lutidine was heated for 10 half-lives in a sealed tube. The trifluoroethanol was removed by rotary evaporator, and the residue was taken up into ether, washed with dilute HCl solution, and dried over $MgSO_4$. After solvent removal by rotary evaporator, the products were characterized by standard spectral methods. The following procedure is representative.

A solution of 291 mg of **9**-*m*-F in 15 mL of TFE containing 128 mg of 2,6-lutidine was heated in sealed tubes for 31 h at 125 °C. Workup, as described above, gave 278 mg (94%) of **11** (Ar = *m*-FC_6H_4): NMR ($CDCl_3$) δ 7.6–6.9 (4 H, m), 4.82 (1 H, d, J = 16 Hz), 4.35–3.65 (6 H, m), 1.27 (3 H, t, J = 8 Hz) 1.23 (3 H, t, J = 8 Hz).

Solvolyses of 14. General Procedure. A solution of triflate **14** in the appropriate solvent containing 1.25 equiv of buffering base was heated for 10 half-lives in a sealed tube. The mixture was then taken up into ether, and a standard aqueous workup followed. For reactions in HOAc and HCO_2H, the mixtures were taken up into ether and washed with water and then with NaOH solution. After standard drying procedures, the solvent was removed by rotary evaporator. Products were separated by preparative gas chromatography and identified by standard spectral methods. The following procedure is representative.

A solution of 162 mg of triflate **14** in 7 mL of TFE containing 75 mg of 2,6-lutidine was heated in saled tubes at 139 °C for 25 h. After a standard workup using a minimal amount of water (**16** is appreciably soluble in water), the mixture was analyzed by 300-MHz NMR which showed **15** and **16** in a 39:61 ratio. NMR of **15** (S = CH_2CF_3) ($CDCl_3$): δ 4.3–3.8 (7 H, m), 1.457 (3 H, doublet of doublets, J = 17, 7 Hz), 1.353 (3 H, t, J = 7 Hz), 1.346 (3 H, t, J = 7 Hz). NMR of **16**[20] ($CDCl_3$) δ 6.4–6.0 (3 H, m), 4.099 (4 H, quintet, J = 7 Hz), 1.335 (6 H, t, J = 7 Hz).

Solvolyses of Mesylates and Triflates. Kinetics Procedures. Solvolyses of mesylates **9** were monitored by using the titrimetric methods previously described.[2,21] Maximum standard deviations in duplicate runs were ±3%. The very reactive **9**-*p*-SCH_3 was monitored spectrophotometrically by following the absorbance increase at 260 nm. Benzyl mesylates containing electron donor substituents were also monitored spectrophotometrically. Those containing electron-withdrawing substituents were monitored titrimetrically. Solvolysis rates of **9**-*m*-F in TFA were determined by NMR monitoring the disappearance of the carbinyl doublet of **9**-*m*-F and the appearance of the product trifluoroacetate. Solvolysis rates of **14** and **14**-d_4 were monitored titrimetrically. Maximum standard deviations for the isotope effect data were ±1.5%.

Acknowledgment. The financial support of the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Registry No. **9**-*p*-SCH_3, 96258-44-5; **9**-3,4-$(CH_3)_2$, 96258-45-6; **9**-*p*-CH_3, 96258-46-7; **9**-3,5-$(CH_3)_2$, 96258-47-8; **9**-*p*-H, 51761-45-6; **9**-*m*-CH_2F, 96258-48-9; **9**-*m*-F, 96258-49-0; **9**-*m*-CF_3, 96258-50-3; **9**-*p*-CF_3, 96258-51-4; **11** (Ar = *m*-FC_6H_4), 96258-58-1; **12**-3,5-$(CH_3)_2$, 96258-52-5; **12**-*m*-CH_3, 96258-53-6; **12**-*p*-H, 55791-06-5; **12**-*m*-CH_2F, 96258-54-7; **12**-*m*-CF_3, 96258-55-8; **12**-*p*-CF_3, 96258-56-9; **14**, 96258-57-0; **14**-d_4, 96292-53-4; **15** (S = CH_2CF_3), 96258-61-6; **16**, 682-30-4; **19**, 96258-59-2; **20**, 96258-60-5; TFE, 75-89-8; HFIP, 920-66-1; TFA, 76-05-1; *p*-$SCH_3C_6H_4CHO$, 3446-89-7; 3,4-$(CH_3)_2C_6H_3CHO$, 5973-71-7; *p*-$CH_3C_6H_4CHO$, 104-87-0; 3,5-$(CH_3)_2C_6H_3CHO$, 5779-95-3; C_6H_5CHO, 100-52-7; *m*-$CH_2FC_6H_4CHO$, 96258-62-7; *m*-FC_6H_4CHO, 456-48-4; *m*-$CF_3C_6H_4CHO$, 454-89-7; *p*-$CF_3C_6H_4CHO$, 455-19-6; *p*-$SCH_3C_6H_4CH(OSiMe_3)PO(OEt)_2$, 96258-63-8; 3,4-$(CH_3)_2C_6H_3CH(OSiMe_3)PO(OEt)_2$, 96258-64-9; *p*-$CH_3C_6H_4CH(OSiMe_3)PO(OEt)_2$, 96258-65-0; 3,5-$(CH_3)_2C_6H_3CH(OSiMe_3)PO(OEt)_2$, 96258-66-1; $C_6H_5CH(OSiMe_3)PO(OEt)_2$, 31675-43-1; *m*-$CH_2FC_6H_4CH(OSiMe_3)PO(OEt)_2$, 96258-67-2; *m*-$CF_3C_6H_4CH(OSiMe_3)PO(OEt)_2$, 96258-68-3; *p*-$CF_3C_6H_4CH(OSiMe_3)PO(OEt)_2$, 96258-69-4; *p*-$SCH_3C_6H_4CH(OH)PO(OEt)_2$, 96258-70-7; 3,4-$(CH_3)_2C_6H_3CH(OH)PO(OEt)_2$, 96258-71-8; *p*-$CH_3C_6H_4CH(OH)PO(OEt)_2$, 79158-40-0; 3,5-$(CH_3)_2C_6H_3CH(OH)PO(OEt)_2$, 96258-72-9; $C_6H_5CH(OH)PO(OEt)_2$, 1663-55-4; *m*-$CH_2FC_6H_4CH(OH)PO(OEt)_2$, 96258-73-0; *m*-$CF_3C_6H_4CH(OH)PO(OEt)_2$, 86208-43-7; *p*-$CF_3C_6H_4CH(OH)PO(OEt)_2$, 96258-74-1; 3,5-$(CH_3)_2C_6H_3CH_2OH$, 27129-87-9; *m*-$CH_3C_6H_4CH_2OH$, 587-03-1; $C_6H_5CH_2OH$, 100-51-6; *m*-$CH_2FC_6H_4CH_2OH$, 96258-75-2; *m*-$CF_3C_6H_4CH_2OH$, 349-75-7; *p*-$CF_3C_6H_4CH_2OH$, 349-95-1; $Me_3SiOP(OEt)_2$, 13716-45-5; *m*-$CH_2FC_6H_4Br$, 456-43-9; CD_3CDO, 1632-89-9; HOAc, 64-19-7; HCO_2H, 64-18-6; EtOH, 64-17-5; diethyl (1-hydroxyethyl)phosphonate, 15336-73-9; diethyl (1-(trimethylsiloxy)ethyl)phosphonate-d_4, 96258-76-3; diethyl (1-hydroxyethyl)phosphonate-d_4, 96258-77-4.

(20) Ford-Moore, A. H.; Williams, J. H. *J. Chem. Soc.* **1947**, 1465–7.
(21) Creary, X. *J. Am. Chem. Soc.* **1984**, *106*, 5577–85.

Nonstabilized Imidate Ylides by the Desilylation Method: A Route to the Pyrrolizidine Alkaloids Retronecine and Indicine

Edwin Vedejs,* Scott Larsen, and Frederick G. West

S. M. McElvain Laboratory of Organic Chemistry, Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received August 3, 1984

Imidate ylides, members of the azomethine ylide family, are generated by desilylation of *N*-[(trimethylsilyl)methyl] imidate salts with CsF. This technique is used to prepare monoprotected retronecine **16** starting from butyrolactam. The route is improved over that described in our 1980 communication, in particular in the conversion of enamine ester **8a** into selenides **13** via selective 1,4 reduction with Dibal and in situ selenylation of the aluminum enolate. Synthetic *d,l*-**16** is converted predominantly into *d,l*-indicine by acylation with *d,l*-**19**.

During extensive studies which culminated in the early 1970's, Huisgen et al. established stabilized azomethine ylides as reactive intermediates which readily undergo cycloaddition reactions with dipolarophiles.[1] Many examples were reported of the synthesis of pyrroles, pyrrolines, and pyrrolizidines from suitable combinations of azomethine dipoles with acrylate- or propiolate-derived dipolarophiles. Nonstabilized azomethine ylides, on the other hand, could be generated in only a few specialized systems.[2] Their inaccessibility precluded synthetic ap-

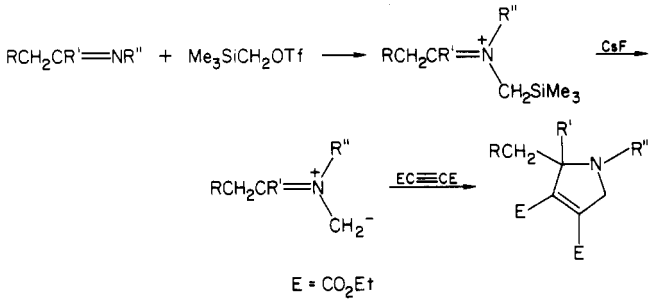
(1) Reviews: (a) Lown, J. W. *Recent Chem. Prog.* **1971**, *32*, 51. (b) Kellogg, R. M. *Tetrahedron* **1976**, *32*, 2165. (c) Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403. See also: Hermann, H.; Huisgen, R.; Mader, H. *J. Am. Chem. Soc.* **1971**, *93*, 1779 and references therein.

(2) Deyrup, J. A.; Szabo, W. A. *J. Org. Chem.* **1975**, *40*, 2048. Deyrup, J. A.; Kuta, G. S. *Ibid.* **1978**, *43*, 501. Burger, K.; Meffert, A.; Bauer, S. *J. Fluorine Chem.* **1977**, *10*, 57. Beugelmans, R.; Negron, G.; Roussi, G. *J. Chem. Soc., Chem. Commun.* **1983**, *31*.

0022-3263/85/1950-2170$01.50/0

plications for the construction of relatively simple five-membered nitrogen heterocycles.

In 1979 we published a preliminary account demonstrating that nonstabilized ylides of nitrogen, sulfur, and phosphorus can be generated by the fluoride ion induced desilylation of the corresponding (trimethylsilyl)methyl "onium" salts.[3] This paper included the first examples of nonstabilized azomethine ylide generation from imines and their trapping with dipolarophiles according to the following procedure. The desilylation route proved capable of generating ylides even in systems where formation of enamine via α-deprotonation of the iminium salt should be especially facile (R = phenyl, below).



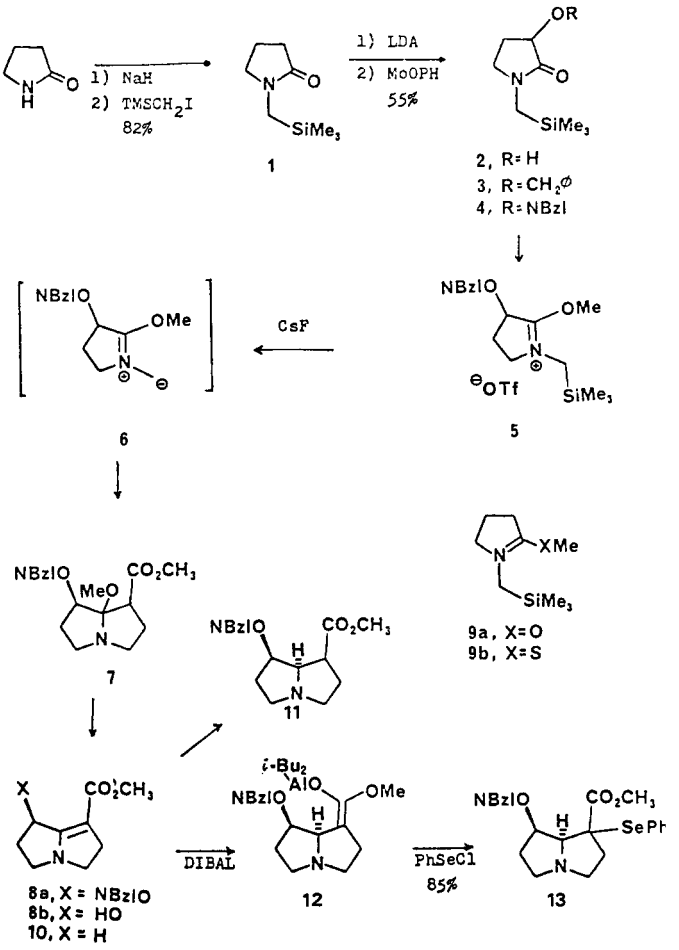
In 1980 we described the extension of this process to nonstabilized imidate ylides,[4] and more recently, an improved procedure involving thioimidate analogues which are convenient precursors of pyrrolines and pyrroles.[5] Several variations on the desilylation technique have now appeared from other laboratories and have helped to establish the method as a general route to five-membered nitrogen rings.[6]

Our studies have focused on the use of imidate ylides for the synthesis of pyrrolizidine alkaloids derived from retronecine (**17**). Important target compounds include biologically potent retronecine esters such as indicine (**20**)[7] or the macrocyclic dilactones (monocrotaline, crispatine, fulvine, etc.).[8] In principle, these substances are available from a derivative of retronecine protected at secondary hydroxyl by the photolabile *o*-nitrobenzyl (NBzl) ether group as in **16**. In this paper, we describe the synthesis of **16** by using imidate ylide strategy, as well as its conversion to *d,l*-retronecine and *d,l*-indicine. The synthetic sequence includes several improvements compared to our short communication which used benzyl-protected intermediates.

In the first step, the (trimethylsilyl)methyl group is attached to butyrolactam nitrogen by using ICH_2SiMe_3[9] + NaH to give **1**, 82% yield. Introduction of the secondary hydroxyl of retronecine is then accomplished by enolate hydroxylation with MoO_5·Py·HMPA (MoOPH).[10] The yield of crystallized product **2** is unexpectedly low (55%), but the procedure is convenient. The next step, hydroxyl protection with *o*-nitrobenzyl bromide, works well (91%, NaH in DME at −23 °C) but extensive experimentation was required to obtain this result due to the base sensitivity of the nitrobenzyl substituent. In particular, it was essential to perform the reaction at −23 °C to avoid the formation of intensely colored decomposition products. The latter predominate under the room temperature conditions we had used earlier to prepare **3**.[4]

The critical cycladdition of imidate ylide **6** with acrylate ester must now be performed. Its net result is to convert **4** into the enamine ester **8a** in a single operation. In the first stage, **4** is treated with methyl triflate to generate imidate salt **5**. The crude salt is then desilylated with anhydrous CsF/DME in the presence of methyl acrylate at 20 °C. Neither the ylide **6** nor the cycloadduct **7** has been observed directly, but the derived enamine **8a** can be isolated in 51% overall yield from **4**. Regioisomeric adducts have not been detected in this reaction, but they would not be likely to survive isolation procedures.

In our recent study, it was demonstrated that thioimidate ylides undergo the [2 + 3] cycloaddition process in higher yield than their oxygen counterparts.[5] For example, treatment of thioimidate salt **9b** with CsF + acrylate affords the adduct **10** in 66% yield while the corresponding imidate ylide from **9a** gives the same product in 37% yield.



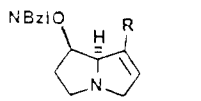
Preliminary experiments suggest that the thioimidate ylide would also work in the retronecine series. However, the conversion of lactam **4** into the analogous thiolactam

(3) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452.
(4) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1980**, *102*, 7993.
(5) Vedejs, E.; West, F. G. *J. Org. Chem.* **1983**, *48*, 4773.
(6) Achiwa, K.; Sekiya, M. *Chem. Lett.* **1981**, 1213. Achiwa, K.; Sekiya, M. *Tetrahedron Lett.* **1982**, *23*, 2589. Teraro, Y.; Imai, N.; Achiwa, K., Sekiya, M. *Chem. Pharm. Bull.* **1983**, *30*, 3167. Chen, S.-F.; Ullrich, J. W.; Mariano, P. S. *J. Am. Chem. Soc.* **1983**, *105*, 6160. Padwa, A.; Chen, Y.-Y. *Tetrahedron Lett.* **1983**, *24*, 3447. Smith, R.; Livinghouse, T. *J. Org. Chem.* **1983**, *48*, 1554. Padwa, A.; Haffmanns, G.; Tomas, M. *Tetrahedron Lett.* **1983**, *24*, 4303.
(7) (a) Mattocks, A. R.; Schoental, R.; Crowley, H. C.; Culvenor, C. C. J. *J. Chem. Soc.* **1961**, 5400. Culvenor, C. C. J.; Smith, L. W. *Aust. J. Chem.* **1966**, *19*, 1955. (b) Indicine *N*-oxide as an antitumor agent: Powis, G.; Ames, M. M.; Kovach, J. S. *Cancer Res.* **1979**, *39*, 3564. Kovach, J. S.; Ames, M. M.; Powis, G.; Moertel, C. G.; Hahn, R. G.; Creagan, E. T. *Ibid.* **1979**, *39*, 4540.
(8) For synthetic results on retronecine dilactones (fulvine, crispatine, etc.): Vedejs, E.; Larsen, S. D. *J. Am. Chem. Soc.* **1984**, *106*, 3030.
(9) Ambasht, S.; Chin, S. K.; Peterson, P. E.; Queen, J. *Synthesis* **1980**, 318.
(10) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

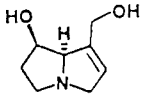
by using Lawesson's reagent proceeds in unusually low yield (70%), perhaps due to interference by the *o*-nitrobenzyl protecting group. This result offsets any expected advantage of a thioimidate cycloaddition, and the imidate ylide procedure remains the method of choice in this specific case.

The next stage of synthesis requires stereochemical and redox adjustments to transform **8a** into the isomer **14**. In our earlier study this was accomplished in three steps by α-face-selective olefin hydrogenation followed by standard lithium enolate selenylation and selenoxide elimination.[4] In the NBzl sequence, the hydrogenation step is precluded by the presence of a nitro group, but the desired product **11** can be easily obtained by reduction of **8a** with $NaCNBH_3$. Conditions for the base-induced enolization–selenylation of **11** have not been found, however. All attempts to generate the lithium enolate gave intensely colored side products suggesting involvement of the base sensitive nitrobenzyl group.

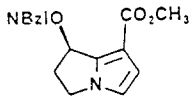
Fortunately, the problem can be avoided by a shorter alternative route. Reduction of **8a** with diisobutylaluminum hydride at −45 °C followed by addition of PhSeCl to the aluminum enolate derived from 1,4-addition[11] affords the selenides **13** in a single step and in good yield. Best results in the conversion to the unsaturated ester **14** are obtained by treating the crude selenide mixture with aqueous acid to protonate the amine nitrogen and then performing the usual selenium oxidation (MCPBA, −78 °C) and thermal elimination. In this way, **14** is formed in 65% overall yield from **8a**, together with approximately 10% of the aromatized pyrrole **15**. If the N-protonation step is omitted, significantly more of the pyrrole can be isolated, suggesting some competing N-oxidation in the sequence from selenide **13** to unsaturated ester **14**.



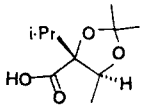
14, R = CO_2CH_3
16, R = CH_2OH



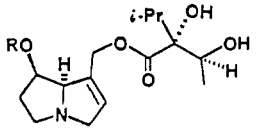
17



15



19



18, R = NBzl
20, R = H

Reduction of **14** to the monoprotected retronecine with Dibal poses no further problems. Likewise, the deprotection to retronecine **17** is relatively routine (sunlamp, CH_3OH, 71%), although it is important to separate **17** from photolysis byproducts without delay.

Overall, this sequence affords the monoprotected retronecine **16** via five isolated intermediates from butyrolactam. There are now too many syntheses of retronecine for simple comparisons.[12] However, the route of Yamada et al. is of interest in the present context because it uses the unsaturated enamine **10** as a substrate for LDA-induced MoOPH hydroxylation to form **8b**.[12g] Subsequent reduction and selenoxide steps can be performed without hydroxyl protection and give retronecine in good yield. Since we have prepared **10** by the thioimidate ylide cycloaddition with acrylate ester (66%, two steps from **1**),[5] the combination with Yamada's sequence from **10** to **17** (four steps) results in a very short synthesis of unprotected retronecine.

We will now turn briefly to the synthesis of *d,l*-indicine **20**, a monoester of retronecine which has been of interest due to the antitumor properties of the corresponding *N*-oxide.[7b] Coupling of naturally derived, unprotected, retronecine with optically pure trachelanthic acid acetonide **19** has been reported by using the Steglich method (DCC + DMAP), 50% after acetonide hydrolysis.[13] We have used similar conditions to couple racemic monoprotected **16** with a 2-fold excess of racemic **19**, resulting in a 71% yield of esters after acetonide hydrolysis. There is a significant kinetic preferrence of 3:1 in favor of the natural diastereomer **18** (together with enantiomer, *d,l*-product), confirmed by *o*-nitrobenzyl ether cleavage to form *d,l*-indicine **20** as the predominant diastereomer.

In conclusion, we have demonstrated the application of imidate ylide 1,3-cycloadditions for synthesis of pyrrolizidine alkaloids. The use of synthetic *d,l*-retronecine **17** and its *o*-nitrobenzyl ether **16** for the preparation of seco acids related to fulvine and crispatine is described elsewhere.[8]

Experimental Section

Ether solvents (THF, DME) were dried over sodium benzophenone and freshly distilled; chlorocarbons and CH_3CN were distilled over P_2O_5. All reactions were performed in a nitrogen atmosphere.

1-[(Trimethylsilyl)methyl]-2-pyrrolidinone (1). 2-Pyrrolidinone (0.68 g, 8.0 mmol) was added neat to a suspension of sodium hydride (0.192 g, 8.0 mmol) in dry Me_2SO (10 mL) at 20 °C with efficient mechanical stirring, N_2 atmosphere. After 90 min at room temperature, (iodomethyl)trimethylsilane[9] (1.88 g, 8.8 mmol) was added neat while the reaction was cooled in a water bath (20 °C). The bath was removed and stirring was continued overnight at ambient temperature. The reaction was poured into water (10 mL) and extracted with ether (6 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated (aspirator) and the resulting oil was eluted through a short column of alumina with ether (140 mL) to remove residual Me_2SO. The solvent was evaporated and the crude product distilled in a Kugelrohr apparatus (100–110 °C (0.2 mm)) to yield 1.12 g (81.8%) of colorless crystals (mp approximately 25 °C), pure enough for the next step.

3-Hydroxy-1-[(trimethylsilyl)methyl]-2-pyrrolidinone (2). To a −78 °C solution of lactam **1** (171 mg, 1.00 mmol) from above in dry THF (5 mL) under N_2 was added lithium diisopropylamide (LDA) (1.49 mL, 0.74 M in hexane/THF, 1.10 mmol). The reaction was stirred for 15 min at −78 °C before warming to −45 °C and adding solid MoOPH[10] (0.65 g, 1.50 mmol) all at once. Stirring was continued at −45 °C for 1.5 h during which time the MoOPH slowly dissolved and the solution went from deep red to orange. The reaction was quenched at −45 °C by addition of

(11) For analogous trapping of aluminum enolates generated by 1,4-addition of Dibal see: Itoh, A.; Ozawa, S.; Oshima, S.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 274.

(12) (a) Geissman, T. A.; Weiss, A. C. *J. Org. Chem.* **1962**, *27*, 139. (b) Tufariello, J. J.; Lee, G. E. *J. Am. Chem. Soc.* **1980**, *102*, 373. (c) Keck, G. E.; Mickel, D. G. *Ibid.* **1980**, *102*, 3632. (d) Osawa, T. Ihara, M.; Fukumoto, K.; Kametani, T. *Heterocycles* **1982**, *19*, 2075: *J. Org. Chem.* **1983**, *48*, 3644. (e) Narasaka, K.; Sakakura, T.; Uchimura, T.; Morimoto, K.; Mukaiyama, T. *Chem. Lett.* **1982**, 455. (f) Rueger, H.; Benn, M. *Heterocycles* **1983**, *20*, 1331. (g) Niwa, H.; Kuroda, A.; Yamada, K. *Chem. Lett.* **1983**, 125.

(13) Piper, J. R.; Kari, P.; Shealy, Y. F. *J. Labelled Compd. Radiopharm.* **1981**, *18*, 1579.

saturated aqueous Na_2SO_3 (4 mL) and vigorous stirring for 10 min while warming to 25 °C. Saturated aqueous NaCl (4 mL) was added and the mixture was extracted with ether (3 × 5 mL) and chloroform (1 × 7 mL). The combined organic extracts were washed successively with 10% aqueous HCl (4 mL) and saturated aqueous NaCl (4 mL). The aqueous phase was back extracted with ether (2 × 5 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to yield a light yellow oil which was eluted through a short column of silica gel (10 g) with ethyl acetate (R_f 0.25, silica gel, ethyl acetate). Evaporation of solvent gave a nearly colorless oil which crystallized on standing. Recrystallization from hexane gave 103 mg of **2** (55.1%) as white needles (mp 65–70): IR ($CHCl_3$, cm^{-1}) 3540 (w), 3320 (m), 1690 (s); NMR ($CDCl_3$, ppm) 4.68 (1 H, bs), 4.36 (1 H, t, J = 8 Hz), 3.30 (2 H, m), 2.82 (2 H, s), 2.40 (1 H, m), 2.00 (1 H, m), 0.10 (9 H, s); exact mass calcd for $C_8H_{17}NO_2Si$ 187.10285, observed 187.1032.

3-[(*o*-Nitrobenzyl)oxy]-1-[(trimethylsilyl)methyl]-2-pyrrolidinone (4). A solution of hydroxy lactam **2** (2.00 g, 10.7 mmol) in glyme (7 mL) was added to a 0 °C suspension of sodium hydride (0.257 g, 10.7 mmol) in glyme (35 mL). The reaction was stirred for 10 min at 0 °C and for 20 min at ambient temperature and then cooled to −23 °C before addition of a solution of *o*-nitrobenzyl bromide (3.47 g, 16.1 mmol) in glyme (7 mL). The reaction immediately turned a deep reddish purple. While stirring at −23 °C for 1 h and 0 °C for $2^1/_2$ h the reaction gradually became a milky tan color as much precipitate formed. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL) followed by saturated aqueous NaCl (10 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated, yielding 4.7 g of brown oil which was purified by column chromatography (silica gel, 100 g, elution with 4:1 hexane–ethyl acetate until product appears (R_f 0.4 in 1:1 hexane–ethyl acetate) followed by 1:1 hexane–ethyl acetate), affording 3.15 g (91%) of pale amber oil: IR (neat, cm^{-1}) 1690 (s), 1525 (s); NMR ($CDCl_3$, 270 MHz, ppm) 8.01 (1 H, d, J = 7.4 Hz), 7.85 (1 H, d, J = 7.4 Hz), 7.62 (1 H, t, J = 7.4 Hz), 7.42 (1 H, t, J = 7.4 Hz), 5.13, 5.24 (2 H, AB, J = 14.6 Hz), 4.19 (1 H, dd, J = 7.5, 6.3 Hz), 3.45 (1 H, m), 3.30 (1 H, m), 2.89, 2.81 (2 H, AB, J = 15.2 Hz), 2.40 (1 H, m), 2.05 (1 H, m), 0.11 (9 H, s); exact mass calcd for $C_{15}H_{22}N_2O_4$ 322.1343, observed 322.1348.

[2 + 3] Cycloadduct 8a. A solution of **4** (5.72 g, 17.8 mmol) and methyl trifluoromethanesulfonate (2.91 g, 17.8 mmol) in methylene chloride (18 mL) was stirred overnight under N_2. Solvent was removed with a stream of dry nitrogen and replaced with dry glyme (180 mL). Methyl acrylate (4.60 g, 53.6 mmol, freshly distilled) was added and the entire suspension was transferred via large gauge cannula into a N_2 swept flask containing anhydrous cesium fluoride (flame dried under vacuum, 6.46 g, 42.7 mmol). The reaction immediately turned a clear orange color. After stirring for 24 h, solvent was evaporated and the residue was dissolved in water (60 mL). Saturated aqueous NaCl (30 mL) was added followed by extraction with chloroform (3 × 40 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to yield a deep red oil which was eluted through a short column of silica gel (75 g) with ethyl acetate. Evaporation yielded 5.2 g of red oil which was dissolved in warm ether and cooled to yield 2.58 g (46%) of light orange prisms, sufficiently pure to use in the next step. The supernatant could be purified by thick-layer chromatography (silica gel, 1:1 ethyl acetate–hexane, R_f 0.45) to yield an additional 0.28 g (5%). A small sample of **8a** was recrystallized from ether to yield yellow needles: mp 93–95 °C; IR ($CHCl_3$, cm^{-1}) 1665 (s), 1615 (s), 1525 (s), 1345 (m); NMR ($CDCl_3$, 270 MHz, ppm) 8.03 (1 H, d, J = 7.4 Hz), 7.80 (1 H, d, J = 7.4 Hz), 7.62 (1 H, t, J = 7.4 Hz), 7.35 (1 H, t, J = 7.4 Hz), 5.03, 5.10 (2 H, AB, J = 14.7 Hz), 4.84 (1 H, dd, J = 6.1, 2.0 Hz), 3.65 (3 H, s), 3.24–3.53 (3 H, m), 2.91–3.07 (3 H, m), 2.37–2.58 (2 H, m); exact mass calcd for $C_{16}H_{18}N_2O_5$ 318.1211, observed 318.1215.

Selenide 13. A solution of **8a** (1.00 g, 3.15 mmol) in THF (10 mL) was cooled to −45 °C under N_2 before addition of a hexane solution of diisobutylaluminum hydride (Dibal) (4.5 mL, 1 M, 4.5 mmol). The reaction was stirred at −45 °C for 1 h and cooled to −78 °C before dropwise addition of a solution of phenylselenenyl chloride (1.02 g, 5.35 mmol) in THF (7 mL). After stirring for 15 min at −78 °C, the reaction was quenched by dropwise addition of methanol (3 mL). The mixture was warmed to room temperature and poured into saturated aqueous NH_4Cl (25 mL) and ether (25 mL). Any resulting emulsions were cleared with 5% aqueous H_2SO_4 (approximately 0.5 mL). The mixture was extracted with ether (2 × 25 mL) and then chloroform (2 × 25 mL) and the combined extracts were evaporated. The resulting oil was purified by elution through a short column of alumina (100 g) with 1:1 chloroform–hexane until high R_f impurities were eluted followed by 1:2 CH_3OH–$CHCl_3$ until product was completely recovered. The best overall yields were realized by taking the resulting light brown oil (1.55 g) directly onto the next step.

Unsaturated Ester 14. A solution of crude selenides **13** (1.55 g) from the previous experiment in methylene chloride (30 mL) was added dropwise via cannula over 25 min to a vigorously stirred suspension of *m*-chloroperbenzoic acid (80%, 1.32 g, 6.4 mmol) in methylene chloride (15 mL) at −78 °C. The reaction was stirred for 2 h at −78 °C and then dimethyl sulfide (1.25 mL) was slowly added and stirring continued for an additional hour at −78 °C. After addition of pyridine (1.70 mL), the reaction was rapidly transferred via cannula into refluxing carbon tetrachloride (120 mL). The solution was immediately cooled to room temperature with an ice bath and poured into saturated aqueous NaCl (70 mL) containing potassium carbonate (2.1 g). Extraction with chloroform (3 × 50 mL), drying over $MgSO_4$, and evaporation yielded an oil which was purified by elution through a short column of alumina (14 × 2.2 cm) with 7:3 chloroform–hexane followed by 7:3 chloroform–methanol. The methanolic eluant (approximately 1 g) was further purified by preparative thick-layer chromatography with CH_3OH (silica gel, R_f 0.3) to afford a pale yellow oil. Crystallization from hexane gave pale yellow prisms of **14** (614 mg, 61% overall from **8**, mp 81–83 °C). The pyrrole **15** could also be obtained in about 9% yield by preparative thick-layer chromatography of the hexane–chloroform eluant from the alumina column (silica gel, 2:3 ethyl acetate–hexane, R_f 0.4) and crystallized from ether–hexane as light tan prisms: mp 105–106 °C. IR (CCl_4, cm^{-1}). **14**: 1715 (s), 1520 (s), 1340 (s); **15**: 1720 (s), 1540 (s), 1355 (m). NMR ($CDCl_3$, 270 MHz, ppm). **14**: 8.05 (1 H, d, J = 7.5 Hz), 7.62 (2 H, m), 7.41 (1 H, m), 6.78 (1 H, d, J = 2.2 Hz), 4.96, 4.73 (2 H, AB, J = 15.1 Hz), 4.55 (1 H, m), 4.28 (1 H, t, J = 3.7 Hz), 4.05 (1 H, ddd, J = 18.0, 3.3, 2.2 Hz), 3.71 (3 H, s), 3.55 (1 H, ddd, J = 18.0, 5.9, 2.2 Hz), 3.28 (1 H, t, J = 8.1 Hz), 2.66 (1 H, m), 2.20 (1 H, dd, J = 13.2, 5.1 Hz), 1.92 (1 H, m). **15**: 8.02 (1 H, d, J = 8.5 Hz), 7.72 (1 H, d, J = 7.4 Hz), 7.58 (1 H, t, J = 7.4 Hz), 7.40 (1 H, t, J = 7.4 Hz), 6.64 (2 H, s), 5.19 (1 H, d, J = 5.9 Hz), 5.08, 4.96 (2 H, AB, J = 14.7 Hz), 4.23 (1 H, m), 3.97 (1 H, t, J = 9.9 Hz), 3.81 (3 H, s), 2.68 (2 H, m). Exact mass. **14**: calcd for $C_{16}H_{18}N_2O_5$ 318.1211, observed 318.1215. **15**: calcd for $C_{16}H_{16}N_2O_5$ 316.1055, observed 316.1072.

Protected Retronecine 16. A solution of unsaturated ester **14** (453 mg, 1.42 mmol) in methylene chloride (23 mL) was cooled to −23 °C under N_2 before addition of Dibal (5.0 mL, 1 M in hexane, 5 mmol). The reaction was stirred for 1 h at −23 °C and then quenched by addition of Glauber's salt. The mixture was warmed to room temperature and alumina (approximately 1 g) was added. After stirring for 15 min, or until gas evolution ceased, the entire mixture was loaded onto a short column of alumina (50 g) and eluted with 2:3 methanol–ethyl acetate. This required assistance by an aspirator-induced vacuum at the bottom of the column. Evaporation of the eluant afforded 415 mg (100%) of pure **16** as pale yellow crystalline solid. Recrystallization of a small sample from methylene chloride–hexane gave pale yellow prisms: mp 105–108 °C; IR ($CHCl_3$, cm^{-1}) 2400–3600 (s), 1530 (s), 1345 (s); NMR ($CDCl_3$, 270 MHz, ppm) 8.05 (1 H, d, J = 8.5 Hz), 7.64 (2 H, m), 7.44 (1 H, t, J = 6.6 Hz), 5.67 (1 H, bs), 4.98, 4.75 (2 H, AB, J = 15.1 Hz), 4.33 (1 H, bs), 4.20 (2 H,AB, J = 14.3 Hz), 3.90 (1 H, bd, J = 14.7 Hz), 4.20 (1 H, bs), 3.36 (1 H, dd, J = 14.7, 4.8 Hz), 3.24 (1 H, t, J = 8.4 Hz), 2.64 (1 H, m), 2.23 (1 H, dd, J = 13.5, 5.8 Hz), 1.88 (1 H, m); exact mass calcd for $C_{15}H_{18}N_2O_4$ 290.1262, observed 290.1267.

(±)-Retronecine 17. Protected retronecine **16** (25 mg, 0.086 mmol) in methanol (25 mL) was irradiated with a 275-W sun lamp through a Pyrex filter while cooled in a water bath (20–25 °C) for 60 min. The amber solution was then evaporated (aspirator) to a volume of approximately 1 mL before addition of water (3 mL). After washing with chloroform (3 × 2 mL), the aqueous phase was evaporated. The resulting brown oil was dissolved in chloroform and filtered through a plug of anhydrous Na_2CO_3 and

$MgSO_4$. Evaporation of the eluant gave an amber oil (9.5 mg, 71%). Pure (±)-retronecine could be prepared by sublimation (100 °C (0.01 mm)) of the crude base in 70% yield, followed by recrystallization of the solid sublimate from acetone to give a crystalline white solid, mp 129–130 °C (lit.[11a] mp 130–131 °C). The NMR spectrum and TLC mobility of (±)-17 were identical with an authentic sample of racemic retronecine.[14]

Coupling of Retronecine and 19. Conversion to *d,l*-Indicine. Monoprotected retronecine 16 (*d,l*) (14.5 mg, 0.050 mmol), *d,l*-acetonide 19 (20.2 mg, 0.10 mmol), *N,N'*-dicyclohexylcarbodiimide (20.6 mg, 0.10 mmol), and (*N,N*-dimethylamino)pyridine (1.7 mg, 0.014 mmol) were stirred in dry toluene (0.9 mL) for 14 h according to the procedure used for unprotected retronecine.[13] (A white precipitate, dicyclohexylurea, appeared during this time.) The resulting suspension was filtered, and the filtrate was diluted with toluene to a volume of 5 mL and extracted with 5% aqueous HCl (3 × 4 mL). The combined acid extracts were allowed to stand overnight at ambient temperature, and then were brought to pH 11 with 28% aqueous NH_4OH. The resulting cloudy suspension was extracted with ether (10 mL), saturated with NaCl, and extracted additionally with ether (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated (aspirator) to give 20.6 mg of pale yellow glass consisting of a ca. 3:1 ratio of diastereomeric products together with DMAP. PTLC (silica gel, 20% methanol–chloroform) separated the coupling products (R_f 0.40) from DMAP (R_f 0.19) but failed to resolve the unequal mixture of diastereomers, giving 15.5 mg (71%) of the esters: IR (neat film, cm^{-1}) 1730 (s); partial 270 MHz NMR ($CDCl_3$, ppm) major diastereomer, 1.20 (methyl, d, J = 6.2 Hz), minor diastereomer, 1.18 (methyl, d, J = 6.2 Hz).

The unequal mixture of diastereomeric coupling products (10.4 mg, 0.024 mmol) was dissolved in dry THF (10 mL) and photolyzed (275-W sunlamp through Pyrex, cooling to maintain ≤28 °C) for 30 min, after which TLC (33% CH_3OH–CH_2Cl_2) showed total consumption of starting material (R_f 0.50) and appearance of a new high R_f spot (*o*-nitrobenzaldehyde derived products) and one at R_f 0.07 (deprotected product). Solvent was removed (aspirator) and the residue taken up in water (2 mL). The aqueous layer was washed with chloroform (2 × 1 mL) and evaporated to yield 5.0 mg of yellow oil (70%) which was identified as protonated indicine and its diastereomer. The material was dissolved in THF and stirred over excess solid, anhydrous K_2CO_3 for 15 min. Removal of solvent gave a mixture of the free bases: IR (KBr, cm^{-1}) 1725 (s); partial 270 MHz NMR ($CDCl_3$, ppm) minor (unnatural) diastereomer 1.21 (methyl, d, J = 5.5 Hz), 1.11, 0.83 (isopropyl, two d, J = 6.2 Hz), major diastereomer[15] (indicine) 1.17 (methyl, d, J = 6.5 Hz), 0.92, 0.91 (isopropyl, two d, J = 7.2 Hz).

Acknowledgment. This work was supported by the National Institutes of Health (CA 17918) and by an NSF predoctoral fellowship (FGW).

Registry No. 1, 76596-19-5; 2, 76596-20-8; 4, 96246-59-2; 8a, 96246-60-5; 13, 96246-61-6; 14, 96246-62-7; 15, 96246-63-8; 16, 96246-64-9; 17, 73466-19-0; 18 (isomer 1), 96246-65-0; 18 (isomer 2), 96346-14-4; 19, 96291-80-4; 20 (isomer 1), 96291-81-5; 20 (isomer 2), 96291-82-6; 2-pyrrolidinone, 616-45-5; (iodomethyl)trimethylsilane, 4206-67-1; *o*-nitrobenzyl bromide, 3958-60-9; methyl acrylate, 96-33-3; phenylselenenyl chloride, 5707-04-0.

(14) Kindly provided by Dr. A. R. Mattocks, Medical Research Council Laboratories, United Kingdom.

(15) Identical with spectra of natural indicine, a sample of which was kindly provided by the National Cancer Institute.

Rearrangement of Unsaturated (Acyloxy)benzotriazoles

Srinivasan Nagarajan, Scott R. Wilson, and Kenneth L. Rinehart, Jr.*

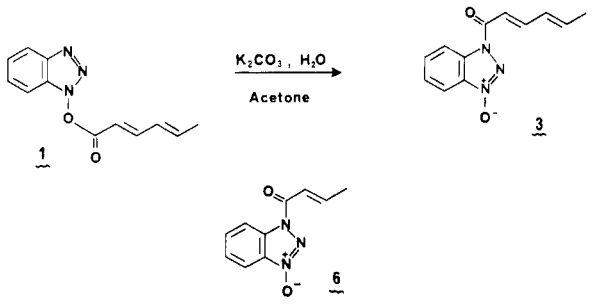
School of Chemical Sciences, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

Received July 20, 1984

In an attempt to use hydroxybenzotriazole to synthesize *C*-acyl tetramic acid analogues of streptolydigin and tirandamycin, preformed 1-(crotonyloxy)benzotriazole rearranged to give β-methyl-3-benzotriazolepropionic acid 1-oxide (7) through the intermediate ketene. 1-(Crotonyloxy)benzotriazole (formed in situ) and 1-(sorbyloxy)benzotriazole (in situ or preformed) were found to rearrange to give the corresponding 3-acylbenzotriazole oxides (6 and 3). Structures of 3 and 7 were established by X-ray crystallography. The ^{15}N NMR spectra of the rearrangement products and related compounds are also discussed.

Hydroxybenzotriazole has been used widely as a coupling agent for forming peptide bonds[1] and as a phosphorylating agent[2] and, recently, has been successfully employed to effect C-acylation of a pyrrolidinedione to give malonomicin,[3] an acyl tetramic acid antibiotic. In our continuing studies of potential routes to the acyl pyrrolidinedione antibiotics tirandamycin and streptolydigin,[4] we attempted to acylate α-(1-methyl-2,4-dioxo-5-pyrrolidinyl)-*N*-methylacetamide, employing preformed 1-(sorbyloxy)benzotriazole (1, Scheme I) and 1-(crotonyloxy)benzotriazole (2, Scheme II) rather than in situ generated esters; however, unexpected rearrangements were observed instead.

Scheme I



Results and Discussion

During the preparation of 1-(sorbyloxy)benzotriazole (1) from the potassium salt of 1-hydroxybenzotriazole and sorbyl chloride in acetone, a small amount of rearrangement product 3 was obtained. This compound could also be obtained when the sorbyl ester 1 was stored for several weeks or, in large quantities, when the sorbyl ester was

(1) For a review, see: Munekata, E.; Sakakibara, S. *J. Synth. Org. Chem., Jpn.* **1973**, *31*, 853–858.
(2) van Boeckel, S. A. A.; van der Marel, G.; Wille, G.; van Boom, J. H. *Chem. Lett.* **1981**, 1725–1728.
(3) van der Baan, J. L.; Barnick, J. W. F. K.; Bickelhaupt, F. *Tetrahedron* **1978**, *34*, 223–231.
(4) Lee, V. J.; Branfman, A. R.; Herrin, T. R.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 4225–4236.

0022-3263/85/1950-2174$01.50/0