accounting for the observed selectivity.[12,13]

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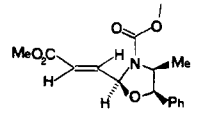
Registry No. 2, 105226-55-9; 3a, 105140-27-0; 3b, 105140-28-1; 3c, 105140-29-2; 3d, 105140-32-7; 3e, 105140-30-5; 3f, 105140-31-6; 4a, 105226-56-0; 4a (1,4-diol), 70423-38-0; 4b, 71633-61-9; 4c, 71464-83-0; 4d, 71464-84-1; Bu_2CuLi, 24406-16-4; Me_2CuLi, 15681-48-8; Et_2CuLi, 38297-20-0; $(CH_2{=}CH)_2CuLi$, 22903-99-7; $(CH_2{=}CHCH_2)_2CuLi$, 21500-57-2.

Supplementary Material Available: ^1H and ^{13}C NMR data for compounds **3a–f** and ^1H NMR data for ester **2** and for aldehydes **4a–d** (2 pages). Ordering information is given on any current masthead page.

(12) To assess this point we performed MM calculations on model compound **5** which, upon cuprate addition, shows the same stereoselectivity as **2**. It turned out that, at ground-state level, B-type conformer is disfavored over A-type by 1.5 kcal/mol.



5

(13) As pointed out by one of the referees, metal coordination phenomena, by either the allylic oxygen or the carbamate group could also be important in determining the stereochemical outcome. Further work is in progress to clarify this aspect.

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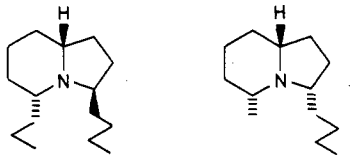
A Short Total Synthesis of (±)-Gephyrotoxin-223AB

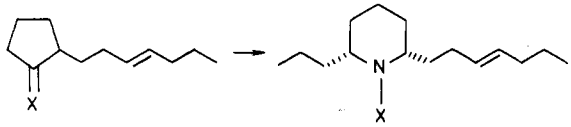
Summary: (±)-Gephyrotoxin-223AB has been synthesized from 2-carbomethoxycyclopentanone in nine steps by a route utilizing the stereoselective homolytic cyclization of an alkenyl-substituted *N*-chloropiperidine.

Sir: Recent years have witnessed a proliferation of synthetic strategies based upon the intramolecular cyclization reactions of carbon-centered radicals.[1] By contrast, the synthetic potential of nitrogen-centered radicals[2] has not been as frequently exploited. Surzur and Stella[3] have shown that metal-complexed aminyl radicals can be generated under mild conditions by treatment of the corresponding *N*-chloramines with a variety of reducing metal salts including titanium trichloride, iron(II) chloride, and copper(I) chloride (with or without added copper(II) chloride). The species so produced undergo intramolecular addition to double bonds in much the same manner as their carbon-centered radical counterparts. The facility of these cyclizations coupled with the ready availability of both *cis*- and *trans*-2,6-dialkylpiperidines[4] suggested to us the possibility of using aminyl radical heterocyclizations for the construction of indolizidine alkaloids such as gephyrotoxin-223AB (**1**)[5] and monomorine (**2**).[6] We now report a short stereoselective synthesis of gephyrotoxin-223AB,[7] a constituent of the skin extracts of neotropical poison-dart frogs (family Dendrobatidae).



1 2

Alkylation of the dianion of 3-butynol[8] with *n*-propyl bromide [*n*-PrBr (1.1 equiv), THF–HMPA (3:1), −78 → 20 °C, 6 h] generated 3-heptynol in 91% yield. Reduction of this material with sodium in liquid ammonia [1 h, NH_4Cl quench] provided (*E*)-3-heptenol in 95% yield (stereohomogeneous by ^{13}C NMR). This alcohol was converted to its mesylate [MsCl (1.1 equiv), NEt_3, CH_2Cl_2, 0 °C, 1 h] in quantitative yield and the crude mesylate was used to alkylate the sodium enolate of 2-carbomethoxycyclopentanone[9] [toluene, reflux, 6 h]. Decarbomethoxylation[10] of the resulting crude β-keto ester [NaCN, H_2O, Me_2SO, 140 °C, 70 min] gave the (*E*)-alkenylcyclopentanone **3**[11] in 53% overall yield from 2-carbomethoxycyclopentanone.



3, X = O
4, X = NOH

5, X = H
6, X = Cl

Treatment of **3** with hydroxylamine hydrochloride and sodium acetate in methanol gave the anti oxime **4** (70%). Oxime **4** was then converted into the 2,6-cis-disubstituted piperidine **5** under the conditions defined by Yamamoto[4a] [(i) MsCl, NEt_3, CH_2Cl_2, −20 °C, 30 min; (ii) Al(*n*-Pr)$_3$ (3 equiv), CH_2Cl_2–toluene (7:2), −78 → 20 °C, 1 h; (iii) DIBAL (2 equiv), CH_2Cl_2, −78 °C/2 h, 0 °C/2 h]. Piperidine **5** was obtained in 41% yield after flash chromatography on silica

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(2) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337.
(3) (a) Surzur, J. M.; Stella, L.; Tordo, P. *Bull. Soc. Chim. Fr.* **1970**, 115. (b) Surzur, J. M.; Stella, L.; Tordo, P. *Tetrahedron Lett.* **1970**, 3107. (c) Surzur, J. M.; Stella, L.; Nouguier, R. *Tetrahedron Lett.* **1971**, 903. (d) Surzur, J. M.; Stella, L. *Tetrahedron Lett.* **1974**, 2191. (e) Bougeois, J.-C.; Stella, L; Surzur, J. M. *Tetrahedron Lett.* **1981**, 61.

(4) For instance: (a) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, M.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831. (b) Meyers, A. I.; Edwards, P. D.; Bailey, T. R.; Jagdmann, G. E. *J. Org. Chem.* **1985**, *50*, 1019. (c) Nakazono, Y.; Yamaguchi, R.; Kawanisi, M. *Chem. Lett.* **1984**, 1129. (d) Clive, D. L. J.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Org. Chem.* **1980**, *45*, 2120. (e) Harding, K. E.; Marmah, T. H. *J. Org. Chem.* **1984**, *49*, 2838. (f) Abe, K.; Okumura, H.; Tsugoshi, T.; Nakamura, N. *Synthesis* **1984**, 597.
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(6) Ritter, F. J.; Rotgans, I. E. M.; Talman, E.; Vermiel, P. E. J.; Stein, F. *Experientia* **1973**, *29*, 530.
(7) For other syntheses of 1, see: (a) Macdonald, T. L. *J. Org. Chem.* **1980**, *45*, 193. (b) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534. (c) Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, 1515. For syntheses of stereoisomers of 1, see: (d) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 103. (e) Hart, D. J.; Tsai, Y. M. *J. Org. Chem.* **1982**, *47*, 4403. For two more recent syntheses of 1 and a comprehensive review of work in this area, see: Daly, J. W.; Spande, Th. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1986; Vol. 4, p 1.
(8) See: Chin, S. K.; Peterson, P. E. *Tetrahedron Lett.* **1980**, 4047.
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(10) Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. *Tetrahedron Lett.* **1967**, 215.
(11) New compounds except **6**, **8**, and **10** were fully characterized by ^1H NMR, IR, and HRMS and/or microanalysis. The rather labile chloramines were characterized by ^1H and ^{13}C NMR. All were stereohomogeneous.

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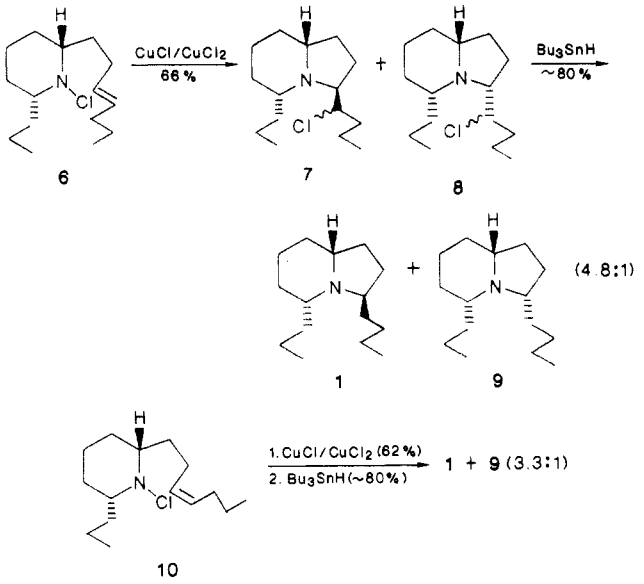
gel (eluting with a solution of 12% methanolic ammonia in chloroform). The DIBAL reduction of the intermediate imine proceed with near total stereoselectivity as expected.[4a] The 2,6-cis stereochemistry of piperidine **5** was established by examination of its ^{13}C NMR spectrum which showed azamethine signals at 56.4 and 56.6 ppm, characteristically downfield from their typical values in 2,6-trans-disubstituted piperidine systems.[12] Chlorination of piperidine **5** [NCS (1.05 equiv), Et_2O, 0 °C/1 h] gave *N*-chloroamine derivative **6** in 86% yield.

The *Z* double bond isomer of *N*-chloroamine **6** was also prepared. Hydrogenation of 3-heptynol [Lindlar catalyst, 1 atm H_2, benzene containing a trace of quinoline] gave (*Z*)-3-heptenol in 97% yield (stereohomogeneous by ^{13}C NMR). Conversion of the *Z* alcohol to the (*Z*)-*N*-chloropiperidine **10** was accomplished in the manner described for the *E* isomer.



Cyclization of chloroamines **6** and **10** was best effected at −45 °C in THF–acetic acid–water (6:1:1) by using the copper(I) chloride–copper(II) chloride redox system.[13] The diastereomeric chloroindolizidines **7** and **8** were obtained in good yield after chromatography (silica gel, 2% MeOH in dichloromethane). Under these conditions regeneration of the parent secondary amines did not take place to any significant extent. Dechlorination of **7** and **8** proceeded with remarkable ease [Bu_3SnH (2.5 equiv), AIBN (0.25 equiv), benzene, reflux, chloroindolizidines added over 20 min and reaction continued 45 min longer], giving **1** and **9**. Synthetic **1** had MS,[14] IR, and ^{13}C NMR[15] spectra which were in agreement with those reported for gephyrotoxin-223AB.[16] The ^{13}C NMR and mass spectra of the epimer **9** also matched closely those reported in the literature.[5]

Thin-layer chromatography and ^{13}C NMR showed the chloroindolizidine mixtures to consist primarily of two diastereomers (ratio 3–5:1 depending on reaction conditions and double bond geometry of the *N*-chloropiperidine starting material) accounting for at least 85% of the material as well as two minor diastereomers. Careful chromatographic separation gave pure samples of the major diastereomers. Tributyltin hydride reduction of the first-eluted compound, which was invariably formed in lesser amount, gave epimer **9**, whereas reduction of the other gave **1**. The yields obtained in both reductions were essentially identical. Structure **8** can therefore be assigned to the former diastereomer and structure **7** to the latter. One may also conclude that the ratio of **1** to **9** obtained on reduction of the unseparated chloroindolizidine mixtures[17] provides a reasonably accurate reflection of the stereoselectivity of the initial radical cyclization. We have not been able to assign the stereochemistry at the chlorine-bearing carbons of our major diastereomers with confidence. It is interesting that the same two major diastereomers are produced in the cyclizations of both the (*E*)- and (*Z*)-*N*-chloropiperidines.[18]

The factors responsible for the stereoselectivity demonstrated in the cyclizations of **6** and **10** are not easily identified. The two side chains effectively lock the piperidine ring in that chair conformation in which both are equatorial. If it is assumed that in the transition state the newly forming carbon–nitrogen bond is disposed equatorially with respect to the piperidine ring, the stereoselectivity displayed by these cyclizations parallels that observed in comparable cyclizations of cyclohexyl and cyclohexenyl radicals.[19]

In conclusion we have shown that the homolytic cyclization of alkenyl substituted *N*-chloropiperidines provides a facile and stereoselective route to the indolizidine ring system. Cyclization followed by dechlorination of the resulting products affords, in overall effect, a means of adding a secondary amine across an unactive carbon–carbon double bond. We expect that variations of this method will prove useful for the synthesis of a number of alkaloids, and our studies in this area will continue.

Acknowledgment. We thank the Research Board of the University of Illinois, Research Corporation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

Registry No. (±)-**1**, 81076-50-8; (±)-(*E*)-**3**, 105281-69-4; (±)-(*Z*)-**3**, 105281-70-7; (±)-(*E,E*)-**4**, 105281-71-8; (±)-(*E,E*)-**4** (mesylate), 105281-73-0; (±)-(*E,Z*)-**4**, 105281-72-9; (±)-(*E,Z*)-**4** (mesylate), 105281-74-1; (±)-(*E*)-**5**, 105281-75-2; (±)-(*Z*)-**5**, 105369-38-8; (±)-(*E*)-**6**, 105281-76-3; (±)-(*Z*)-**6**, 105369-39-9; **7**, 105281-77-4; (±)-**9**, 81076-52-0; (*E*)-3-hepten-1-ol, 2108-05-6; (*Z*)-3-hepten-7-ol, 1708-81-2; (*E*)-3-heptenyl mesylate, 105281-65-0;

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(13) A solution of chloramine **6** or **10** (0.33 mmol) in 4 mL of THF was cooled to −45 °C (under argon) and treated over 2 min with a solution of CuCl (0.1 equiv) and $CuCl_2$ (1.0 equiv) in 4 mL of THF/AcOH/H_2O (2:1:1). (Solvents were purged with argon to remove dissolved oxygen). The solution was stirred at −45 °C for 40 min. Some freezing of the solvent invariably takes place but has no detrimental effect on the reaction. It was allowed to warm to 0 °C and stirred 2 min and again cooled to −45 °C. The reaction mixture was basified with excess 5 N NaOH solution and the product quickly extracted with CH_2Cl_2. These cyclizations can be performed at higher temperatures; however, their stereoselectivity is eroded considerably.

(14) Mass spectrum of synthetic gephyrotoxin-223AB (70-eV electron impact): *m/z* (relative intensity) 223 (4), 222 (3), 181 (15), 180 (99), 167 (17), 166 (100), 124 (23), 122 (6), 96 (6), 81 (9), 67 (11), 55 (16), 41 (18).

(15) ^{13}C NMR ($CDCl_3$) spectrum of synthetic gephyrotoxin-223AB: δ 59.2, 58.5, 56.8, 35.5, 31.9, 30.5, 29.8, 29.0, 26.2, 25.1, 24.5, 22.9, 18.9, 14.4, 14.1.

(16) For mass spectra of gephyrotoxin-223AB see ref 5 and 7b. For ^{13}C NMR spectra of gephyrotoxin-223AB see ref 5 and 7a–c.

(17) Determined by GC analysis[5] of crude reaction mixtures.

(18) It has been reported[3e] that (*E*)- and (*Z*)-*N*-chloro-*N*-methyl-4-hexenylamine cyclize with high stereospecificity in the presence of copper(I) chloride/copper(II) chloride giving diastereomeric chloroethyl pyrrolidines resulting from the formal anti addition of nitrogen and chlorine radicals across the double bond. It was suggested that this stereospecificity might derive from simultaneous complexation of the newly formed carbon-centered radical and the nitrogen lone pair by the metal salt leading to hindered rotation of the radical center around that bond connecting it to the pyrrolidine ring. In our less conformationally flexible indolizidine ring system such intramolecular complexation would be expected to prove energetically disadvantageous.

(19) Beckwith, A. L. J.; Phillipov, G.; Serelis, A. K. *Tetrahedron Lett.* **1981**, 2811. (b) Chuang, C.-P.; Hart, D. J. *J. Org. Chem.* **1983**, *48*, 1782.

(Z)-3-heptenyl mesylate, 105281-66-1; (±)-2-carbomethoxycyclopentanone, 53229-93-9; (±)-2-(3(E)-hepten-1-yl)-2-carbomethoxycyclopentanone, 105281-67-2; (±)-2-(3(Z)-hepten-1-yl)-2-carbomethoxycyclopentanone, 105281-68-3; 3-heptynol, 14916-79-1.

Supplementary Material Available: Experimental procedures for compounds 1 and 3–9 (5 pages). Ordering information is given on any current masthead page.

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Reaction of (α-Thioalkyl)chromium Compounds Prepared by Chromium(II) Reduction of α-Halo Sulfides

Summary: Reduction of α-chloroalkyl phenyl (or methyl) sulfides with chromium(II) chloride in THF proceeds smoothly in the presence of LiI. The resulting (α-thioalkyl)chromium reagents add to aldehydes in a chemo- and stereoselective manner.

Sir: Because of the versatility of sulfur, carbanions stabilized by adjacent sulfur are widely employed in organic synthesis.[1] The preparation of α-thio carbanions, compared to their sulfinyl[2] or sulfonyl counterparts,[3] requires very strong base combinations such as BuLi–DABCO,[4a] BuLi–TMEDA,[4b] or *t*-BuLi–HMPA.[4c,5] We report here that α-phenyl (or -methyl) thio carbanions are produced smoothly by chromium(II) reduction[6,7] of the corresponding α-halo sulfides (Scheme I).[8] The resulting (α-thioalkyl)chromium reagents add to aldehydes in a chemo- and stereoselective manner which could not be achieved by employing the former strong-base combinations.

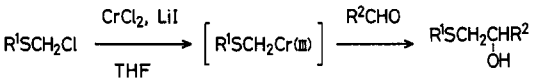
A typical procedure is as follows. To a stirring suspension of commercial $CrCl_2$[9] (0.49 g, 4.0 mmol) in THF (6 mL) at 25 °C under an argon atmosphere was added successively a solution of benzaldehyde (0.11 g, 1.0 mmol) in THF (2 mL), chloromethyl methyl sulfide (0.17 mL, 2.0 mmol), and a THF solution of LiI (1.0 M, 2.0 mL, 2.0 mmol). The resulting mixture was stirred at 40 °C for 5 h and then poured into water (25 mL). The mixture was extracted with ether (3 × 15 mL), and the combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel column (5:1 hexane–ethyl acetate) gave 2-(methylthio)-1-phenyl-1-ethanol (1) in 88% (0.15 g) yield.[10,11] The yield of 1 without LiI was 16% even at 60 °C for 6 h. Lithium iodide is added to generate in situ iodomethyl methyl sulfide[12] which is reduced smoothly with $CrCl_2$.

Table I. Reaction of α-Halo Sulfides with Aldehydes Using $CrCl_2$[a]

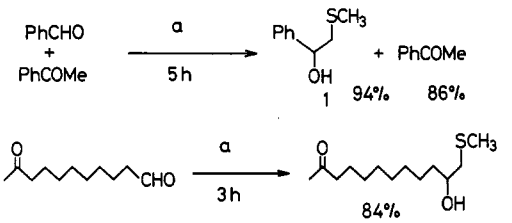
run	α-halo sulfide, R^1	aldehyde, R^2	temp, °C	time, h	yeild,[b] %
1	Me	Ph	40	5	88
2		Oct	40	9	72
3		PrCH=CH	40	13	64
4	Ph	Ph	60	10	63[c]
5		Oct	40	10	48[d]

[a] The aldehyde (1.0 mmol) was treated with α-halo sulfide (2.0 mmol), LiI (2.0 mmol), and $CrCl_2$ (4.0 mmol) in THF. [b] Isolated yields. [c] Reaction was conducted without LiI. [d] Four mmoles of α-halo sulfide, 4.0 mmol of LiI, and 8.0 mmol of $CrCl_2$ were employed per mol of the aldehyde.

Scheme I



Scheme II



(a) CH_3SCH_2Cl, $CrCl_2$, LiI, THF, 40°C

The addition of the [(methylthio)methyl]chromium (or [(phenylthio)methyl]chromium) reagent to several aldehydes is summarized in Table I. In the reaction of an α,β-unsaturated aldehyde, the 1,2-addition product was produced exclusively (run 3).[6]

Treatment of a mixture of benzaldehyde and acetophenone at −78 °C with [(methylthio)methyl]lithium, prepared by using the BuLi–TMEDA system, gave a mixture of 1 and 1-(methylthio)-2-phenyl-2-propanol (2) in a 7:5 ratio, in our hands. In contrast, the chromium reagent reported here reacts with an aldehyde selectively (Scheme II).[6]

(1) For reviews, see: Peterson, D. J. *Organomet. Chem. Rev. A* **1972**, *7*, 295. Stowell, J. C. *Carbanions in Organic Synthesis*; Wiley: New York, 1979; pp 90–115.

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(6) For reactions with organochromium reagents, see: (a) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048 and references cited therein.

(7) Other reducing agents have been examined in the reaction between chloromethyl methyl sulfide and benzaldehyde. Among them, zinc has also proved to promote the reaction (23% yield of 1). Little or no adduct was obtained with the following reducing agents: VCl_3–$LiAlH_4$, Mn, $MnCl_2$–$LiAlH_4$, Sn, $SnCl_2$, SmI_2, and Bi.

(8) α-Halo sulfides were prepared by chlorination of the corresponding sulfides with *N*-chlorosuccinimide in CCl_4 and were used after filtration and removal of the solvent in vacuo. Tuleen, D. L.; Stephens, T. B. *Chem. Ind. (London)* **1966**, 1555.

(9) Anhydrous $CrCl_2$ (90% assay) was purchased from Aldrich Chemical Co.

(10) During the reaction, benzyl alcohol and 1,2-diphenyl-1,2-ethanediol were not observed (<1%).

(11) Treatment of a mixture of benzaldehyde and $CrCl_2$ with (or without) LiI in THF at 40 °C for 5 h resulted in recovery of benzaldehyde (93% or 94%) along with 1,2-diphenyl-1,2-ethanediol (<5%). Benzyl alcohol was not detected. These observations suggest to eliminate another possibility for the reaction path that the carbonyl moiety is attacked first by Cr(II) to yield Cr(III)–O–CRH–Cr(III) and this anion attacks the (phenyl- or (methylthio)methyl iodide. See, Castro, C. E.; Kray, W. C., Jr. *J. Am. Chem. Soc.* **1966**, *88*, 4447. Davis, D. D.; Bigelow, W. B. Ibid. **1970**, *92*, 5127.

(12) Ronald, R. C. *Tetrahedron Lett.* **1973**, 3831.

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