3, giving 1,8-dihydropentalene **5** and thence other DHPs, that is the slow step.[4,7] A portion of the C_8H_8 energy hypersurface involving SBV (**1**), COT (**2**), and intermediate **3** is shown in Figure 1.

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Registry No. 1, 6909-37-1; **2**, 629-20-9.

Stereospecific Total Synthesis of (±)-Gephyrotoxin 223AB

Hideo Iida, Yohya Watanabe, and Chihiro Kibayashi*

Tokyo College of Pharmacy
Horinouchi, Hachioji, Tokyo 192-03, Japan

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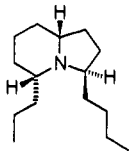
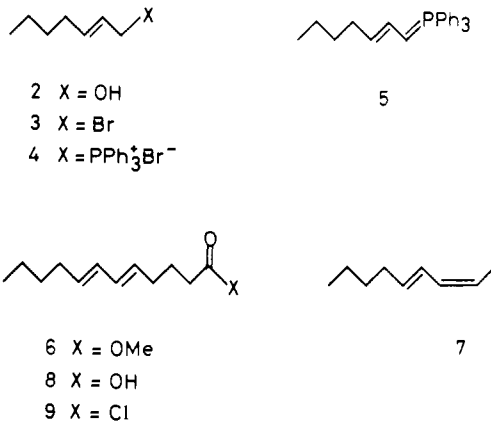
Gephyrotoxin (GTX) 223AB (**1**), one of the neurotoxin alka-



1

loids isolated in minute quantity from skin extracts of neotropical poison-dart frogs (family Dendrobatidae),[1,2] has attracted a vast amount of interest because of its unusual biological characteristics. Numerous groups have thus been involved in the development of methodology for the total synthesis of this molecule. These efforts have recently resulted in the syntheses of stereoisomers of **1**[3-5] and also (−)-**1**.[6] Herein, we report on the efficient preparation of (±)-GTX 223AB based upon an acyl nitroso Diels–Alder reaction[7] with *complete* stereochemical control. Our synthesis is distinguished from these previous efforts[3-6] by the fact that *the entire sequence provided single stereoisomers in the desired sense and thus met with no separation problems.*

Reduction of ethyl (*E*)-2-heptenoate, prepared by the Wittig reaction of 4-pentanal with (ethoxycarbonyl)methylene triphenylphosphorane, with AlH_3 in ether afforded the alcohol **2** (80%), bp 78–80 °C (16 mmHg). Bromination of **2** with PBr_3 (petroleum ether, −10 °C) followed by treatment of the resultant bromide **3**, bp 64–65 °C (16 mmHg), with Ph_3P provided the phosphonium bromide **4**, mp 159–161 °C. The ylide **5** derived from **4** (*n*-BuLi, THF, −5 °C) was treated with methyl 5-oxopentanoate[8] in THF–HMPA (9:1) at −5 °C to produce methyl 5,7-dodecadienoate in 89% yield. Since the resulting material included 25% (by ^1H NMR) of the 5*Z*,7*E* isomer **7**, it was con-



2 X = OH
3 X = Br
4 X = $PPh_3^+Br^-$

5

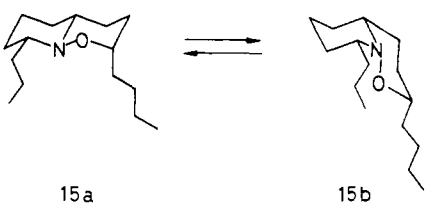
6 X = OMe
8 X = OH
9 X = Cl

7

verted to the isomerically pure (5*E*,7*E*)-ester **6** by irradiation (hexane, I_2). Saponification of **6** and chlorination (ClCOCOCl, benzene) of the resultant acid **8** gave the acid chloride **9**, which was allowed to react with hydroxylamine under aqueous alkaline conditions to form hydroxamic acid **10**, mp 78–80 °C, in 58% overall yield from the ester **6**. The yield of this construction was improved when the ester **6** was exposed to hydroxylamine in methanolic KOH at room temperature (15 h). In this manner the pure hydroxamic acid **10** was directly obtained from the ester **6** in 81% yield after collecting crystalline product followed by simple recrystallization (hexane).

Treatment of this hydroxamic acid with tetrapropylammonium (meta)periodate in chloroform (0–5 °C) generated in situ the acyl nitroso compound **11**. Under the reaction conditions, **11** underwent intramolecular [4 + 2] cycloaddition to give as the sole product the 1,2-oxazine derivative **12** in 82% yield after purification by silica gel chromatography (benzene/chloroform, 1:1). Hydrogenation (Pd/C, H_2, MeOH) of **12** provided **13** in 90% yield. Then **13** was treated with the Grignard reagent in ether at ambient temperature to give somewhat unstable enamine **14** (89%), which was subsequently subjected to reduction with $NaCNBH_3$ in methanol at pH 3.8–5.4 (10% HCl/MeOH, bromcresol green) resulting in the exclusive formation of **15** (70%).

The ^{13}C NMR spectrum[9] of **15** at 24 °C showed pairs of resonances for each of the carbons in the molecule. The relative intensity of each doublet was nearly unit independent of temperature and the doublet collapsed into a single line at high temperature depending on its peak separation. These observations strongly indicate that **15** exists in conformational equilibrium between **15a** and **15b** (eq 1) due to nitrogen inversion with nearly



15a 15b (1)

equal population energy barrier ($\Delta G^{\ddagger}$), estimated to be about 8.0 kcal mol^{-1}.[10]

The ^1H NMR spectra (270 MHz) in pyridine-d_5 of **15** at 27.5 °C showed two sets of multiplets at δ 3.87 ($W_{1/4}$ = 23.9 Hz) and 3.72 ($W_{1/4}$ = 31.6 Hz) with an integration ratio of 10:9 for the C-2 proton, indicative of the equatorial hydrogen in **15a** and the axial hydrogen in **15b**, respectively. These C-2 proton signals converged to a single resonance centered at δ 3.88 at 100 °C.

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(4) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 103.
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(7) For recent entries into natural products utilizing nitroso Diels–Alder reaction, see: (a) Leonard, N. J. Playtis, A. J. *J. Chem. Soc., Chem. Commun.* **1972**, 133. (b) Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632. (c) Keck, G. E.; Webb, R. R., II *J. Org. Chem.* **1982**, *47*, 1302. (d) Baldwin, J. E.; Bailey, P. D.; Gallacher, G.; Singleton, K. A.; Wallace, P. M. *J. Chem. Soc., Chem. Commun.* **1983**, 1049. (e) Iida, H.; Watanabe, Y.; Kibayashi, C. *Tetrahedron Lett.* **1984**, *25*, 5091.
(8) Prepared from 5-pentanolide according to: Huckstep, M.; Taylor, R. J. K.; Caton, M. P. L. *Synthesis* **1982**, 881.
(9) A series of ^{13}C NMR spectra (50.1 MHz) of **15** were taken under the gated proton-decoupled condition without NOE as a function of temperature in the range of 24 to 100 °C.
(10) The exchange rates (R) between **15a** and **15b** were calculated from temperature dependence of the peak separations for several sets of doublets in the spectrum using the exchanged Bloch equation.[11] Plots of ln R vs. $1/T$ exhibited a straight line, from which the $\Delta G^{\ddagger}$ was calculated.
(11) Becker, E. D. "High Resolution NMR", 2nd ed.; Academic Press: New York, 1980; p 243.

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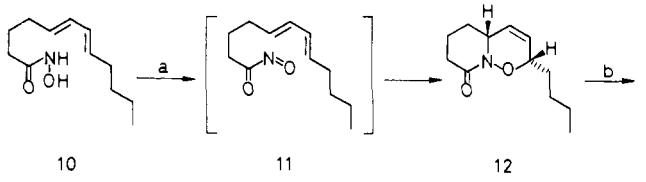
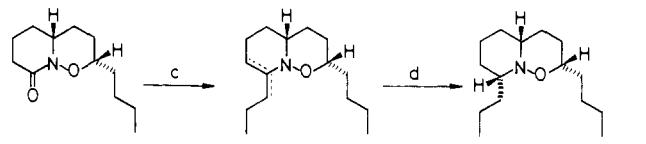
Scheme I



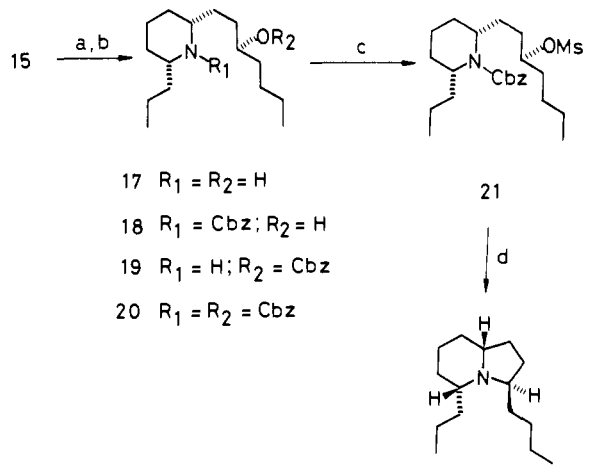
10 11 12



13 14 15

[a] (a) n-$Pr_4N(IO_4)$, $CHCl_3$, 0 → 5 °C, 1 h; (b) H_2, 5% Pd/C, MeOH. (c) n-PrMgBr, Et_2O, 0 °C → room temperature, 1 h. (d) $NaCNBH_3$, MeOH, pH 3.8-5.4 (HCl/MeOH, bromcresol green), 0 °C → room temperature, 1 h.

Scheme II[a]



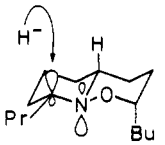
17 $R_1 = R_2 = H$
18 R_1 = Cbz; $R_2 = H$
19 $R_1 = H$; R_2 = Cbz
20 $R_1 = R_2$ = Cbz

21

1

[a] (a) Zn, AcOH-H_2O (6:4), 60 °C, 90 h; (b) $PhCH_2OCOCl$, aqueous Na_2CO_3, $CHCl_3$, 0 °C → room temperature, 2 h; (c) MsCl, NEt_3, CH_2Cl_2, -10 °C, 5 min; (d) H_2 (1 atm), 5% Pd/C, MeOH, room temperature, 5 h.

The exclusive formation of **15** can be rationalized to be a result of stereoelectronically controlled reaction of the transient iminium salt generated from **14** under acidic conditions. Due to inversion at nitrogen, there are thus four possible transition states[12] which maintain maximum orbital overap with respect to the approaching hydride ion and the developing nitrogen lone pair. Two of these are boat shaped and the other two are of more stable chair shape. One of the latter is disfavored due to a strong peri interaction between the butyl group and the incoming hydride ion. On the other hand, transition state **16** can accommodate the entering



16

hydride ion without steric interference of the 2-alkyl side chain thereby leading to **15**.

With the required stereochemistry thus established, the only requirement in order to complete the synthesis was constructing the pyrrolidine moiety of the target molecule. Reductive cleavage (Zn, aqueous AcOH) of the N-O bond in **15** gave the amino alcohol **17** (85%), mp 52-55 °C. Exposure of this material to benzyl chloroformate in an alkaline solution furnished the hydroxy carbamate **18** (36%), along with **19** (24%) and **20** (25%), the latter two product of which could easily be hydrogenated back to the amino alcohol **17**. Thus actual yield of **18** based on recovered **17** was 71%.

Finally, the hydroxy carbamate **18** was converted to the mesylate **21** (MsCl, NEt_3, -10 °C, ca. 5 min; 83%) which upon hydrogenation (Pd/C, MeOH, 1 atm) provided GTX 223AB (**1**) in 81% yield as the sole product. Synthetic material thus prepared was found to have identical spectra (^1H NMR, ^{13}C NMR,[13] and mass[14]) with those of natural GTX 223AB.[15,16]

Acknowledgment. We thank Dr. H. Shindo, Tokyo College of Pharmacy, for his helpful discussion in estimation of $\Delta G^{\ddagger}$.

(12) Stevens, R. F.; Lee, A. W. *J. Am. Chem. Soc.* **1979**, *101*, 7032.

(13) The ^{13}C NMR spectrum ($CDCl_3$, 67.8 MHz) of synthetic GTX 223AB was as follows: δ 14.2 (q), 14.5 (q), 19.0 (t), 23.0 (t), 24.6 (t), 25.1 (t), 26.4 (t), 29.1 (t), 30.0 (t), 30.8 (t), 32.2 (t), 35.8 (t), 56.8 (d), 58.6 (d), 59.3 (d).

(14) The mass spectrum of synthetic GTX 223AB was as follows: m/z (relative intensity) 223 (2), 222 (3), 181 (14), 180 (99), 167 (14), 166 (100), 124 (6), 122 (3), 81 (6), 55 (13); exact mass calcd for $C_{15}H_{29}N$, m/z 223.2300, found 223.2297.

(15) We thank Drs. J. W. Daly, NIH, and T. Tokuyama, Osaka City University, for the ^{13}C NMR data and ^1H NMR spectrum of natural GTX 223AB.

(16) The mass spectrum of natural GTX 223AB has appeared in ref 2.

Internal Molecular Motion as Forerunner of a Phase Change Involving Conformational Isomerization

Qing-Chuan Yang,† Mary Frances Richardson,‡ and Jack D. Dunitz*

Organic Chemistry Laboratory of the Swiss Federal Institute of Technology CH-8092 Zürich, Switzerland

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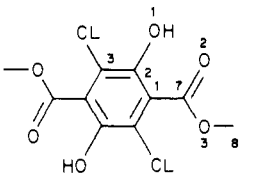
The notion that the vibrational behavior of a molecule in its electronic ground state is related to the pathways for its unimolecular reactions is intuitively appealing.[1] Experimental evidence relevant to this question is, however, hard to come by. Nevertheless, information about internal motions of molecules in crystals can be obtained, in principle and sometimes in practice, by analysis of the anisotropic Gaussian displacement parameters from diffraction studies.[2] In this paper we describe variable-temperature x-ray diffraction results that show a connection between internal molecular motion and conformational isomerization for dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate (**1**).



1

The thermally induced solid-state transformation of a yellow into a white crystalline modification of **1** was observed by Hantzsch[3] and studied extensively in recent years.[4-6] The yellow

† On leave from Peking University, China.
‡ On leave from Brock University, St. Catharines, Ontario, Canada.

(1) See: Swanson, B. I. *J. Am. Chem. Soc.* **1976**, *98*, 3067-3071 for a more formal statement of the relationship between molecular vibrations and reaction coordinates.

(2) Trueblood, K. N.; Dunitz, J. D. *Acta Crystallogr., Sect. B* **1983**, *39B*, 120-133.

(3) Hantzsch, A. *Chem. Ber.* **1915**, *48*, 797-816.

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