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SYNTHESIS AND CD MEASUREMENT OF CHIRAL 1-ETHYL-3-CARBOXY-1,2,3,4-TETRAHYDRO-β-CARBOLINES: C1 CONFIGURATION AND SECOND SPHERE CHIRALITY

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Abstract – Chiral diastereomers, (1*S*)-ethyl-(3*S*)-carboxy-1,2,3,4-tetrahydro-β-carboline and (1*R*)-ethyl-(3*S*)-carboxy-1,2,3,4-tetrahydro-β-carboline, were synthesized. Complete ^{1}H and ^{13}C NMR spectral assignments were made and the C-ring conformations were clarified by NMR spectral measurements and DFT potential energy calculation using the 6-31G(d) basis set. CD spectra were measured and the $^{1}L_b$ band Cotton effects were found to be controlled by both the C1 absolute configuration and the C-ring conformation.

Corynanthe-type alkaloids, yohimbanes, and heteroyohimbanes are three major types of monoterpenoid indole alkaloids characterized by an indolo[2,3-*a*]quinolizidine framework in their A to D ring moieties. The CD Cotton effect associated with the longest UV absorption wavelength ($^{1}L_b$ band)[1] has been widely used for the structure determination of such molecules. A positive Cotton effect near 275-250 nm

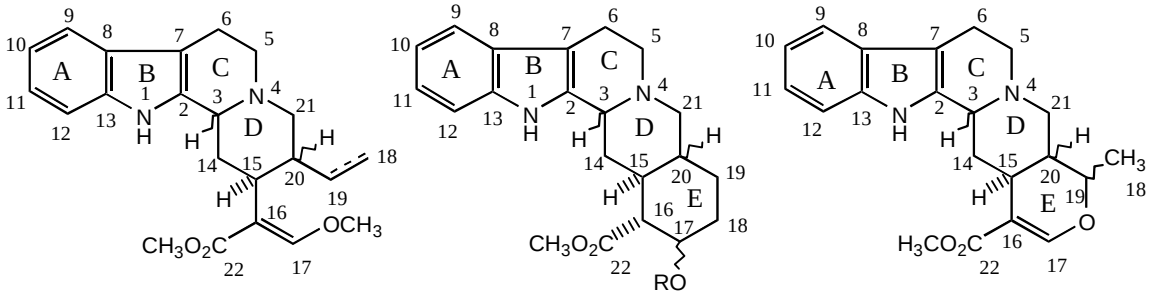
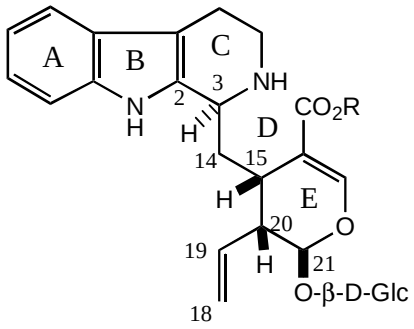


Figure 1

corresponds to a C3-*S* (or C3-αH) configuration and a negative one, to C3-*R* (or C3-βH).[2,3] This rule has been widely accepted and applied to the structure determination of various types of indole alkaloids. In most cases, the deduced C3 configurations are further supported by other spectroscopic observations.

NMR and other spectral methods reveal the relative stereochemistry among the chiral centers as well as the orientation of paired electrons on N4 of the conformationally rigid molecules. The C15 configuration is known to be (*S*) and therefore the correct absolute configuration is safely attributed to C3.

Strictiosidine (**1**) and related glycosidic alkaloids are another class of indole alkaloids. Here the D ring is not closed, so that the C3 chiral center is separated from the nearest chiral center, C15, by achiral C14 methylene carbon. Because of the two intervening freely rotating single bonds, the stereochemical correlation between the two chiral centers is quite difficult to establish by conventional spectroscopic methods, except X-Ray crystallography. For this type of molecule the above CD spectral rule is almost the sole tool to deduce the absolute configuration at C3. It is apparent that caution is needed in applying an empirical CD spectral rule to this type of molecule. We reported previously that strictosidinic acid (**2**) with the C3(*S*) configuration shows a negative Cotton effect in the longest wavelength region although a positive one was expected.[4] In this paper, we report the synthesis and CD spectral studies of simple 1,3-disubstituted tetrahydro-β-carbolines. To clarify the C-ring conformations, the DFT (Density Functional Theory) MO calculation was employed besides conventional ^{1}H and ^{13}C NMR spectral measurements.



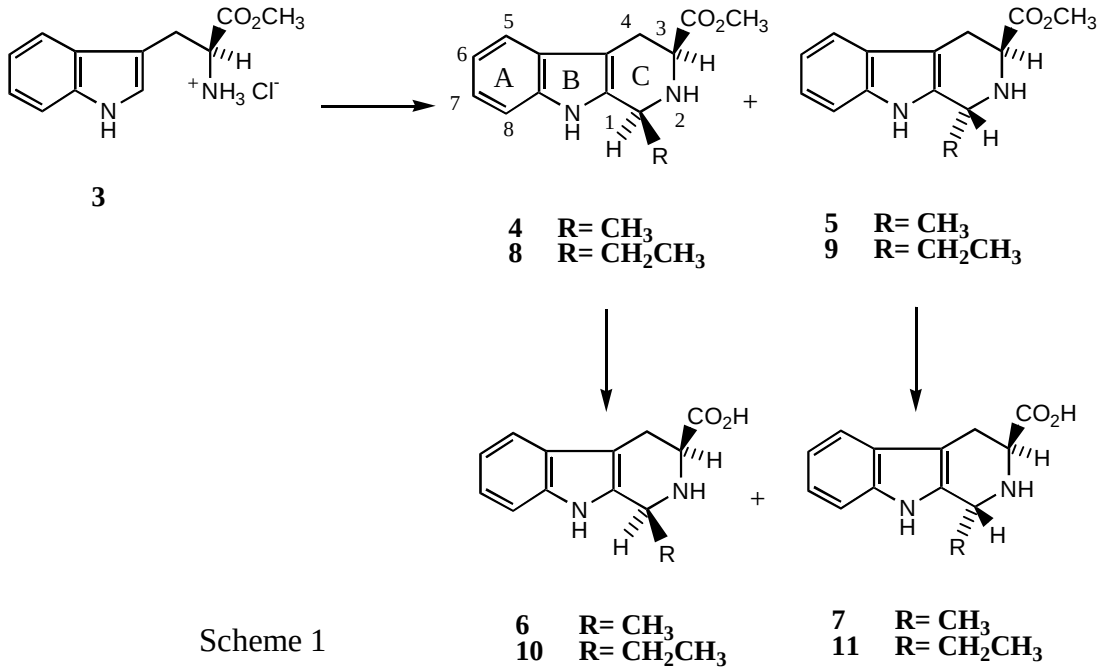
R = CH_3 (**1**)

R = H (**2**)

Figure 2

Chiral amino acids (**6**) and (**7**) with known absolute configurations were synthesized by Brossi *et al.* and their chiroptical properties were reported.[5] Recent studies have shown the presence of the same compounds in some foodstuffs together with their structural analogues.[6,7] Although 1-ethyl analogues have been reported in the literatures,[8,9] detailed studies on their spectroscopic and chiroptic properties are lacking. We synthesized two diastereomeric chiral esters (**8**) and (**9**), according to the procedure reported by Ungemach *et al.* for the racemic congeners.[10] Commercially available L-tryptophan methyl ester hydrochloride (**3**) was subjected to the Pictet-Spengler reaction with propionic aldehyde. The resulting diastereomeric mixture was separated in single epimers (**8**), $[\alpha]_D$ –89.6° and (**9**), $[\alpha]_D$ +8.0°. The ^{13}C NMR spectra of **8** and **9** were identical to those reported for the *cis*- and *trans*-isomers respectively. *Cis*-isomer (**8**) shows a double doublet at δ 3.78 indicative of axial H3, with the expected *J* values of $J_{3,4\beta}$= 11.3 Hz and $J_{3,4\alpha}$= 4.4 Hz. The *trans*-epimer (**9**) shows the corresponding coupling

constants of 7.2 and 5.1 Hz, indicating the presence of two chair forms of the 1,3-*trans*-diastereomer.



Scheme 1

Detailed NOE measurements further supported the structural assignments. Each of the 1,3-*cis*- **8** and 1,3-*trans* **9** diastereomers was subjected to hydrolysis of the ester groups and the corresponding *cis*-amino acid (**10**)[11] and *trans*-amino acid (**11**)[12] were obtained.

The CD spectra of **10** and **11** *did not* show antipodal CD curves in the region of 260 – 300 nm, the region of the ^1L_b UV band. Compound (**10**) with C1(*S*) configuration shows a negative CD band ($\Delta\varepsilon_{265}$ -1.1). Compound (**11**) with C1(*R*) configuration showed a broad negative CD band ($\Delta\varepsilon_{283}$ -0.65) of much lower intensity . It is apparent that second sphere helicity contributes to the CD curve. We then studied the respective conformations of compounds (**10**) and (**11**). As expected, compound (**10**) adopted a half-chair conformation, conformer 1 (Figure 3), having 1eq ethyl group and 3eq carboxyl group as evidenced by the NMR spectral coupling constants of C3-H with two adjacent protons, $J_{3\alpha H,4\beta H}$= 12.1 Hz, and $J_{3\alpha H,4\alpha H}$= 4.8 Hz. On the other hand, the *trans*-isomer (**11**) showed coupling constants of 6.7 and 5.9 Hz between C3-H and C4-Hα, Hβ, indicating the presence of two conformers, conformers 3 (minor) and 4 (major).

To obtain further information about their C-ring conformations, DFT MO calculation of the potential energy of the stable conformations was carried out. Optimization was done using the B3LYP/6-31G(d) level of theory set on Gaussian 98.[13] The difference in potential energy between the two conformations of the 1,3-*cis*-diastereomer (**10**) was 2.63 kcal mol^{-1}. This value indicates that the Boltzmann population of the 1eq-ethyl-3eq-carboxyl conformer (conformer 1) predominates over that of the

1ax-ethyl-3ax-carboxyl conformer (conformer 2) by 98.9 to 1.1. In the case of *trans*-diastereomer (**11**), the stable conformer is the 1eq-ethyl-3ax-carboxyl conformer (conformer 4) and the less stable one is the 1ax-ethyl-3eq-carboxyl conformer (conformer 3), the difference in potential energy being 0.752 kcal mol^{-1}. This value suggests that *trans*- diastereomer (**11**) exists in a conformational mixture

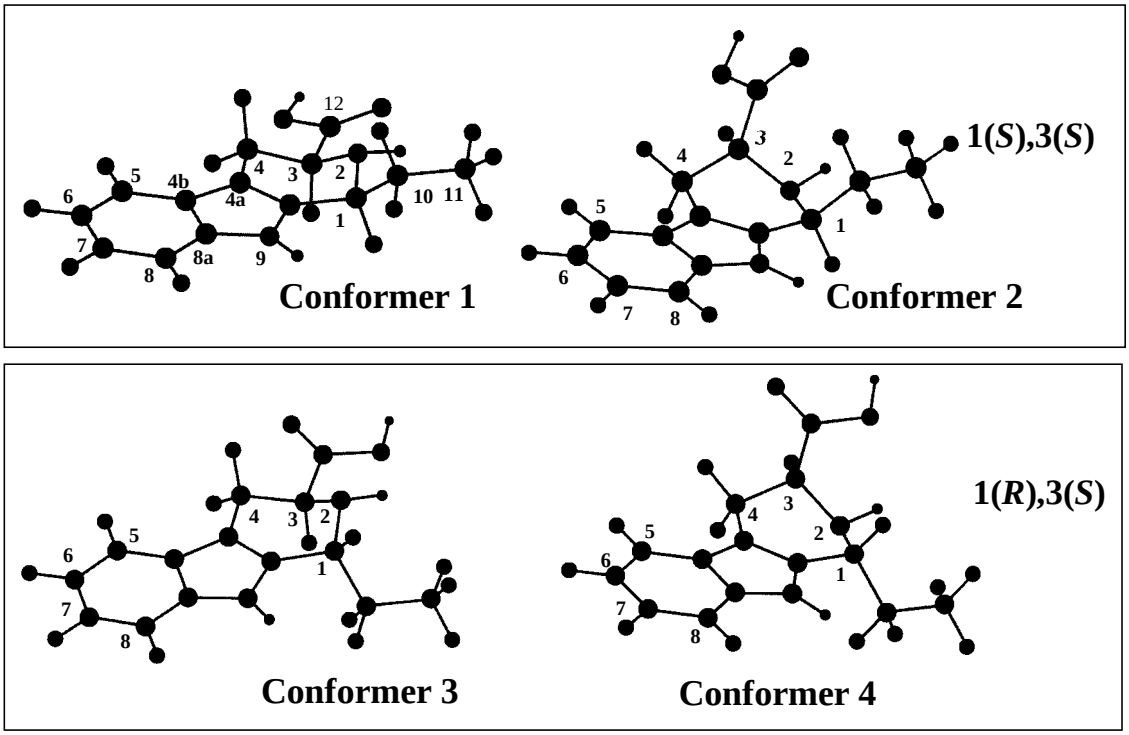
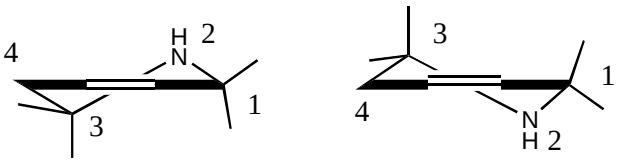


Figure 3

consisting of 78% conformer 4 and 22% conformer 3. The difference in population of the P-type and M-type conformers of the two diastereomers prevents the CD curve from becoming antipodal in the region of the ^1L_b UV absorption band. Further accumulation of fundamental data is required to distinguish the contribution of the C1 (and C3)-chiral substituents from that of the C-ring helicity. Studies of the CD spectra of a series of chiral 1-monosubstituted tetrahydro-β-carbolines are under way.



M-type conformation **P-type conformation**

Figure 4

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11. (1*S*,3*S*)-1-Ethyl-3-carboxy-1,2,3,4-tetrahydro-β-carboline; mp 240-242 °C (from EtOH-H_2O 1:1), $[\alpha]^{25}_D$= -173 ° (c=0.13, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6+D_2O) δ 1.04 (3H, dd, *J*=7.6, 7.6 Hz, $CH_2C\underline{H}_3$), 1.89, 2.19 (each 1H, m, $C\underline{H}_2CH_3$), 2.81 (1H, ddd, *J*=2.8, 12.6, 15.8 Hz, H-4β), 3.22 (1H, dd, *J*=3.7, 16.2 Hz, H-4α), 3.62 (1H, dd, *J*=4.8, 12.1 Hz, H-3), 4.45 (1H, br d, *J*=8.2 Hz, H-1), 6.99 (1H, dd, *J*=7.6, 7.6 Hz, H-6), 7.08 (1H, dd, *J*=7.6, 7.6 Hz, H-7), 7.33 (1H, d, *J*=8.2 Hz, H-8), 7.43 (1H, d, *J*=7.6 Hz, H-5). ^{13}C-NMR (125 MHz, DMSO-d_6+D_2O) δ 9.90 ($CH_2\underline{C}H_3$), 23.09 (C-4), 24.81 ($\underline{C}H_2CH_3$), 54.70 (C-1), 58.32 (C-3), 107.52 (C-4a), 111.87 (C-8), 118.64 (C-5), 119.66 (C-6), 122.28 (C-7), 126.35 (C-4b), 130.64 (C-9a), 136.93 (C-8a), 170.76 (COOH). HRMS *m/z*: Calcd for $C_{14}H_{17}N_2O_2$, 245.1290. Found 245.1291 ($[M+H]^+$). *Anal.* Calcd for $C_{14}H_{16}N_2O_2$+1/2H_2O: C, 66.39; H, 6.76; N, 11.06. Found: C, 66.33; H, 6.85; N, 11.17. UV(MeOH):λ_{max} 221.5, 273.0 nm. CD (MeOH), λ nm(Δε): 209.6 (-10.5), 220.8 (0), 226.8 (+6.26), 234.8 (0), 238.0 (-0.54), 283.0 (-0.65), 323.6 (0).
12. (1*R*,3*S*)-1-Ethyl-3-carboxy-1,2,3,4-tetrahydro-β-carboline; Colorless powder, $[\alpha]^{25}_D$= -31 °(c=0.18, MeOH), ^{1}H NMR (500 MHz, DMSO-d_6+D_2O) δ 1.07 (3H, dd, *J*=7.4, 7.4 Hz, $CH_2C\underline{H}_3$), 2.03 (2H, m, $C\underline{H}_2CH_3$), 3.10 (1H, dd, *J*=6.7, 16.0 Hz, H-4α), 3.19 (1H, dd, *J*=5.9, 16.1 Hz, H-4β), 3.90 (under H_2O, H-3), 4.67 (1H, dd, *J*=6.3, 6.3 Hz, H-1), 7.03 (1H, dd, *J*=7.5, 7.5 Hz, H-6), 7.13 (1H, dd, *J*=7.6, 7.6 Hz, H-7), 7.37 (1H, d, *J*=8.2 Hz, H-8), 7.46 (1H, d, *J*=7.7 Hz, H-5). ^{13}C NMR (125 MHz, DMSO-d_6 + D_2O) δ 10.38 ($CH_2\underline{C}H_3$), 22.45 (C-4), 25.72 ($\underline{C}H_2CH_3$), 52.39 (C-1), 54.16 (C-3), 106.12 (C-4a), 111.78 (C-8), 118.50 (C-5), 119.45 (C-6), 122.19 (C-7), 126.38 (C-4b), 130.43 (C-9a), 136.66 (C-8a), 170.84 (COOH). HRMS *m/z*: Calcd for $C_{14}H_{17}N_2O_2$, 245.1290. Found 245.1307 ($[M+H]^+$). UV(MeOH): λ_{max} 222.0, 272.5 nm. CD (MeOH), λ nm(Δε): 215.2 (+2.48), 219.0 (0), 227.8 (-5.52), 243.8 (-0.38), 264.8 (-1.09), 294.6 (-0.15), 325.4 (0).
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