lowed by a stereo- and regioselective hydrozirconation reaction[10] that gave rise to the vinyl bromide **3** in 86% yield after treatment of the vinylzirconium intermediate with *N*-bromosuccinimide (NBS).

The union of **3** and the previously reported **4** (TIPS = TBS)[1k,11] required considerable experimentation in order to find conditions that resulted in an efficient and stereoselective outcome. First, the reaction of **3** with 2.5 equiv of tBuLi resulted in halogen–metal exchange. The resultant alkenyllithium was sequentially treated with 1.0 equiv of magnesium bromide and aldehyde **4**. The coupling resulted in the predominant formation of α-carbinol **5** together with the readily separable diastereomeric β-carbinol (α:β = 5.8:1) in 66% yield, with 20% yield of recovered **4**. Evidence that the major diastereomer corresponded to that of a Cram-selective addition was obtained by a chemical correlation[12] with material prepared by the previously described route.[1k]

The acylation of **5** occurred smoothly at −20 °C with (*S*)-tBOC-*N*-pipecolinic acid, DCC, and 4-pyrrolidinopyridine to provide **6** in 88% yield. When the same conditions were used with racemic tBOC-*N*-pipecolinic acid, the reaction yielded two readily separable (silica gel (sg) chromatography) isomeric products, thereby confirming that epimerization at C_2 did not occur in the reaction with the nonracemic amino acid derivative.

In order to evaluate the compatibility of the pipecolinate ester toward conditions required to introduce the C_{19}–C_{20} olefin, the coupling of **7** and phosphonamide **8**[1j] was examined (Scheme II). Treatment of **6** with zinc dust in the presence of ammonium chloride unmasked the C_{21} allyl side chain. Swern oxidation of the resulting primary alcohol gave aldehyde **7** in 89% overall yield from **6**. The reaction of the α-lithio derivative of **8** with **7** resulted in the formation of readily separable diastereomeric adducts in nearly quantitative yield. The more rapidly eluting (R_f = 0.5 (sg); 2:1 hexane/ethyl acetate) and major pair of diastereomers underwent stereospecific elimination to the trans olefin **9** (yield of **9** from **7** = 35%) upon heating in toluene.[13,14] The more polar and minor diastereomeric pair (R_f = 0.3 (sg); 2:1 hexanes/ethyl acetate) produced the C_{19}–C_{20} cis isomer (not shown) under similar conditions. We are currently investigating methods to convert the polar pair of diastereomers into **9** in order to improve upon the coupling efficiency.

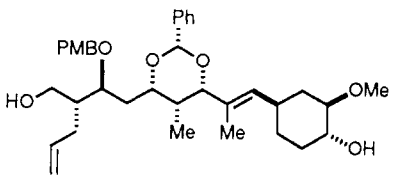
Spectroscopic and chemical analyses of **9** provided evidence that the olefination conditions did not result in appreciable epimerization of the stereocenter on the pipecolinate ring and thereby suggest that the early and direct introduction of this moiety, as detailed in the present paper, will be of utility in studies relating to the synthesis of FK-506.

Supplementary Material Available: ^{1}H NMR spectra for all compounds (16 pages). Ordering information is given on any current masthead page.

(10) (a) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679. (b) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333. (c) Corey, E. J.; Trybulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4618. (d) Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620.

(11) The stereochemistry at the carbon bearing the iodomethyl group of the tetrahydrofuran has not been determined and is arbitrarily rendered with the β-configuration. This stereocenter is removed upon treatment of **6** with Zn/NH_4Cl.

(12) Compound **5** was converted into diol **10** by the following sequence: (i) Zn, NH_4Cl, EtOH; (ii) Bu_4NF, THF, (iii) PhCHO, TsOH, benzene. The 500-MHz ^{1}H NMR spectra of both **10** and its derived bisacetate (Ac_2O, Et_3N, DMAP, CH_2Cl_2) were identical with the spectra of the corresponding materials prepared by the previously described route.[1k]



10

(13) Corey, E. J.; Kwiatkowski *J. Am. Chem. Soc.* **1968**, *90*, 6816.

(14) The assignment of the C_{19}–C_{20} olefin geometry is based on the characteristic resonances of the C_{19} methyl substituent in (*E*)-**9** (16.0 ppm) and (*Z*)-**9** (23.5 ppm) as observed in related systems.[4]

Synthesis of the Macrolactone Alkaloid (+)-Usaramine via Necic Acid Coupling to a Pyrrolizidine Borane

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Received March 31, 1989

Summary: The protected necic acid **19**, prepared from (*R*)-(+)-β-citronellol, was converted to the *Crotalaria* alkaloid (+)-usaramine (**2**) by regioselective coupling to the pyrrolizidine borane **22**.

Sir: The dilactones integerrimine (**1**), usaramine (**2**), and its geometrical isomer retrorsine (**3**) are members of a broadly distributed family of pyrrolizidine alkaloids (PAs) that have been shown to possess powerful hepatotoxic and carcinogenic properties.[1] Earlier investigations of the chemistry of macrolactone PAs[2] that included syntheses of **1**[3] and related systems[4] have laid the groundwork for approaches to more highly functionalized members of the group. Recently, a flexible route to the necic acid of **1** was opened from (*R*)-(+)-β-citronellol (**4**)[5] that, in principle, can be extended to **2** and **3**. We now describe the first

(1) Mattocks, A. R. *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic Press: London, U.K., 1986.

(2) Robins, D. J. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 115.

(3) (a) Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guedin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954. (b) White, J. D.; Ohira, S. *J. Org. Chem.* **1986**, *51*, 5492. (c) Niwa, H.; Miyachi, Y.; Uosaki, Y.; Yamada, K. *Tetrahedron Lett.* **1986**, *27*, 4601. (d) Niwa, H.; Miyachi, Y.; Uosaki, Y.; Kuroda, A.; Ishiwata, H.; Yamada, K. *Tetrahedron Lett.* **1986**, *27*, 4609.

(4) (a) Vedejs, E.; Larsen, S. D. *J. Am. Chem. Soc.* **1984**, *106*, 3030. (b) Brown, K.; Devlin, J. A.; Robins, D. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1819. (c) Huang, J.; Meinwald, J. *J. Am. Chem. Soc.* **1981**, *103*, 861.

(5) White, J. D.; Jayasinghe, L. J. *Tetrahedron Lett.* **1988**, *29*, 2139.

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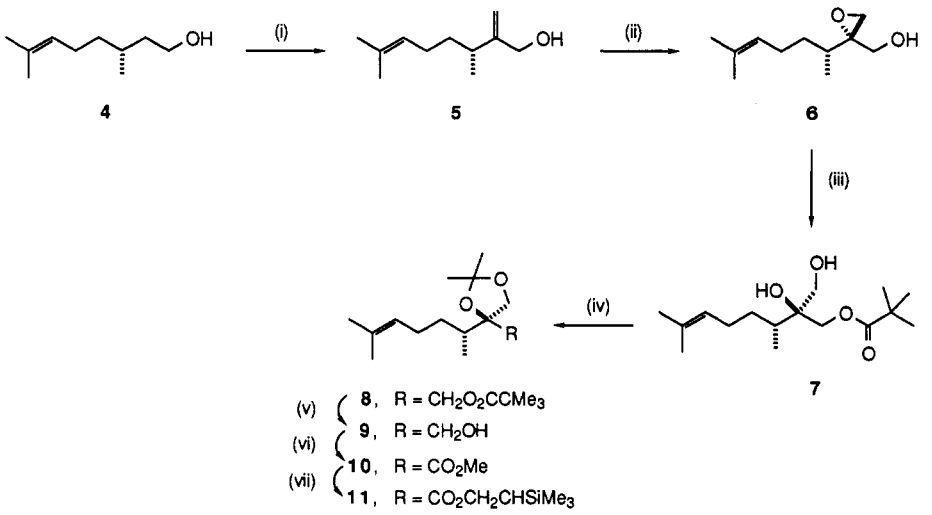
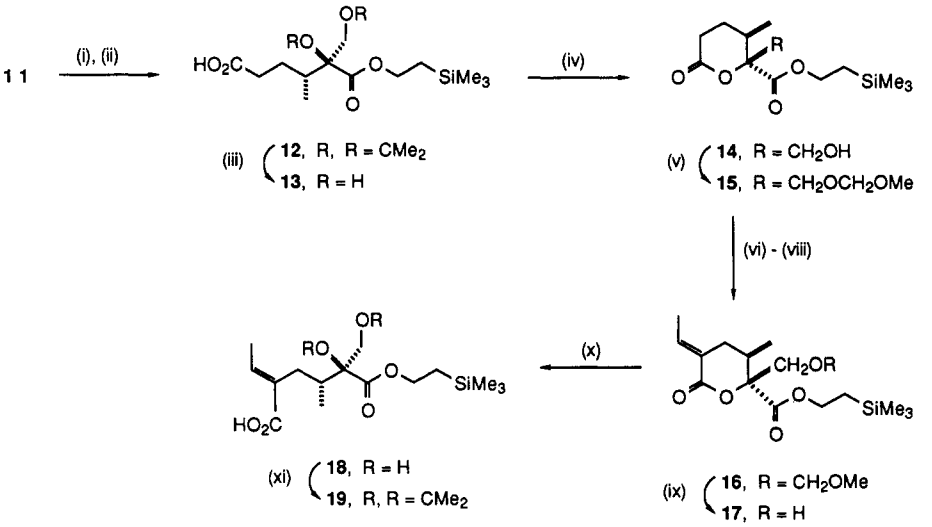
Scheme I[a]



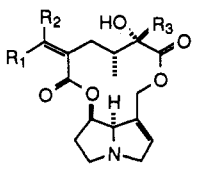
[a] (i) Reference 5; (ii) $C_6H_5CMe_2OOH$, $Ti(O^iPr)_4$ (cat.), (+)-diisopropyl tartrate (cat.) (81%); (iii) Me_3CCO_2H, $Ti(O^iPr)_4$, toluene (69%); (iv) $Me_2C(OMe)_2$, CSA (cat.) (80%); (v) $LiAlH_4$, Et_2O, reflux (90%); (vi) PDC, CH_2Cl_2, then CH_2N_2, Et_2O (65%); (vii) $Me_3SiCH_2CH_2OH$, $Ti(OEt)_4$, 100 °C (93%).

Scheme II[a]



[a] (i) O_3, CH_2Cl_2, −78 °C, then Me_2S; (ii) $NaIO_4$, $RuCl_3 \cdot H_2O$ (cat.), 15 min (66% from 11); (iii) HOAc, 80 °C, 7 h (55%); (iv) 2-chloro-1-methylpyridinium iodide, DMAP, MeCN (95%); (v) $ClCH_2OMe$, $^iPrNEt_2$, THF, 40 °C (91%); (vi) MeCHO, LDA, THF, −60 °C; (vii) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2; (viii) DBU, CH_2Cl_2, 4 °C (74% from 15); (ix) 3 N HCl, THF (86%); (x) LiOH, H_2O_2, THF–H_2O (58%); (xi) $Me_2C(OMe)_2$, CSA (cat.), $CHCl_3$ (86%).

synthesis of (+)-usaramine (**2**), a constituent of *Crotalaria usaramoensis*[6a,b] and *Senecio vulgaris*,[6c] using a novel protection of retronecine as its borane for linkage to the necic acid.



1, $R_1 = H$, $R_2 = R_3 = Me$

2, $R_1 = H$, $R_2 = Me$, $R_3 = CH_2OH$

3, $R_1 = Me$, $R_2 = H$, $R_3 = CH_2OH$

Allylic alcohol **5**, prepared from **4** as described previously,[5] was submitted to the catalytic version of the Sharpless epoxidation[7] using (+)-diisopropyl tartrate. This afforded a 96:4 mixture of diastereomeric epoxides in favor of **6**. Opening of this epoxide with pivalic acid, assisted by intramolecular complexation with titanium(IV),[8] gave diol **7**, which was protected as its acetonide **8** (Scheme I). The pivalate **8** was reduced to alcohol **9**, and the latter was oxidized to an unstable acid, which was isolated as its methyl ester **10**. Transesterification of **10** with (trimethylsilyl)ethanol in the presence of titanium ethoxide[9] yielded the protected ester **11**.

The isopropylidene terminus of **11** was cleanly truncated by an ozonolysis–oxidation sequence that led to **12**

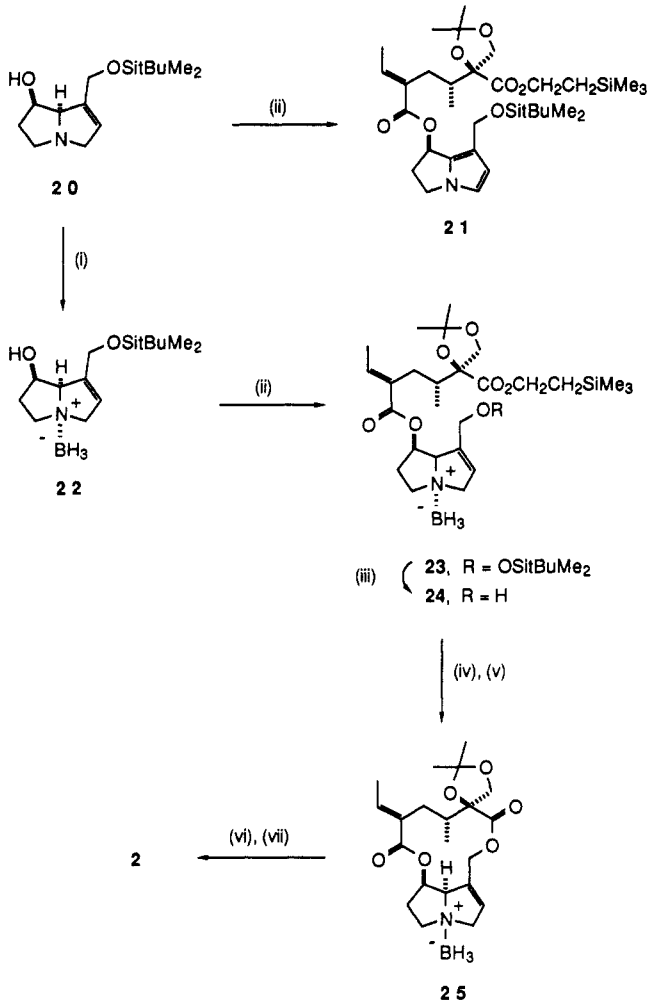
(6) (a) Culvenor, C. C. J.; Smith, L. W. *Aust. J. Chem.* **1967**, *20*, 2499. (b) Sawhney, R. S.; Girotra, R. N.; Atal, C. K.; Culvenor, C. C. J.; Smith, L. W. *Indian J. Chem.* **1967**, *5*, 655. (c) Pieters, L. A.; Vlietinck, A. J. *Planta Med.* **1988**, *54*, 178.

(7) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Do, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(8) (a) Sharpless, K. B.; Caron, M. *J. Org. Chem.* **1985**, *50*, 1557. (b) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.

(9) Imwinkelried, R.; Schiess, M.; Seebach, D. *Org. Synth.* **1987**, *65*, 230.

Scheme III[a]



[a] (i) BH_3·THF, THF (86%); (ii) **19**, $(EtO)_2POCl$, Et_3N, THF, 0 °C → room temperature; **20** or **22**, *n*-BuLi, DMAP (cat.), THF, 0 °C, then mix (55%); (iii) NH_4F, MeOH–H_2O, 60–65 °C (65%); (iv) MsCl, Et_3N, CH_2Cl_2; (v) *n*-Bu_4F, MeCN (75% from **24**); (vi) EtOH, 80 °C; (vii) 1 N HCl–THF (1:1) (67% from **25**).

(Scheme II). Unfortunately, condensation of this material with acetaldehyde was thwarted by a facile Dieckmann condensation, and it was necessary to convert **12** to a δ-lactone for introduction of the ethylidene group. This was accomplished by hydrolysis of the acetonide **12** and treatment of the resulting dihydroxy acid **13** with Mukaiyama's reagent.[10] After protection as its MOM ether (**15**), the lactone was condensed with acetaldehyde, and the resulting β-hydroxy lactone was acetylated. Elimination of acetic acid with 1,5-diazabicyclo[5.4.0]undec-5-ene afforded the *E* olefin **16** with only a trace of the *Z* isomer. Removal of the MOM group and hydrolysis of the lactone **17** furnished **18**, which was protected as acetonide **19** in anticipation of its coupling with **20**.[11]

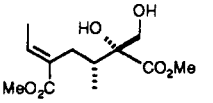
Esterification of the *tert*-butyldimethylsilyl ether **20**[3a] of retronecine[12] with **19** unexpectedly gave the unstable pyrrole **21** in addition to the desired Δ^3-pyrroline ester.[13] It was surmised that protection of **20** against pyrrole formation could be ensured via the pyrrolizidine borane,[14] and when it was found that **20** was converted to **22** in high yield by treatment with borane–THF, the latter became our focal substrate for coupling studies (Scheme III). Thus, **22** was converted to its *O*-lithio derivative and was treated with the acyl phosphate from **19** to give **23**, from which the primary silyl ether was removed to furnish **24**. Treatment of **24** with methanesulfonyl chloride,[15] deprotection of the resulting (trimethylsilyl)ethyl ester, and in situ lactonization to **25** parallels earlier precedent[3b,4a,16] and gave **25** in good yield. Ethanolysis quantitatively removed the borane from **25**, and a final acidic hydrolysis of the acetonide afforded usaramine (**2**, $[\alpha]_D^{24} = +6.8°$), identical with natural material ($[\alpha]_D^{20} + 7.1°$) by comparison of TLC behavior, IR, ^1H and ^{13}C NMR, and mass spectra. Since usaramine has been isomerized photochemically to retrorsine (**3**),[6a] this synthesis also constitutes a route to the latter alkaloid.

Acknowledgment. We are grateful to Dr. C. C. J. Culvenor, Animal Health Research Laboratory, Melbourne, Australia, for a sample of natural usaramine. Financial support was provided by the National Institute for Environmental Health Sciences (ES 03334). Funds for the purchase of a Bruker AM 300 NMR spectrometer were provided by the National Science Foundation (Grant CHE-8216190), the National Institutes of Health (Grant RR04039), and the M. J. Murdock Charitable Trust.

Supplementary Material Available: Spectral and characterization data for compounds **5–19**, **22–25**, and **2** (6 pages). Ordering information is given on any current masthead page.

(10) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707.

(11) A parallel sequence from **10** led to the dimethyl ester (i) of (+)-retronecic acid, with spectroscopic properties identical with those reported for (±)-(i) [Ameer, F.; Drewes, S.; Hoole, R.; Kaye, P.; Pitchford, A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2713].



(i)

(12) Retronecine was obtained by hydrolysis of monocrotaline [Crout, D. H. G.; Davies, N. M.; Smith, E. H.; Whitehouse, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 671].

(13) It was shown by rigorous exclusion of air that this formal dehydrogenation is not the result of aerial oxidation.

(14) Cf.: Schwartz, M. A.; Rose, B. F.; Vishnuvajjala, B. *J. Am. Chem. Soc.* **1973**, *95*, 612.

(15) The intermediate isolated at this stage was shown by mass spectrometry to be the allylic chloride rather than the mesylate [Jayasinghe, L. R. Ph.D. Thesis, Oregon State University, 1988].

(16) Vedejs, E.; Ahmad, S.; Larsen, S. D.; Westwood, S. *J. Org. Chem.* **1987**, *52*, 3938.

Stereochemical Course of Solvolytic 1,3-Deoxysilylation

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Received June 21, 1989

Summary: The stereochemistry of the solvolytic 1,3-deoxysilylation of 4-(trimethylsilyl)-2-butyl *p*-bromobenzenesulfonate has been determined at both reaction centers.

0022-3263/89/1954-4270$01.50/0