Enantioselective Ru-Mediated Synthesis of (−)-Indolizidine 223AB

Douglass F. Taber,* P. Bruce Deker, and Lee J. Silverberg

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

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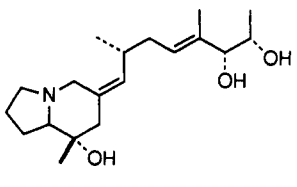
Triphenylphosphine/CCl_4-mediated cyclization of amino alcohol **17** proceeded smoothly, *with single inversion*, to provide (−)-indolizidine 223AB **4**. Amino alcohol **17** was prepared by thermolysis of azide **16**, followed by DIBAL reduction of the intermediate imine. Symchiral aldehyde **12** and phosphonium salt **15**, precursors to **16**, were prepared by BINAP·Ru*-mediated hydrogenation of the corresponding β-keto esters. A simplified procedure allows this hydrogenation to be carried out in a Parr shaker, at 80 °C and 50 psig of H_2.

The alkaloids exuded by the skin of the Central American frog species of the genus *Dendrobates* have been under intensive investigation for the last 20 years.[1] Although this mixture, in contrast to that of the related *Phyllobates*, was not used as an arrow poison, many of the constituent alkaloids, including pumiliotoxin A (**1**), gephyrotoxin (**2**), histrionicotoxin (**3**), and indolizidine 223AB (**4**), show pronounced neuromuscular activity.



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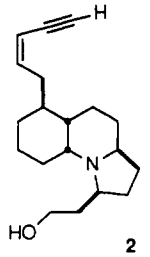

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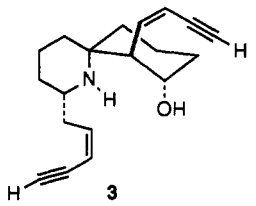

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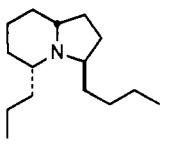

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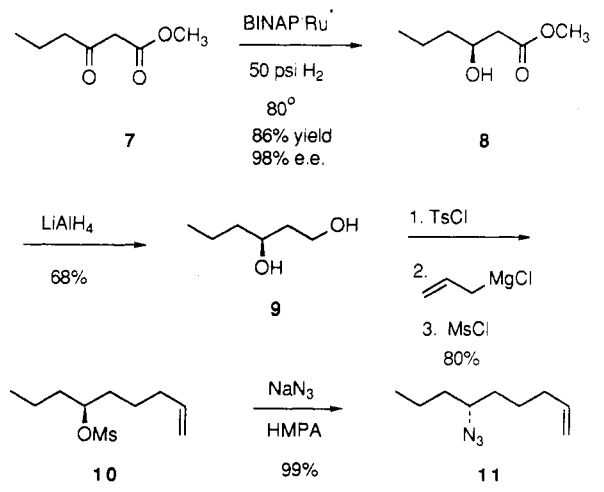
We report an efficient strategy for the assembly of (−)-indolizidine 223AB (**4**), with control of both relative and absolute configuration. The key to our approach is the enantioselective $RuCl_2$/BINAP-mediated reduction[2,3] of β-keto esters.

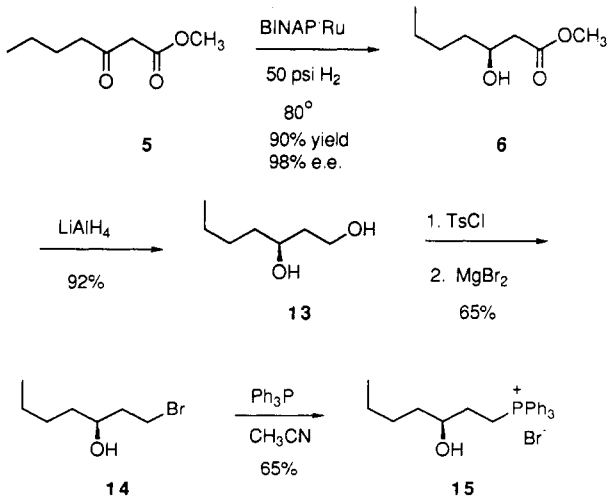
Background

When indolizidine 223AB (**4**) was first isolated,[1] only the gross structure was deduced. Elucidation of the relative and absolute configuration depended on an intense series of synthetic investigations, in the course of which all four possible diastereomers were prepared.[4-6]

Scheme I



Scheme II



Previous syntheses of **4** have been either cumbersome or nonselective, hindering further investigation in this

(1) For a detailed account of the isolation and structure of the *Dendrobates* alkaloids, including indolizidine 223AB, see: Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1, pp 1–274.

(2) For the original report of BINAP/Ru-mediated reduction of β-keto esters, see: (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, A. *J. Am. Chem. Soc.* **1987**, *109*, 5856. For later references, see: (b) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, A.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629. (c) Kitamura, M.; Ohkuma, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 1555. (d) Nishi, T.; Kitamura, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 6327. (e) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134.

(3) For an improved procedure for BINAP/Ru-mediated reduction of β-keto esters, see: (a) Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227. (b) Taber, D. F.; Silverberg, L. J.; Robinson, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6639. (c) For related work, see: Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163. (d) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Org. Chem.* **1992**, *57*, 4053.

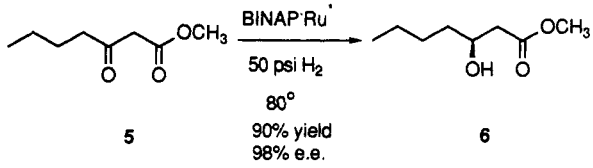
(4) For syntheses of racemic indolizidine 223AB, see: (a) Macdonald, T. L. *J. Org. Chem.* **1980**, *45*, 193. (b) Spande, T. F.; Daly, J. W.; Tsai, Y.-M.; Macdonald, T. L. *Experientia* **1981**, *37*, 1242. (c) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534. (d) Broka, C. A.; Eng, K. K. *J. Org. Chem.* **1986**, *51*, 5043. (e) Brandi, A.; Cordero, F.; Querci, C. *J. Org. Chem.* **1989**, *54*, 1788. (f) Edwards, O. E.; Greaves, A. M.; Sy, W. W. *Can. J. Chem.* **1988**, *66*, 1163. (g) Watanabe, Y.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 4088.

0022-3263/92/1957-5990$03.00/0

series. We envisioned a simple synthetic approach to **4**, based on cyclization of **7** and subsequent reduction of the intermediate imine[7] (Scheme I). We now report the successful execution of this approach, which is especially noteworthy in that it proceeds without resort to *any* functional-group protection.

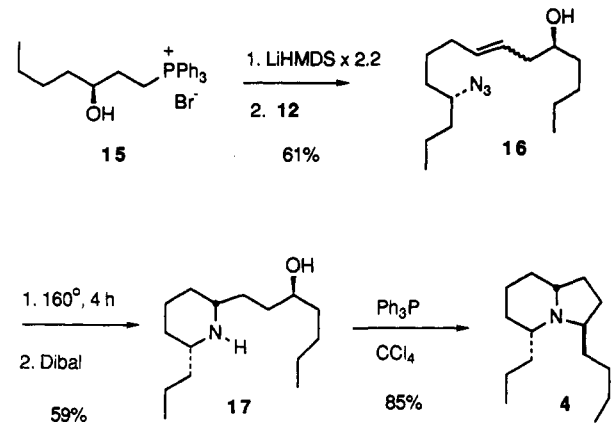
A Simplified Procedure for the Enantioselective Hydrogenation of β-Keto Esters. The key to this approach to **4** was the enantioselective preparation of aldehyde **12** and phosphonium salt **15**. We envisioned that each (Scheme I and Scheme II) could be prepared from a precursor symchiral[8] β-hydroxy ester.

Originally, we had projected that the β-hydroxy esters would be prepared by the method we had developed[9] for chiral auxiliary-directed reduction. As this project commenced, however, the Nagoya and Takasago groups, working in collaboration, reported[2] that a solution prepared by treating BINAP ruthenium diacetate with methanolic HCl would catalyze the reduction of β-keto ester **5** to **6** with excellent turnover and stunning enantioselectivity (99:1). There were, however, two practical difficulties with this procedure: the ruthenium complex must be prepared (two steps) and stored under controlled atmosphere conditions (Schlenkware or glovebox). Further, the hydrogenations were effected at 1500 psi H_2, a pressure not routinely available to the organic synthesis chemist.



We have found[3] that direct combination of commercially available BINAP and $(RuCl_2$·cyclooctadiene$)_n$ in the presence of triethylamine, followed by heating, leads to a very active catalyst.[10] Further, we have found that neither lowering the hydrogen overpressure nor raising the temperature of the reaction adversely affects the enantiomeric excess of the product. Thus, the hydrogenation can be carried out in a conventional Parr shaker[11,12] using catalyst

Scheme III



prepared in a single step from commercial materials. It is particularly important that under these conditions, in contrast to those previously reported,[2] an isolated alkene survives.[3]

Preparation of Aldehyde 12. As we have previously reported,[3a] hydrogenation of β-keto ester **7** (Scheme I) proceeded smoothly to give **8**. $LiAlH_4$ reduction then delivered diol **9**. Coupling of the derived monotosylate with allylmagnesium chloride[7b] gave the secondary alcohol, which was most efficiently isolated as the derived mesylate **10**. Azide **11** is prone to cyclization, but could be stored at 0 °C for a few days, if desired, prior to ozonolysis to aldehyde **12**.

Preparation of Phosphonium Salt 15. $LiAlH_4$ reduction of **6** (Scheme II) provided diol **7**. Bromide **14** was prepared by exposure of the primary monotosylate of **13** to an excess of $MgBr_2$ (prepared from Mg turnings and allyl bromide) in THF at reflux. Heating of **14** with triphenylphosphine in dry THF gave the hygroscopic phosphonium salt **15**, which was purified to a dry white powder by silica gel chromatography followed by trituration with diethyl ether.

Synthesis of Indolizidine 223AB. Wittig condensation[13] of phosphonium salt **15** (Scheme III) with aldehyde **12** provided **16** as a mixture of geometric isomers. This mixture was of no consequence, as both the *Z* and *E* alkenes participated efficiently in the subsequent dipolar addition/fragmentation. Thus, thermolysis of the coupled alkene followed by selective reduction[7,14] proceeded smoothly to give the *cis*-dialkylpiperidine **17**.

With **17** in hand, we were prepared to investigate cyclodehydration to **4**. Previously,[4] this had been effected by a three-step sequence of N-acylation, mesylation, and N-deacylation with concomitant cyclization. There was literature precedent for alcohol activation in the presence of an amine,[15-17] but the stereochemical course of cyclization with a secondary alcohol had not been investigated.[18] In fact, we have found that the cyclization proceeds *with single inversion* to give the desired indolizidine 223AB

(5) For an enantioselective synthesis of indolizidine 223AB, see: Royer, J.; Husson, H. P. *Tetrahedron Lett.* **1985**, *26*, 1515.

(6) For enantioselective routes to related indolizidines, see: (a) Nagao, Y.; Dai, W.-M.; Chiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289. (b) Yamazaki, M.; Kibayashi, C. *Tetrahedron Lett.* **1988**, *29*, 5767. (c) Smith, A. L.; Williams, S. F.; Holmes, A. B.; Hughes, L. L.; Lidert, Z.; Swithenbank, C. *J. Am. Chem. Soc.* **1988**, *110*, 8696. (d) Yamazaki, M.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396. (e) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Org. Chem.* **1990**, *55*, 1148. (f) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. (g) Holmes, A. B.; Smith, A. L.; Williams, S. W.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393.

(7) (a) For the first report of cyclic imine construction by intramolecular azide cycloaddition, see: Logothetis, A. L. *J. Am. Chem. Soc.* **1965**, *85*, 749. For applications to natural product synthesis, see: (b) Taber, D. F.; Deker, P. B.; Fales, H. M.; Jones, T. H.; Lloyd, H. A. *J. Org. Chem.* **1988**, *53*, 2968. (c) Bennett, R. B., III; Choi, J. R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2581. (d) Hudlicky, T.; Seoane, G.; Lovelace, T. C. *J. Org. Chem.* **1988**, *53*, 2094. (e) Pearson, W. H. *Tetrahedron Lett.* **1985**, *26*, 3527.

(8) For the use of "symchiral" to mean "having high enantiomeric purity", see: (a) Taber, D. F. *Chem. Eng. News* Aug 19, 1991, 5. (b) Magar, S. S.; Fuchs, P. L. *Tetrahedron Lett.* **1992**, *33*, 745.

(9) Taber, D. F.; Deker, P. B.; Gaul, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 7488.

(10) We would like to thank Dr. S. Akutagawa and co-workers of Takasago International Corp., Tokyo, for suggesting this catalyst preparation.

(11) The Parr shaker bottle was modified by replacing the usual rubber stopper, not compatible with the ruthenium catalyst, with a 24/40 female ground glass joint having an outside thread. Into this was inserted a 24/40 male ground glass straight gas inlet tube having a threaded plastic retaining ring and an O-ring seal. Parr bottles modified in this way are available from Mr. Douglas Nixon of this department.

(12) Heating of the Parr bottle was effected with a Parr bottle heating mantle, available from Fisher Scientific.

(13) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emsweiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 218.

(14) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831.

(15) Stoilova, V.; Trifonov, L. S.; Orahovats, A. S. *Synthesis* **1979**, *2*, 105.

(16) Sonnet, P. E.; Oliver, J. E. *J. Heterocycl. Chem.* **1975**, *12*, 289.

(17) Okada, I.; Ichimura, K.; Sudo, R. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1185.

(18) A related cyclization of an amino alcohol under Mitsunobu conditions, with clean inversion, was reported after the initial phase of this work was completed: Bernota, R. C. *Tetrahedron Lett.* **1990**, *31*, 469.

(4), $[\alpha]_D$ = −102° (lit.[5] $[\alpha]_D$ −101°), identical (^1H, ^{13}C NMR, TLC) with natural material.

Conclusion

The modification[3] of the Noyori–Akutagawa hydrogenation[2] that we have developed makes symchiral secondary alcohols such as **9** and **13** very easy to prepare. The strategies outlined here for the efficient coupling of these fragments then allow the convergent assembly of longer acyclic intermediates such as **16**. This approach could be used to selectively prepare any of the eight diastereomers of **4**, with control of both relative and absolute configuration.

Experimental Section

General. ^1H and ^{13}C NMR spectra were obtained as solutions in $CDCl_3$. Carbon signals were assigned by an INEPT pulse sequence, u = methylene or quaternary carbon, d = methyl or methine. The infrared (IR) spectra were obtained neat or as solutions in CCl_4 and are reported in cm^{-1}. Substances for which C,H analysis are not reported were purified as specified and gave spectroscopic data consistent with being >95% of the assigned structure. Optical rotations were measured as solutions, 1.0 g/100 mL in absolute ethanol unless otherwise specified. Organic chemicals were purchased from Aldrich Chemical Co. THF and Et_2O were distilled from sodium/benzophenone. The solvent mixtures used for chromatography are volume/volume mixtures. R_f values indicated refer to thin-layer chromatography on Analtech 2.5 × 10 cm, 250-μm analytical plates coated with silica gel GF. Column chromatography was carried out with TLC-mesh silica gel, using the procedure we have described.[19] Unless otherwise specified, all reactions were carried out in flame-dried glassware under an atmosphere of N_2.

Catalyst Preparation. All manipulations were carried out in an N_2 atmosphere. Following the procedure we have developed,[3] 39 mg of $(RuCl_2$·cyclooctadiene$)_n$, 100 mg of (*S*)-(−)-**2**, 2′-bis(diphenyylphosphino)-1,1′-binaphthyl, 4.5 mL of toluene, and 0.0275 mL of triethylamine were sealed in a 5-mL reactivial. Stirring was continued at 140 °C until the solution was a clear homogeneous red (2–4 h). Solvent was removed in vacuo, and the residue was taken up in 10 mL of THF. The resultant orange-brown suspension was divided into five equal portions, each of which was stored in a stoppered vial under N_2 until use.

Methyl (*S*)-3-Hydroxyheptanoate (6) and Methyl (*S*)-3-Hydroxyhexanoate (8). Keto ester **5** (5.0 g, 35.2 mmol), methanol (20 mL), catalyst as prepared above (2 mL; from 20 mg of BINAP), and Dowex-50 resin (350 mg; washed with water, methanol, diethyl ether, and methanol and then pressed to remove most of the methanol) were combined in a modified[11] Parr bottle. Hydrogenation was carried out at 50 psig of H_2 and 80 °C for 5.5 h. After filtration through glass wool and evaporation, the residue was distilled bulb-to-bulb at 0.5 mm (bath = 85 °C) to give **6** as a colorless oil (4.57 g, 31.7 mmol, 90%): $[\alpha]_D$ 1.85°; ^1H NMR (δ) 4.01 (m, 1 H), 3.71 (s, 3 H), 3.1 (bs, 1), 2.36–2.56 (m, 2 H), 1.3–1.55 (m, 6 H), 0.91 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (δ) 173.3, 67.9, 51.6, 41.1, 36.2, 27.5, 22.5, 13.9. IR (cm^{-1}) 3436 (b), 2957, 2931, 2864, 1742, 1437, 1291, 1171, 1125, 1045, 872, 733.

Methyl (*S*)-3-hydroxyhexanoate **8** was prepared analogously: TLC R_f (20% ethyl acetate/petroleum ether) = 0.25; $[\alpha]_D$ 4.6° (*c* 1.0, ethanol); ^1H NMR (δ) 4.01 (m, 1 H), 3.72 (s, 3 H), 2.90 (bs, 1 H), 2.36–2.56 (m, 2 H), 1.3–1.55 (m, 4 H), 0.94 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (δ) 173.3, 67.7, 51.6, 41.1, 38.6, 18.6, 13.8; IR (cm^{-1}) 3600–3200 (b), 2959–2875 (b), 2741, 2031, 1735, 1652.

(*S*)-(+)-1,3-Hexanediol (9). Methyl (*S*)-3-hydroxyhexanoate (**8**) (1.02 g, 6.96 mmol) in THF (35 mL, 0.2 M) was added dropwise with stirring to $LiAlH_4$ (0.528 g, 2 equiv) in 100 mL of THF at 0 °C. After 1 h of warming the mixture was cooled again in ice and quenched by sequential addition of water (1.3 mL), 10% aqueous NaOH (1.3 mL), and water (2.6 mL). The resultant salts were washed with ether, and the combined filtrates were dried (Na_2SO_4) and chromatographed to give **9** (0.557 18 g, 68% yield) as a colorless oil. A middle cut was distilled bulb-to-bulb (bath = 100 °C (0.5 mm)): $[\alpha]_D$ 11.4° (*c* 3.2, ethanol); ^1H NMR (δ) 0.94 (t, *J* = 6.7 Hz, 3 H), 1.24–1.54 (m, 4 H), 1.54–1.80 (m, 2 H), 3.65–3.95 (br m, 3 H), 4.45 (br s, dilution dependent, 1 H), 4.67 (br s, dilution dependent, 1 H); ^{13}C NMR (δ) d: 13.9, 70.8; u: 18.6, 38.3, 39.7, 60.7; IR (cm^{-1}) 3507, 3440, 3286, 3169, 2960, 2892, 2843, 1471, 1434, 1089, 1053, 1022; MS (CH_4, CI; *m/z*) 119 ($(M + H)^+$, 11), 117 (1), 101 ($(M + H - H_2O)^+$, 18), 99 (3), 83 ($(M + H - 2H_2O)^+$, 100), 81 (2); EI ($M^+ - H_2O$) 100.0910, calcd 100.0888.

(*S*)-8-Nonen-4-yl Methanesulfonate (10). Diol **9** (9.14, 72.7 mmol) in CH_2Cl_2 (75 mL) at 0 °C was treated sequentially with pyridine (5.75 g, 1.0 equiv) and triethylamine (7.34 g, 1.0 equiv), followed by *p*-toluenesulfonyl chloride (6 × 2.78 g, 0.2 equiv each time) over 1.5 h. After an additional 0.5 h, the reaction mixture was partioned between brine and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residual oil was chromatographed to give a mixture (6.90 g) containing some of the desired primary monotosylate, followed by the pure primary monotosylate as a colorless oil (14.19 g): TLC R_f (30% EtOAc/pentane) = 0.58; ^1H NMR (δ) 0.88 (t, *J* = 6.8 Hz, 3 H), 1.10–1.50 (m, 4 H), 1.62 (m, 1 H), 1.80 (m, 1 H), 2.28 (s, dilution dependent, 1 H), 2.44 (s, 3 H), 3.69 (br s, 1 H), 4.02–4.35 (m, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.78 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (δ) d: 14.0, 21.6, 67.6, 127.9, 130.0; u: 18.7, 36.3, 39.7, 68.1, 133.1, 144.9; IR (cm^{-1}) 3619, 3580, 3451, 2952, 2933, 2851, 1365, 1180, 1095, 965; MS (CH_4, CI; *m/z*) 275 (4), 274 (10), 273 ($(M + H)^+$, 60), 257 (3), 256 (6), 255 (42), 173 (3), 101 (2), 83 (100).

The pure primary monotosylate (13.32 g, 22.75 mmol) in 50 mL of THF was added all at once to a stirred solution of allylmagnesium chloride (2 M in THF, 245 mL, 489 mmol). After 20 min, the mixture was warmed to reflux for 3 h and then partitioned between 10% aqueous HCl and Et_2O. In a similar manner 6.49 g of the mixture containing primary monotosylate was treated with allylmagnesium chloride (114 mL, 228 mmol). The combined organic phases from both runs were washed with brine, dried (Na_2SO_4), concentrated, and chromatographed to give a mixture (5.00 g) containing the alkenyl alcohol, followed by pure alkenyl alcohol (7.15 g) as a faintly yellow oil; TLC R_f (20% Et_2O/pentane) = 0.42. Bulb-to-bulb distillation of 0.0821 g (bath ≈ 75 °C, 0.5 mmHg) gave a clear oil: 0.0816 g; $[\alpha]_D$ 1.06° (*c* 2.1, EtOH); ^1H NMR (δ) 0.90 (t, *J* = 6.7 Hz, 3 H), 1.25–1.60 (m, 8 H), 1.95–2.15 (m, 2 H), 2.20 (s, dilution dependent, 1 H), 3.59 (br s, 1 H), 4.90–5.07 (m, 2 H), 5.70–5.90 (m, 1 H); ^{13}C NMR (δ) d: 14.1, 71.4, 138.8; u: 18.9, 25.0, 33.8, 36.9, 39.7, 114.5; IR (cm^{-1}) 3628, 3375, 2945, 2930, 2907, 2855, 1462, 1375; MS (CH_4, CI; *m/z*) 143 ($(M + H)^+$, 17), 141 (5), 126 (6), 125 ($(M + H - H_2O)^+$, 61), 123 (15), 111 (3), 109 (5), 97 (10), 83 (100).

Methanesulfonyl chloride (7.62 mL, 98.5 mmol) followed by Et_3N (20.60 mL, 147.7 mmol) were added dropwise to the alkenyl alcohol (7.00 g, 49.2 mmol) in dry Et_2O (100 mL) at 0 °C. After 2 h the mixture was partitioned between brine and Et_2O. In a like manner 4.90 g of the crude fraction containing the alkenyl alcohol was treated with methanesulfonyl chloride (5.44 mL, 70.3 mmol). The combined organic phases from both runs were washed with brine, dried (Na_2SO_4), concentrated, and chromatographed to give mesylate **10** as a clear oil: 11.85 g (80% from diol); TLC R_f (20% Et_2O/pentane) = 0.49; ^1H NMR (δ) 0.95 (t, *J* = 6.8 Hz, 1 H), 1.30–1.60 (m, 6 H), 1.60–1.80 (m, 4 H), 2.09 (q, *J* = 6.4 Hz, 2 H), 2.98 (s, 3 H), 4.73 (m, 1 H), 4.90–5.10 (m, 2 H), 5.70–5.87 (m, 1 H); ^{13}C NMR (δ) d: 13.6, 38.5, 83.5, 137.8; u: 18.1, 23.9, 33.1, 33.6, 36.4, 114.9; IR (cm^{-1}) 3090, 2961, 2940, 2922, 1374, 1356, 1346, 1332, 1181, 968, 896; MS (NH_4, CI; *m/z*) 255 (2), 238 ($(M + NH_4)^+$, 100), 223 (1), 158 (1), 142 (2), 131 (1), 114 (2), 95 (1).

(*R*)-6-Azido-1-nonene (11). NaN_3 (17.48 g, 268.7 mmol) was added to mesylate **10** (11.85 g, 53.78 mmol) in dry HMPA (27.0 mL). After 2 h at 40 °C the mixture was partitioned between brine and Et_2O. The combined organic phases were dried (Na_2SO_4), concentrated, and chromatographed to give azide **11** as a faintly green-yellow oil: 8.88 g (99%); TLC R_f (10% Et_2O/pentane) = 0.91; ^1H NMR (δ) 0.93 (t, *J* = 7.1 Hz, 3 H), 1.30–1.65 (m, 8 H), 2.08 (m, 2 H), 3.24 (br s, 1 H), 4.92–5.07 (m, 2 H), 5.70–5.90 (m, 1 H); ^{13}C NMR (δ) d: 13.9, 62.8, 138.3; u: 19.4, 25.4, 33.5, 33.8, 36.6, 115.0; IR (cm^{-1}) 3070, 2954, 2920, 2850, 2090, 1482, 1461, 1439; MS (CH_4, CI; *m/z*) 180 (7), 168 ($(M + H)^+$, 24), 140 ($(M - N_2 + H)^+$, 100), 139 ($(M - N_2)^+$, 21), 138 (25), 124 (7), 96 (8).

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(*R*)-(+)-6-Azidooctanal (12). Azide 11 (8.88 g, 53.10 mmol) was subjected to ozonolysis in four aliquots of 2.22 g each. Thus, alkenyl azide (2.22 g, 13.28 mmol) in MeOH (≈130 mL) was chilled to −78 °C, and O_3 was bubbled through the rapidly stirred mixture for 12.5 min (after 12 min a slight purple haze due to excess O_3 was detectable). Excess O_3 was purged from the −78 °C solution with O_2 (2 min) and N_2 (3 min). The reaction mixture, still at −78 °C, was charged with dimethyl sulfide (≈20 mL) and allowed to warm overnight. The four aliquots were combined, concentrated in vacuo (35 °C, H_2O aspirator), and chromatographed to give 12 as a slightly yellow oil: 7.08 g (79%); TLC R_f (10% Et_2O/pentane) = 0.28. Bulb-to-bulb distillation of 0.865 g (≈110 °C, 0.5 mmHg) gave a clear oil: 0.848 g (62% from the diol); $[\alpha]_D$ 4.85° (*c* 3.26, EtOH). Long-term storage of this material requires refrigeration and a dry atmosphere of N_2. Storage as a mixture with dimethyl sulfide is effective as well: ^{1}H NMR (δ) 0.92 (t, *J* = 6.5 Hz, 3 H), 1.30–1.60 (m, 6 H), 1.60–1.90 (m, 2 H), 2.49 (t, *J* = 6.6 Hz, 2 H), 3.15–3.35 (m, 1 H), 9.77 (s, 1 H); ^{13}C NMR (δ) d: 13.9, 62.5, 201.9; u: 18.7, 19.3, 33.7, 36.5, 43.5; IR (cm^{-1}) 2972, 2961, 2941, 2925, 2874, 2100, 1730, 1713, 1253; MS (*m*/*z*) 167 (M^+, 2), 156 (52), 140 (78), 127 ($(M - N_3)^+$, 91), 124 (50), 112 (100), 109 (65), 101 (40).

(*S*)-(+)-1,3-Heptanediol (13). Methyl 3-hydroxyheptanoate (6) (1.00 g, 6.24 mmol) in THF (11.2 mL) was added dropwise to $LiAlH_4$ (0.71 g, 18.7 mmol) in THF (20 mL) at 0 °C. After being warmed for 1 h, the mixture was cooled to 0 °C and quenched sequentially with water (0.71 mL), 10% aqueous NaOH (0.71 mL), and water (1.42 mL). The salts were removed by vacuum filtration and rinsed with ether. The combined filtrates were dried (Na_2SO_4) and chromatographed and then distilled bulb-to-bulb (bath = 120 °C, 0.5 mm) to give 13 as a viscous colorless oil (0.757 g, 5.74 mmol, 92% yield): $[\alpha]_D$ 9.6° (*c* 5.0, EtOH); ^{1}H NMR (δ) 0.91 (t, *J* = 6.9 Hz, 3 H), 1.12–1.50 (m, 6 H), 1.50–1.83 (m, 2 H), 3.78 (m, 3 H), 3.90–4.40 (br s, br s overlapping and concentration dependent, 2 H); ^{13}C NMR (δ) d: 14.1, 71.2; u: 22.7, 27.8, 37.4, 38.5, 60.9; IR (cm^{-1}) 3620, 3425, 2927, 2850, 1465, 1430, 1376, 1065; MS (CH_4, CI; *m*/*z*) 133 ($(M + H)^+$, 8), 115 ($M + H - H_2O)^+$, 22), 97 ($(M + H - 2H_2O)^+$, 100), 85 (3).

(*S*)-(+)-1-Bromo-3-heptanol (14). Diol 13 (6.85 g, 51.8 mmol) in CH_2Cl_2 (50 mL) in an ice/water bath was treated sequentially with pyridine (4.1 g, 1.0 equiv) and triethylamine (5.23 g, 1.0 equiv), followed by *p*-toluenesulfonyl chloride (6 × 1.98 g, 0.2 equiv each time) over 1.5 h. After an additional 0.5 h, the reaction mixture was partitioned between brine and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), filtered, concentrated, and chromatographed to give the desired primary monotosylate as a faintly yellow oil: 10.29 g, plus an additional 1.82 g from rechromatography of mixed fractions (total = 82%); TLC R_f (40% EtOAc/hexane) = 0.58; ^{1}H NMR (δ) 0.88 (t, *J* = 6.7 Hz, 3 H), 1.10–1.50 (m, 6 H), 1.64 (m, 1 H), 1.84 (m, 1 H), 1.99 (br s, dilution dependent 1 H), 2.45 (s, 3 H), 3.71 (br s, 1 H), 4.12 (m, 1 H), 4.25 (m, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (δ) d: 14.1, 21.7, 67.9, 128.0, 130.0; u: 22.7, 27.8, 36.4, 37.3, 68.1, 133.1, 145.0; IR (cm^{-1}) 3620, 3582, 3465, 2955, 2920, 2851, 1374, 1185, 1090, 974; MS (CH_4, CI; *m*/*z*) 289 (4), 288 (9), 287 ($(M + H)^+$, 54), 270 (4), 269 (22), 229 (2), 213 (2), 201 (11), 173 (8), 97 (100).

Mg turnings (5.24 g, 216 mmol) and I_2 (catalytic amount) were heated with a flame under an N_2 atmosphere and the purple I_2 vapor removed after 5 min by a flow of N_2. Dry THF (180 mL) was added followed by dropwise addition of allyl bromide (38.0 mL, 442 mmol) so as to maintain a gentle reflux (typically additional allyl bromide was needed to consume all of the magnesium). The resultant $MgBr_2$ solution was cooled to rt. The primary monotosylate (10.29 g, 35.93 mmol) in dry THF (180 mL) was added dropwise over 15 min. The mixture was stirred 1 h at rt and then warmed to reflux for 1 h. After being cooled to rt, the mixture was partitioned between brine and Et_2O. The combined organic extracts were dried (Na_2SO_4), concentrated, and chromatographed to give 6.7 g of 14 as a colorless oil (65%); TLC R_f (Et_2O/pentane) = 0.16. Bulb-to-bulb distillation of 0.236 g (≈60 °C, 0.5 mmHg) gave 0.230 g of a colorless oil: $[\alpha]_D$ 31.6° (*c* 7.84, EtOH); ^{1}H NMR (δ) 0.94 (t, *J* = 6.7 Hz, 3 H), 1.15–1.60 (m, 6 H), 1.82–2.08 (m, 2 H), 3.08 (br s, 1 H), 3.50–3.59 (m, 2 H), 3.71–3.85 (br m, 1 H); ^{13}C NMR (δ) d: 14.0, 69.6; u: 22.6, 27.7, 30.6, 37.1, 40.1; IR (cm^{-1}) 3366, 2973, 2905, 2861, 1465, 1262, 1151, 1120, 1046, 911; MS (CH_4, CI; *m*/*z*) 195 ($(M + H)^+$, 1), 180 (2), 179 (30), 177 (30), 137 (4), 115 (4), 97 (100).

((*S*)-3-Hydroxyhept-1-yl)triphenylphosphonium Bromide (15). Bromo alcohol 14 (6.50 g, 33.5 mmol), triphenylphosphine (16.68 g, 63.60 mmol), and dry CH_3CN (1.34 mL, distilled from CaH_2) were combined in a sealed tube and heated to 150 °C for 24 h. The solution was bulb-to-bulb distilled to remove CH_3CN (≈40 °C, 0.1 mmHg). The crude residue (24.79 g) was chromatographed on 50 g of silica gel to give 15 as a gummy white solid. This was triturated with dry Et_2O (2 × 200 mL) and vacuum dried to give 15 as a fine white powder: 15.25 g (99.8%); TLC R_f (2% MeOH/CH_2Cl_2) = 0.26 (streak); mp 54–57 °C. This material is best stored under vacuum with P_2O_5 desiccant; ^{1}H NMR (δ) 0.82 (t, *J* = 6.7 Hz, 3 H), 1.15–1.82 (m, 8 H), 2.4 (br s, dilution dependent, 0.5 H), 3.45–3.67 (m, 1 H), 3.75–4.15 (m, 2 H), 5.25 (br s, dilution dependent, 0.5 H), 7.65–8.00 (m, 15 H); ^{13}C NMR (δ) d: 13.7, 69.3, 69.5, 130.2, 130.4, 133.1, 133.2, 134.8; u: 19.2, 20.0, 22.2, 27.7, 29.8, 29.9, 36.4, 117.4, 118.7; MS (CH_4, CI; *m*/*z*) (M^+ = loss of Br^-) 417 ($(M + C_3H_5)^+$, 2), 405 ($(M + C_2H_5)^+$, 11), 377 ($(M + H)^+$, 100), 375 (21), 299 (97), 263 (9), 223 (14), 185 (11).

(3*R*,10*S*)-3-Azido-7-pentadecen-10-ol (16). Wittig condensation was effected by a modification of the procedure of Maryanoff.[12] Thus, $LiN(SiMe_3)_2$ (1.0 M in THF; 26.1 mL) was added dropwise to phosphonium salt 15 (5.68 g, 12.4 mmol) suspended in 6 mL of dry THF at 0 °C. The cooling bath was removed, and the solution was stirred at rt for 30 min before being chilled to −78 °C. While at −78 °C aldehyde 12 (2.53 g, 14.9 mmol) in dry THF (5.6 mL) was added dropwise over 15 min. Immediately following aldehyde addition the cooling bath was allowed to warm to 0 °C (≈2 h) and then stirred an additional 15 min before being partitioned between saturated aqueous NH_4Cl and Et_2O. The aqueous phase was extracted twice with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4), concentrated, triturated twice with Et_2O, and then vacuum dried to give recovered phosphonium salt 15: 1.79 g (32%). The combined Et_2O and THF extracts were dried (Na_2SO_4), concentrated, and chromatographed to give recovered aldehyde 12 (0.668 g, 26%) followed by the desired condensation product 16 as a faintly yellow oil (1.79 g, 54%, 61%, and 79%, respectively, based on consumed 12 and 15): ^{1}H NMR (δ) 0.92 (m, 6 H), 1.20–1.60 (m, 14 H), 1.70 (bs, dilution dependent, 1 H), 1.98–2.30 (m, 4 H), 3.25 (bs, 1 H), 3.59 (bs, 1 H), 5.37–5.70 (m, 2 H); ^{13}C NMR (δ) (major geometric isomer of mixture) d: 14.0, 14.2, 62.9, 71.2, 126.9, 133.8; u: 19.5, 22.9, 26.1, 28.1, 32.5, 34.0, 36.7, 36.7, 40.9; ^{13}C NMR (δ) (additional peaks due to minor geometric isomer in mixture) d: 71.7, 126.2, 132.6; u: 26.3, 27.3, 28.1, 34.1, 35.6, 36.8; IR (cm^{-1}) 3354, 2966, 2948, 2905, 2856, 2087, 1545, 1459, 1250, 973; MS (CH_4, CI; *m*/*z*) 268 ($(M + H)^+$, 7), 240 (36), 222 (100), 207 (44), 182 (5), 139 (6), 137 (6), 123 (22), 109 (81).

(2*R*,6*R*)-(−)-2-((3*S*)-3-Hydroxy-1-heptyl)-6-(1-propyl)-piperidine (17). Azide 16 (0.344 g, 1.29 mmol) in *o*-dichlorobenzene (2.6 mL) was heated to 165 °C for 4 h in a sealed reactivial. The solvent was removed by bulb-to-bulb distillation (bath ≈37 °C, 0.5 mmHg). The residual dark viscous crude concentrate in CH_2Cl_2 (7.0 mL) at −78 °C was treated with diisobutylaluminum hydride (1.0 M in CH_2Cl_2, 6.43 mL) dropwise via syringe over 15 min. After 30 min, the mixture was maintained at −45 °C for 1 h, at −20 °C for 1 h, and at 0 °C for 1 h. While still at 0 °C, the mixture was diluted with Et_2O (20 mL) and treated with solid NaF (1.05 g, 25.7 mmol), followed by the cautious dropwise addition of H_2O (0.35 mL, 19 mmol). After being stirred for 15 min, the resulting slurry was filtered through a short pad of Celite that was subsequently washed with 200 mL of 10% Et_2NH/Et_2O. The combined filtrate and washings were dried (Na_2SO_4), concentrated, and chromatographed to give the *cis*-dialkylpiperidine 17 as a yellow crystalline solid: 0.183 g (59%); TLC R_f (10% Et_2NH/petroleum ether) = 0.64; mp 57–58 °C. Bulb-to-bulb distillation of 0.074 g of this mixture (≈120 °C, 0.5 mmHg) gave a white crystalline solid: 0.067 g (54% from 16); $[\alpha]_D$ −6.6° (*c* 0.95, EtOH); ^{1}H NMR (δ) 0.91 (m, 6 H), 1.20–1.48 (m, 14 H), 1.48–1.87 (m, 9 H), 2.44–2.57 (m, 1 H), 2.57–2.68 (m, 1 H); ^{13}C NMR (δ) d: 14.1, 14.2, 56.2, 56.7, 71.3; u: 19.2, 22.9, 24.7, 28.3, 31.5, 32.2, 33.3, 34.2, 37.4, 39.5; IR (cm^{-1}) 3189, 2956, 2931, 2863, 1735, 1466, 1455, 1377, 1331, 1258, 1129, 1093, 1051, 901; MS (*m*/*z*) 241 (M^+, 2), 240 (3), 222 (3), 198 (61), 180 (34), 166 (8), 152 (3), 126 (100), 112 (6). Anal. Calcd for $C_{15}H_{31}NO$: C, 74.63; H, 12.98. Found: C, 74.62; H, 12.59.

Further elution gave the *trans*-dialkylpiperidine as a dark viscous oil: 0.012 g (3.8%); TLC R_f (10% Et_2NH/petroleum ether) = 0.41; ^1H NMR (δ) 0.90 (m, 6 H), 1.10–1.55 (m, 14 H), 1.55–1.95 (m, 5 H), 2.49–2.65 (m, 1 H), 2.76–2.97 (m, 2 H), 3.00–3.55 (br s, dilution dependent, 2 H), 3.59–3.76 (m, 1 H); ^{13}C NMR (δ) d: 14.2, 14.2, 36.6, 60.3, 69.3; u: 19.7, 22.9, 24.7, 28.2, 34.0, 37.7, 38.0, 39.8, 42.8, 51.5; IR (cm^{-1}) 3300, 2960, 2937, 2862, 2811, 1468, 1446, 1377, 1135; MS (*m/z*) 241 (M^+, 2), 240 (1), 212 (2), 198 (100), 180 (24), 166 (4), 140 (15), 126 (4), 112 (16).

(*R*,*R*,*R*)-(−)-Indolizidine 223AB (4). Dehydrative cyclization was accomplished using the method of Orahovats.[13] Thus, Et_3N (0.082 mL, 0.58 mmol), CCl_4 (0.056 mL, 0.58 mmol), and CH_3CN (0.4 mL) were added to a stirred mixture of *cis*-piperidine 17 (0.109 g, 0.450 mmol) and triphenylphosphine (0.153 g, 0.585 mmol) at 0 °C. After 5 min the cooling bath was removed. After 14 h the mixture was chromatographed directly (eluting with 110 mL of NH_4OH/Et_2O/pentane in a ratio of 1/12/87) to give indolizidine 223AB 4 as a yellow oil: 0.0849 g (85%); TLC R_f (10% Et_2NH/petroleum ether) = 0.54; $[\alpha]_D$ −99° (*c* 0.96, *n*-pentane). Bulb-to-bulb distillation of 0.0283 g (≈70 °C, 0.5 mmHg) gave a clear oil: 0.0251 g (76% from 17); $[\alpha]_D$ −102° (*c* 1.1, *n*-hexane) (lit.[5] $[\alpha]_D$ −101° (*c* 2.3, *n*-hexane)); ^1H NMR (δ) 0.87–0.98 (m, 6 H), 0.98–1.07 (m, 4 H), 1.07–1.38 (m, 6 H), 1.38–1.56 (m, 4 H), 1.56–1.98 (m, 6 H), 2.28–2.48 (m, 2 H), 3.27–3.34 (t, J = 7.4 Hz, 1 H); ^{13}C NMR (δ) d: 14.3, 14.7, 56.8, 58.7, 59.2; u: 19.1, 23.1, 24.8, 25.2, 26.5, 29.3, 30.2, 31.1, 32.5, 36.0; IR (cm^{-1}) 2959, 2931, 2861, 2798, 1581, 1553, 1455, 1384, 1342, 1236, 1096, 1004; MS (*m/z*) 223 (M^+, 2), 222 (3), 181 (12), 180 (100), 178 (3), 167 (12), 166 (94), 164 (2), 152 (3), 150 (3), 124 (10), 122 (8), 108 (18). These data (^1H, ^{13}C NMR, TLC) were identical with those recorded by us for natural material.

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Supplementary Material Available: ^{13}C spectra for compounds 4, 6, 9–17 (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Zirconium-Mediated Reactions of Alkylpyrazines and Alkynes. Synthesis of Highly Substituted Alkylpyrazines

Anil S. Guram and Richard F. Jordan*

Department of Chemistry, The University of Iowa, Iowa City, Iowa 52242

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Sequential one-pot addition of alkylpyrazines, alkynes, and a proton source to a solution of $Cp_2Zr(Me)(THF)^+$ (1) in CH_2Cl_2 at room temperature affords (*E*)-alkenyl-substituted alkylpyrazines **2–10** in excellent yields. The regio- and stereoselectively observed in these reactions is similar to those observed previously for related early transition metal-mediated reactions and is ascribed to steric and Si electronic effects. Conventional synthetic organic manipulation of the alkenylpyrazines provides easy access to a variety of highly substituted alkylpyrazines including tri- and tetrasubstituted alkylpyrazines **13**, **17–20**, dibromoalkylpyrazine **14**, bromoalkylpyrazine **15**, and epoxyalkylpyrazine **16**.

Introduction

Alkylpyrazines have been recognized as flavor components in foods,[1] as pheromones in various insect species,[2] and as versatile synthetic intermediates.[3] In the past, condensation reactions[3a] and nucleophilic addition of alkyllithium reagents[4] were commonly employed for the preparation of alkylpyrazines. These methods suffer from poor yields resulting from incomplete conversions/side reactions and exhibit poor regioselectivity in the preparation of unsymmetrically substituted pyrazines. More recently, synthetic methods based on electrocyclization reactions[5] and transition metal-mediated reactions[6] have been described. Herein we describe a facile zirconium-mediated reaction of alkylpyrazines and alkynes which offers a simple route to alkenyl-substituted alkylpyrazines. Conventional synthetic organic manipulations of these alkenylpyrazines provide access to a variety of highly substituted alkylpyrazines.

As a part of our ongoing efforts to develop synthetic organic applications of cationic $Cp_2Zr(R)(L)^+$ complexes,[7,8] we recently reported that complex $Cp_2Zr(CH_3)(THF)^+$ (1) reacts with pyridines under mild conditions via C–H ac-

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