrichim. Acta* **1985,** *18,* 3.

[9] M. C. Desai, J. L. Doty, L. M. Stephens, K. E. Brighty, *Tetrahedron Lett.* **1993,** *34,* 961.

[10] D. Seebach, I. M. P. Huber, *Chimia* **1985,** *39,* 233; D. Seebach, I. M. P. Huber, M. A. Syfrig, *Helv. Chim. Acta* **1987,** *70,* 1357.

[11] H. Rapoport, R. T. Dean, *J. Org. Chem.* **1978,** *43,* 2115.

[12] H. R. Kricheldorf, *Liebigs Ann. Chem.* **1972,** *763,* 17.

[13] D. Seebach, Th. Gees, F. Schuler, *Liebigs Ann. Chem.* **1993,** 785.

[14] T. Maetzke, C. P. Hidber, D. Seebach, *J. Am. Chem. Soc.* **1990,** *112,* 8248; T. Maetzke, D. Seebach, *Organometallics* **1990,** *9,* 3032.

[15] U. Schöllkopf, *Angew. Chem.* **1970,** *82,* 795; *ibid. Int. Ed.* **1970,** *9,* 763.

[16] J. H. Brewster, M. W. Kline, *J. Am. Chem. Soc.* **1952,** *74,* 5179.

[17] D. Seebach, J. Hansen, P. Seiler, J. M. Gromek, *J. Organomet. Chem.* **1985,** *285,* 1.

[18] R. J. Murray, N. H. Cromwell, *J. Heterocycl. Chem.* **1974,** *11,* 979; E. Didier, B. Loubinoux, G. M. Ramos Tombo, G. Rihs, *Tetrahedron* **1991,** *47,* 4941; J. P. Vacca, J. P. Guare, S. J. deSolms, W. M. Sanders, E. A. Giuliani, S. D. Young, P. L. Darke, J. Zugay, I. S. Sigal, W. A. Schleif, J. C. Quintero, E. A. Emini, P. S. Anderson, J. R. Huff, *J. Med. Chem.* **1991,** *34,* 1228.

[19] D. Seebach, S. Roggo, T. Maetzke, H. Braunschweiger, J. Cercus, M. Krieger, *Helv. Chim. Acta* **1987,** *70,* 1605.

[20] T. Minami, Y. Yamaguchi, Y. Ohshiro, T. Agawa, S. Murai, N. Sonoda, *J. Chem. Soc., Perkin Trans. 1* **1977,** 904.

[21] D. Seebach, H. Estermann, *Tetrahedron Lett.* **1987,** *28,* 3103; H. Estermann, D. Seebach, *Helv. Chim. Acta* **1988,** *71,* 1824.

[22] E. Juaristi, D. Quintana, B. Lamatsch, D. Seebach, *J. Org. Chem.* **1991,** *56,* 2553; E. Juaristi, J. Escalante, B. Lamatsch, D. Seebach, *ibid.* **1992,** *57,* 2396.

[23] E. Pfammatter, D. Seebach, *Liebigs Ann. Chem.* **1991,** 1323.

[24] S. C. Watson, J. F. Eastham, *J. Organomet. Chem.* **1967,** *9,* 165.

[25] D. Seebach, A. K. Beck, J. Golinski, J. N. Hay, Th. Laube, *Helv. Chim. Acta* **1985,** *68,* 162.

[26] A. Giannis, K. Sandhoff, *Angew. Chem.* **1989,** *101,* 220; *ibid. Int. Ed.* **1989,** *28,* 218.

[27] G. M. Sheldrick, C. Krüger, R. Goodard, Crystallographic Computing 3, Oxford University Press, 1985, pp. 175–189.

[28] SHELX76 G. M. Sheldrick, SHELX76. Program for Crystal Structure Determination, University of Cambridge, England; SHELX-92 (beta/gamma release) G. M. Sheldrick, *Current Contents* (Physical, Chemical and Earth Sciences) **1989,** *29,* 14.