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# Notes

## New Neoclerodane Diterpenoid Containing an Oxetane Ring Isolated from *Teucrium chamaedrys*. X-ray Structure Determination

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Continuing our studies on diterpenic compounds from the *Teucrium* species (family Labiatae),[2–5] we now report the isolation and structure determination of a new compound from *T. chamaedrys* L., a species in which several new neoclerodane diterpenoids have been previously found.[6–12] The structre of this new diterpenoid, chamaedroxide, has been shown to be 4β, 6β:15,16-diepoxy-2β-hydroxyneocleroda-13(16),14-diene-18,19:20,12(*S*)-diolide (1),[13] and it was established as follows.

Combustion analysis and mass spectrometry indicated the molecular formula $C_{20}H_{22}O_7$ for chamaedroxide (1). Its IR spectrum was consistent with the presence of a furan ring (3150, 3135, 1502, 883 $\text{cm}^{-1}$), two γ-lactone groups (1765, 1760 $\text{cm}^{-1}$), and an OH group (3500 $\text{cm}^{-1}$). The presence of a hydroxyl group was confirmed by the formation, on treatment with $Ac_2O$–pyridine, of a monoacetate, $C_{22}H_{24}O_8$ (2), the IR spectrum of which showed no OH absorption.

However, it was the $^1H$ NMR spectrum of chamaedroxide that provided the most information and established a clerodane structure such as 1 for this new diterpenoid. Effectively, this spectrum showed signals of a secondary methyl group at $\delta$ 0.88 (d, $J = 7$ Hz, 3 H-17), and of a β-substituted furan ring (an ABX system, two α-furan protons having their resonance at $\delta$ 7.73 and 7.65 and one β-furan proton at $\delta$ 6.54, H-16, H-15, and H-14, respectively).[14] An ABX system at $\delta$ 5.62 (1 H, dd, $J_{XB} = 8$ Hz, $J_{XA} = 5$ Hz), 2.95 (1 H, dd, $J_{AB} = 13.5$ Hz, $J_{BX} = 8$ Hz) and 2.41 (1 H, dd, $J_{AX} = 5$ Hz) was assigned to the C-12 methyne and the C-11 methylene groups,[3,14] and an AB system at $\delta$ 4.56 and 4.43 ($J_{AB} = 11$ Hz) was attributed to the C-19 methylene grouping.[3,15] A one-proton signal at $\delta$ 4.18 was assigned to the geminal proton of the secondary hydroxyl group of chamaedroxide, because it was downfield shifted ($\delta$ 4.72) in the $^1H$ NMR spectrum of the acetyl derivative 2. This signal showed that this alcohol function must be placed between two methylene groups, because it appeared as a broad multiplet in compounds 1 ($W_{1/2} = 25$ Hz) and 2 (16-line signal, $W_{1/2} = 28$ Hz). Thus, in a clerodane skeleton, only the C-2 position is likely for this hydroxyl group. On the other hand, the C-6β position of chamaedroxide (1) must be substituted, because neither of the two protons at C-19 in compounds 1 and 2 showed any long-range coupling in their $^1H$ NMR spectra. The requirement for the existence of such a long-range coupling, which has been observed ($J = 2$ Hz) in some clerodan-18,19-olides lacking a substituent at C-6,[15] is the existence of an axial (β) proton at C-6.[3,4] Consequently, a one-proton double doublet signal at $\delta$ 5.17 ($J_1 = 7.5$, $J_2 = 6$ Hz) in the $^1H$ NMR spectrum of chamaedroxide (1) must be assigned to the C-6α proton. Moreover, a one-proton double doublet at $\delta$ 2.10 was attributed to the C-7β proton, which is coupled with its geminal proton ($J_{7\beta,7\alpha} = 12$ Hz) and with the C-6α proton ($J_{7\beta,6\alpha} = 6$ Hz) but not with the C-8β proton,[2,16] since a value close to zero for $J_{7\beta,8\beta}$ is consistent with a H-7,H-8 dihedral angle of ca. 90°, as can be seen in the Dreiding model of chamaedroxide (1). Finally, a one-proton doublet of double doublets at $\delta$ 1.84 was assigned to the C-7α proton, which is coupled with its geminal proton (see above) and with both C-6α and C-8β protons ($J_{7\alpha,6\alpha} = 7.5$ Hz, $J_{7\alpha,8\beta} = 8$ Hz).

In order to confirm the above assignments, a series of proton-decoupling experiments was carried out. As a result of irradiation at $\delta$ 5.62 (H-12), the double doublet signals at $\delta$ 2.95 and 2.41 (H-11 and H′-11) collapsed into an AB system. Irradiation at $\delta$ 5.17 (H-6α) caused modifications of the signals at $\delta$ 2.10 (H-7β, now appearing as a doublet, $J_{7\beta,7\alpha} = 12$ Hz) and at $\delta$ 1.84 (H-7α, now a double doublet, $J_{7\alpha,7\beta} = 12$ Hz, $J_{7\alpha,8\beta} = 8$ Hz). Furthermore, on irradiation at $\delta$ 4.18 (H-2) no modifications were observed in any of the well-resolved signals, but a pattern of complex signals appearing between $\delta$ 2.20 and 2.50 was drastically modified.

As a consequence of all the above data, it is evident that the C-6β position of chamaedroxide (1) is occupied by an oxygen atom, which must be forming a cyclic ether linkage with a trisubstituted carbon atom (C-4 or C-10 in the clerodane skeleton), since only a proton (H-6α) appeared in the $^1H$ NMR spectra of compounds 1 and 2 for this cyclic ether structural moiety. On the other hand, the presence in the $^1H$ NMR spectrum of chamaedroxide of a one-proton triplet at $\delta$ 3.25 ($J = 10$ Hz) may be attributed not only to the C-10β axial proton in structure 1 but also

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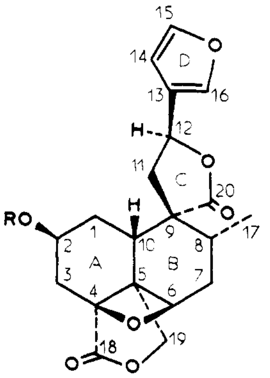
**Table I. Cremer's Parameters and Torsional Angles in the Junction A/B for Decalines of Some *Teucrium* Diterpenoids**

| compd | $\theta_A$ | $\Phi_A$ | $Q_A$ | $\tau_A$ | $\lvert\tau_A\rvert + \lvert\tau_B\rvert$ | $\tau_B$ | $Q_B$ | $\Phi_B$ | $\theta_B$ |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Neoclerodanes | | | | | |
| chamaedroxide (1a) | 89 | 281 | 0.78 | −66.1 | 128.7 | 62.6 | 0.73 | 80 | 90 |
| chamaedroxide (1b) | 89 | 280 | 0.78 | −66.5 | 131.5 | 65.0 | 0.80 | 78 | 91 |
| auropolin[2] | 18 | 259 | 0.62 | −68.8 | 101.3 | 32.5 | 0.67 | 293 | 30 |
| 19-acetyl gnaphalin[22] | 6 | 222 | 0.60 | −57.8 | 102.9 | 45.1 | 0.50 | 223 | 6 |
| teucrin $P_1$[22] | 7 | 350 | 0.57 | −55.2 | 107.2 | 52.0 | 0.80 | 39 | 80 |
| capitatin[23] | 9 | 251 | 0.61 | −62.5 | 109.4 | 46.9 | 0.76 | 71 | 98 |
| eriocephalin[24] | 16 | 293 | 0.62 | −65.9 | 103.2 | 37.3 | 0.74 | 72 | 104 |
| teuspinin[25] | 18 | 309 | 0.59 | −64.2 | 114.4 | 50.2 | 0.51 | 1 | 4 |
| | | | | Neoclerod-3-ene | | | | | |
| lolin[27] | 51 | 304 | 0.55 | −60.2 | 108.0 | 47.8 | 0.51 | 192 | 8 |
| | | | | 19-Norneoclerod-4-ene | | | | | |
| teuflin[26] | 47 | 359 | 0.56 | −34.7 | 60.2 | 25.5 | 0.84 | 28 | 94 |
| | | | | 10α-19-Norneoclerod-4-enes | | | | | |
| teuflidin[28] | 125 | 229 | 0.50 | 1.1 | 49.3 | −48.2 | 0.57 | 118 | 166 |
| teucvidin[29] | 123 | 226 | 0.50 | −0.6 | 50.4 | −49.8 | 0.57 | 128 | 169 |

to the C-4β axial proton[17] in an alternative structure with the oxetane ring between the C-6 and C-10 positions.

A single-crystal X-ray determination was undertaken in order to elucidate this last question, to determine the configurations at C-2 and C-12, and to establish the absolute configuration of chamaedroxide. Figure 1 shows the final X-ray model confirming all the above assignments and establishing the oxetane ring between the C-4β and C-6β positions, a C-2β configuration for the secondary hydroxyl group, a C-12(*S*) configuration, and a neoclerodane absolute stereochemistry[13] for this new diterpenoid (1).



**1** R = H

**2** R = Ac

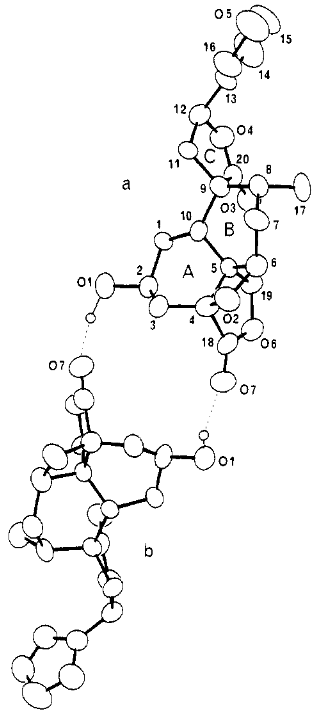


**Figure 1.** X-ray molecular model of the two crystallographycally independent molecules of chamaedroxide (1).

Crystals of chamaedroxide (1) are built upon dimers of two crystallographically independent molecules, which bond together through two hydrogen bonds O(1)–H···O(7) of 2.746 (5) and 2.964 (5) Å, as shown in Figure 1. The X-ray-determined absolute configuration shows that the two molecules belong to the neoclerodane-type configuration.[13]

The conformations of both molecules, omiting the orientation of the furan rings, are very similar. A half-normal probability plot[18] with all intramolecular distances less than 4.1 Å gives a correlation coefficient of 0.98 with a $\chi_{\min}^2$ of 0.11, the interexperimental *R* value being of 0.007. The orientation of the furan rings is different for the two molecules, and both also differ from the usual orientation found for several *Teucrium* diterpenoids. In most of these compounds, ring C is an envelope with the flap C-11 at the C-8 side, which allows the planar furan ring to bisect C-(11)–C(12)–O(4). In the molecules of chamaedroxide (Figure 1), however, the flap C-11 is at the C-10 side, and the furan rings have to rotate out of their usual positions.

Nevertheless, the oxetane moiety is the most interesting structural feature of chamaedroxide, because this is the first report on the X-ray geometry of an oxetane bridging a *trans*-decaline between the C-4 and C-6 carbon atoms. Bond lengths and angles are the usual for an oxetane group, and the dihedral angles for both molecules are 14.6° and 15.3°, which are between the reported values running from 0° to 16°.[19,20] A cyclobutane ring equally substituted in a *cis*-decaline has a dihedral angle of 17.7°.[21]

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The oxetane ring of chamaedroxide gives to its decaline moiety a special conformation, which departs much from the reported decaline conformations in other *Teucrium* diterpenoids.[2,22-29] In order to analyze the decaline deformation of chamaedroxide (**1**), it is also worth reviewing the reported decaline conformations for those compounds. We define the conformation of each six-membered ring with the three puckering parameters of Cremer:[30] the out of chair $\theta$ (in degrees), the pseudorotation $\phi$ (in degrees), and the total amplitude $Q$ (in angstroms). Table I shows these parameters and their torsions through the junction C(5)–C(10): $\tau_A$ = C(1)–C(10)–C(5)–C(4) and $\tau_B$ = C(6)–C(5)–C(10)–C(9) for the *Teucrium* diterpenoids studied by diffraction methods.

Usually the axial–axial interactions of ring B deform it from a chair, and some of this deformation is transmited to ring A, which has no axial–axial interactions other than H–H. When the oxetane ring is present (**1a** and **1b**, Figure 1), $|\tau_A| + |\tau_B|$ increases very much, and rings A and B become twists symmetrically disposed ($\phi_A = -80°$ and $\phi_B = 80°$) at both sides of C(5)–C(10). These rings could be also described as deformed boats with the flaps at C-3, C-10, and C-7, their deformations to twist being due to the H(3)–H(10)–H(7) axial interactions.

The oxetane ring moiety is a rare feature in natural products, and to date, only a few compounds possessing this function, e.g., montanin D,[31] laureatin,[32] and pseudoanisatin,[33] have been described.

## Experimental Section

Melting points were determined in a Kofler apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter with a 1-dm cell. Elemental analyses were carried out in Madrid[1b] with the help of a Perkin-Elmer 240 analyzer. IR spectra were determined on a Perkin-Elmer 257 spectrometer. $^1$H NMR spectra were measured at 100 MHz, in pyridine-$d_5$ or $CDCl_3$ solution with $Me_4Si$ as an internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6MG instrument.

**Isolation of Chamaedroxide (1).** Dried and finely powdered *T. chamaedrys* L. (aerial parts, 770 g), collected near Ciruelos del Pinar (Guadalajara, Spain), were extracted with acetone as previously described.[12] The chromatographic fraction (350 mg) obtained before elution of teugin[3,12] was repeatedly chromatographed over silica gel columns eluted with petroleum ether–EtOAc (1:1), yielding pure chamaedroxide (**1**): 67 mg; mp 255–257 °C (from $Me_2CO$–$Et_2O$); $[\alpha]^{20}{}_D$ +37.1° (*c* 0.42, pyridine); IR (KBr) 3500, 3150, 3135, 3000, 2980, 2960, 2920, 2885, 1765,1760, 1502, 1460, 1380, 1320, 1195, 1163, 1120, 1033, 1005, 990, 977, 883, 870, 785 cm$^{-1}$; UV (EtOH) $\lambda_{max}$ 217.5 nm (log $\epsilon$ 3.72), furan ring; $^1$H NMR (pyridine-$d_5$): see the text; mass spectrum (75 eV, direct inlet), *m/z* (relative intensity) 374 (M$^+$, 4), 356 (2), 346 (2), 330 (6), 316 (4), 236 (8), 213 (7), 203 (7), 177 (11), 161 (14), 145 (24), 133 ( 20), 131 (18), 119 (24), 105 (44), 96 (60), 95 (96), 94 (100, base peak), 91 (51), 81 (68), 77 (44), 65 (29), 53 (40). Anal. Calcd. for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 64.03; H, 6.05.

**Compound 2.** A solution of 27 mg of chamaedroxide in 2 mL of pyridine and 0.5 mL of acetic anhydride was allowed to stand overnight at room temperature. The reaction mixture was poured into ice–water and extracted with $CHCl_3$. A workup in the usual manner yielded, after purification by column chromatography, 24 mg of **2**: amorphous solid which melts at 120–126 °C; $[\alpha]^{20}{}_D$ +71.2° (*c* 0.62, $CHCl_3$); IR (KBr) 3150, 3130, 2960, 2870, 1770, 1765, 1735, 1505, 1455, 1365, 1240, 1190, 1165, 1100, 1030, 990, 975, 880, 805, 780 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.46 (2 H, m, $W_{1/2}$ = 4 Hz, H-15 and H-16), 6.36 (1 H, m, $W_{1/2}$ = 4 Hz, H-14), 5.49 (1 H, dd, $J_1$ = 4.5 Hz, $J_2$ = 8 Hz, H-12), 5.15 (1 H, dd, $J_1$ = 6 Hz, $J_2$ = 6.5 Hz, H-6), 4.72 (1 H, 16 lines, $W_{1/2}$ = 28 Hz, H-2), 4.42 and 4.28 (AB system, $J$ = 11.5 Hz, 2 H-19), 2.76 (1 H, dd, $J_{gem}$ = 13.5 Hz, $J_{11,12}$ = 8 Hz, H-11), 2.33 (1 H, dd, $J_{gem}$ = 13.5 Hz, $J_{11',12}$ = 4.5 Hz, H′-11), 2.04 (3 H, s, OAc), 0.90 (3 H, d, $J$ = 7 Hz, 3 H-17); mass spectrum (75 eV, direct inlet), *m/z* (relative intensity) 416 (M$^+$, 4), 372 (3), 356 (1), 329 (2), 312 (2), 298 (4), 267 (3), 253 (3), 218 (6), 199 (16), 159 (14), 145 (15), 133 (11), 131 (12), 119 (13), 105 (26), 96 (14), 95 (42), 94 (68), 91 (26), 81 (30), 77 (16), 65 (13), 53 (17), 43 (100, base peak). Anal. Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.25; H, 5.99.

**X-ray Structure Determination of 1.** $C_{20}H_{22}O_7$ crystallizes in the space group $P2_12_12_1$ with $Z = 8$ and $a$ = 30.139 (1), $b$ = 11.3698 (3), and $c$ = 10.3159 (2) Å. The molecular weight is 374.39, and the calculated density is 1.407 g cm$^{-3}$. A single crystal of 0.2 × 0.2 × 0.3 mm dimensions was used to measure the intensities of 2525 independent Friedel pairs, alternately collected on a computer-controlled four-circle diffractometer. Some experimental details are as follows: $\omega/2\theta$ scan mode; 1.20° scan width; 0.040 s g$^{-1}$ scan spead with the same measurement time for both backgrounds as for the peak. Graphite-monochromated Cu K$\alpha$ radiation (1.5418 Å) was used up to a Bragg angle of 55°. No intensity decay was observed during the data collection process. After the usual correction for Lorentz and polarization effects, 2038 Friedel pairs were considered as observed according to the criterion $I > 2\sigma(I)$ and were used for the structure determination and refinement. No absorption correction was applied. The atomic scattering factors and the anomalous dispersion corrections were taken from the literature.[34] The structure was solved by direct methods.[35] and refined by full-matrix least-squares methods with anisotropic thermal parameters for the nonhydrogen atoms using (*hkl*) reflections. The hydrogen atoms were placed at their expected positions, but they were checked in a Fourier difference map and were included as fixed isotropic contributors in the refinement.

A weighting scheme was selected to prevent bias in $\langle \omega\Delta^2F \rangle$ vs. $\langle |F_o| \rangle$ and $\langle \sin\theta/\lambda \rangle$. Several cycles of weighted anisotropic refinement including both (*hkl*) and ($\bar{h}\bar{k}\bar{l}$) reflections gave for the correct enantiomer the following unweighted and weighted discrepancy indices: $R$= 0.061 and $R_w$ = 0.057.[36,37]

The absolute configuration was determined by comparing the more relevant Bijvoet pairs. The absorption correction was not necessary because the crystal was almost centrosymmetric, and this effect could be considered the same for both reflexions of each measured pair. On consideration of reflexions with $F_o > 10\sigma(F_o)$, there are 56 Bijvoet pairs with $\Delta F_c > 0.16$ showing an averaged Bijvoet difference ($\Delta^+$) of 0.661 for the correct enantiomer vs. 0.757 for the wrong one ($\Delta^-$). Taking $\Delta F_c > 0.08$, there are 290 Bijvoet pairs with $\Delta^+ = 0.875$ and $\Delta^- = 0.926$. These results support the molecular absolute configuration showed in Figure 1.

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**Registry No.** 1, 82679-43-4; 2, 82679-44-5.

**Supplementary Material Available:** A list of atomic parameters, bond distances, bond angles, and torsion angles (18 pages). Ordering information is given on any current masthead page.

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# Absolute Configuration of 2-Amino-4-phenylbutyric Acid (Homophenylalanine)

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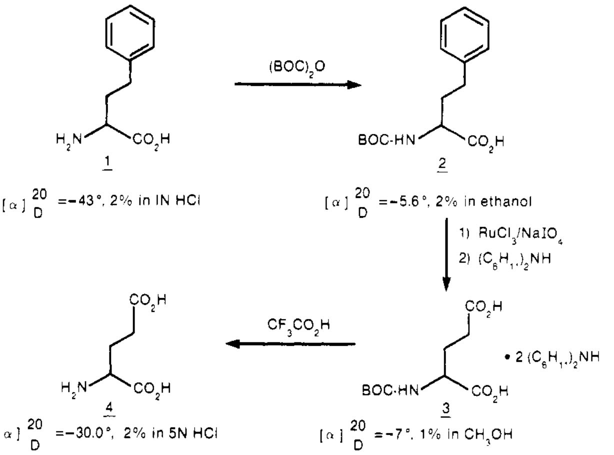
In the design of novel inhibitors of peptidase enzymes our efforts are often guided by results obtained with model peptides, some of which may contain uncommon or nonnaturally occurring amino acids. Recently, our attention has been directed toward 2-amino-4-phenylbutyric acid (1). This compound, which may be viewed as a homologue of the naturally occurring amino acid phenylalanine ("homophenylalanine"),[1] is a component of new agents of pharmacological interest.[2] We thus became aware that a considerable amount of confusion has existed in the literature for some time with respect to assignment of absolute configuration to the enantiomers of this unusual amino acid.

Resolution of 2-amino-4-phenylbutyric acid, by crystallization of the *N*-formyl derivative as its brucine salt, was first reported by du Vigneaud and Irish in 1938.[3] These workers assigned the natural L-configuration to the dextrorotatory isomer ($[\alpha]^{30}_D$ +48.8°, 1% in 1 N HCl) on the basis of comparison of the pH dependence of its specific rotation with that of naturally occurring amino acids. Additionally, in a series of feeding experiments initiated by Knoop[4] and verified by du Vigneaud,[3] it was concluded that the *N*-acetyl derivative of the levorotatory isomer is "less readily handled by the body" and thus corresponds to the unnatural D isomer. In 1964, Dirkx and Sixma[5] correlated the positive Cotton effect observed for the dextrotatory isomer ($[\alpha]^{25}_{600}$ +47°, 0.1% in 0.1 N HCl) with that observed for naturally occurring isomers of a number of other amino acids, including phenylalanine. Also in 1964, preparation of isotopically labeled L-homophenylalanine by submitting racemic material to D-amino acid oxidase and recovering unchanged amino acid was reported but without physical data.[6] In 1970, Sakota and coworkers[7] subjected *N*-acetyl-*dl*-$\alpha$-amino-$\beta$-benzalpropionic acid to hydrolysis with "Biodiastase". Hydrogenation of the resulting free amino acid gave levorotatory 2-amino-4-phenylbutyric acid ($[\alpha]^{20}_D$ −18°, 1% in HCl), which was claimed as the naturally occurring L isomer; a literature citation used to support this claim refers only to a synthesis of the racemic material.[8] In 1976, Arold and co-workers[9] reported resolution of 1 by a procedure virtually identical with that reported earlier by du Vigneaud;[3] the levorotatory isomer ($[\alpha]^{20}_D$ −45.6°, 1% in 1 N HCl), however, was assigned the natural L configuration without comment. This material was subsequently incorporated into a nonapeptide bradykinin analogue. Indeed, the levorotatory isomer ($[\alpha]^{30}_D$ −47°, 1% in HCl) was offered commercially as "L-$\alpha$-amino-4-phenylbutyric acid" as late as 1981.[10]

Confusion concerning the absolute configuration of 2-amino-4-phenylbutyric acid is related to the fact that this substance has not been chemically converted to a compound of known absolute configuration. Such a transformation has now been accomplished, thus unambiguously establishing the absolute configuration of this important amino acid.

Reaction of the sodium salt of (−)-2-amino-4-phenylbutryic acid[11] with di-*tert*-butyl dicarbonate in aqueous *tert*-butyl alcohol afforded *t*-BOC derivative 2, which was characterized as its dicyclohexylammonium salt. Ruthenium tetraoxide oxidation of 2 (free acid) using the modification recently reported by Sharpless and co-



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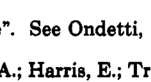
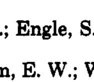
[1] Note that other *types* of homologues of phenylalanine can also exist (i, ii). For example, i has been reported and referred to as "$\beta$-



i



ii

homophenylalanine". See Ondetti, M. A.; Engle, S. L. *J. Med. Chem.* **1975**, *18*, 761.

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[10] "Chemalog Hi Lites", Vol. 5 (Chemical Dynamics Corp., South Plainfield, NJ, April 1981). This designation has recently been changed to (−)-$\alpha$-amino-4-phenylbutyric acid.

[11] Chemical Dynamics Corp. Stock No. 05-4525-00, see ref 10.

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