Tetrahedron Vol. 48, No. 35, pp. 7071-7082, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Oxidation of Ylide Precursors to Vicinal Tricarbonyls. Applications in Vincamine Alkaloid Synthesis.

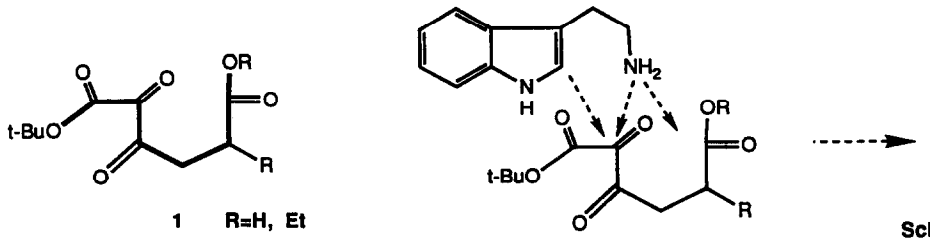
Harry H. Wasserman* and Gee-Hong Kuo
Department of Chemistry, Yale University, New Haven, CT 06511 USA

(*Received in USA* 8 *May* 1992)

Abstract: Attachment of carbethoxyalkyl residues to an α,β-diketo ester provides dielectrophilic species applicable to the synthesis of the vincamine alkaloids, eburnamonine and tacamonine. The required vicinal tricarbonyl aggregates were formed by oxidation of suitable ylide precursors with ozone or singlet oxygen.

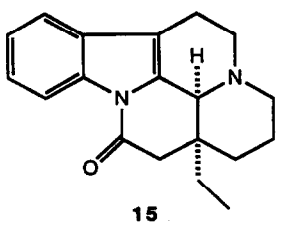
We have reported the use of vicinal tricarbonyl derivatives attached to various acceptor residues as polyelectrophiles in synthetic applications leading to the formation of natural products. In the syntheses of prodigiosin,[1] vasicine[2] and 3-demethoxyerythratidinone,[3] the attachment of a vinyl group to the tricarbonyl aggregate provided sites for tandem addition of dinucleophiles leading to the key intermediates for further elaboration to the target alkaloids.

In the present work, we describe the generation of other tricarbonyl units which may undergo reactions as polyelectrophiles leading to key intermediates in the synthesis of vincamine-related alkaloids. Our synthons in this work were monohydrates of tricarbonyl esters containing auxiliary carbonyl groups attached by two-carbon spacers to the main functionality as in **1**. Formation of the tetracyclic framework in eburnamonine **15**[4] and tacamonine **16**[5] would then take place by stepwise reaction with tryptamine (Scheme 1).[6]

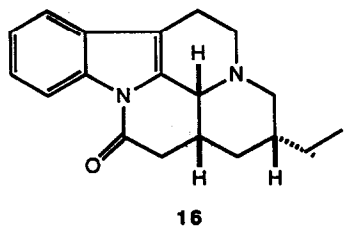


1 R=H, Et

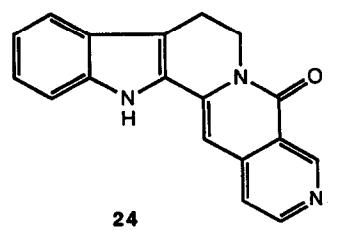
Scheme 1



15
eburnamonine



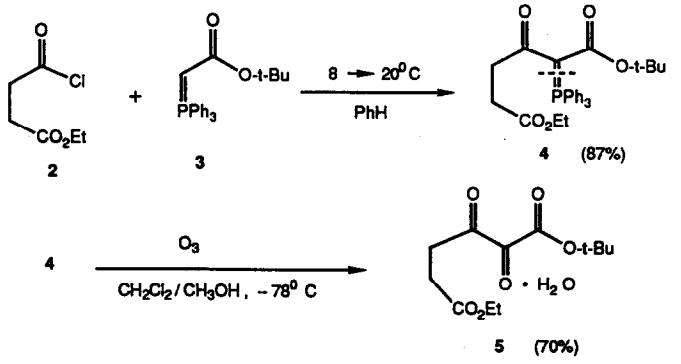
16
tacamonine



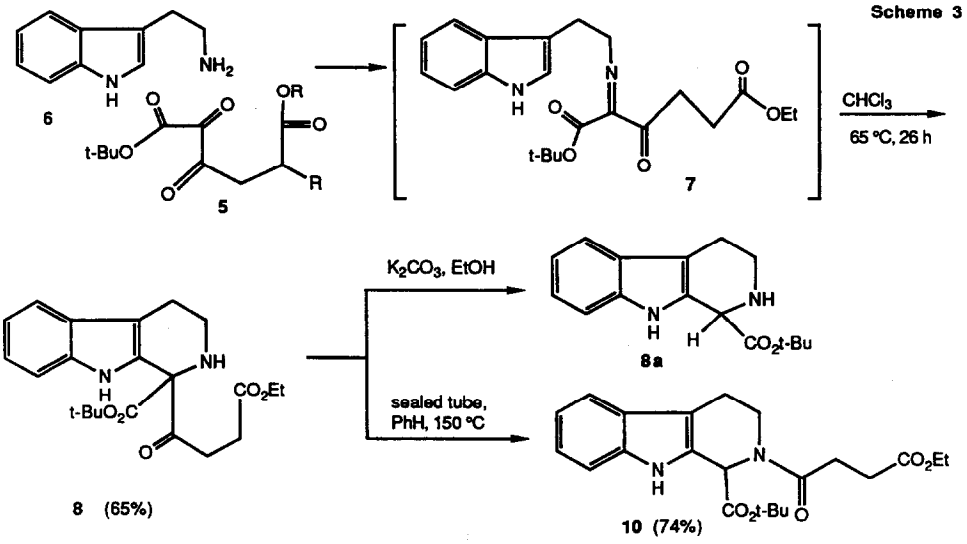
24
nauclefine

Our synthesis of eburnamonine began with the formation of 1, R=H from ethyl succinyl chloride 2. Reaction of 2 with two equivalents of t-butyl (triphenylphosphoranylidine)acetate 3 along the lines of Cook's procedure[7] yielded the ylide 4 (87%). Recently,[8] we have found that reactions of acid chlorides with ylides such as 3 require only one equivalent of phosphorane if the coupling is carried out in the presence of a proton acceptor such as bis(trimethylsilyl)acetamide (BSA). We have also found that, in many cases, the free carboxylic acid will undergo coupling directly with the ylide in the presence of DCC or EDCl.

The ylide 4 was then subjected to oxidative cleavage. Our initial studies on cleavage of the carbon-phosphorus double bond in 4 employed singlet oxygen or ozone. In general, singlet oxygen is more selective than ozone in this type of reaction, providing a gentler oxidant in the presence of sensitive substituents.[9] In this case, while either oxidant appeared to be effective, it was found more convenient to use ozone, which accomplished the conversion to the tricarbonyl hydrate 5 in 70% yield (Scheme 2). The latter crystallized in the form of long white needles m.p. 48-49°C.

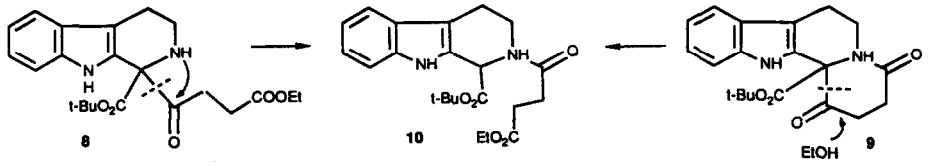


Scheme 2



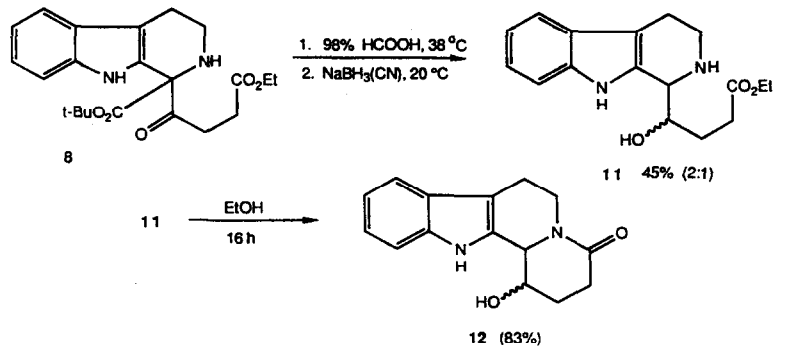
Scheme 3

The reaction of tryptamine **6** with the tricarbonyl **5** in methylene chloride at room temperature initially gave disappointing results in that only the imine **7** was formed in low yield. However, under warm chloroform reflux for one day, the reaction took a more promising course, yielding the tricyclic β-carboline **8** directly (65%) (Scheme 3). At this stage, we attempted to form the lactam **9** by heating **8** with or without potassium carbonate in ethanol,[10] but, under these conditions, the β-keto ester residue in **8** underwent a reverse-Claisen type of cleavage yielding **8a**. When **8** was heated in a sealed tube in benzene at 150°C, the amide **10** was isolated (74%). This product was formed most probably by intramolecular attack of the neighboring amino group (Scheme 4) or by ethanol-promoted ring-opening of the transient intermediate **9**.

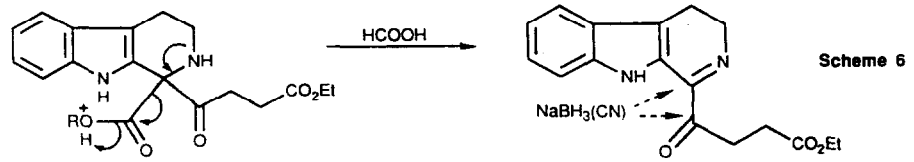


Scheme 4

We were able to solve the problem of β-keto ester cleavage by removing the t-butyl ester group. This was accomplished (Scheme 5) by treating **8** with 98% formic acid at 38°C for one hour, followed by reduction of the expected intermediate imine with sodium cyanoborohydride. Previous observations on the reactions of systems similar to **8** with THF or formic acid[2] suggest (Scheme 6) that the loss of the ester group may take place by decarbonylation, with accompanying formation of an imino group, although an alternative decarboxylation-air oxidation pathway has not been ruled out.. This combined degradation-reduction process yielded product **11** as a mixture of diastereomers which could be converted on heating in ethanol to the desired lactam **12**. Reduction of

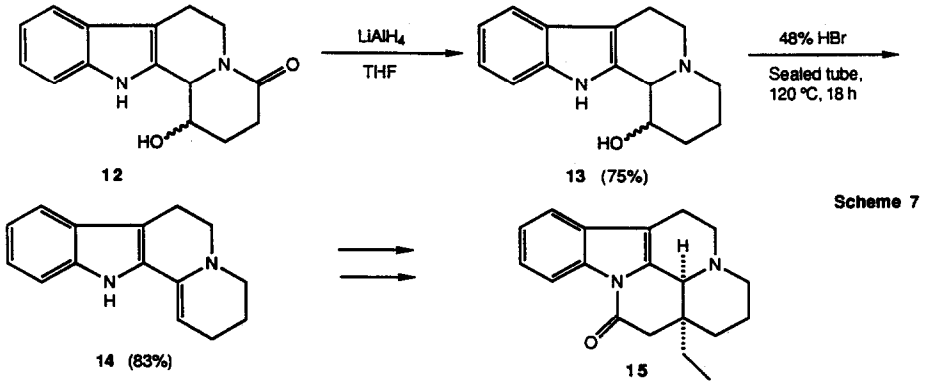


Scheme 5



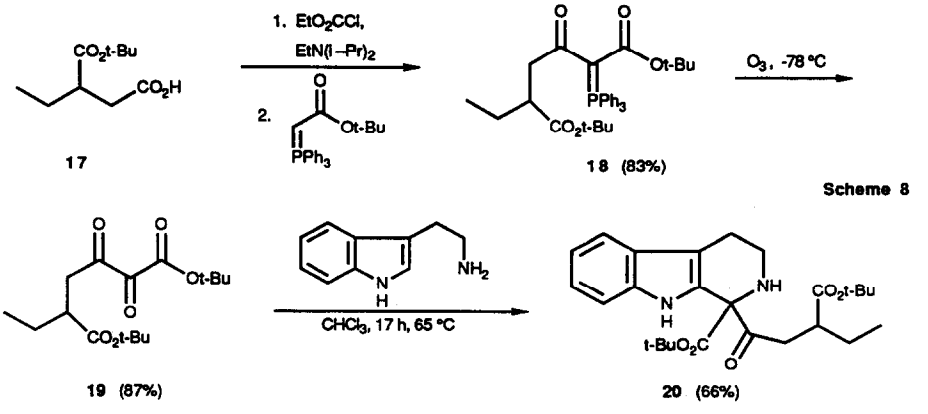
Scheme 6

12 with $LiAlH_4$ (Scheme 7) gave the corresponding mixture of amino alcohols 13 (75%). When 13 was heated under nitrogen in a sealed tube at 120° for 18 hours in the presence of 48% HBr, it was converted (83%) to the pure enamine 14,[11a] exhibiting physical and spectroscopic properties in excellent accord with those reported by Martel[11c] who has previously transformed this compound to eburnamonine 15 by standard enamine coupling reactions.

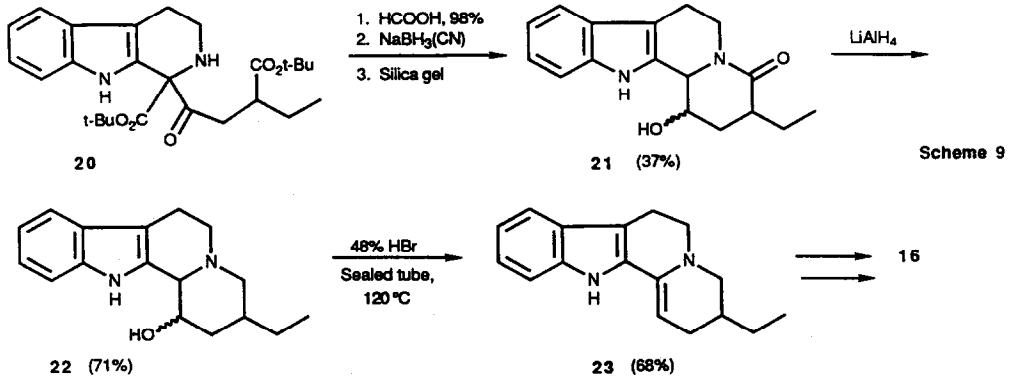


Scheme 7

In extending this approach to the synthesis of tacamonine 16, (Scheme 8) we found that while the coupling reaction outlined in Scheme 2 worked poorly with the acid chloride, it yielded 18 in excellent yields when the mixed anhydride was used instead. The latter anhydride was formed by the procedure of Overman[13] from the half acid-ester 17[12] using ethyl chloroformate in the presence of diisopropylethylamine, and treated with 3, directly, without isolation. As in the conversion of 4 to 5, ozonolysis of 18 led smoothly to the tricarbonyl hydrate 19 (87%). Heating 19 with tryptamine in chloroform for 17 hours yielded the tricyclic product 20 (66%) which was then subjected to the action of 98% formic acid followed by $NaBH_3(CN)$ (Scheme 9). Removal of solvent, addition of ethanol, and warming with silica gel at 78° for 48 hours yielded the lactam 21 as a mixture of four diastereomers (37% yield for the three steps from 20).



Scheme 8

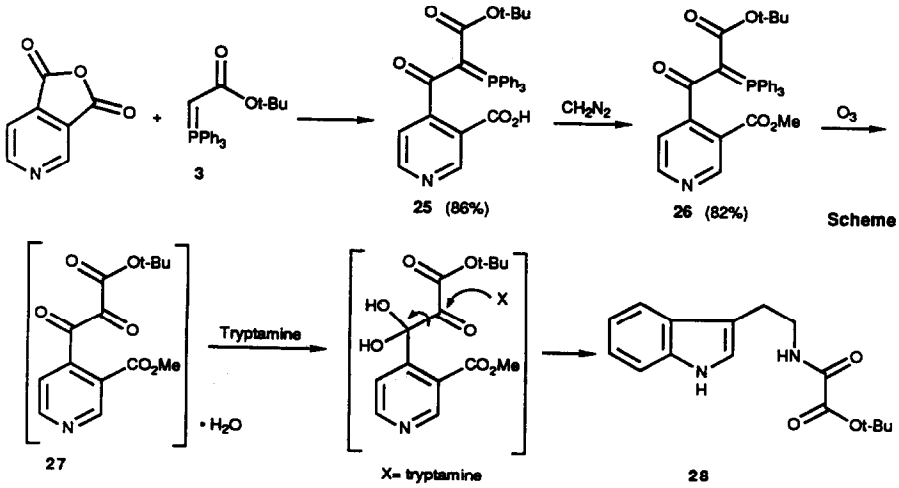


20 21 (37%) Scheme 9

22 (71%) 23 (68%)

Reduction of **21** with $LiAlH_4$ yielded the amino alcohol **22** as a mixture of two *syn* and two *anti* diastereomers (71%) which could be dehydrated by heating with 48% aqueous HBr to form the enamine **23** (68%). The 250 MHz ^1H NMR, IR, MS and HRMS of this product are in complete accord with the assigned structure of **23**, which has been converted to tacamonine **16** by Massiot in a three-step procedure involving reaction with ethyl iodoacetate, zinc/acetic acid reduction and ring closure with sodium ethoxide.[5]

In our most recent work, we sought to extend this methodology to the synthesis of the alkaloid nauclefine[14] **24**, according to the sequence outlined in Scheme 10. In accord with this plan, commercially available 3,4-pyridinedicarboxylic acid anhydride was coupled with **3** to form the ylide **25** (86%), which was converted to the methyl ester **26** with diazomethane (82%). Ozonolysis of **26** yielded a vicinal tricarbonyl product **27** corresponding most probably to a mixture of the two different hydrates. Thus far, we have not found conditions for the addition of tryptamine to this tricarbonyl mixture which parallels the reaction of **5** with **6** to form **8**. Product **27** appears to be particularly sensitive to cleavage by base, since reaction with tryptamine yielded only the cleavage product **28**. Related cleavage reactions of tricarbonyl hydrates have been observed by Danishefsky in his studies on the reactions of FK-506 with nucleophiles.[15]



3 25 (86%) 26 (82%) Scheme 10

27 X= tryptamine 28

Experimental Section

General Information

Melting points were determined on a Thomas Hoover capillary melting point apparatus. All melting points and boiling points were uncorrected. Infrared spectra were recorded on a Perkin Elmer 1420 Spectrophotometer or Nicolet S-5X FT-IR. Proton and carbon nuclear magnetic resonance spectra were determined in the indicated solvent on a Bruker HX-270, Bruker WM-250, Bruker WM-500 spectrometer as noted. In most cases, $CDCl_3$ was used as the internal standard (δ 7.27 ppm). Low-resolution mass spectra were recorded on a Hewlett Packard 5985A or 5989A mass spectrometer using electron ionization (20 EV). High-resolution mass spectra, using either electron ionization (EI) or chemical ionization (CI), were performed by Mr. Dan Pentek on a Kratos MS-80RFA at Yale University, Instrument Center.

Flash chromatography was performed on silica gel 60 (230-400 mesh, EM laboratories). All chromatographic solvents were distilled prior to use with the exception of diethyl ether which was obtained in anhydrous form. Thin layer chromatography (TLC) was performed on glass plates pre-coated with silica gel 60 F_{254} (0.25 mm, EM laboratories). Visualization was carried out using UV lamp, iodine, phosphomolybdic acid, or *p*-anisaldehyde stain.

Anhydrous solvents were distilled prior to use: THF was distilled from sodium/benzophenone ketyl; acetonitrile, benzene, methylene chloride, pyridine, triethylamine and dimethyl sulfoxide were distilled from calcium hydride.

t-Butyl (Triphenylphosphoranylidine) Acetate 3. This preparation followed the published procedure of Cooke and Burman[7] with minor modifications. The spectroscopic information is essentially the same as that reported by these authors. A solution of triphenylphosphine (94.4 g, 0.36 mol) and t-butyl chloroacetate (50 g, 0.33 mol) in benzene (400 mL) was heated at reflux for 48 h. After cooling the solution to room temperature, the resulting salt was collected by suction filtration and washed with benzene (2 x 400 mL). Drying the phosphonium salt *in vacuo* yielded t-butyl(triphenylphosphoranylidine) acetate as a white solid (104 g, 77%). To a solution of the crude phosphonium salt (30 g, 72.7 mmol) in water (550 mL), cooled to 5°C, was added a solution of NaOH (3.37 g, 84 mmol) in H_2O (110 mL) with vigorous stirring. After six minutes of stirring at 5 °C, the precipitate was collected by suction filtration and washed well with cold water. This solid was dried *in vacuo* to yield the ylide as a white powder (25 g, 92%): IR ($CDCl_3$) 3000, 2980, 1605, 1435, 1360, 1162, 1102 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.2-8.1 (m, 15 H), 2.78 (br d, 1H), 1.26 (br s, 9 H).

t-Butyl 5-Ethoxycarbonyl-3-oxo-2-(triphenylphosphoranylidine)-pentanoate 4. To a stirred solution of the ylide 3 (26 g, 69.1 mmol) in dry benzene (172 mL), cooled to 8°C, was added ethyl succinoyl chloride (5.2 g, 31.4 mmol) dropwise in benzene (28 mL). The reaction mixture was stirred at 8 °C for 5 min and then at room temperature for an additional 1.5 h. Afterwards, ether (206 mL) was added and the precipitated phosphonium salt was removed by suction filtration. The filtrate was concentrated *in vacuo* to give a thick,

yellow oil. The crude product was purified by silica gel column chromatography (CH_2Cl_2/EtOAc= 7/1) to afford compound **4** as a white crystalline solid (13.7 g, 87%): mp 135-137°C; IR ($CDCl_3$) 3001, 1731, 1661, 1552, 1482, 1440 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.94-7.37 (m, 15H), 4.03 (q, J= 7.1 Hz, 2H), 3.22 (t, J= 7.1 Hz, 2H), 2.53 (t, J= 7.1 Hz, 2H), 1.17 (t, J= 7.1 Hz, 3H), 1.06 (s, 9H); MS, m/e 506 (0.6, M+2), 505 (3.6, M+1), 504 (10.9, M), 459 (3) 431 (3.4), 403 (12.4), 376 (6.5), 348 (22.7), 347 (100), 320 (16.5), 319 (13.5), 304 (6.8), 303 (29.5), 276 (4.8), 262 (3.3); exact mass calcd for $C_{30}H_{33}O_5P$: 504.2067, found: 504.2073.

t-Butyl 2,3-Dioxo-5-ethoxycarbonylpentanoate Monohydrate **5**. A solution of the ylide **4** (13.7 g, 27.2 mmol) in CH_2Cl_2 (150 mL) and methanol (30 mL) was cooled to -78 °C. Ozone was passed through the light yellow solution to the persistence of a green color. Excess ozone was then removed from the reaction mixture by purging with N_2 gas. After the solution was warmed to 20°C, the solvent was removed *in vacuo* to give the tricarbonyl derivative as a yellow oil. The crude product was purified by silica gel column chromatography (CH_2Cl_2/EtOAc=12/1--10/1--8/1) to afford **5** as a yellow oil (5.3 g, 70%) which solidified to a yellow oily semisolid upon storage in the freezer overnight. Long white needles were obtained after the oily solid was recrystallized from cyclohexane: mp 48-49 °C; IR ($CDCl_3$) 3500-3450, 1724 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.95 (s, 2H), 4.15 (q, J+7.1 Hz, 2H), 2.93 (t, J= 6.7 Hz, 2H), 2.65 (t, J= 6.7 Hz, 2H), 1.52 (s, 9H), 1.26 (t, J= 7.1 Hz, 3H); MS, m/e 175 (2, M- $CO_2C(CH_3)_3$), 157 (1.4), 131 (1.4), 130 (5.7), 129 (57.9), 102 (13.8), 101 (48.8), 74 (3.5), 58 (39), 57 (100); exact mass calcd for $C_{12}H_{19}O_6$ (CI, M + H-H_2O): 259.1182, found: 259.1172.

1-(t-Butoxycarbonyl)-1-(3-ethoxycarbonyl-1-oxo-propyl)-2,3,4-trihydro-β-carboline **8**. The mixture of tryptamine **6** (1.74 g, 10.88 mmol) and tricarbonyl derivative **5** (3 g, 10.87 mmol) in chloroform (150 mL) was heated at 65 °C for 26 h. The solvent was removed under vacuum. The crude product was purified by a short silica gel column (5 cm height, 2% EtOAc/CH_2Cl_2) to afford compound **8** as a yellow oil (2.83 g, 65%): IR ($CDCl_3$) 3490, 3010, 1730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 7.54 (d, J= 8.0 Hz, 1H), 7.37 (d, J= 8.0 Hz, 1H), 7.21 (t, J= 7.6 Hz, 1H), 7.11 (t, J= 7.7 Hz, 1H), 4.10 (q, J= 7.1 Hz, 2H), 3.13 (t, J= 5.6 Hz, 2H), 2.91 (m, 2H), 2.80 (m, 2H), 2.52 (m, 2H), 1.52 (s, 10 H), 1.22 (t, J= 7.1 Hz, 3H); MS, m/e 400 (1.6 M), 300 (1.8), 299 (7.9), 272 (3.6), 271 (17.2), 216 (14.2), 215 (100), 197 (3.5), 170 (5), 169 (4.8), 129 (2.4); exact mass calcd for $C_{22}H_{28}N_2O_5$: 400.1999, found: 400.1978.

1-(t-Butoxycarbonyl)-2-(3-ethoxycarbonyl-1-oxo-propyl)-1,2,3,4-tetrahydro-β-carboline **10**. The solution of compound **8** (15 mg, 0.0375 mmol) in benzene (2 mL) was heated at 150 °C in a sealed tube for 63 h. The solvent was removed under vacuum. The crude product was purified by silica gel column chromatograpy (EtOAc/CH_2Cl_2= 4% --8%) to afford compound **10** as a yellow oil (11 mg, 74%): IR ($CDCl_3$, FT) 3471, 3316, 3006, 2927, 2847, 1737, 1727, 1651, 1149 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.38 (brs, 1H), 7.50 (d, J= 7.8 Hz, 1H), 7.37 (d, J= 7.8 Hz, 1H), 7.20 (t, J= 7.8 Hz, 1H), 7.11 (t, J= 7.8 Hz, 1H), 6.02 (s, 1H), 4.22 (brd, J= 13.5 Hz, 1H), 4.15 (q, J= 7.1 Hz, 2H), 3.60 (m, 1H), 2.86-2.73 (m, 6H), 1.46 (s, 9H), 1.26 (t, J= 7.1 Hz, 3H); MS, m/e 401 (1.3, M+1), 400 (5.4, M), 355 (3.9), 344 (12.7), 327 (3.6), 326 (12), 300 (20.4), 299 (18), 271 (1.1), 225 (3.3), 216 (13), 215 (78.8), 172 (15.7), 171 (100), 170 (33.5), 129 (31.5), 101 (26).

1-(3-Ethoxycarbonyl-1-hydroxy-propyl)-1,2,3,4-tetrahydro-β-carboline **11**. The orange-red solution of the indole ester **8** (2.56 g, 6.4 mmol) in 98% HCOOH (60 mL) was stirred at 38 °C for 1 h. The solution was then cooled to 20 °C before addition of $NaBH_3(CN)$ (1.21 g, 19.2 mmol). The resulting yellow solution was stirred at 20 °C for 2 h, the solvent removed, and the residue dissolved in EtOAc (200 mL). The organic phase was washed with $NaHCO_3$ (aq) to alkaline pH, and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and the solvent was evaporated. The crude product was purified by silica gel column chromatography (dry loading, methylene chloride/methanol=15/1) to afford compound **11** as a white solid (870 mg, 45%, 2:1 mixture of two diastereomers): IR ($CDCl_3$) 3485, 3375, 3040-2850, 1720 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.94 (brs, 1H), 7.47 (d, J= 7.6 Hz, 1H), 7.37 (d, J= 7.6 Hz, 1H), 7.18 (t, J= 7.6 Hz, 1H), 7.10 (t, J= 7.6 Hz, 1H), 4.14 (q, J= 7.0 Hz, 2H), 4.08 (br s, 1H), 3.94 (br s, 1H), 3.30 (m, 1H), 3.23 (m, 1H), 2.98-2.62 (m, 4H), 2.54 (m, 1H), 2.03 (m, 1H), 1.95 (m, 1H), 1.25 (t, J= 7.0 Hz, 3H); MS, m/e 256 (10, M-EtOH), 172 (16.4), 171 (100), 149 (16.4), 144 (7.9), 129 (7.9), 97 (14.3), 96 (9.3), 85 (17.1), 84 (16.4), 73 (20), 71 (22.9), 69 (19.3), 60 (34.3); exact mass calcd for $C_{17}H_{23}N_2O_3$ (CI, M+H): 303.1710, found: 303.1702.

Lactam **12**. The solution of compound **11** (870 mg, 2.88 mmol) in dry EtOH (45 mL) was heated at 78 °C for 16 h after which the solvent was removed. The crude product was purified by silica gel column chromatography (dry loading, methylene chloride/methanol = 16/1) to afford compound **12** as a white solid (612 mg, 83%, 3:1 mixture of two diastereomers): IR ($CDCl_3$) 3495, 3450, 2950, 1634, 1298 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.24 (brs, 1H), 7.53 (d, J= 7.1 Hz, 1H), 7.37 (d, J= 7.1 Hz, 1H), 7.22 (t, J= 7.2 Hz, 1H), 7.14 (t, J= 7.2 Hz, 1H), 5.14 (m, 1H), 4.94 (brs, 1H), 4.53 (m, 1H), 2.96-2.64 (m, 5H), 2.57-2.44 (m, 1H), 2.16-2.01 (m, 2H); MS, m/e 258 (1.8, M+1), 257 (17, M+1), 256 (100, M), 238 (13.1), 227 (6.6), 211 (14.3), 172 (6.4), 171 (24.4), 170 (66.6), 169 (60.4), 155 (19.9), 144(11.9), 143 (29.6); exact mass calcd for $C_{15}H_{16}N_2O_2$: 256.1213, found: 256.1216.

Amino Alcohol **13**. The lactam **12** (612 mg, 2.39 mmol) was refluxed for 3 h in THF (100 mL) containing lithium aluminum hydride (15 mL, 1M, 15 mmol). Water was added carefully until a heavy gel formed after which the solvent was removed under vacuum. The residue was extracted with methanol (3 x 120 mL) and filtered through celite. The filtrate was concentrated yielding a crude product which was purified by column chromatography (dry loading, methylene chloride/methanol=9/1) to afford compound **13** as a white solid (432 mg, 75%, 2.3:1 mixture of two diastereomers). Major isomer: IR ($CDCl_3$) 3498, 3080, 3020, 1422, 1262 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.10 (brs, 1 H), 7.46 (d, J= 7.9 Hz, 1H), 7.31 (d, J= 7.9 Hz, 1 H), 7.11 (m, 2H), 4.18 (brs, 1H), 3.54 (brs, 1H), 3.05 (m, 1H), 2.94 (m, 2H), 2.71 (m, 2H), 2.46 (brt, J= 11.3 Hz, 1H), 1.96 (m, 2H), 1.71-1.54 (m, 3H), ; MS, m/e 244 (1.5, M+2), 243 (14.8, M+1), 242 (100, M), 241 (88.5), 224 (3.5), 223 (3.5), 197 (35), 171 (28), 170 (40.7), 169 (49.2), 156 (7.8); exact mass calcd for $C_{15}H_{18}N_2O$: 242.1420, found: 242.1424. Minor isomer: IR ($CDCl_3$) 3640, 3480, 2975, 1470 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3 + D_2O$) δ 7.48 (d, J= 7.5 Hz, 1H), 7.32 (d, J= 7.5 Hz, 1H), 7.10 (m, 2H), 3.78 (td, J= 10, 4.5 Hz, 1H), 3.13 (br s, 1H), 3.09 (br s, 1H), 2.98 (m, 2H), 2.78-2.56 (m, 2H) , 2.37 (m, 1H), 2.17 (m, 1H), 1.80 (m, 2H), 1.48 (m, 1H); MS, m/e 244 (1.5, M+1), 243 (15.5,

M+1), 242 (100), 241 (86.4), 197 (44.4), 185 (8.3), 171 (42.2), 170 (67.7), 169 (85.2), 156 (11.2), 144 (15.5), 143 (23.6); exact mass calcd for $C_{15}H_{18}N_2O$: 242.1420, found: 242.1427.

2,3,4,6,7,12-Hexahydroindolo[2,3-a]quinolizine, Enamine **14**. A solution of compound **13** (191 mg, 0.79 mmol) in 48% aqueous HBr (6 mL) was heated under nitrogen in a sealed tube at 120 °C for 18 h. The reaction mixture was made basic with 13% potassium hydroxide at 0 °C, whereupon a light yellow solid was formed. The product was collected, washed thoroughly with water, and dried under vacuum to afford enamine **14** as a light yellow solid (147 mg, 83%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87 (brs, 1H), 7.47 (d, J=7.9 Hz, 1H), 7.29 (d, J= 8.1 Hz, 1H), 7.15 (brt, J=7.3 Hz, 1H), 7.07 (brt, J= 7.7 Hz, 1H), 4.95 (brs, 1H), 3.08 (m, 4H), 2.93 (m, 2H), 2.25 (m, 2H), 2.02 (m, 2H); MS, m/e 226 (1.8, M+2), 225 (15.7, M+1), 224 (100), 223 (75.4), 209 (27.9), 195 (9.1), 180 (2.7), 169 (2.6), 168 (6.1), 167 (5.9), 129 (4), 112 (4.7); exact mass calcd for $C_{15}H_{16}N_2$: 224.1315, found: 224.1308.

Keto Ylide Diester **18**. The acid-ester **17** prepared by the method of Overman (8.8 g, 43.5 mmol) was added to N,N-diisopropylethylamine (14.1 g, 108.9 mmol) in methylene chloride (50 mL). The resulting solution was stirred and cooled to 0 °C. A solution of ethyl chloroformate (5.91 g, 54.5 mmol) in methylene choride (20 mL) was then added dropwise at 0°C and stirred for another 0.5 h at 0°C to form the mixed anhydride **19**. To this mixture was then added a solution of ylide **3** (40.95 g, 108.9 mmol) in methylene chloride (70 mL) at 0°C and the solution was stirred for 18 h at 20 °C. The solvent was removed, then the dark pink-red residue was extracted with ether (3 x 500 mL), filtered thru celite and then concentrated. The product was subjected to silica gel column chromatography (ether) to afford compound **18** as a yellow oil (18.3 g, 75%). Final purification was accomplished by further column chromatography (CH_2Cl_2/EtOAc=8/1) yielding a white solid . IR ($CDCl_3$) 2985, 1714, 1660, 1542 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.73-7.61 (m, 6H), 7.53-7.35 (m, 9H), 3.33 (m, 1H), 2.93 (m, 1H), 2.68 (m, 1H), 1.53 (m, 2H), 1.29 (s, 9 H), 1.07 (s, 9H), 0.89 (t, J= 7.2 Hz, 3H); MS, m/e 562 (2, M+2), 561 (7, M+1), 560 (19, M), 487 (21), 418 (38), 403 (16), 376 (25), 362 (21), 361 (25), 347 (100), 319 (41), 303 (30), 262 (66); exact mass calcd for $C_{34}H_{41}O_5P$: 560.2693, found: 560.2665.

t-Butyl 2,3-Dioxo-5-ethoxycarbonylheptanoate, Hydrate **19**. A solution of the ylide **18** (1.39 g, 2.5 mmol) in methylene chloride (45 mL) and methanol (9 mL) was cooled to -78 °C. Ozone was passed through the solution to the persistence of a green color. Excess ozone was removed from the reaction mixture by prging the solution with nitrogen. After the solution was warmed up to 20 °C, the solvent was evaporated to give the tricarbonyl derivative **19** as a yellow oil. The product was purified by column chromatography (11 cm in height, methylene chloride-CH_2Cl_2/EtOAc=20/1) to afford **19** as a yellow oil (725 mg, 87%) which solidified to a yellow solid upon storage overnight in the freezer. White crystals were obtained on recrystallization from cyclohexane: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.00 (d, J= 5.8 Hz, 2H), 2.96 (m, 1H), 2.82-2.61 (m, 2H), 1.68-1.53 (m, 2H), 1.51 (2, 9H), 1.45 (2, 9H), 0.92 (t, J= 7.3 Hz, 3H); MS, m/e 248 (1), 220 (5), 217 (3), 203 (14), 185 (33), 175 (12), 158 (12), 157 (10), 148 (7), 130 (8), 129 (100), 92 (22), 57 (64); exact mass calcd for $C_{16}H_{27}O_6$ (CI, M+H-H_2O): 315.1808, found: 315.1803.

Keto-Diester **20**. The mixture of tryptamine (291 mg, 1.82 mmol) and compound **19** (403 mg, 1.21 mmol) in chloroform (18 mL) was heated at 65°C for 17 h. The solvent was evaporated and the resulting crude product was purified by a short column (5 cm height, 0.5% EtOAc/methylene chloride) to isolate compound **20** as a yellow oil (364 mg, 66%, mixture of two diastereomers). Major isomer: IR ($CDCl_3$) 3479, 3415, 3063-2802, 1738-1711, 1450 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.37 (brs, 1 H), 7.53 (d, J= 8 Hz, 1H), 7.36 (d, J= 7.7 Hz, 1H), 7.20 (t, J= 7.3 Hz, 1H), 7.10 (t, J= 7.7 Hz, 1H), 3.19-2.49 (m, 7H), 1.95 (brs 1 H), 1.51 (s, 9 H), 1.43 (s, 9 H), 1.41 (m, 2 H), 0.84 (t, J= 7.3 Hz, 3 H); MS, m/e 458 (.2, M+2), 457 (.9, M+1), 456 (3, M), 355 (4), 327 (5), 299 (6), 271 (30), 216 (15), 215 (100); exact mass calcd for $C_{26}H_{36}N_2O_5$: 456.2626, found: 456.2618.

Amide-Alcohol **21**. The keto diester **20** (2.18 g, 4.77 mmol) in 98% HCOOH (56 mL) was stirred at 40 °C for 1 h. Sodium cyanoborohydride (1.1 g, 17.4 mmol) was added to the red solution, and the mixture was stirred at 20 °C for 4 h. The solvent was removed by rotary evaporation (~70 °C water bath), and dry ethanol (112 mL) and silica gel (16 g) were added. The mixture was heated at reflux for 24 h, after which the solvent was removed. The product was purified by column chromatography (dry loading, methylene chloride/methanol = 15/1, two columns) to afford compound **21** as a yellow powder (500 mg, 37%, mixture of four diastereomers): IR ($CDCl_3$) 3458, 2992-2824, 1774, 1626, 1457 cm^{-1}; MS, m/e 285 (20, M+1), 284 (99, M), 266 (11), 256 (9), 240 (11), 200 (32), 199 (33), 172 (10), 171 (37), 170 (100), 169 (59), 155 (11), 144 (13), 143 (18); exact mass calcd for $C_{17}H_{20}N_2O_2$: 284.1526, found: 284.1529.

Amino-Alcohol **22** A mixture of the amide-alcohol **21** (500 mg, 1.76 mmol) and lithium aluminum hydride (8.8 mL, 1 M, 8.8 mmol) in THF (35 mL) was refluxed for 18 h. Water was added carefully until a heavy gel formed, the solvent was then removed, the residue was extracted with methanol, followed by filtration through celite and concentration. The product was then purified by column chromatography (dry loading, methylene chloride/methanol=9/1) to afford compound **22** as a yellow powder (341 mg, 71%, 1:1 mixture of two *syn*-diastereomers and two *anti*-diastereomers): Two *syn* diastereomers: IR ($CDCl_3$) 3612, 3458, 2985-2802 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.02 (brs, 1 H), 7.48 (d, J= 7.7 Hz, 1H), 7.29 (d, J= 7.7 Hz, 1 H), 7.17-7.02 (m, 2H), 3.89 (td, J= 10.3, 4.5 Hz, 1 H), 3.13-2.88 (m, 3 H), 2.86-2.57 (m, 3 H), 2.54-2.43 (m, 1 H), 2.07-1.93 (m, 1 H), 1.80-1.39 (m, 4H), 0.92 (t, J= 7.3 Hz, 3 H); MS, m/e 272 (2, M+2), 271 (19, M+1), 270 (100), 269 (87), 241 (8), 225 (11), 213 (3), 185 (9), 184 (8), 171 (25), 170 (59), 169 (40); exact mass calcd for $C_{17}H_{22}N_2O$: 270.1734, found: 270.1713.

Two *anti* diastereomers: IR ($CDCl_3$) 3464, 2978-2851 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.92 (brs, 1 H), 7.47 (d, J= 6.8 Hz, 1 H), 7.31 (d, J= 7 Hz, 1 H), 7.18-7.05 (m, 2 H), 4.19 (brs, 1 H), 3.38 (brs, 1 H), 3.12-2.88 (m, 3 H), 2.80-2.62 (m, 2 H), 2.21-1.91 (m, 3 H), 1.38-1.17 (m, 3 H), 0.94 (t, J= 7.7 Hz, 3 H); MS, m/e 271 (19, M+1), 270 (100, M), 269 (82), 241 (10), 225 (14), 211 (4) 185 (15), 184 (14), 171 (46), 170 (99), 169 (63), 144 (11), 143 (16); exact mass calcd for $C_{17}H_{22}N_2O$: 270.1734, found: 270.1718.

Enamine **23** A solution of compound **22** (90 mg, 0.33 mmol) in 48% aqueous HBr (3 mL) was heated under nitrogen in a sealed tube at 120 °C for 20 h. The reaction mixture was made basic with 13% KOH at 0 °C, whereupon a yellow solid formed immediately. The product was collected, washed thoroughly

with water and then dried under vacuum to afford the enamine **23** as a light-yellow solid (65 mg, 77%): IR ($CDCl_3$) 3479, 2986-2816, 1626, 1549, 1450 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.92 (brs, 1 H), 7.47 (d, J= 7.7 Hz, 1 H), 7.31-7.04 (m, 3 H), 4.94 (brs, 1 H), 3.26-2.48 (m, 6H), 2.40-2.10 (m, 1 H), 2.05-1.66 (m, 2 H), 1.48-1.25 (m, 2 H), 0.97 (t, J= 7.3 Hz, 3 H); MS m/e 254 (s, M+2), 253 (13, M+1), 252 (63, M), 251 (14), 237 (10), 224 (23), 223 (100), 221 (8), 209 (16), 195 (12); exact mass calcd for $C_{17}H_{20}N_2$: 252.1628, found: 252.1632.

Carboxylic Acid-Ylide **25.** To a stirred solution of the ylide **3** (30.3 g, 80.5 mmol) in dry benzene (240 mL), cooled to 8 °C, was slowly added a solution of 3,4-pyridinedicarboxylic acid anhydride (<10 g, 67.1 mmol) in THF (200 mL). The reaction mixture was stirred at 20 °C for 6 h, and ether (400 mL) was added. The white powder was collected by suction filtration, and further washed with ether (2 x 100 mL). The product was dried under vacuum to afford **25** (30.2 g, 86%) as a white powder: ^1H NMR (250 MHz, $CDCl_3$) δ 9.19 (s, 1 H), 8.69 (d, J = 5.0 Hz, 1 H), 7.86-7.76 (m, 6 H), 7.61-7.47 (m, 9 H), 7.27 (d, J = 5.0 Hz, 1 H), 0.92 (s, 9 H)

Methyl Ester-Ylide **26** A solution of carboxylic acid-ylide **25** (14 g, 26.7 mmol) in methylene chloride (200 mL) was added to a diazomethane etherate solution freshly prepared from Diazald (11.25 g, 51.75 mmol), KOH (11.25 g), water (18 mL), ethanol (95%, 22.5 mL) and ether (123 mL). A titration-pipet was used to transfer the diazomethane etherate solution to the methylene chloride solution of the carboxylic acid-ylide. After the reaction was complete, nitrogen gas was bubbled through the titration-pipet in order to evaporate the solvent. The dark red residue was purified by column chromatography to give the product **26** as a light yellow solid (11.8 g, 82%): IR ($CDCl_3$) 3100-2900, 1740, 1668, 1550 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.10 (s, 1 H), 8.65 (d, J = 5.1 Hz, 1 H), 7.91-7.81 (m, 6 H), 7.63-7.45 (m, 9 H), 7.19 (d, J = 5.1 Hz, 1 H), 3.82 (s, 3 H), 0.91 (s, 9 H): MS, m/e 541 (6, M+2), 540 (27, M+1), 539 (74, M), 483 (19), 464 (12), 439 (41), 438 (100), 425 (19), 424 (70), 407 (15), 406 (36), 380 (16), 347 (18), 331(17), 330(76), 303(13), 262 (12); exact mass calcd for $C_{32}H_{30}NO_5P$: 539.1863, found: 539.1855.

Ester-Amide **28.** Ozone was passed through a solution of ester-ylide (100 mg, 0.186 mmol) in methylene chloride (6 mL) and methanol (3 mL) at -78 °C for 3.5 min, after which the solution was purged with N_2 for 10 min. To this solution containing the tricarbonyl product was added a solution of tryptamine (149 mg, 0.93 mmol) in methylene chloride (2 mL) at -78 °C, and the reaction mixture allowed to warm up slowly to 20 °C. After concentrating the solution by evaporation, a crude product was obtained which was purified by column chromatography (methylene chloride / ETOAc = 15 / 1) affording compound **28** as a colorless oil: IR ($CDCl_3$) 3500, 3430, 1736, 1718 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.09 (brs, 1 H), 7.62 (d, J = 7.5 Hz, 1 H), 7.35 (d, J = 7.8 Hz, 1 H), 7.27-7.09 (m, 3 H), 7.07 (brs, 1 H), 3.66 (q, J = 6.7 Hz, 2 H), 3.03 (t, J = 6.8 Hz, 1 H), 1.52 (s, 9 H); MS, m/e 290 (0.6, M+2), 289 (5, M+1), 288 (27, M), 232 (5), 187 (17), 144 (27), 143 (100), 130 (76), 57(8); exact mass calcd for $C_{16}H_{20}N_2O_3$: 288.1475, found: 288.1463

REFERENCES

(1) Wasserman, H.H. ; Lombardo, L.J. *Tetrahedron Lett.* **1989**, *30*, 1725.

(2) Wasserman, H.H.; Kuo, G.-H. *Tetrahedron Lett.* **1991**, *32*, 7131.

(3) Wasserman H.H. ; Amici, R. *J. Org Chem.* **1989**, *54*, 5843.

(4) Fuji, K.; Node, M.; Nagasawa, H. *J. Am. Chem. Soc.* **1987**, *109*, 7901. (b) Wenkert, E.; Wickberg, B.; *J. Am. Chem. Soc.* **1965**, *87*, 1580.

(5) Massiot, G.; Oliveira, F.S.; Levy J. *Bull Soc Chem France* II **1982**, 185.

(6) For a preliminary report of this work, see: Wasserman, H.H.; Kuo, G.-H. *Tetrahedron Lett.* **1989**, *30*, 873.

(7) Cooke, M.P., Jr.; Burman, D. L. *J. Org. Chem.* **1982**, *47*, 4955.

(8) Wasserman, H.H.; Ennis, D.; Rotello, V.M.; in publication.

(9) More recently, we have employed Oxone® for oxidative cleavage of ylide tricarbonyl precursors in the presence of electron rich double bonds: Wasserman, H.H.; Vu, C.B. *Tetrahedron Lett.* **1990**, *31*, 5205.

(10) van Tamelen, E. E.; Shamma, M.; Aldrich, P. *J. Am. Chem. Soc.* **1956**,*78*, 4628.

(11) (a) Schut, R. N.; Leipzig, T. J. *J. Heter. Chem.* **1966**, *3*, 101 (b) Sakai, S-i; Yamanaka, E.; Kasamatsu, S.; Aimi, N. *Tetrahedron Lett.* **1983**, *24*, 3861; (c) Martel, J.; Toromanoff, E.; Buendia, J.; Costerousse, G. *Bull. Soc. Chem. France* II **1978**, 355.

(12) Szantay, C.; Novak, L.; Robaly, J. *Heterocycles* **1977**, *6*, 1149.

(13) Jessup, P.J.; Petty, C.B.; Roos, J.; Overman, L.E. *Org. Syn.* **1979**,*59*, 1.

(14) Wanner, M.J. *Tetrahedron* **1983**, *39*, 3673.

(15) Fisher, M.J.; Chow, K.; Villalobos, A.; Danishefsky, S.J. *J. Org. Chem.* **1991**, *56*, 2900.

Acknowledgment: Support of this work by the General Medical Sciences Institute of the National Institutes of Health is gratefuly acknowledged.