A New Modified Amino Acid: 2-Amino-3-mercapto-3-phenylpropionic Acid (3-Mercaptophenylalanine). Synthesis of Derivatives, Separation of Stereoisomers, and Assignment of Absolute Configuration

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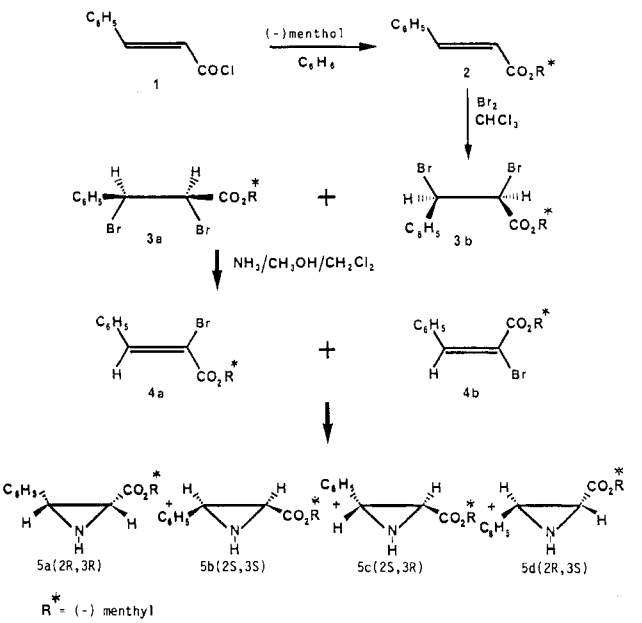
The two stereoisomers of *N*-(*tert*-butyloxycarbonyl)-3-((3-nitro-2-pyridinesulfenyl)thio)-L-phenylalanine were prepared in order to synthesize cyclic analogues of the neuropeptide Substance P. Starting from (*E*)-cinnamoyl chloride (1), the *cis*- and *trans*-aziridines **5a,b** and **5c,d** were obtained by the Gabriel reaction. The formation of the three-membered ring was not stereospecific, contrary to a previous report.[6] Compounds **5a–d** were then opened regio- and stereoselectively by an excess of 4-methoxybenzyl mercaptan in the presence of BF_3·Et_2O to afford **6a–d**. The absolute configuration of these derivatives was assigned by chemical correlation to (–)-menthyl *N*-(trifluoroacetyl)phenylalaninates (**7a,b**). The 4-methoxybenzyl groups of these compounds were substituted by the 3-nitro-2-pyridinesulfenyl group. The hydrolysis of the menthyl ester was successfully achieved by using liquid HF.

Cyclic analogues of linear peptides, designed to restrict the conformational mobility and to favor some conformations, are often used for the investigation of peptide–receptor interactions.[1] A classical cyclization involving the formation of a disulfide bridge, usually achieved by replacement of two amino acids by two cysteinyl (or homocysteinyl) residues, removes the side chains, which may be important for the interactions. It would be interesting to restore these side chains by introduction in the sequence of 3-substituted cysteines.

As part of a general program on Substance P, Arg^1-Pro^2-Lys^3-Pro^4-Gln^5-Gln^6-Phe^7-Phe^8-Gly^9-Leu^{10}-Met^{11}-NH_2, and especially in a search for the bioactive conformation(s) of this neuropeptide, we have synthesized a number of cyclic analogues of this molecule.[2] Primary structure–activity relationship results have revealed that Phe^7 and Phe^8 are very important for the recognition by the receptor.[3] To achieve cyclizations involving these positions while keeping the phenyl group, we have prepared new amino acids, namely (2*R*,3*R*)- and (2*R*,3*S*)-2-amino-3-mercapto-3-phenylpropionic acid. We propose 3-mercaptophenylalanine as semisystematic nomenclature and 3-Mrp as a symbol for these amino acids.[4] They were synthesized under the protected form useful for the solid-phase cyclization that we have previously described,[5] namely, the *N*-*tert*-butyloxycarbonyl-3-((3-nitro-2-pyridinesulfenyl)thio)phenylalanine derivatives.

We chose the route involving the addition of a mercaptan to an aziridine derivative, taking advantage of the fact that the *cis*-2-((–)-menthyloxycarbonyl)-3-phenylaziridines have been described by Lown et al.[6]

Scheme I. Synthesis of the Four Diastereoisomeric Aziridines



We report here the synthesis of 3-mercaptophenylalanine derivatives, the separation of stereoisomers, and the determination of their absolute configuration. These data enable us to revise the absolute configuration of the *cis*-aziridine tentatively proposed by Lown et al.[6]

Results and Discussion

Synthesis of the Aziridines. We have only slightly modified the method of Lown et al.,[6] but we were able to elucidate several major points of the mechanism of formation of the three-membered ring, which remained obscure in the original work.

(*E*)-Cinnamoyl chloride (1) was converted into its (–)-menthyl ester **2** as previously described.[6] Treatment of **2** with bromine gave a mixture of two products **3a** and **3b** in a 1/1 ratio, to which we have assigned the erythro configuration assuming a trans addition of bromine.[7] This was confirmed by the identity of the $^3J_{H_2H_3}$ coupling constants in both compounds. Treatment of the mixture **3a,b** with a saturated solution of ammonia in methanol–di-

(1) Hruby, V. J. *Life Sci.* **1982**, *31*, 189.
(2) (a) Chassaing, G.; Lavielle, S.; Ploux, O.; Julien, S.; Convert, O.; Marquet, A.; Beaujouan, J. C.; Torrens, Y.; Glowinski, J. *Proceedings of 18th European Symposium, 1985*; Brundfelt, K., Ed.; Djurönäset: Sweden, 1985; pp 345–348. (b) Ploux, O.; Lavielle, S.; Chassaing, G.; Julien, S.; Marquet, A.; D'Orléans Juste, P.; Dion, S.; Regoli, D.; Beaujouan, J. C.; Bergström, L.; Torrens, Y.; Glowinski, J. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 8095.
(3) (a) Couture, R.; Fournier, A.; Mangon, J.; Saint-Pierre, S.; Regoli, D. *Can. J. Physiol. Pharmacol.* **1979**, *57*, 1427. (b) Lavielle, S.; Chassaing, G.; Julien, S.; Besseyre, J.; Marquet, A.; Beaujouan, J. C.; Torrens, Y.; Glowinski, J. *J. Neuropept.* **1986**, *7*, 191.
(4) Symbols and abbreviations are in accordance with the recommendations of the IUPAC–IUB Commission on Biochemical Nomenclature (*J. Biol. Chem.* **1971**, *247*, 977). Other abbreviations used are as follows: 3-Mrp, 3-mercaptophenylalanine; Npys, 3-nitro-2-pyridinesulfenyl.
(5) Ploux, O.; Chassaing, G.; Marquet, A. *Int. J. Pept. Protein Res.* **1987**, *29*, 162.
(6) Lown, J. W.; Itoh, T.; Ono, N. *Can. J. Chem.* **1973**, *51*, 856.
(7) Fahey, R. L. *Top. Stereochem.* **1968**, *3*, 237.

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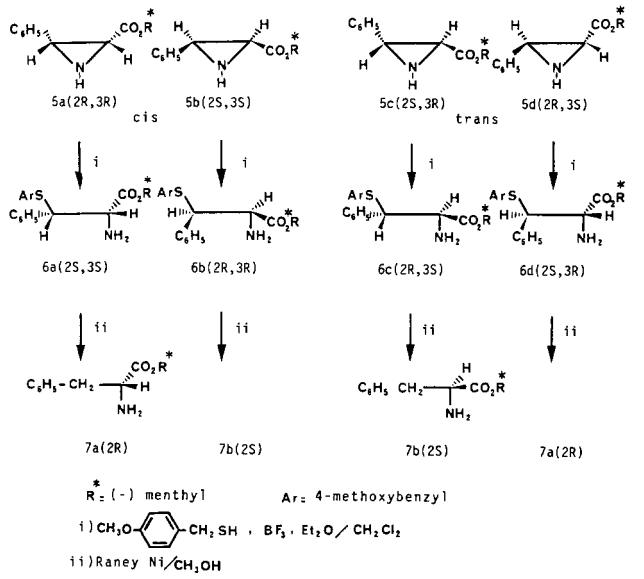
Scheme II. Ring Opening of the Aziridines and Correlation to the Phenylalanine Derivatives



chloromethane yielded the four diastereoisomeric aziridines **5a–d** (Scheme I).

In fact, this reaction proceeded in two steps: a fast elimination of HBr, affording a 1/1 mixture of (*Z*)- and (*E*)-(–)-menthyl 2-bromocinnamates (**4a** and **4b**), followed by a slow addition of ammonia to the double bond. These two compounds have been isolated and separated, and their structure has been assigned by ^1H and ^{13}C NMR. **4a**: $\delta(H_3)$ = 8.2 (calcd according to ref 8a, δ = 8.36), $^3J_{C_1H_3}$ = 5.3 Hz. **4b**: $\delta(H_3)$ = 7.2 (calcd[8a] δ = 7.63 ppm), $^3J_{C_1H_3}$ = 10.7 Hz ($^3J_{CH^{cis}} < {}^3J_{CH^{trans}}$[8b]).

The addition of ammonia to the double bond of **4a** or **4b** yielded a mixture of the four diastereoisomeric aziridines.[9] *cis*- and *trans*-aziridines **5a,b** and **5c,d** were readily separated by chromatography on silica gel. Their stereochemistry was assigned on the basis of the H_2H_3 scalar coupling constant: $^3J_{H_2H_3}$ = 6.5 Hz for **5a,b** and 2.3 Hz for **5c,d** ($^3J_{cis} > {}^3J_{trans}$[10]).

Recrystallization of the *cis*-aziridines as previously described[6] afforded two fractions: pure **5a** and fraction **5b**, which is indeed a 75/25 mixture of **5b** and **5a** (determined by 200-MHz ^1H NMR). Comparison of analytical data showed that the corresponding compound (**5b**) isolated by Lown et al.[6] was also a mixture. A small sample of the *trans*-aziridines was also recrystallized, giving pure **5c**.

In conclusion, the formation of the aziridines is not at all stereospecific during each step, contrary to the previous report.[6] Consequently, the separations of diastereoisomers **3a/3b** and **4a/4b** are not synthetically useful.

Ring Opening of the Aziridines. Treatment of the aziridines with a free mercaptan in liquid ammonia or with a sodium mercaptide in DMF did not lead to any ring opening.[11] A clean addition of 4-methoxybenzyl mercaptan on the aziridines **5a–d** could be achieved with $BF_3{\cdot}Et_2O$ as a catalyst, according to Bernstein et al.[12] (Scheme II). This thiol was selected because of its good reactivity during the exchange with the Npys group.[5]

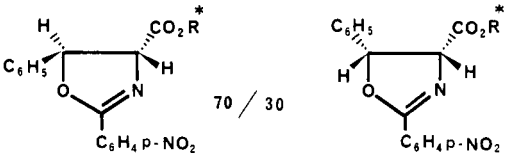


Figure 1. Oxazoline i (cis/trans ratio = 30/70) involved in the correlation described by Lown.[6]

The adducts were purified on silica gel. Diastereoisomers **6c** and **6d**, which coelute, could be separated by crystallization of their chlorhydrate salts. The purity of each compound **6a–d** was checked by HPLC. The regioselectivity of the opening reaction was demonstrated by desulfurization with Raney nickel,[13] which gave compounds identified with authentic samples of (–)-menthyl phenylalaninate.

The fact that no common compound was found (HPLC) in the opening products of **5a** and fraction **5b** on the one hand and **5c,d** on the other hand proves that the opening is stereospecific. Assuming thus inversion of configuration at C_3 as already observed,[14] we can assign the relative configurations 2*S*,3*S* or 2*R*,3*R* to **6a** and **6b** and 2*R*,3*S* or 2*S*,3*R* to **6c** and **6d** (Scheme II). The 25/75 mixture of **6a** and **6b** obtained by the opening of fraction **5b** confirms that this isomer contained 25% of **5a** not separated by crystallization.

Determination of the Absolute Configuration. The absolute configuration was deduced from that of the desulfurization product (Scheme II). Reference compounds **7a** (2*R*) and **7b** (2*S*) were prepared from D- and L-phenylalanine.[15,16] They showed the same retention time by HPLC, but the corresponding *N*-trifluoroacetates were separated. The major compounds obtained after desulfurization and *N*-trifluoroacetylation of **6a** and **6d** showed the same retention time as *N*-trifluoroacetyl **7a**. Desulfurization of **6b** and **6c** led to *N*-trifluoroacetyl **7b**. Some epimerization (~10%) at C_2 took place during the desulfurization since pure **6a**, **6c**, or **6d** led to a mixture of **7a** and **7b**. However, the diastereoisomeric excess of these products was large enough to establish the absolute configuration unambiguously.

The opposite absolute configuration had been tentatively assigned to the *cis*-aziridines by Lown[6] using a chemical correlation. Besides the fact that the starting aziridine sample (mp 124 °C; $[\alpha]^{23}_D$ –51.7°) had a diastereoisomeric excess of only 50%, this route involved an oxazoline i which can epimerize at C_2 during hydrolysis, thus preventing any correlation.

Synthesis of the Protected 3-Mercapto-L-phenylalanines. The exchange of the S-protecting group, that is the transformation of the adduct **6c** into **12c**, was achieved in three steps (Scheme III). First the 4-methoxybenzyl group was substituted by the 3-nitro-2-pyridinesulfenyl group as described by Matsueda et al.[17] The hydrolysis of the menthyl ester did not occur in 6 N HCl but was readily achieved in anhydrous liquid HF as described by Tam et al.[18] for the deprotection of Asp(*O*-

(8) (a) Abraham, R. J.; Loftus, P. *Proton and Carbon-13 NMR Spectroscopy*; Wiley: New York, 1983; p 18. (b) *Ibid.*, pp 57.

(9) In a similar reaction of ammonia with diethyl bromofumarate or diethyl bromomaleate, a mixture of *trans*-aziridine and trans enamine was obtained: Berlin, K. D.; Williams, L. G.; Dermer, O. C. *Tetrahedron Lett.* **1968**, 873.

(10) Dermer, O. C.; Ham, G. E. *Ethylenimine and Other Aziridines*; Academic: New York, 1969; pp 99–101.

(11) *N*-Tosylaziridines reacted readily with mercaptan in liquid ammonia. Unfortunately, this route was not suitable because the N-deprotection using Na/NH_3 yielded several products presumably arising from the reduction of benzylic C–S bonds. Ring opening did not occur if the tosyl group was placed by a Boc or a diphenylphosphinoyl ($(C_6H_5)_2P$) group.

(12) Bernstein, Z.; Ben-Ishai, D. *Tetrahedron* **1977**, *33*, 881.

(13) Petit, G. R.; Von Tamelen, E. E. *Org. React.* **1962**, *12*, 356.

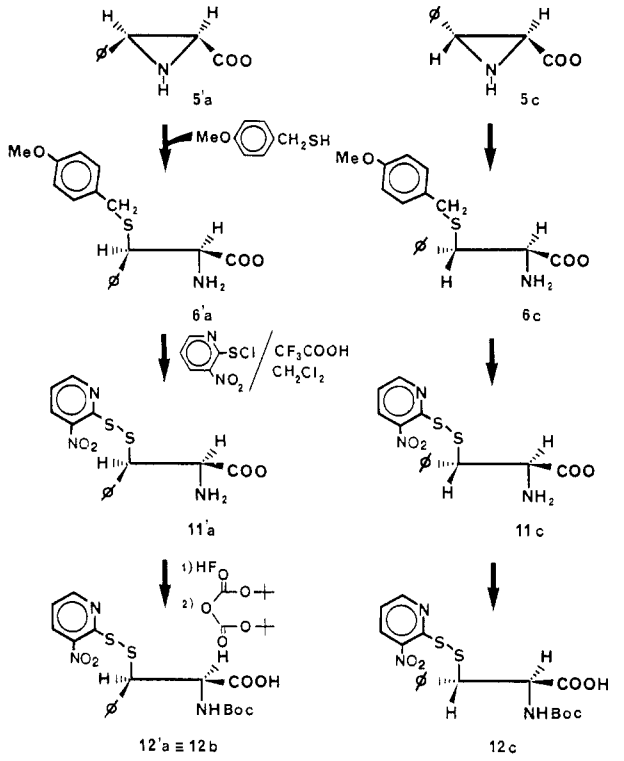
(14) Taguchi, T.; Kojima, M.; Muro, T. *J. Am. Chem. Soc.* **1959**, *81*, 4222.

(15) Hareda, K.; Hayakawa, T. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 191.

(16) Haregawa, M.; Matsubara, I. *Anal. Biochem.* **1975**, *63*, 108.

(17) Matsueda, R.; Higashida, S.; Ridge, R. J.; Matsueda, G. R. *Chem. Lett.* **1982**, 921.

Scheme III. Synthesis of the L-Boc-3-Mrp(Npys) Derivatives from the Aziridines



cyclohexyl). The amino acid thus obtained was not isolated but transformed into its Boc derivative by a classical procedure. No epimerization had been detected during this sequence of reactions (checked by TLC and HPLC).

The other L isomer **12b** could not be obtained enantiomerically pure from aziridine **5b** since this compound was impure. Thus we prepared pure **12b** starting from (*E*)-(+)-menthyl cinnamate. **5a'** (the enantiomer of **5a**), **6a'**, **11a'**, and **12a'** (equivalent to **12b**) were successively obtained by the route described for the preparation of **12c** (Scheme III).

Experimental Section

General Methods. Melting points were determined with a Kofler hot stage apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter using a 10-cm path length cell. TLC was performed on precoated silica gel plates (Merck 60F, 0.25 mm thick). The abbreviations used to designate the solvent systems are the following: A, acetic acid; B, 1-butanol; C, chloroform; DCM, dichloromethane; EA, ethyl acetate; H, hexane; M, methanol; Py, pyridine; W, water. The spots were detected by UV, ninhydrin reagent, or molybdophosphoric acid. Silica gel (70–230 mesh) supplied by Merck was used for column chromatography. HPLC was performed with a Waters Associates Model 204 liquid chromatography system, and separations were accomplished either on a C18 μ-Bondapak (Waters) column or on a μ-Porasil (Merck) column. Detection was accomplished with a Shoeffel UV apparatus at 270 nm unless otherwise stated. The elution systems were in the isocratic mode: a mixture of a 0.25 M triethylamine–phosphate buffer, pH 3.0, and acetonitrile at the indicated percentage for reverse-phase separation, and a mixture of hexane and ethyl acetate at the indicated percentage for normal-phase separation. ^{1}H and ^{13}C NMR spectra were recorded at 90 MHz on a JEOL FX90Q spectrometer or at 200 MHz on a Bruker AM200 spectrometer. NMR spectra were run in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Perkin-Elmer 237 apparatus. Elemental analyses were performed by the Service Central de Microanalyse at the Université Pierre et Marie Curie. HF was handled in a Daiflon reaction apparatus (Protein Research Foundation, Minoh, Osaka).

(*E*)-(−)-Menthyl Cinnamate (2). **2** was prepared in 87% yield as previously described[6] starting from (*E*)-cinnamoyl chloride (**1**); $[\alpha]^{23}_D$ −63.7° (*c* 1, EtOH) (lit.[6] $[\alpha]^{23}_D$ −76.4° (*c* 1.06, EtOH)).

***erythro*-(−)-Menthyl 2,3-Dibromo-3-phenylpropionates (3a,b).** To a solution of **2** (15.2 g, 0.054 mol) in $CHCl_3$ (100 mL) was added dropwise a solution of Br_2 (3 mL, 0.054 mol) dissolved in $CHCl_3$ (10 mL). The resulting mixture was stirred at room temperature and rapidly (3 h) discolorated. After evaporation of the solvent in vacuo, the oily residue crystallized upon cooling to yield 20 g (85%) of **3a,b**: mp 76–78 °C (lit.[6] mp 74–76 °C); ^{1}H NMR (200 MHz) δ 0.7–2.3 (18 H, m, menthyl protons), 4.85 (1 H, m, 6 lines >CH–O menthyl), 4.80 (**3a** or **3b**, 0.5 H, d, J = 11.7 Hz), 5.35 (**3a** or **3b**, 0.5 H, d, J = 11.7 Hz), 4.81 (**3a** or **3b**, 0.5 H, d, J = 11.7 Hz), 5.34 (**3a** or **3b**, 0.5 H, d, J = 11.7 Hz), 7.4 (5 H, s, C_6H_5).

(*Z*)- and (*E*)-(−)-Menthyl 2-Bromocinnamates (4a,b). The reaction was performed in a pressurized bottle. **3a,b** (14.0 g, 0.089 mol) was dissolved in a mixture of CH_2Cl_2 and CH_3OH (100 mL/300 mL). The solution was cooled to −78 °C and then liquid ammonia (200 mL), previously condensed, was carefully added. The bottle was closed and shaken at room temperature for 1 h. After removal of the solvents under reduced pressure, the residue was dissolved in CH_2Cl_2, and the solution was filtered off to eliminate NH_4Br. The filtrate was evaporated and the residue crystallized upon cooling to yield 30.9 g (95%) of a white product. NMR analysis showed the presence of two compounds: (*Z*)- and (*E*)-(−)-menthyl 2-bromocinnamates (**4a** and **4b**) in a 1/1 ratio.[19] Recrystallization of the mixture (CH_3OH) afforded two fractions: 50% of **4a** and **25%** of **4b**. The latter contained 5% of **4a**.

4a (*Z*): mp 98 °C; $[\alpha]^{22}_D$ −57.5° (*c* 1, $CHCl_3$); TLC (H, EA: 95, 5) R_f 0.5; ^{1}H NMR δ 0.7–2.2 (18 H, m, menthyl protons), 4.85 (1 H, m, 6 lines, >CH–O menthyl), 7.4–8.0 (5 H, m, aromatic protons), 8.2 (1 H, s, =CH–); ^{13}C NMR (uncoupled) δ 16.33, 20.47, 21.74, 23.46, 26.30, 31.18, 34.00, 40.49, 46.91 (menthyl carbons), 76.77 (>C–O menthyl), 113.50 (C–Br), 128.07, 129.74, 129.97 (aromatic carbons), 133.61 (aromatic quaternary carbon), 140.08 (=C–H), 162.41 (carbonyl); IR (Nujol) ν_{max} 1715 cm^{-1}.

4b (*E*): mp 70 °C; $[\alpha]^{22}_D$ −46.0° (*c* 1, $CHCl_3$); TLC (H, EA: 95, 5) R_f 0.5; ^{1}H NMR δ 0.7–2.2 (18 H, m, menthyl protons), 4.75 (1 H, m, 6 lines, >CH–O menthyl), 7.3 (1 H, s, =CH–), 7.4–8.0 (5 H, m, aromatic protons); ^{13}C NMR (uncoupled) δ 15.72, 20.35, 21.60, 22.91, 25.47, 30.97, 33.75, 39.69, 46.48 (menthyl carbons), 76.10 (>C–O menthyl), 111.75 (=C–Br), 127.72, 127.92, 129.63 (aromatic C), 133.30 (quaternary aromatic carbon), 137.41 (=C–H–), 165.00 (carbonyl); IR (Nujol) ν_{max} 1715 cm^{-1}. Anal. Calcd for $C_{19}H_{25}O_2Br$: C, 62.05; H, 6.88; Br, 21.82. Found: C, 62.24; H, 6.76.

***cis*- and *trans*-2-((−)-Menthyloxycarbonyl)-3-phenylaziridines (5a,b and 5c,d).** This reaction was performed starting with the mixture **3a,b** as described for the isolation of **4a,b** except for the reaction time, which was 3–5 days. After elimination of NH_4Br the residue was purified by column chromatography on silica gel (H, EA, C: 6, 2, 2) to yield 45% of **4a,b**, which could be recycled, 10% of **5a,b**, and 14% of **5c,d**. Corrected yields: **5a,b**, 20%; **5c,d**, 25%. After recrystallization (CH_3OH) of **5a,b** (8 g), **5a** (2.5 g) and **5b** (3 g) were obtained. The *cis*-aziridine/*trans*-aziridine proportion, determined by ^{1}H NMR, varies slightly along the course of the reaction. This is probably due to some aminolysis of the *trans*-aziridines. (The resulting amides have been observed, whereas the *cis*-aziridines are not transformed.)

5a (2*R*,3*R*): mp 158–160 °C; $[\alpha]^{23}_D$ −17.7° (*c* 1, C_6H_6) (lit.[6] mp 156–158 °C; $[\alpha]^{23}_D$ −18.78° (*c* 0.74, C_6H_6)); ^{1}H NMR δ 0.3 (3 H, d, methyl or menthyl), 0.3–1.8 (16 H, m, menthyl protons and NH), 2.98 (1 H, d, J = 6.5 Hz), 3.49 (1 H, d, J = 6.5 Hz), 4.50 (1 H, m, 6 lines, >CH–O–), 7.3 (5 H, s, C_6H_5).

Fraction **5b (2*S*,3*S*)**: mp 130–131 °C; $[\alpha]^{23}_D$ −56.6 (*c* 1, C_6H_6) (lit.[6] mp 124 °C; $[\alpha]^{23}_D$ −51.75° (*c* 0.80, C_6H_6)). Fraction **5b**

(18) Tam, J. P.; Wong, T. W.; Riemen, M. W.; Tjoeng, F. S.; Merrifield, R. B. *Tetrahedron Lett.* **1979**, *42*, 4033.

(19) Although **4a** has been described by Lown et al.[6] but without any structural study (lit.[6] mp 93–95 °C), the presence of **4b** was not detected. Surprisingly, by reproducing the described[6] synthesis of **4a** (HBr elimination, starting from **3a,b** by 1 equiv of NEt_3 in C_6H_6), we have observed the formation of **4a** and **4b** in a 60/40 ratio.

contains 75% of **5b** and 25% of **5a**, measured by integration of methyl and >CH–O of menthyl. ^{1}H NMR (**5b**) δ 0.63 (3 H, d, methyl of menthyl), 0.7–1.8 (16 H, m, menthyl protons and NH), 2.99 (1 H, d, J = 6.5 Hz), 3.47 (1 H, d, J = 6.5 Hz), 4.53 (1 H, m, 6 lines, >CH–O–), 7.3 (5 H, s, C_6H_5).

5c (2*S*,3*R*): mp 74–75 °C; $[\alpha]^{23}_D$ 97.4° (*c* 1, $CHCl_3$); ^{1}H NMR δ 0.78 (3 H, d, methyl of menthyl), 0.8–2.1 (16 H, m, menthyl protons and NH), 2.58 (1 H, dd, J = 2.3, 8.1 Hz), 3.23 (1 H, dd, J = 2.3, 9.5 Hz), 4.77 (1 H, m, 6 lines, >CH–O–), 7.3 (5 H, s, C_6H_5).

Fraction **5d (2*R*,3*S*)** contains 77% of **5d** and 23% of **5c**, measured by integration of >CH–O– of menthyl. ^{1}H NMR (**5d**) δ 0.78 (3 H, d, methyl of menthyl), 0.8–2.1 (16 H, m, menthyl protons and NH), 2.57 (1 H, d, J = 2.3 Hz), 3.23 (1 H, d, J = 2.3 Hz), 4.79 (1 H, m, 6 lines, >CH–O–), 7.3 (5 H, s, C_6H_5). Elemental analysis was performed on a 1/1 mixture of **5c** and **5d**. Anal. Calcd for $C_{19}H_{27}O_2N$: C, 75.71; H, 9.03; N, 4.05. Found: C, 74.57; H, 8.89; N, 4.56.

After recrystallization from the (+)-menthyl series, **5a′** was obtained. **5a′ (2*S*,3*S*)**: mp 158–160 °C; $[\alpha]^{23}_D$ +17.7° (*c* 1, C_6H_6).

(–)-Menthyl 2-Amino-3-((4-methoxybenzyl)thio)-3-phenylpropionates (6a–d). General Procedure. To a solution of aziridine (2 g, 0.066 mol) and 4-methoxybenzyl mercaptan (2.8 mL, 0.18 mol) in CH_2Cl_2 (10 mL) was added dropwise $BF_3{\cdot}Et_2O$ (0.81 mL, 0.066 mol) at 0 °C under an inert atmosphere. The solution was stirred for 15 h at room temperature. The solution was then poured on ice and treated with 5% $NaHCO_3$ until the aqueous phase was basic (pH 8). The organic phase was collected, washed with 5% $NaHCO_3$ and H_2O, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (H, EA: 7, 3) to yield ca. 2 g of **6a**, fraction **6b**, or fraction **6c,d**. The yields varied from 60% to 70%.

6a (2*S*,3*S*): mp 85 °C; $[\alpha]^{23}_D$ 124.5° (*c* 1, $CHCl_3$); TLC (H, EA: 7, 3) R_f 0.39; ^{1}H NMR δ 0.4–2.0 (20 H, m, NH_2 and menthyl protons), 3.39 (1 H, d, J = 13 Hz, CH_A–S), 3.49 (1 H, d, J = 13 Hz, CH_B–S), 3.69 (1 H, d, J = 8 Hz, H_3), 4.04 (1 H, J = 8 Hz, H_2), 3.77 (3 H, s, CH_3), 4.55 (1 H, m, 6 lines, menthyl H), 6.7–7.5 (9 H, m, aromatic protons); HPLC (μ-Bondapack C18, iso 56% CH_3CN), R_t 16.4 min; HPLC (μ-Porasil, iso 20% AcOEt), R_t 15.6 min. Anal. Calcd for $C_{27}H_{37}NO_3S$: C, 71.18; H, 8.19; N, 3.07. Found: C, 71.09; H, 8.17; N, 3.07.

6b (2*R*,3*R*) was obtained as an oil: TLC (H, EA: 7, 3) R_f 0.39; ^{1}H NMR δ 0.5–2.0 (20 H, m, NH_2 and menthyl protons), 3.34 (1 H, d, J = 13 Hz, CH_A–S), 3.53 (1 H, d, J = 13 Hz, CH_B–S), 3.77 (1 H, d, J = 7.0 Hz, H_3), 4.00 (1 H, d, J = 7.0 Hz, H_2), 3.79 (3 H, s, CH_3), 4.55 (1 H, m, 6 lines, CH–O menthyl), 6.7–7.5 (9 H, m, aromatic protons); HPLC (μ-Bondapack C18, iso 56% CH_3CN) R_t 14.85 min; HPLC (μ-Porasil, iso 20% AcOEt), R_t 14.85 min. NMR and HPLC data showed that **6b** contained 23% of **6a**. The chlorhydrate salt of **6b** was recrystallized in CH_3OH: mp 250 °C dec; $[\alpha]^{23}_D$ –61.0° (*c* 1, CH_3OH). Anal. Calcd for $C_{27}H_{38}NO_3SCl$: C, 65.88; H, 7.79; N, 2.84; S, 6.51; Cl, 7.20. Found: C, 65.29; H, 7.62: N, 2.89.

Fraction **6c,d** was dissolved in $CHCl_3$ and treated with HCl. Evaporation of the solvent afforded a residue that was further recrystallized to give two fractions, **6c·HCl** and **6d·HCl**.

6c·HCl (2*R*,3*S*): mp 172–174 °C; $[\alpha]^{25}_D$ 106.6° (*c* 1, CH_3OH). The regenerated amine **6c** showed the following: TLC (H, EA: 7, 3) R_f 0.40; HPLC (μ-Bondapack C18, iso 56% CH_3CN) R_t 15.0 min; HPLC (μ-Porasil, iso 20% AcOEt) R_t 21.1 min; ^{1}H NMR δ 0.6–2.0 (20 H, m, NH_2 and menthyl protons), 3.60 (1 H, d, J = 13.4 Hz, CH_A–S), 3.74 (1 H, d, J = 13.4 Hz, CH_B–S), 3.82 (3 H, s, CH_3), 4.3 (2 H, m, H_2H_3), 4.7 (1 H, m, CH–O menthyl), 6.7–7.5 (9 H, m, aromatic protons).

6d·HCl (2*S*,3*R*): mp 166 °C; $[\alpha]^{23}_D$ –148.2° (*c* 1, CH_3OH). The regenerated amine **6d** showed the following: TLC (H, EA: 7, 3) R_f 0.40; HPLC (μ-Bondapack C18, iso 56% CH_3CN) R_t 15.9 min; HPLC (μ-Porasil, iso 20% AcOEt) R_t 21.1 min. The ^{1}H NMR spectrum for **6d** was the same as that for **6c**. Elemental analysis was performed on a 1/1 mixture of **6c,d·HCl**. Anal. Calcd for $C_{27}H_{38}NO_3SCl$: C, 65.88; H, 7.79; N, 2.84; S, 6.51; Cl, 7.20. Found: C, 65.63; H, 7.78; N, 2.89.

From the (+)-menthyl series **6a′ (2*S*,3*R*)** was obtained: mp 85–86 °C; $[\alpha]^{23}_D$ –128° (*c* 1, $CHCl_3$).

(–)-Menthyl 2-Amino-3-((*S*-3-nitro-2-pyridinesulfenyl)-thio)phenylpropionates (11a′, 11c). General Procedure. 6a′ and **6c** (1.0 g, 2.2 mmol) were dissolved in a solution of CF_3COOH and CH_2Cl_2 (5 mL/5 mL) at 0 °C. Under vigorous stirring, 3-nitro-2-pyridinesulfenyl chloride[20] (0.5 g, 2.6 mmol) was added portionwise. After all the material was dissolved, the solution was stirred 15 min at 0 °C. The solution was then evaporated under reduced pressure, and the residual oil was dissolved in CH_2Cl_2. The resulting solution was successively washed with 5% $NaHCO_3$ and H_2O, dried over $MgSO_4$, and evaporated. The residue was then purified by column chromatography on silica gel (C, M: 98, 2) to yield 1.02 g (95%) of a yellow oil.

11a′ (2*R*,3*R*): TLC (C, M: 98, 2) R_f 0.52; $[\alpha]^{25}_D$ –37.2° (*c* 2.5, $CHCl_3$); ^{1}H NMR δ 0.3–1.9 (18 H, m, menthyl protons), 2.1 (2 H, s, NH_2), 3.88 (1 H, d, J = 9.3 Hz, H_2), 3.38 (1 H, d, J = 9.3 Hz, H_3), 4.45 (1 H, m 6 lines, CH–O menthyl), 7.1–7.3 (6 H, m, C_6H_5 and Npys), 8.4–8.8 (2 H, two dd, Npys protons); HPLC (μ-Bondapack C18, iso 53% CH_3CN) R_t 15.3 min.

11c (2*R*,3*S*): TLC (C, M,: 98, 2) R_f 0.57; $[\alpha]^{23}_D$ 268.4° (*c* 0.80, $CHCl_3$); ^{1}H NMR δ 0.5–2.1 (20 H, m, NH_2 and menthyl protons), 4.14 (1 H, d, J = 5.1 Hz, H_3), 4.60 (1 H, d, J = 5.1 Hz, H_2), 4.60 (1 H, m, >CH–O menthyl), 7.2–7.5 (6 H, m, C_6H_5 and Npys), 8.45–8.7 (2 H, two dd, Npys protons); HPLC (μ-Bondapack C18, iso 53% CH_3CN) R_t 20.3 min.

2-((*tert*-Butyloxycarbonyl)amino)-3-((*S*-3-nitro-2-pyridinesulfenyl)thio)-3-phenylpropionic Acids (12a′, 12c). General Procedure. In a Daiflon reactor **11a′** or **11c** (452 mg, 0.92 mmol) was dissolved in HF (10 mL). The mixture was stirred for 1 h at 0 °C. After removal of HF in vacuo, the residue [TLC (B, A, W: 4, 1, 5) R_f 0.40] was suspended in DMF (20 mL) at 0 °C. NEt_3 was then added dropwise until pH 8 (measured on wet litmus paper). Then di-*tert*-butyl dicarbonate (285 mg, 1.31 mmol) was added to the solution, which was stirred at room temperature for 3 h. After removal of DMF in vacuo, the residue was purified by column chromatography on silica gel (C, M, A: 95, 5, 3) to yield 321 mg (77%) of **12a′** or **12c**.

12a′ (2*R*,3*R*): mp 165 °C; $[\alpha]^{22}$ –327.9° (*c* 1, $CHCl_3$); TLC (C, M, A: 95, 5, 3) R_f 0.63; HPLC (reverse phase, iso 41% CH_3CN) R_t 33.0 min; ^{1}H NMR δ 1.4 (9 H, s, Boc), 4.6 (2 H, m, H_3, H_2), 6.20 (1 H, m, NH), 7.3 (5 H, s, C_6H_5), 7.5–8.6, 8.9 (3 H, three dd, Npys protons). Anal. Calcd for $C_{19}H_{21}N_3O_6S_2$: C, 50.55; H, 4.69; N, 9.31; S, 7.22. Found: C, 50.40; H, 4.82; N, 9.12.

12c (2*R*,3*S*) was obtained as an oil. TLC (C, M, A: 95, 5, 3) R_f 0.59; $[\alpha]^{23}$ 152.6° (*c* 1, $CHCl_3$); HPLC (μ-Bondapack C18, iso 41% CH_3CN) R_t 27.3 min; ^{1}H NMR δ 1.45 (9 H, s, Boc), 4.58 (1 H, d, J = 5.7 Hz, H_3) 4.95 (1 H, m, H_2), 5.85 (1 H, d, J = 8.0 Hz, NH), 7.25–7.50 (6 H, m, C_6H_5 and Npys), 8.0 (1 H, s, COOH), 8.50–8.85 (2 H, two dd, Npys protons).

(–)-Menthyl phenylalaninate chlorhydrates (10a, 10b) were synthesized as previously described[15] starting from L- or D-phenylalanine (**9a, 9b**) in 50% yield. **10a (2*S*)**: mp 165 °C; $[\alpha]^{23}$ –20.3° (*c* 1, EtOH), (lit.[15] mp 165 °C; $[\alpha]^{26}$ –20.8° (*c* 0.77, EtOH). **10b (2*R*)**: mp 180 °C; $[\alpha]^{22}$ –71.0° (*c* 1, EtOH) (lit.[15] mp 185–186 °C; $[\alpha]^{26}$ –75.1° (*c* 1.07, EtOH).

(–)-Menthyl *N*-(trifluoroacetyl)phenylalaninates (8a, 8b)[17] were prepared by action of excess trifluoroacetic anhydride (TFAA) in CH_2Cl_2 on **10a** or **10b** in 70% yield. **8a (2*S*)**: mp 112–113 °C; $[\alpha]^{22}$ –56.9° (*c* 0.5, EtOH). **8b (2*R*)**: mp 72 °C; $[\alpha]^{22}$ –71.0° (*c* 1, EtOH). HPLC (reverse phase, iso 56% CH_3CN, detection at 260 nm): **8a**, R_t 35.4 min; **8b**, R_t 33.8 min.

Desulfurization and Trifluoroacetylation of Compounds 6a, 6c, and 6d and Fraction 6b. Compounds **6** (20 mg, 0.04 mmol) were dissolved in CH_3OH (2 mL). To this solution were added NEt_3 (11.4 μL, 0.04 mmol) and Raney Ni (100 mg) previously washed with MeOH. The mixture was then vigorously stirred and refluxed for 30 min. After filtration, the solution was evaporated in vacuo and treated with an excess of TFAA (50 μL, 0.4 mmol) in CH_2Cl_2 (1.5 mL). The solution was stirred for 1 h at room temperature and then evaporated. The residue was analyzed by TLC ((H, EA: 8, 2) R_f 0.53) and HPLC (reverse phase, iso 56% CH_3CN, detection at 260 nm). Degradation of **6a** and **6d** afforded the D-Phe derivative, and **6c** gave the L-Phe derivative. In the three cases, about 10% of the C_2 epimerized product was present. Fraction **6b** led to the L-Phe derivative as major product.

(20) NpysCl was synthesized as previously described: Mastueda, R.; Aiba, K. *Chem. Lett.* **1978**, 951.

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Registry No. 2, 5033-95-4; **3a**, 114529-80-5; **3b**, 114529-81-6; **4a**, 50707-54-5; **4b**, 114466-82-9; **5a**, 50896-31-6; **5'a**, 114529-88-3; **5b**, 50707-55-6; **5c**, 114529-82-7; **5d**, 114529-83-8; **6a**, 114466-83-0; **6'a**, 114529-89-4; **6b**, 114529-84-9; **6b**·HCl, 114578-92-6; **6c**, 114529-85-0; **6c**·HCl, 114578-90-4; **6d**, 114529-86-1; **6d**·HCl, 114578-91-5; **7a**, 114529-87-2; **7b**, 47226-25-5; **8a**, 21772-58-7; **8b**, 56994-38-8; **11'a**, 114466-84-1; **11c**, 114529-90-7; **12'a**, 114466-85-2; **12c**, 114466-86-3; NpysCl, 68206-45-1; *p*-$MeOC_6H_4CH_2SH$, 6258-60-2.

Reaction of Raney Nickel with Alcohols

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The reaction of Raney nickel with a variety of functional groups was studied. Ethers, esters, and alkyl chlorides were found to be stable to Raney nickel in refluxing toluene; however, alcohols were found to be reactive. Primary alcohols were oxidized to aldehydes and then subsequently decarbonylated, secondary alcohols were oxidized to the corresponding ketone, and tertiary alcohols were deoxygenated.

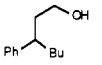
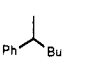
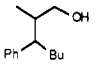
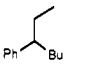
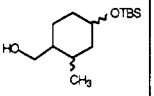
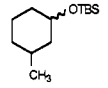
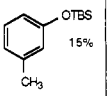
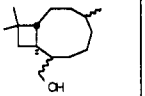
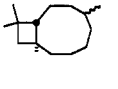
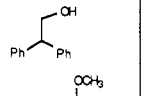
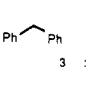
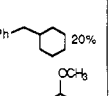
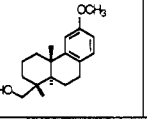
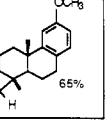
Over the years, Raney nickel has been used for many purposes, including reductive desulfurization reactions,[1] reductive alkylations of amines,[2a] and as a hydrogenation catalyst in the reduction of olefins, aromatic rings, nitro groups,[3] isoxazolidines,[4] and imines.[5] Recently we reported the use of Raney nickel in the oxidation of secondary alcohols to ketones[6] and in the deoxygenation of tertiary alcohols.[7] We have concluded our investigations of the reactivity of Raney nickel toward a variety of functional groups and now summarize the results obtained for the reaction of Raney nickel with primary, secondary, and tertiary alcohols.

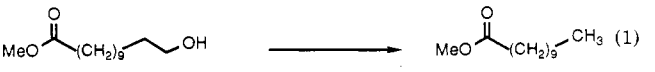
Primary Alcohols

In the presence of Raney nickel in refluxing toluene primary alcohols were oxidized to aldehydes, which subsequently underwent decarbonylation. Aldehydes have been decarbonylated with a variety of transition metals, including rhodium,[8-10] ruthenium,[10] and palladium.[10,11]

Primary alcohols, when refluxed with Raney nickel in toluene, gave rise to new, deoxygenated compounds that contained one less carbon. For example, heating a toluene solution of methyl 12-hydroxydodecanoate with Raney nickel for 3.5 h gave rise to a 73% isolated yield of methyl undecanoate (eq 1). This dehydroxymethylation procedure was found to be suitable for use with a number of substrates, and the results are summarized in Table I.

Table I

Entry	Alcohol	Product(s)	
1	$CH_3O_2C(CH_2)_{10}CH_2OH$	$CH_3O_2C(CH_2)_9CH_3$	73%
2	TBSO-$(CH_2)_{11}CH_2OH$	TBSO-$(CH_2)_{10}CH_3$: TBSO-$(CH_2)_{11}CH_3$ (100 : 1)	69%
3		 (10 : 1)	72%
4		 (23 : 1)	73%
5			62%  15%
6			72%
7		 (3 : 1)	70%  20%
8			 65%



A plausible mechanism for the transformation involves a reversible dehydrogenation (i.e., oxidation) of the alcohol to the aldehyde, followed by an irreversible decarbonylation. The aldehyde intermediates were observed by

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