Absolute Configuration of Natural Diastereoisomers of 6*β*-Hydroxyhyoscyamine by Vibrational Circular Dichroism

Marcelo A. Muñoz,[†] Orlando Muñoz,[†] and Pedro Joseph-Nathan*[,‡]

Departamento de Química, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile, and Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado 14-740, México, D. F., 07000 México

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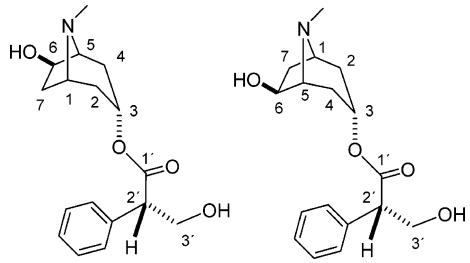
The absolute configuration of the two natural diastereoisomers of 6*β*-hydroxyhyoscyamine has been determined using vibrational circular dichroism (VCD) spectroscopy. The predicted VCD and IR spectra of (3*R*,6*R*,2′*S*)-6*β*-hydroxyhyoscyamine (**1**) and (3*S*,6*S*,2′*S*)-6*β*-hydroxyhyoscyamine (**2**) were calculated using density functional theory (DFT) with the B3LYP functional and 6-31G(d) basis set and considering the eight lower energy conformations of each diastereoisomer. In both cases, the first four conformers showed the N-Me group in the *syn* orientation, permitting the formation of a hydrogen bond between the hydroxy group at the tropane ring and the tertiary nitrogen atom. In addition the eight conformers showed an intramolecular hydrogen bond between the hydroxy and carbonyl groups of the tropic ester moiety. The calculated IR spectra of both molecules showed good agreement with the experimental spectra, while comparison of the experimental and calculated VCD spectra showed that the absolute configuration of dextrorotatory 6*β*-hydroxyhyoscyamine is (3*R*,6*R*,2′*S*), while the levorotatory isomer is (3*S*,6*S*,2′*S*).

Anisodamine, or 6*β*-hydroxyhyoscyamine, is a well-known tropane alkaloid found in the roots and leaves of various species of *Physochlaina*, *Scopolia*, *Duboisia*, and *Datura* genera.[1] It possesses a number of pharmacological uses, e.g., against cardiovascular disorders,[2,3] acute ischemic renal failure,[4] and snakebites.[5] Some interest has been shown for the separation and analysis of this drug in different matrixes such as vegetable material,[6,7] pharmaceutical samples,[8,9] and urine[10] using different chromatographic methodologies. While pharmaceutical formulations comprise the four possible stereoisomers,[11] only (3*R*,6*R*,2′*S*)-6*β*-hydroxy-hyoscyamine (**1**) and (3*S*,6*S*,2*S*)-6*β*-hydroxy-hyoscyamine (**2**), also known as 7*β*-hydroxyhyoscyamine[12] and 6*β*-hydroxy-hyoscyamine,[13] respectively, have been isolated from plant material.[12] These two molecules have the same (*S*) absolute configuration at the tropic ester moiety,[14] like other related alkaloids, and therefore they differ only in the relative position of the hydroxy group attached to the tropane ring. The C-3 stereocenter is responsible for the diastereoisomeric relationship of these two molecules.

The absolute configuration of tropane alkaloids of this type is commonly established using chemical correlation with the corresponding 3α,6*β*-tropanediol of known configuration.[15,16] The absolute configuration of 3α,6*β*-tropanediol was established[17,18] as (3*R*,6*R*) for the levorotatory free base ($[\alpha]_D = -23.3$) and (3*S*,6*S*) for the enantiomer ($[\alpha]_D = +24.1$) adopting the lactone rule of Hudson.[19] Also, a levorotatory form of 6*β*-hydroxyhyoscyamine hydrobromide ($[\alpha]_D = -10.5$) was correlated with (+)-3α,6*β*-tropanediol hydrobromide ($[\alpha]_D = +1.4$) and assigned the (3*R*,6*R*) absolute configuration.[20] The same authors corrected the absolute configurations of both enantiomeric 3α,6*β*-tropanediols by using chemical correlation with (*S*)-methoxysuccinic acid, leading to the opposite conclusion.[21,22] Different articles concerning the isolation of (−)-6*β*-hydroxyhyoscyamine are found, most of which do not report specific rotation data. For a few exceptions negative values were reported for the hydrobromide form of the alkaloid when measured in water.[23,24]

In addition, diastereoisomers **1** and **2** where found in the hairy roots of *Hyoscyamus albus*, one being levorotatory ($[\alpha]_D = -13.0$) and the other dextrorotatory ($[\alpha]_D = +1.2$), when measured as free bases.[12] Although the hydrolyses of these alkaloids were conducted, and the absolute configuration of (+)-6*β*-hydroxyhyoscyamine and (−)-6*β*-hydroxyhyoscyamine were defined as (3*R*,6*R*) and (3*S*,6*S*), respectively, some confusion has arisen from the specific rotation values of the two obtained tropanediols. The reported values of $[\alpha]_D = -1.8$ and $[\alpha]_D = -1.0$ for the hydrochlorides of the diols obtained from levorotatory and dextrorotatory 6*β*-hydroxyhyoscyamine, respectively, do not provide sufficient information to establish the absolute configuration of these tropane alkaloids. Owing to the confusing information, we decided to use an independent contemporary methodology to establish the absolute configuration of these molecules. This methodology can further be useful for the absolute configuration determination of related tropane alkaloids, like those isolated from the bark of *Erythroxylum vaccinifolium*, for which no absolute configuration is discussed.[25]



Recently, vibrational circular dichroism (VCD) spectroscopy has been shown to be an excellent and reliable technique to ascertain the absolute configuration of chiral molecules.[26] The methodology involves the calculation of all significantly populated conformations followed by generation of the weighted vibrational spectra using ab initio calculations,[27] which are in turn compared to the experimental VCD spectra.[28] The computational time needed for these calculations has limited the use of VCD data of natural products, due to the relative size and complexity of these molecules, with the exception of a few recently reported examples.[29−32] Also, most of the applications of VCD spectroscopy on organic molecules dealt with the differentiation of enantiomeric species.[33−38] The use of these calculations for the differentiation of diastereoisomeric pairs is very restricted[38−40] and has not yet been applied in the natural products field. Here, we present the first use of experimental and

* To whom correspondence should be addressed. Tel: +5255 5747 7112. Fax: +5255 5747 7137. E-mail: pjoseph@nathan.cinvestav.mx.

[†] Universidad de Chile.

[‡] Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional.

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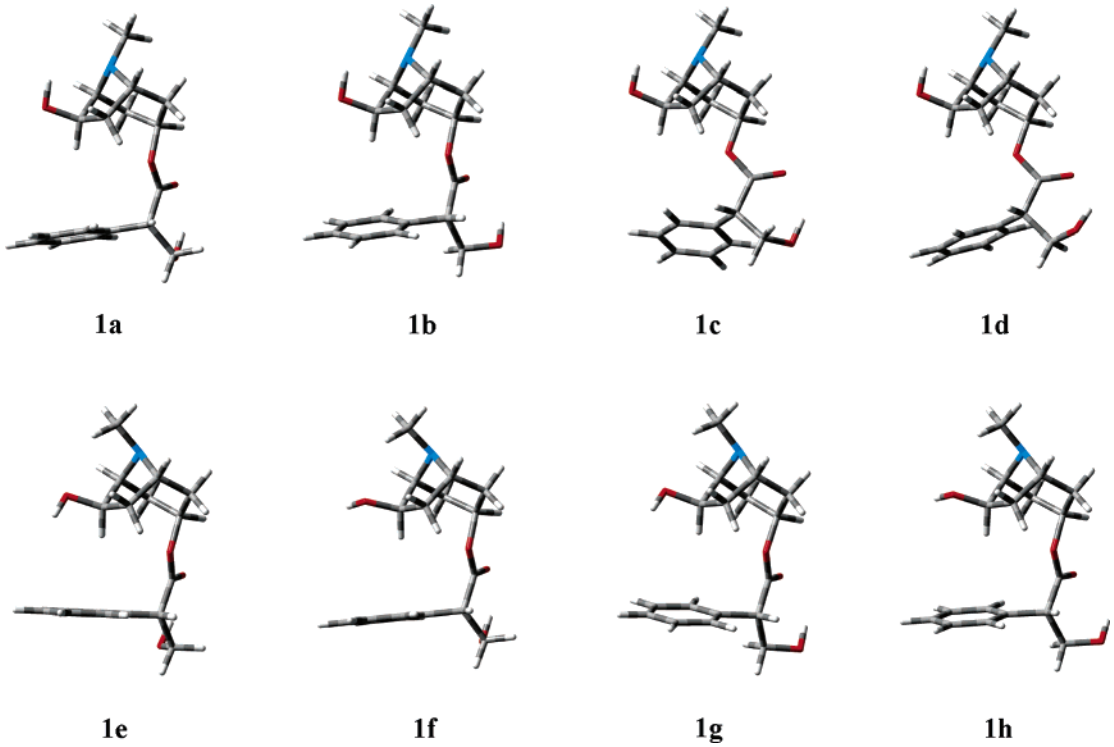

Figure 1. DFT-optimized structures of the eight more stable conformers of (3*R*,6*R*)-6β-hydroxyhyoscyamine (**1**). For relative energies and abundances, see Table 1.

Table 1. Calculated Relative Energies (kcal/mol) and Abundances (%) of the Eight More Stable Conformers of **1** and **2**, Using MMFF94 Systematic Search and B3LYP/6-31G(d) Single-Point and Geometry Optimization Level of Theory[a]

conf	E_{MMFF}[b]	E_{SP}[b]	$\%_{SP}$[c]	E_{OE}[b]	$\%_{OE}$[d]
1a	2.02	0.00	25.54	0.00	25.66
1b	1.14	0.20	18.28	0.08	22.42
1c	2.29	0.01	25.02	0.24	17.11
1d	1.41	0.51	10.85	0.25	16.83
1e	1.54	0.92	5.39	0.87	5.91
1f	1.90	0.74	7.30	0.93	5.34
1g	0.84	1.66	1.54	1.12	3.88
1h	1.46	1.30	2.85	1.30	2.85
2a	1.97	0.00	34.88	0.00	30.45
2b	1.39	0.46	16.13	0.23	20.66
2c	2.81	0.23	23.54	0.25	19.97
2d	2.00	0.71	10.43	0.43	14.74
2e	1.47	1.25	4.20	1.19	4.09
2f	0.87	1.94	1.32	1.24	3.76
2g	2.30	1.23	4.40	1.27	3.57
2h	1.53	1.82	1.61	1.42	2.76

[a] The conformers of each diastereoisomer are arranged according to the optimized energy calculations. [b] Relative to the lowest energy conformer of each diastereoisomer. [c] Calculated using the single-point energies in the first 5 kcal/mol. [d] Calculated using the optimization energies of the relevant conformers.

calculated VCD spectra for the determination of the absolute configuration of two diastereoisomeric secondary metabolites.

Results and Discussion

The conformational distribution of **1** and **2** (Table 1), calculated using MMFF94 systematic conformational searches followed by single-point energy calculations at the B3LYP/6-31G(d) level of theory, shows a clear tendency of the two hydroxy groups to form intramolecular hydrogen bonds. The eight most populated conformations of **1** and **2** shown in Figures 1 and 2, respectively, display this type of association between the hydroxy and the carbonyl groups on the tropic ester, forming a six-membered ring. On the other hand, the possibility of the C-6 hydroxy group of forming a hydrogen bond with the tertiary amine nitrogen in a five-atom arrangement strongly depends on the N-Me orientation. While a *syn* disposition of the N-Me group leaves the nitrogen electron pair oriented to the hydroxy group, permitting the formation of the hydrogen bond, an *anti* orientation precludes this association completely. In both isomers (**1** and **2**) the four more stable conformers show a *syn* N-Me group orientation, and therefore the two possible intramolecular hydrogen bonds are present, while the next four conformers show the *anti* N-Me group orientation with only the tropic ester hydrogen bond. The preference for the *syn* N-Me group orientation of **1** and **2** has been suggested previously based on the ^{13}C NMR chemical shift of the methyl group attached to the nitrogen.[41] The five-membered intramolecular hydrogen bond to the nitrogen atom seems to contribute less than 1.5 kcal/mol to the molecular stabilization. This is probably due to the geometry of the atom arrangement in combination with the basis set used. Both isomers show exactly the same conformational order in the energy scale, confirming the relationship between the relative position of the hydroxy group in the tropane ring and the conformational preferences of the molecules. These eight more significant conformations, accounting for 96.8% and 96.5% of the total population in the first 5 kcal/mol range of **1** and **2**, respectively, were energy optimized by means of B3LYP/6-31G(d) calculations, and the pertinent results are given in Table 1 as E_{OE} values, together with the corresponding values of the relative abundances of these optimized geometries ($\%_{OE}$).

The difficulty in distinguishing these two diastereoisomeric molecules is due to the fact that not all bands in the VCD spectra of the two stereoisomers are mirror images, as would be the case for a pair of enantiomers. This implies the need to identify the vibrational bands that are related to the asymmetric centers that differ in the two diastereoisomers. Also, it is necessary to perform the conformational analysis and calculation of vibrational spectra for both stereoisomers, since this information cannot be inferred from one molecule to the other, as in enantiomers.

The calculated vibrational spectra (IR and VCD) of the lowest energy conformers of **1** and **2** using the B3LYP/6-31G(d) level of theory are shown in Figures 3 and 4, respectively. The combination

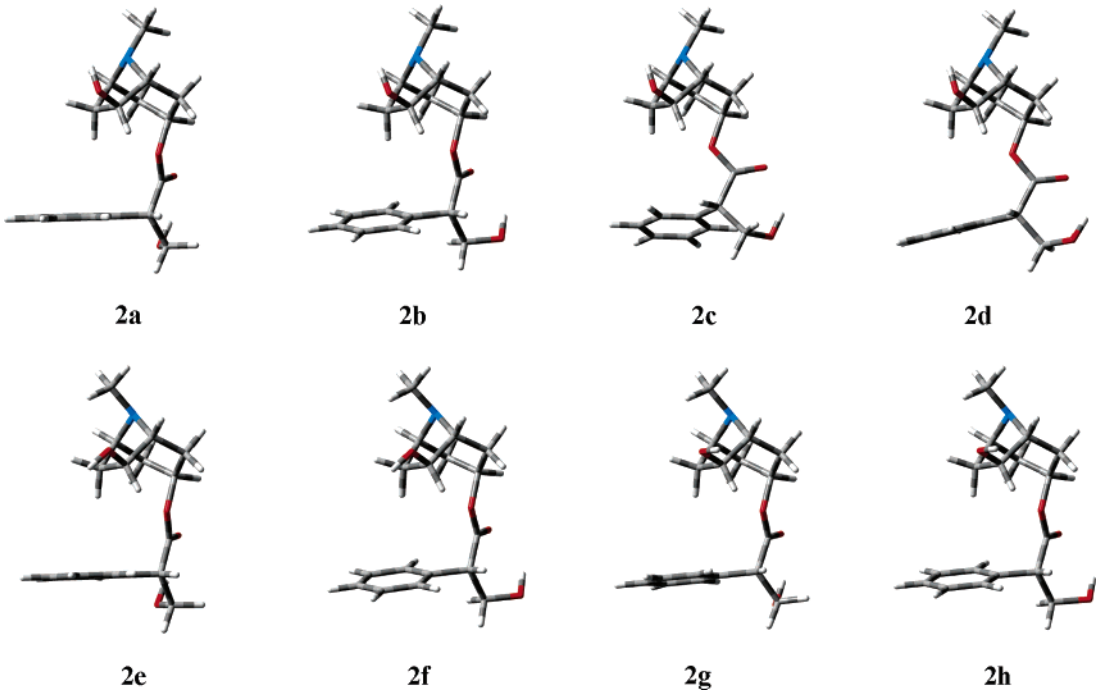

Figure 2. DFT-optimized structures of the eight more stable conformers of (3*S*,6*S*)-6*β*-hydroxyhyoscyamine (**2**). For relative energies and abundances, see Table 1.

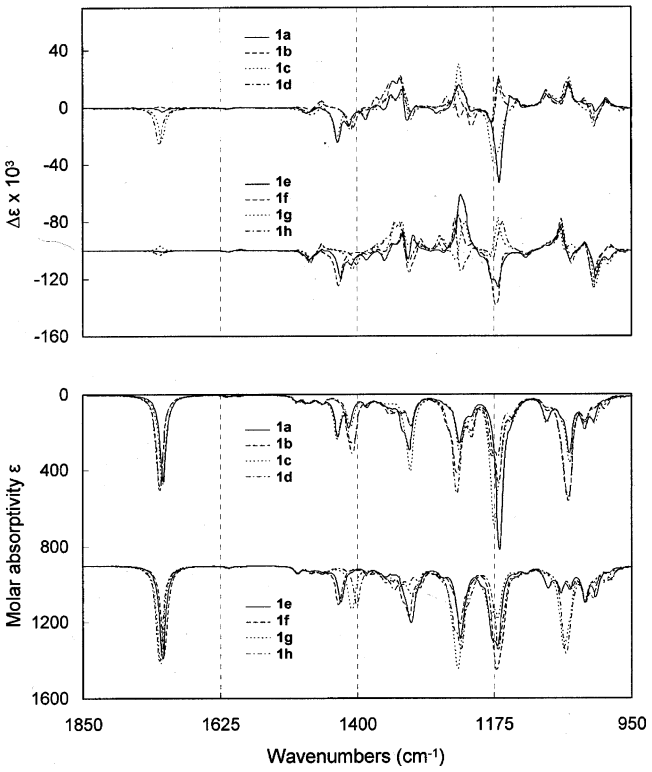

Figure 3. Calculated IR absortion (bottom) and VCD spectra (top) for the eight lowest energy conformers of (3*R*,6*R*)-6*β*-hydroxyhyoscyamine (**1**) at the B3LYP/6-31G(d) level of theory. Half of the spectra is offset for clarity. Frequencies are scaled by a factor of 0.97.[26]

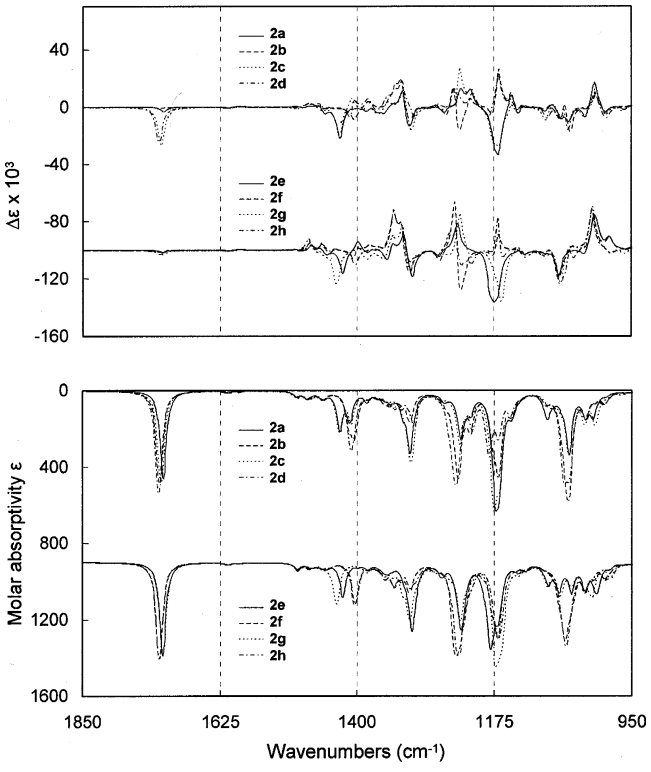

Figure 4. Calculated IR absortion (bottom) and VCD spectra (top) for the eight lowest energy conformers of (3*S*,6*S*)-6*β*-hydroxyhyoscyamine (**2**) at the B3LYP/6-31G(d) level of theory. Half of the spectra is offset for clarity. Frequencies are scaled by a factor of 0.97.[26]

of DFT functionals and basis set used was selected considering its good agreement with experiment and reasonable consumption of computer time that this level of theory has shown in the past.[42] Recently published examples[30,43] confirm that indeed calculations at the B3LYP/6-31G(d) level of theory provide a nice balance between computing time and spectral similarity. In any event, the use of a larger basis set will not modify the goal of this work, which is the diastereoisomeric distinction of **1** and **2**. Some additional considerations regarding limitations imposed by very large computing time requirements for bigger basis sets are given in the Experimental Section, and in the Supporting Information are shown some results obtained using the 6-311G++(d) basis set.

The calculated IR spectra do not show significant differences between the considered conformers. In severe contrast, the VCD

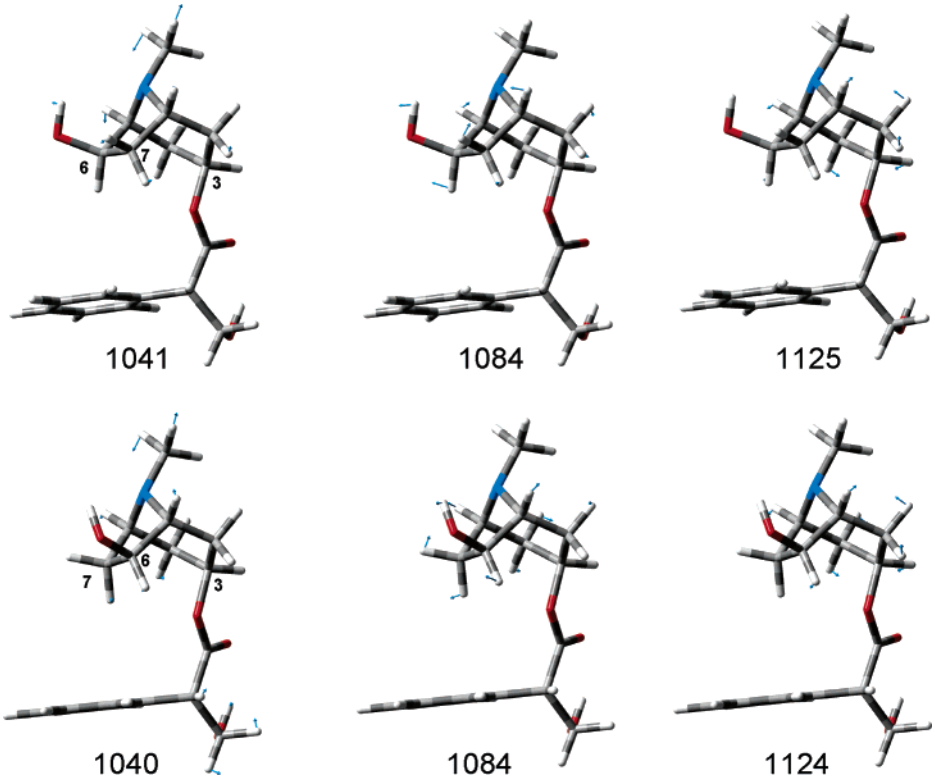

Figure 5. Relative amplitudes of selected vibrational modes (values in cm^{-1} under each structure) for the lowest energy conformer of **1** (top) and **2** (bottom). The vibrational modes are characterized: 1040 and 1041 cm^{-1}, asymmetric stretching between C1−N−C5, N−C1−C2, N−C5−C4, and O−C6−C7; 1084 cm^{-1}, asymmetric stretching between O−C6−C7 and N−C1−C2; 1124 and 1125 cm^{-1}, asymmetric stretching between C2−C3−C4, C1−C2−C3, and C3−C4−C5 and symmetric stretching between O−C6−C5. Note the small arrows pointing to the atoms of interest for a particular transition, drawn using the GaussianView software package.

spectra of the lowest energy conformers of **1** and **2** show a series of bands that depend on the conformational preferences, particularly of the tropic ester. Since these vibrations are related to a more flexible part of the molecule, the correlation between theoretical and experimental bands is expected to be less accurate than those arising from conformationally more restricted parts of the molecule, especially when a small-size basis set is used to calculate geometries, energies, and vibrational behavior. Additionally, these bands are not usable for absolute configuration determination of the whole molecule since they arise from an asymmetric center with the same configuration in both stereoisomers. Nevertheless, the spectral range between 950 and 1100 cm^{-1} shows at least three bands that can be assigned mainly to vibrations on the tropane ring (Figure 5), which remain unchanged in all low-energy conformers. Each band is composed by coupled interactions between different vibrations of the bonds in the tropane ring. The most intense of these three bands (1040 and 1041 cm^{-1} for **1** and **2**, respectively) is due to a coupled interaction between the four asymmetric stretching vibrations of C1−N−C5, N−C1−C2, N−C5−C4, and O−C6−C7. The band at 1084 cm^{-1} for both molecules is produced by the asymmetric stretching of O−C6−C7 and N−C1−C2, while the band at 1125 cm^{-1} is due to the asymmetric vibrations of C2−C3−C4, C1−C2−C3, and C3−C4−C5 and the symmetric stretching of O−C6−C6. These motions are mirror images between the diasteroisomers, and consequently, the produced bands show opposite intensities when comparing the spectra of **1** and **2**, and therefore can be used to assign the diastereoisomeric compounds. Since the C-H absorption of $CHCl_3$ occurs around 1200 cm^{-1}, the VCD spectra were acquired from $CDCl_3$ solutions whereby the C-D absorption is shifted to around 900 cm^{-1}.

When the calculated VCD spectra obtained from the low-energy conformers of **1** and **2**, using the Boltzmann distribution, derived from the energies of the optimized structures, are combined for each molecule in a single weighed plot, which is then compared

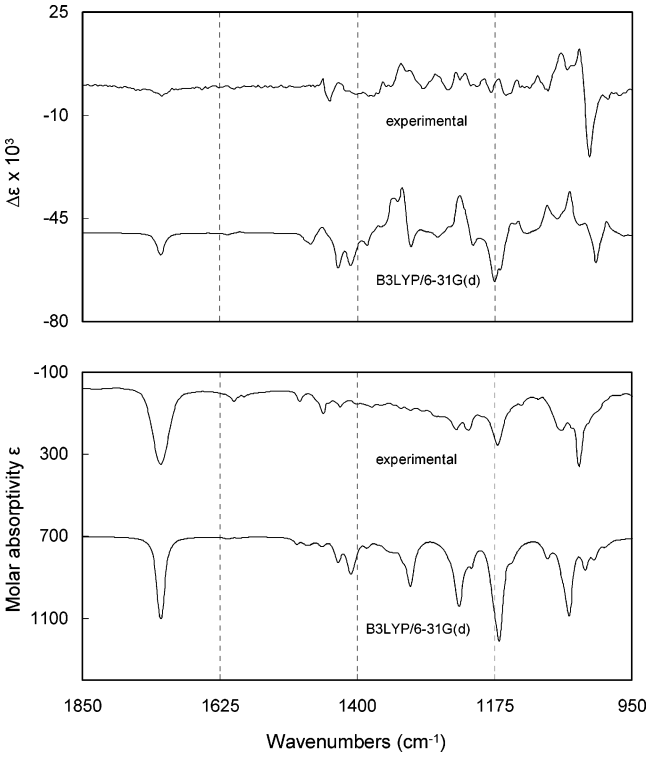

Figure 6. Comparison of observed and calculated IR absortion (bottom) and VCD spectra (top) of (3*R*,6*R*)-6β-hydroxyhyoscyamine (**1**).

with the experimental VCD spectra, as shown in Figures 6 and 7, respectively, the absolute configuration of both diastereoisomers follows unequivocally. The bands assigned to the tropane ring

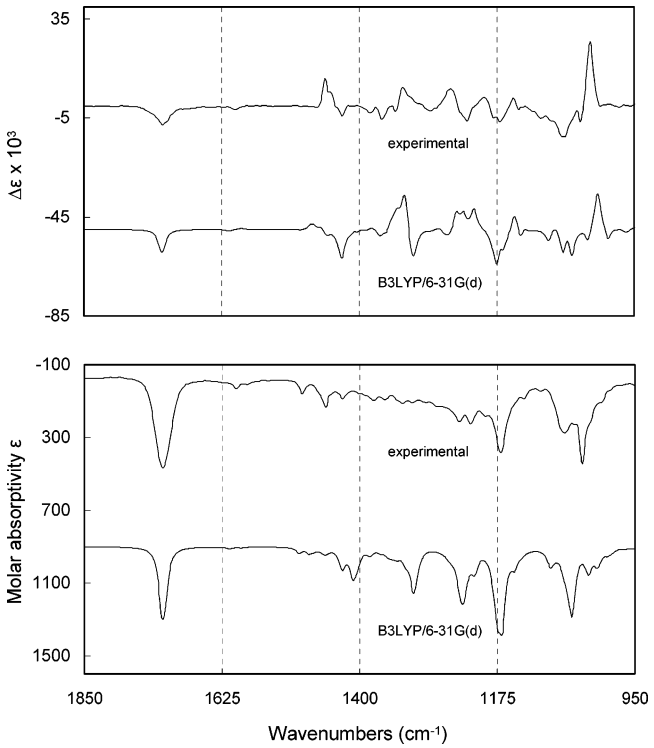

Figure 7. Comparison of observed and calculated IR absorption (bottom) and VCD spectra (top) of (3*S*,6*S*)-6*β*-hydroxyhyoscyamine (**2**).

vibrations clearly differentiate **1** from **2**, showing that the absolute configuration of (+)-6*β*-hydroxyhyoscyamine (**1**) is (3*R*,6*R*,2′*S*), and that for the diastereoisomeric (−)-6*β*-hydroxyhyoscyamine (**2**) is (3*S*,6*S*,2′*S*), as previously reported.[12] It further follows that, since some early publications[17,18,20] are already amended,[21,22] verification of configurational assignments, either by chemical correlation or by VDC measurements, remains to be done in some cases.[15,16,21−24]

Experimental Section

General Experimental Procedures. VCD measurements were performed on a dualPEM Chiral*IR* FT-VCD spectrophotometer at BioTools, Inc, Wauconda, IL. Samples of 10 mg were disolved in 200 μL of $CDCl_3$, placed in a BaF_2 cell with a path length of 100 μm, and data were acquired at a resolution of 4 cm^{-1} during 9 h. ^1H and ^{13}C NMR measurements were performed on Varian Mercury spectrometers using $CDCl_3$ solutions containing TMS as internal standard. Optical rotations $[\alpha]_D$ were measured using a Perkin-Elmer 341 polarimeter at 25 °C.

Computational Methods. Conformational searches were started using a Dreiding model guided systematic conformational search considering an initial energy cutoff of 10 kcal/mol above the global minimum. The minimum energy conformers were generated by varying the endocyclic tropane ring torsion angles in steps of 20° within the range allowed by the constrained geometry of the ring system and by allowing free rotation of other bonds in 30° increments. The searches were conducted independently starting from *syn* and *anti* N-Me group geometries and performing single-point energy calculations at the B3LYP/6-31G(d) level of theory for all MMFF94 conformations derived from the conformational searches. The different sets of conformers derived from the two N-Me group orientations in **1** and **2** were mixed, and the DFT energies were used in a Boltzmann distribution. The eight relevant conformations (accounting for 96.8% and 96.5% of the first 5 kcal/mol for **1** and **2**, respectively) were submitted to geometry optimizations and vibrational calculations using the DFT B3LYP hybrid functional, 6-31G(d) basis set, and the default integration grid size, FineGrid, corresponding to 75 radial shells and 302 angular points per shell. Conformational searches and single-point energy calculations were made using the Spartan'04 software package, while geometry optimizations and vibrational spectra were calculated using the Gaussian 03W software package. The conformational search was done only with the indicated force field method, while the ab initio calculations were performed with the described limited basis set size and a finite integration grid without considering solvent effects. Typical calculations required between 30 and 40 h of computational time per conformer when using a desktop personal computer (PC) with 2 Gb RAM operated at 3 GHz. Calculated dipole and rotational strengths were converted to molecular absorptivities (M^{-1} cm^{-1}) and then plotted as Lorentzian bands with half-widths of 6 cm^{-1}. The four lower energy conformers of **1**, which accounted for 82% of the conformational population in the initial 2 kcal/mol, were also calculated at the higher B3LYP/6-311G++(d) level of theory. On average, each conformer required some 200 h computing time, making this an inpractical procedure. The weighted calculated and experimental VCD curves are compared in Figure 1 of the Supporting Information and provide further evidence that calculations at the B3LYP/6-31G(d) level of theory are reliable for the diastereoisomeric distinction of **1** and **2**.

Preparation of 1 and 2. The two diasteroisomers of 6*β*-hydroxyhyoscyamine were prepared by catalytic hydrogenolysis of commercial (−)-scopolamine hydrobromide (Sigma-Aldrich) with Nickel Raney W1.[44] The separation of the resulting mixture [**1** (33.9%), **2** (41.7%), and (−)-hyoscyamine (19.7%)] was made using ion pair column chromatography with 1-heptanesulfonic acid sodium salt at pH 4 (buffer HOAc/AcONa 50 mM)/MeOH (17:3) as mobile phase and Varian C18 (40 μm) as stationary phase in a one-step procedure. Both methodologies were optimizations of previously reported procedures.[12] The three obtained compounds showed ^1H and ^{13}C NMR chemical shifts and specific rotations identical to those of natural samples.[12]

Supporting Information Available: Comparison of experimental and calculated VCD spectra of **1** using the B3LYP/6-311G++(d) level of theory, and DFT B3LYP/6-31G(d) atom coordinates for the eight low-energy conformers of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Lounasmaa, M.; Tamminen, T. In *The Alkaloids: Chemistry and Pharmacology*; Cordell G. A., Ed.; Academic Press: New York, 1993, Vol. 44, Chapter 1, pp 1−114.
(2) Wang, C.; Zhou, J. A.; Xie, J. Y.; Zhou, J. L.; Guan, H. P. *Thorac. Cardiovasc. Surg.* **1988**, *36*, 141−145.
(3) Zhang, S.; Chang, A. M.; Li, C. F.; Li, Z. J.; Yin, Z. J.; Zhao, X.; Liang, S. L. *Exp. Hematol.* **1987**, *15*, 65−71.
(4) Liu, X.; Zhang, J. *J. Tongji Med. Univ.* **1998**, *18*, 187−189; *Chem. Abstr.* **1999**, *130*, 204840m.
(5) Li, Q-B.; Rei, P.; Wang, G-F.; Tang, S-X. *J. Nat. Toxins* **1999**, *8*, 327−330; *Chem. Abstr.* **2000**, *132*, 116955p.
(6) Kursinszki, L.; Hank, H.; László, I.; Szöke, É. *J. Chrom. A* **2005**, *1091*, 32−39.
(7) Ye, N.; Zhu, R.; Gu, X.; Zou, H. *Biomed. Chromatogr.* **2001**, *15*, 509−512; *Chem. Abstr.* **2002**, *136*, 268264h.
(8) Wei, Y.; Li, J.; Zhu, C.; Hao, A.; Zhao, M. *Anal. Sci.* **2005**, *21*, 959−962; *Chem. Abstr.* **2005**, *143*, 254163g.
(9) Wang, Z.; Huang, A. J.; Sun, Y. L.; Sun, Z. P. *J. High Resolut. Chromatogr.* **1996**, *19*, 697−699; *Chem. Abstr.* **1997**, *126*, 268562x.
(10) Chen, H.; Wang, H.; Chen, Y.; Zhang, H. *J. Chromatogr. B* **2005**, *824*, 21−29.
(11) Fan, G. R.; Hong, Z. Y.; Lin, M.; Yin, X. P.; Wu, Y. T. *J. Chromatogr. B* **2004**, *809*, 265−271.
(12) Ishimaru, K.; Shimomura, K. *Phytochemistry* **1989**, *28*, 3507−3509.
(13) Hashimoto, T.; Kohno, J.; Yamada, Y. *Phytochemistry* **1989**, *28*, 1077−1082.
(14) Fodor, G.; Csepreghy, G. *J. Chem. Soc.* **1961**, 3222−3223.
(15) de la Fuente, G.; Reina, M.; Muñoz, O.; San Martín, A.; Girault, J.-P. *Heterocycles* **1988**, *27*, 1887−1897.
(16) Muñoz, O.; Hartmann, R.; Breitmaier, E. *J. Nat. Prod.* **1991**, *54*, 1094−1096.
(17) Fodor, G.; Vincze, I. W.; Tóth, J. *J. Chem. Soc.* **1961**, 3219−3221.
(18) Fodor, G.; Kovács, Ö. *J. Chem. Soc.* **1953**, 2341−2344.
(19) Hudson, C. S. *J. Am. Chem. Soc.* **1910**, *32*, 338−346.
(20) Fodor, G.; Koczor, I.; Janzsó, G. *Arch. Pharm.* **1962**, *295*, 91−95.
(21) Fodor, G.; Sóti, F. *Tetrahedron Lett.* **1964**, *29*, 1917−1921.
(22) Fodor, G.; Sóti, F. *J. Chem. Soc.* **1965**, 6830-6833.
(23) Romeike, A. *Naturwissenschaften* **1962**, *49*, 281.
(24) Griffin, W. J. *Naturwissenschaften* **1975**, *62*, 97.
(25) Zanolari, B.; Guilet, D.; Marston, A.; Queiroz, E. F.; Paulo, M. Q.; Hostettmann, K. *J. Nat. Prod.* **2005**, *68*, 1153−1158.
(26) Freedman, T. B.; Cao, X.; Dukor, R. K.; Nafie, L. A. *Chirality* **2003**, *15*, 743−758.

(27) Nafie, L. A.; Freedman, T. B. In *Circular Dichroism−Principles and Applications*, 2nd ed.; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: New York, 2000; Chapter 4, pp 97−131.
(28) Keiderling, T. A. In *Circular Dichroism−Principles and Applications*, 2nd ed.; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: New York, 2000; Chapter 22, pp 621−666.
(29) Lassen, P. R.; Skytte, D. M.; Hemmingsen, L.; Nielsen, S. F.; Freedman, T. B.; Nafie, L. A.; Christensen S. B. *J. Nat. Prod.* **2005**, *68*, 1603−1609.
(30) Monde, K.; Taniguchi, T.; Miura, N.; Kutschy, P.; Čurillová, Z.; Pilátová, M.; Mojžiš, J. *Bioorg. Med. Chem.* **2005**, *13*, 5206−5212.
(31) Cichewicz, R. H.; Clifford, L. J.; Lassen, P. R.; Cao, X.; Freedman, T. B.; Nafie, L. A.; Deschamps, J. D.; Kenyon, V. A.; Flanary, J. R.; Holman, T. R.; Crews, P. *Bioorg. Med. Chem.* **2005**, *13*, 5600−5612.
(32) Vargas, A.; Bonalumi, N.; Ferri, D.; Baiker, A. *J. Chem. Phys. A* **2006**, *110*, 1118−1127.
(33) Stephens, P. J.; McCann, D. M.; Devlin, F. J.; Flood, T. C.; Batkus, E.; Stončius, S.; Cheeseman, J. R. *J. Org. Chem.* **2005**, *70*, 3903−3913.
(34) Cerè V.; Peri, F.; Pollicino, S.; Ricci, A.; Devlin, F. J.; Stephens, P. J.; Gasparrini, F.; Rompietti, R.; Villani, C. *J. Org. Chem.* **2005**, *70*, 664−669.
(35) Nieman, J. A.; Keay, B. A.; Kubicki, M.; Yang, D.; Rauk, A.; Tsankov, D.; Wieser, H. *J. Org. Chem.* **1995**, *60*, 1918−1919.
(36) Bouř, P.; Navrátilová, H.; Setnička, V.; Urbanová, M.; Volka, K. *J. Org. Chem.* **2002**, *67*, 161−168.
(37) Wang, F.; Wang, H.; Polavarapu, P. L.; Rizzo, C. J. *J. Org. Chem.* **2001**, *66*, 3507−3512.
(38) Kuppens, T.; Vandyck, K.; Van der Eycken, J.; Herrebout, W.; van der Veken, B. J.; Bultinck, P. *J. Org. Chem.* **2005**, *70*, 9103−9114.
(39) Marcott, C.; Havel, H. A.; Overend, J.; Moscowitz, A. *J. Am. Chem. Soc.* **1978**, *100*, 7088−7089.
(40) Solladié-Cavallo, A.; Marsol, C.; Yaakoub, M.; Azyat, K.; Klein, A.; Roje, M.; Suteu, C.; Freedman, T. B.; Cao, X.; Nafie, L. A. *J. Org. Chem.* **2003**, *68*, 7308−7315.
(41) Yagudaev, M. R.; Aripova, S. F. *Khim. Prir. Soedin.* **1986**, 80−84; *Chem. Nat. Compd.* **1986**, *22*, 74−78.
(42) Kuppens, T.; Langenaeker, W.; Tollenaere, J. P.; Bultinck, P. *J. Phys. Chem. A* **2003**, *107*, 542−553.
(43) Furo, T.; Mori, T.; Wada, T.; Inoue, Y. *J. Am. Chem. Soc.* **2005**, *127*, 8242−8243.
(44) Augustine, R. L. *Catalytic Hydrogenation: Techniques and Applications in Organic Synthesis*; Marcel Dekker Inc.: New York, 1965; p 27.

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