# Enantioselective Syntheses of 3-Substituted 4-(Alkoxycarbonyl)-2-azetidinones from Malic Acid

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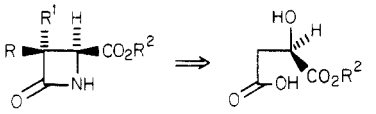
Enantioselective syntheses of 3-substituted 4-(alkoxycarbonyl)-2-azetidinones from malic acid have been developed. Alkylation of diesters of D-malic acid provided primarily the erythro products **15RS**. Base-mediated inversion gave racemic threo isomers **15**. Saponification of **15** and selective monoesterification provided the correspondingly substituted β-hydroxy acids **17**, which could also be epimerized at the hydroxyl position. Separate conversion of the isomers **17** to the hydroxamates **18** followed by cyclization gave the desired β-lactams **19** with complete control of stereochemistry.

4-(Alkoxycarbonyl)-2-azetidinones (1) are versatile intermediates for the synthesis of a variety of bicyclic β-lactams, including the isocephalosporins[1] and carbapenems.[2] However, in most instances, these antibiotic precursors have either been racemic or required introduction of the 3-substituent (R or $R_1$) after formation of the β-lactam. The latter process, alkylation of preformed β-lactams, is usually limited to formation of *trans*-3,4-disubstituted 2-azetidinones. Subsequent to our development of an efficient hydroxamate-mediated synthesis of β-lactams,[3-6] one of our goals has been the synthesis of 3-substituted 4-(alkoxycarbonyl)-2-azetidinones (1) in a manner such that both the chiral centers ($C_3$ and $C_4$) are established before formation of the β-lactam ring. This approach was anticipated to be compatible with the preparation of either *cis*- or *trans*-3,4-disubstituted 2-azetidinones. Malic acid **2** appeared to be an ideal precursor

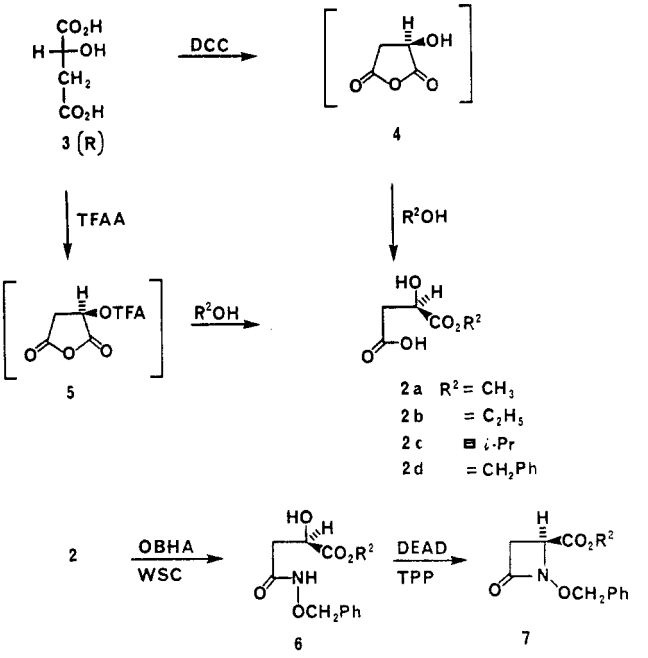


1 2 (1)

to 1. Malic acid is available in both the L and D[7] forms, and, as a β-hydroxy carboxylic acid, it fulfills the primary prerequisite for the hydroxamate-mediated β-lactam synthesis by N–$C_4$ bond closure. In order to convert malic acid to 1, the carboxy group α to the hydroxy group needed to be esterified selectively, and a method was needed for the enantioselective incorporation of substituents (R or $R^1$ of 1) at the methylene position of **2**. Reported here are solutions to both of these problems. The result is a versatile synthesis of optically pure 3-substituted 4-(alkoxycarbonyl)-2-azetidinones.

**Preparation of 3-Unsubstituted 4-(Alkoxycarbonyl)-2-azetidinones.** Simple monosaponification of malic acid diesters provides good yields of monoesters, but for the purposes of this work the wrong esters. However, we found that treatment of malic acid **3** with dicyclohexylcarbodiimide (DCC) to form the anhydride **4** followed by quenching with alcohols provided the desired monoesters **2** in moderate to good yields (Scheme I). Depending on the purity of the malic acid, reagent concentrations, and other subtle changes in reaction conditions, varying amounts of dimeric or polymeric materials were also formed. Alternatively, treatment of malic acid with 2 equiv or more of trifluoroacetic anhydride (TFAA) at 0–25 °C for 0.5–2 h, followed by evaporation of excess TFAA and TFA formed, provided the trifluoroacetate of malic acid anhydride **5** quantitatively. Treatment of the solid residue with an excess of any of a variety of alcohols at room temperature for 3–12 h provided the desired esters **2** in nearly quantitative yield. This very simple process thereby provided the required malic acid carboxyl differentiation.

Scheme I



Before introducing further substituents and the remaining chiral center, we decided to test the compatibility of the malic acid monoester **2** with the conditions required for β-lactam formation. Thus, **2**, derived from D-malic acid, was treated with *O*-benzylhydroxylamine hydrochloride (OBHA) and the water-soluble carbodiimide [*N*-ethyl-*N'*-[3-(dimethylamino)propyl]carbodiimide, Sigma Chemical Co.] in water or water–THF at pH 4.5 and room temperature for 10–30 min.[5] The usual extractive workup with

(1) (a) Huffman, W. F.; Holden, K. G.; Buckley, T. F.; Gleason, J. G.; Wu, L. *J. Am. Chem. Soc.* **1977**, *99*, 2352. (b) Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. E. *Ibid.* **1977**, *99*, 2353.
(2) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6163.
(3) Mattingly, P. G.; Kerwin, J. F., Jr.; Miller, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 3983.
(4) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1980**, *45*, 410.
(5) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026.
(6) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1981**, *46*, 1557.
(7) (a) Corey, E. J.; Marfat, A.; Hoover, D. J. *Tetrahedron Lett.* **1981**, *22*, 1587. (b) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166.

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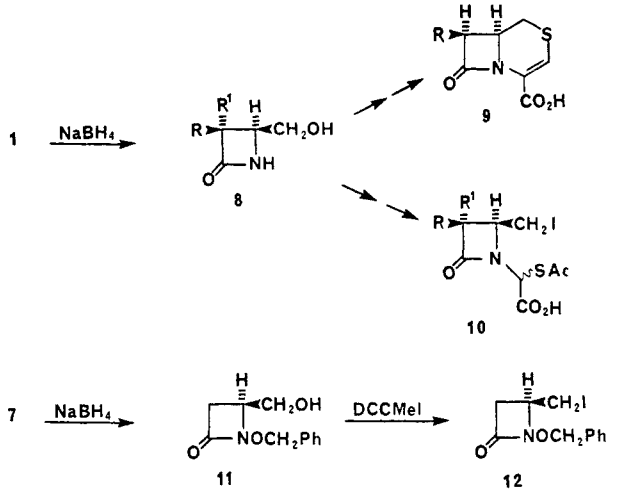
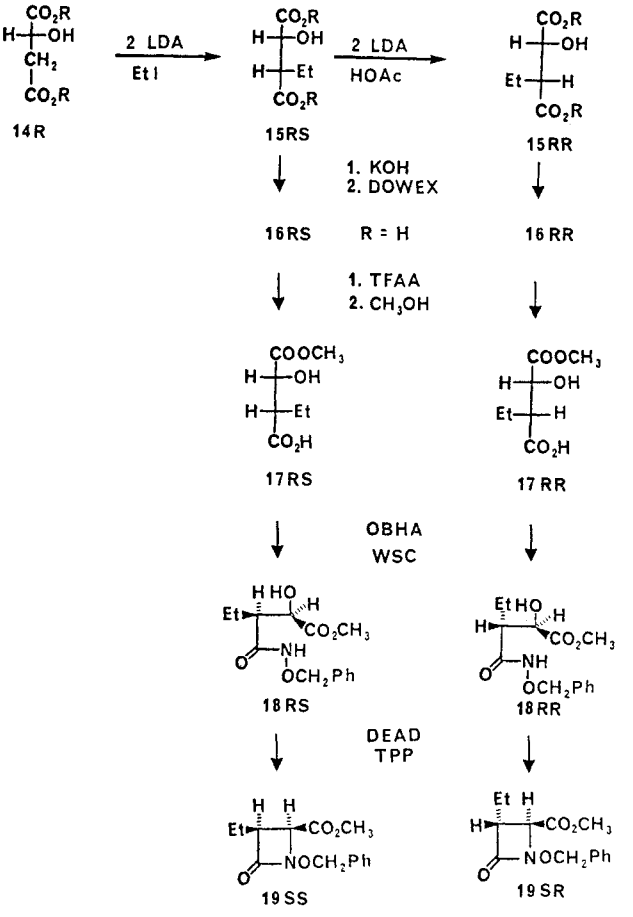
Scheme II



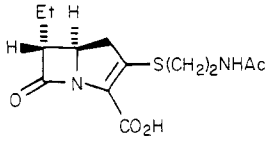
Scheme III



ethyl acetate provided the desired hydroxamates **6** cleanly.[8] Cyclization of **6** to the β-lactam **7** was effected smoothly by the diethyl azodicarboxylate/triphenylphosphine (DEAD/TPP) combination which we utilized earlier.[3-6] These results, coupled with our previous reports of the $TiCl_3$-mediated reduction of the N–O bonds of similar 2-azetidinones,[4] provide an alternative to the aspartic acid route to **1** (R = $R^1$ = H).[2]

As previously reported,[1] one aspect of the versatility of **1** is its facile reduction with $NaBH_4$ to the alcohol **8** (Scheme II). Subsequent multistep elaboration has provided entry to a number of biologically active nuclear analogues of β-lactams (i.e., **9**[1] and **10**[9]). Our recent finding that various substituted *N*-hydroxy-containing β-lactams have interesting chemical[3-5] and biological properties[10] encouraged us to explore similar reactions of the benzyloxy derivatives **7**. Thus treatment of **7** with $NaBH_4$ in $THF/H_2O$ provided the alcohol **11** in 61% yield. Conversion of **11** to iodide **12** was accomplished directly by reaction with dicyclohexylcarbodiimide methiodide (DCCMeI). Elaborations of **11** and **12** to analogues of **9**, **10**, and the carbapenems are being investigated.

**Introduction of the Second Chiral Center.** Initial efforts directed toward introduction of the second chiral center were focused on preparation of a precursor of the antibiotic PS-5, **13**[11] since its side chain corresponding to



**13**

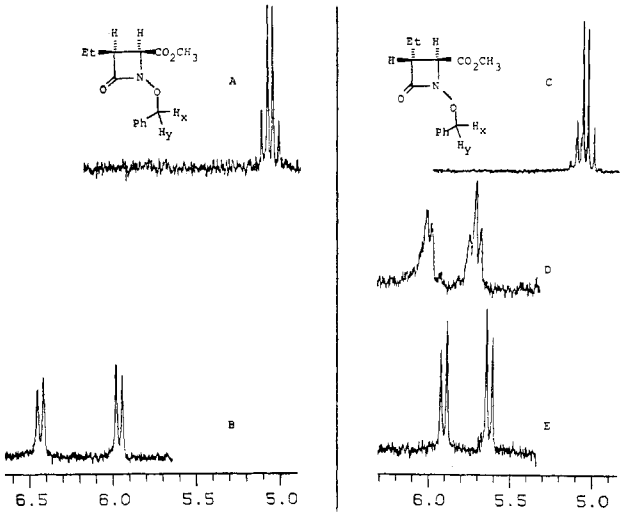
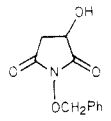


**Figure 1.** Partial 300-MHz $^1$NMR spectra of the cis- (**19SS**) and trans- (**19SR**) substituted β-lactams. The peaks shown are those due to the diastereotopic benzylic protons $H_x$ and $H_y$ were most affected by the chiral shift reagent tris[3-[(heptafluoropropyl)-hydroxymethylene]-*d*-camphorato]europium(III), obtained from Aldrich: (A) 0.25M **19SS** in $CDCl_3$; (B) 0.25M **19SS** in $CDCl_3$ with the chiral shift reagent (0.125 M); (C) 0.25M **19SR** in $CDCl_3$; (D) racemic **19SR** (0.25M) with the chiral shift reagent; (E) Optically pure **19SR** (0.25 M with 0.129 M chiral shift reagent) prepared by the β-lactone inversion process shown in Scheme IV.

$R^1$ of **1** is simply an ethyl group. Thus, following the precedent of Frater[12] and more recently that of Seebach

(8) Variable amounts of 2-hydroxy-3-(benzyloxy)succinimide (i) were



i

occasionally obtained if impure starting acid **2** was used, if the pH of the reaction mixture was allowed to vary during the reaction, if longer reaction times were used, or if acidic aqueous washes (1 M citric acid, 1 M HCl, etc.) were employed in the workup. Characterization for i include the following mp 115–118 °C; IR (KBr) 3500–3200, 1740 $cm^{-1}$; $^1$H NMR δ 2.4–3.2 (2 H, dq, *J* = 4.5, 8.4 Hz), 4.4–4.6 (1 H, dd, *J* = 4.5, 8.4 Hz), 5.8 (2 H, s), 7.4 (5 H, s); mass spectrum (CI with argon), *m/e* 222 (M + 1). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.43; H, 5.02; N, 6.59. Found: C, 59.78; H, 5.02; N, 6.33.

(9) De Marinis, R. M.; Bryan, W. M. *Tetrahedron Lett.* **1982**, *23*, 731.

(10) Unpublished results to be submitted.

(11) Okamura, H.; Hirata, S.; Okamura, Y.; Fukagawa, Y.; Shimauchi, Y.; Kaumo, K.; Ishikura, T.; Lein, J. *J. Antibiot.* **1978**, *31*, 480.

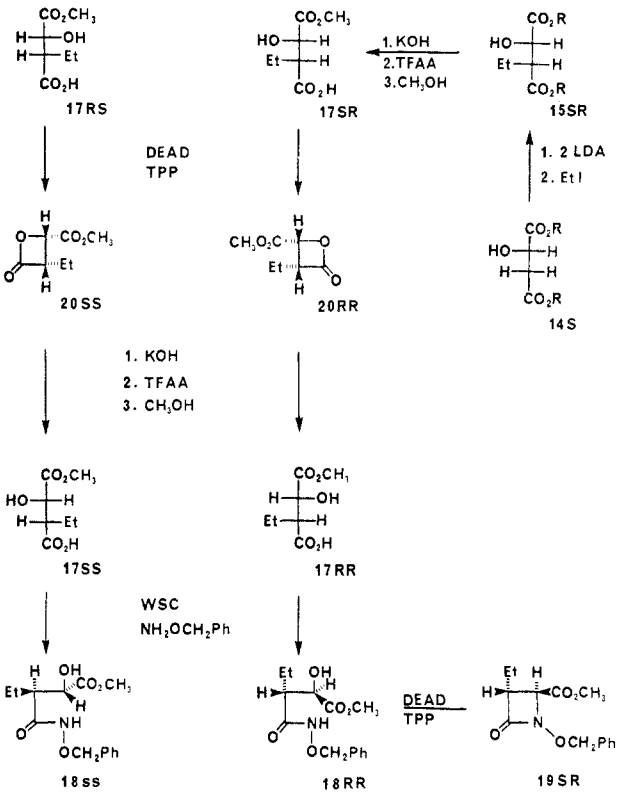
(12) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825.

and Wasmuth,[13] we formed the dianion of diethyl D-malate (**14R**,[14] R = Et; Scheme III) by reaction of **14R** with 220 mol % of LDA in THF containing 100 mol % of HMPA at −78 °C and then quenched the reaction with ethyl iodide to provide an 87:13 ratio of erythro- and threo-ethylated isomers (**15RS** and **15RR**) in 84% yield.[15] Saponification followed by filtration through Dowex 50W-X4 ($SO_3H$) with water gave a 98% yield of the crude mixture of diacids **16RS** and **16RR**. Trituration with ether provided the single diastereomer **16RS**. Treatment of **16RS** with TFAA and then $CH_3OH$, as described earlier for the unsubstituted malic acid, provided the monomethyl ester **17RS** as a colorless oil in 74% yield. The hydroxamate **18RS** was formed in the usual manner[3-6] in 91% yield. Cyclization of **18RS** with DEAD/TPP gave the β-lactam **19SS** in 75% purified yield. As expected, $^1H$ NMR confirmed that **19SS**, derived from the erythro isomer **15RS**, was cis substituted at $C_3$ and $C_4$. Furthermore, NMR chiral shift studies indicated that the product was optically pure (Figure 1). Although several recently discovered carbapenem antibiotics have the cis substitution pattern,[16] PS-5 (**13**) is trans substituted. Consequently, incorporation of an inversion step in the synthetic sequence was necessary.

Inversion at either of the two chiral centers of **15** is conceptually possible. However, eventual conversion of **15RS** to a PS-5 precursor required inversion at $C_3$, the ethyl-bearing carbon. Thus a diastereomeric mixture of **15RS** and **15RR** (isopropyl esters) was treated again with 220 mol % of LDA in THF–HMPA. In contrast to the facile deprotonation of the unsubstituted malic acid esters (**14R**), formation of the dianion of **15** required warming to −20 °C and maintaining the reaction at that temperature for up to 12 h. The reaction mixture was then cooled to −78 °C and quenched with excess acetic acid in THF. Extractive workup provided a new mixture, apparently of **15RS** and **15RR**. $^1H$ NMR of the mixture clearly indicated that **15RR** was now the major isomer (**15RS**/**15RR**, 3:7). Chromatography provided pure **15RR**. However, the observed optical rotation for this compound was suspiciously low. Attempted tests for racemization by NMR chiral shift studies were foiled by excessive peak broadening. Thus **15RR** was subjected to the same sequence as done previously for **15RS** (Scheme III), to provide the trans β-lactam **19**. Only at this stage did an NMR chiral shift study clearly reveal (Figure 1) that racemization had occurred and that the β-lactam **19**, thus obtained, was a mixture of enantiomers (**19SR** and **19RS**).

Conceptually, inversion at the hydroxyl position of malic acid, rather than at the carbon α to the hydroxyl, should permit synthesis of the optically pure β-lactam **19SR** from the much less expensive L-malic acid, **14S**. While several intermolecular inversion processes were considered, most were inefficient or led to elimination products. However, the intramolecular formation of β-lactones from β-hydroxy carboxylic acids with DEAD/TPP is also known to proceed with inversion at the hydroxyl carbon.[17] In order to test

Scheme IV




this approach, we treated the previously prepared mono ester **17RS** with DEAD/TPP. As expected, the β-lactone formed by net inversion to give **20SS** (Scheme IV). The $^1H$ NMR of **20SS** clearly indicated the cis relationship of the α- and β-protons ($J$ = 6.7 Hz). Selective hydrolysis of the lactone of **20SS** in the presence of the methyl ester was not possible. However, complete saponification with 200 mol % of KOH, followed by monoesterification, as described earlier, provided **17SS**,[18] which was converted to the hydroxamate **18SS** ($[\alpha]^{20}_D$ = −5.5° (*c* 1.2, $CH_3OH$)).

Encouraged by these results, we treated the dianion of diisopropyl L-malate (**14S**, diisopropyl ester; Scheme IV) with ethyl iodide and again obtained an 87:13 ratio of erythro (**15SR**) to threo (**15SS**) isomers. Saponification and monoesterification as before gave the carboxylic acid **17SR**. Treatment with DEAD/TPP gave the β-lactone **20RR** which was subjected to the remaining reaction sequence to provide the desired β-lactam **19SR**. The optical purity of **19SR** was confirmed by an NMR chiral shift study (Figure 1).

Consequently, the synthesis of all four optical isomers of β-lactam **1** are possible from either D- or L-malic acid. Extensions to the preparation of both known and potential monocyclic and bicyclic antibiotics are in progress.

## Experimental Section

**General Methods.** Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727b spectrometer. NMR spectra were obtained in chloroform-*d* with tetramethylsilane as a reference on Varian A60, Varian EM390, and Nicolet NB300 300-MHz instruments. Mass spectra were recorded on an AEI Scientific Apparatus 902 or a Du Pont DP102 spectrom-

(13) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197.

(14) The suffixes R and S in this and subsequent structures denote the absolute configuration in malic acid containing two chiral centers; the first designated is that bearing the oxygen. The first chiral center designated in the β-lactams is that attached to the N, in order to remain consistent with the nomenclature.

(15) Use of dimethyl malates resulted in less stereoselectivity in the alkylation. Alkylation of the isopropyl malates also provided an 87:13 erythro/threo ratio. The relative ratios were difficult to assign in the case of the diesters, but were more easily determined after monosaponification.

(16) See for example: Brown, A. G.; Corbett, D. F.; Eglington, A. J.; Howarth, T. T.; *J. Chem. Soc., Chem. Commun.* **1977**, 523. Corbett, D. F.; Eglington, A. J.; Howarth, T. T. *Ibid.* **1977**, 954. Okonogi, K.; Nozaki, Y.; Imada, A.; Kuno, M. J. *J. Antib.* **1981**, *34*, 212.

(17) Mulzer, J.; Brüntrup, G.; Chucholowski, A.; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 622.

(18) For early studies on the hydrolysis of β-lactones see: Olson, R. A.; Miller, R. J. *J. Am. Chem. Soc.* **1938**, *60*, 2687.

eter. Elemental analyses were performed by Midwest Microlabs, Indianapolis, IN, or MHW Laboratories, Phoenix, AZ.

**Synthesis of Malic Acid Monoesters 2. Method A. Synthesis of 2dR (Carbodiimide Procedure).** D-Malic acid (**3R**) was dissolved in 150 mL of freshly distilled THF. Dicyclohexylcarbodiimide (DCC, 110 mol %) was added, and the mixture was stirred at room temperature for 45 min. The precipitated urea (DCU) was removed by filtration and washed with two 50-mL portions of THF. To the combined filtrate was added 200 mol % of benzyl alcohol. The solution was stirred overnight. Evaporation of the solvent gave an oil which was dissolved in 100 mL of ethyl acetate and extracted with three 50-mL portions of 10% $Na_2CO_3$. The combined basic layers were acidified to pH 2 and extracted with three 50-mL portions of ethyl acetate. The ethyl acetate was washed with 25 mL of brine, dried over $MgSO_4$, gravity filtered, and evaporated to yield the desired benzyl ester **2d** as an oil: 64% yield; $^1H$ NMR ($CDCl_3$, 60 MHz) $\delta$ 2.85 (d, 2 H, $J$ = 5.5), 4.55 (t, 1 H, $J$ = 5.5), 5.2 (s, 2 H), 7.35 (s, 5 H), 7.5 (br s, 2 H, $CO_2H$ + OH); IR (neat) 1735 $cm^{-1}$.

**Method B (Preferred Procedure with TFAA). Synthesis of 2aR.** D-Malic acid (10 g, 74.6 mmol) was placed in a 100-mL round-bottomed flask and cooled in an ice bath. Trifluoroacetic anhydride (25 mL) was added, and the suspension was stirred magnetically. Within 15 min the solution became homogeneous. After 1–2 h at 0 °C, the TFA and TFAA were removed by vacuum distillation while the distillation flask was kept at 0 °C. The resulting solid residue of the anhydride trifluoroacetate **5** was then dissolved in 50 mL of anhydrous methanol. After the mixture was stirred for 3.5 h, the solvent was evaporated at reduced pressure to leave a solid residue: 100% yield; mp 75–79 °C. Recrystallization from ethyl acetate–hexanes improved the melting point (79–80 °C): $[\alpha]^{20}_D$ −5 ± 1° (*c* 9.5, $CH_3OH$); $^1H$ NMR ($CDCl_3$, 60 MHz) $\delta$ 2.9 (d, 2 H), 3.8 (s, 2 H), 4.5 (t, 1 H), 6.5–6.9 (br s, OH, $CO_2H$).

In a preliminary experiment, the anhydride **5** obtained from DL-malic acid was isolated and characterized: mp 44–46 °C; IR (KBr) 1880, 1780 $cm^{-1}$; $^1H$ NMR (acetone-$d_6$) $\delta$ 3.51–3.68 (dd, 2 H, $J$ = 6, 4 Hz), 6.16–6.42 (m, 1 H).

The following monoesters were also prepared.

**Compound 2aS** (from L-Malic Acid) by method A: 64.5% yield; $[\alpha]^{20}_D$ +5.8 ± 1° (*c* 9.5, $CH_3OH$); mp 79–80 °C; $^1H$ NMR identical with that for **2aR** from D-malic acid.

**Compound 2bS (R² = Et)** from L-malic acid by method B: 98.7% yield; mp 48–49.5 °C; $^1H$ NMR (90 MHz) $\delta$ 1.3 (t, 3 H), 2.9 (d, 2 H), 4.3 (q, 2 H), 4.57 (t, 1 H), 7.5 (br s, OH, $CO_2H$).

**Compound 2bR (R² = Et)** from D-malic acid by method A: 33% yield; melting point and $^1H$ NMR identical with those of **2bS**.

**Compound 2cR (R = *i*-Pr)** from D-malic acid by method B: 97.7% yield (oil); $^1H$ NMR (60 MHz) $\delta$ 1.25 (d, 6 H), 2.9 (d, 2 H), 4.58 (t, 1 H), 5.14 (m, 1 H), 8.4 (br s, OH, $CO_2H$).

**Malic Acid Monohydroxamate 6.** The procedure for preparing the hydroxamates is essentially the same as that reported previously.[3-6] Thus, in general, the malic acid monoester **2** (10 mmol) was dissolved in 25–50 mL of water or water–THF at pH 4.5 along with 11–15 mmol of *O*-benzylhydroxylamine hydrochloride (Aldrich, Sigma). A solution of 20 mmol of water-soluble carbodiimide [*N*-ethyl-*N'*-[3-(dimethylamino)propyl]carbodiimide, Sigma] was added and the pH maintained at 4.5 with addition of either 1.0 N HCl or 1.0 N NaOH as required. After 30 min the resulting solution or suspension was extracted with three 25-mL portions of ethyl acetate. The combined ethyl acetate was washed with two 20-mL portions of 1 M citric acid, 20 mL of $H_2O$, two 20-mL portions of 5% $NaHCO_3$, and 20 mL of brine, dried over $MgSO_4$, filtered, and evaporated to give an oil or solid residue. The following data are representative of the individual hydroxamates.

**Hydroxamate 6aS (R² = $CH_3$)**: yield 70%; mp 65–67 °C (ethyl acetate–hexanes); $[\alpha]^{23}_D$ = −16.8° (*c* 1.33, $CH_3OH$); $^1H$ NMR (60 MHz) $\delta$ 2.6 (br m, 2 H), 3.75 (s, 3 H), 4.5 (t, 1 H), 4.87 (s, 2 H), 7.37 (s, 5 H). Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.92; H, 5.93; N, 5.53. Found: C, 57.22; H, 5.67; N, 5.43.

**Hydroxamate 6bS (R² = Et)**: yield 60% (oil); $^1H$ NMR (60 MHz) $\delta$ 1.25 (t, 3 H), 2.68 (d, 2 H), 4.23 (q, 2 H), 4.42 (t, 1 H), 4.85 (s, 2 H), 7.32 (s, 5 H); IR (neat film) 3200–3600 $cm^{-1}$ (OH, NH), 1745 (ester), 1690 $cm^{-1}$ (hydroxamate).

**Hydroxamate 6cR (R² = *i*-Pr)**: yield 84%; mp 75–78 °C (ethyl acetate–hexanes); $[\alpha]^{23}_D$ +4.4° (*c* 1.4, $CH_3OH$); $^1H$ NMR (60 MHz) $\delta$ 1.2 (d, 6 H), 2.6 (br, 2 H), 4.1 (m, 1 H), 4.45 (t, 1 H), 4.9 (s, 2 H), 7.36 (s, 5 H). Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.79; H, 6.76; N, 4.98. Found: C, 60.04; H, 7.10; N, 5.04.

**Hydroxamate 6dR (R² = $CH_2Ph$)**: yield 84.5% (ether–hexanes); mp 102–104 °C; $[\alpha]^{20}_D$ +27.2° (*c* 2.5, $CH_3OH$); IR ($CHCl_3$) 3200–3600 (br, OH, NH), 1745 (ester), 1690 $cm^{-1}$ (hydroxmate); $^1H$ NMR (60 MHz) $\delta$ 2.6 (br d, 2 H), 4.48 (t, 1 H), 4.8 (s, 2 H), 5.15 (s, 2 H), 7.32 (s, 1 H). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.65; H, 5.78; N, 4.26. Found: C, 65.48; H, 5.99; H, 4.38.

**β-Lactams 7.** The D-malic acid hydroxamate **6d** (2.64 g, 8.02 mmol) was dissolved in 50 mL of dry THF. Triphenylphosphine (2.0 g, 8 mmol) was added, followed by diethyl azodicarboxylate (DEAD, 1.26 mL). The solution was stirred at room temperature under a drying tube for 11 h. The solution was then concentrated to 10 mL and chromatographed on a medium-pressure apparatus (Michel-Miller; ACE) with ethyl acetate–hexanes (1:4 then 1:1) on silica gel. Evaporation of the appropriate fractions gave 2.4 g (96%) of the desired material **7d** as an oil: $[\alpha]^{20}_D$ −12.6° (*c* 3.6, $CH_3OH$); IR (neat) 1745, 1780 $cm^{-1}$; $^1H$ NMR (60 MHz) $\delta$ 2.8 (m, 2 H), 4.1 (m, 1 H), 4.95 (s, 2 H), 5.2 (s, 2 H), 7.32 (s, 5 H), 7.5 (s, 5 H).

Similarly prepared were the following.

**7a** (R² = $CH_3$): oil; 78% yield; IR (neat) 1740, 1785 $cm^{-1}$; $^1H$ NMR (60 MHz) $\delta$ 2.8 (dd, 2 H), 3.8 (s, 3 H), 4.2 (dd, 1 H), 5.1 (s, 2 H), 7.4 (s, 5 H).

**7b** (R² = $C_2H_5$): oil; 88.5% yield; IR (neat) 1740, 1785 $cm^{-1}$; $^1H$ NMR (60 MHz) $\delta$ 1.25 (t, 3 H), 2.8 (dd, 2 H), 4.15 (m, $C_3H$, $C_4H$, and $OCH_2CH_3$), 5.03 (s, 2 H), 7.4 (s, 5 H).

**Reduction of the 4-Alkoxycarbonyl Group. Preparation of Alcohol 11.** The β-lactam ester **7d** (311 mg, 1 mmol) was dissolved in 10 mL of THF and cooled in an ice bath. $NaBH_4$ (37 mg) in 3 mL of $H_2O$ was added. The solution was stirred at 0 °C (bath temperature for 1 h and then poured into a separatory funnel containing 25 mL of ethyl acetate, 25 mL of $H_2O$, and 2 mL of acetic acid. After the mixture was shaken, the layers were separated. The aqueous layer was extracted with two 25-mL portions of ethyl acetate. The combined ethyl acetate was washed with two 15-mL portions of 5% $NaHCO_3$ and 15 mL of brine, dried over $Na_2SO_4$, filtered, and evaporated to give an oil. Chromatography on silica gel with gradient elution (30% ethyl acetate/70% hexanes to 100% ethyl acetate) gave a fraction [TLC, $R_f$ 0.15 (1:1 ethyl acetate–hexanes)] containing the desired product **11**: 121 mg (oil 61%); IR (neat) 1760 $cm^{-1}$; $^1H$ NMR (60 MHz) $\delta$ 2.5–2.65 (m, 3 H), 3.55–3.65 (br, 3 H), 4.9 (s, 2 H), 7.4 (s, 5 H).

**Iodide 12.** The β-lactam alcohol **11** (786 mg, 3.97 mmol) was dissolved in 30 mL of THF. Dicyclohexylcarbodiimide methiodide (DCCMeI, Alfa, 7.49 mmole) was added and the reaction heated to 40–50 °C (bath) under $N_2$ for 48 h. Evaporation of the solvent followed by chromatography on silica gel with $CH_2Cl_2$–hexanes provided the desired iodide **12** as an oil: 63% yield; IR (neat) 1775 $cm^{-1}$; $^1H$ NMR (60 MHz) $\delta$ 2.5 (d, 1 H, $J$ = 4 Hz), 2.72 (d, 1 H, $J$ = 10 Hz), 3.1 (t, 2 H), 3.63 (m, 1 H), 5.0 (s, 2 H), 7.43 (s, 5 H); mass spectrum, $m/e$ 317.

**Diisopropyl 2(*R*)-Hydroxy-3(*S*)-ethylsuccinate (15RS, R = *i*-Pr).** To a solution of diisopropylamine (16.67 mL, 0.12 mol) in dry THF (150 mL) under $N_2$ at 0 °C was added *n*-BuLi (72.25 mL of a 1.50 M solution, 0.108 mol). After 10 min the solution was cooled to −78 °C and diisopropyl D-malate (**14R**; 11.81 g, 0.054 mol; prepared from D-malic acid and isopropyl alcohol with a catalytic amount of $SOCl_2$) in dry HMPA (9.7 mL, 0.054 mol) and dry THF (10 mL) was added dropwise with a double-tipped needle while the solution was being stirred under $N_2$. The solution turned orange-red. The temperature of the reaction mixture was allowed to rise to −20 °C over about 45 min. The solution was cooled back to −78 °C, and ethyl iodide (6.5 mL, 0.081 mol) was added dropwise. The temperature of the reaction mixture was allowed to rise from −78 °C to room temperature. After stirring at room temperature for 30 min, the reaction was quenched with 1 M citric acid solution and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, and evap-

orated under reduced pressure to give a light yellow oil. NMR of the crude mixture indicated an 87:13 ratio of **15RS/15RR**. The crude product was purified by chromatography over silica gel with ether–hexanes (1:4) to afford **15RS**: 11.2 g (46 mmol, 84%); IR (neat) 3520, 1735 $cm^{-1}$; $^1H$ NMR (90 MHz) $\delta$ 0.98 (t, 3 H, $J$ = 7.5 Hz), 1.25 (d, 6 H, $J$ = 6.5 Hz), 1.28 (d, 6 H, 6.5 Hz), 1.76 (m, 2 H), 2.71 (m, 1 H), 3.28 (d, OH, $J$ = 7.5 Hz), 4.26 (dd, 1 H), 5.06 (m, 2 H).

Diisopropyl L-malate **14S** was ethylated in a similar fashion to provide and 87/13 ratio of **15SR/15SS** in 97% yield. The spectroscopic data for **15SR** were identical with those of **15RS** described above.

The corresponding ethyl esters (**15RS/15RR**, 87:13) were also obtained as oils in an 84% yield from diethyl D-malate. The spectroscopic data for **15RS** are as follows: IR (neat) 3525, 1735 $cm^{-1}$; $^1H$ NMR (90 MHz) $\delta$ 0.98 (t, 3 H, $J$ = 7.5 Hz), 1.15–1.37 (m, 6 H), 1.75 (m, 2 H), 2.77 (m, 1 H), 3.48 (d, OH, $J$ = 7.5 Hz), 4.03–4.37 (m, 5 H); mass spectrum (CI with $CH_4$), $m/e$ 219 (M + 1).

**Hydrolysis of the 3-Ethyl Malates 15 to the Diacids 16. General Procedure.** To a solution of **15** (32 mmol) in dioxane/water (1:1, 200 mL) was added a 20% solution of KOH in water (27 mL, 96 mmol). The reaction mixture was refluxed for 16 h, cooled to room temperature, and passed through a column of Dowex 50W-X4 ($SO_3H$) by elution with water. The resulting aqueous solution was then evaporated to dryness under reduced pressure to give the crude diacid which was usually used without further purification. In one instance, the crude diacid was recrystallized from ether to provide pure 2(*R*)-hydroxy-3(*S*)-ethylsuccinic acid (**16RS**): mp 114–116 °C; $^1H$ NMR ($Me_2SO$-$d_6$, 90 MHz) $\delta$ 0.85 (t, 3 H, $J$ = 7.5 Hz), 1.42 (m, 2 H), 2.56 (m, 1 H), 4.12 (d, 1 H, $J$ = 6 Hz), 7.5 (br, OH, $CO_2H$).

**Methyl hydrogen 2(*R*)-hydroxy-3(*S*)-ethylsuccinate (17RS)** was obtained from 2(*R*)-hydroxy-3(*S*)-ethylsuccinic acid (**16RS**) as an oil in 87% overall yield from the diester **15RS**. The process involved first saponification of **15RS** as above followed by subjection of crude **16RS** to the TFAA-mediated monoesterification process described earlier: IR (neat) 3100–3500, 1740 $cm^{-1}$; $^1H$ NMR (90 MHz) $\delta$ 1.0 (t, 3 H, $J$ = 7.5 Hz), 1.80 (m, 2 H), 2.83 (m, 1 H), 3.80 (s, 3 H), 4.36 (d, 1 H, $J$ = 4.5 Hz), 7.56 (br OH, $CO_2H$); mass spectrum, $m/e$ 176 ($M^+$), 158 (M – $H_2O$).

**Methyl hydrogen 2(*S*)-hydroxy-3(*R*)-ethylsuccinate (17SR)** was obtained in 70% overall yield from the diester **15SR** by saponification to **16SR** followed by the TFAA-mediated monoesterification. Compound **17SR** was an oil with spectroscopic data identical with those reported above for its mirror image **17RS**.

**Methyl Hydrogen 2(*S*)-Hydroxy-3(*S*)-ethylsuccinate (17SS). (a) 3(*S*)-Ethyl-4(*S*)-(methoxycarbonyl) β-Lactone 20SS.** The β-hydroxy acids **17RS** (2.158 g, 12.261 mmol) was dissolved in dry THF (40 mL) containing $PPh_3$ (3.80 g, 14.713 mmol). While being stirred at 0 °C under $N_2$ or a $CaCl_2$ drying tube, a solution of diethyl azodicarboxylate (DEAD, Aldrich; 2.56 g, 14.7 mmol) in dry THF (20 mL) was added dropwise. After 15 min, the ice bath was removed, and the reaction mixture was stirred for 16 h. The solvent was removed under reduced pressure at room temperature, and the residue was triturated with ice cold ether. Insoluble reduced DEAD and $PPh_3O$ were filtered, and the filterate, after concentration, was purified by chromatography over silica gel with 60% methylene chloride in hexanes to give the β-lactone **20SS** as an oil: 1.191 g (7.557 mmole, 61%); IR (neat) 1820, 1725 $cm^{-1}$; NMR (90 MHz) $\delta$ 1.02 (t, $J$ = 7.5 Hz, 3 H), 1.70 (m, 2 H), 3.83 (s, 3 H), 3.67–4.05 (m, 1 H), 4.97 (d, $J$ = 7.2 Hz, 1 H).

**(b) 2(*S*)-Hydroxy-3(*S*)-ethylsuccinic Acid (16SS).** To a solution of the β-lactone **20SS** (300 mg, 1.9 mmol) in dioxane/water (1:1, 30 mL) was added a 20% solution of KOH in water (1.06 mL, 3.8 mmol), and the reaction mixture was stirred at room temperature for 12 h. The basic reaction mixture was passed through $H^+$ resin (Dowex 50W-X4, $SO_3H$), and the aqueous solution was evaporated to dryness under reduced pressure to give the crude diacid **16SS** in nearly quantitative yield.

**(c) 2(*S*)-Hydroxy-3(*S*)-ethylsuccinic acid (16SS)** obtained in the preceding step was treated with trifluoroacetic anhydride followed by methanol in a manner previously described for the preparation of the monoesters to give the title compound **17SS**. The product was purified by silica gel chromatography (ethyl acetate–hexanes, 3:7) to give an oil: 218 mg (1.24 mmol, 65% overall yield from lactone **20SS**); IR (neat) 3100–3500 $cm^{-1}$; NMR (90 MHz) $\delta$ 0.98 (t, $J$ = 7.5 Hz, 3 H), 1.73 (m, 2 H), 2.30 (m, 1 H), 3.85 (s, 3 H), 4.58 (d, $J$ = 5.5 Hz, 1 H), 8.20 (br, OH, $CO_2H$).

**Methyl Hydrogen 2(*R*)-Hydroxy-3(*R*)-ethylsuccinate (17RR).** The β-hydroxy acid **17SR** (3.88 g, 22.05 mmol) in dry THF (40 mL) was treated with $PPh_3$ (6.9 g, 26.4 mmol) and DEAD (4.603 g) under the conditions described for the preparation of β-lactone **20SS**. After the reaction was complete (monitered by IR), excess solvent was removed under reduced pressure at room temperature, and the residue was triturated with ice-cold ether. Insoluble reduced DEAD and $Ph_3PO$ were filtered out, and the filtrate after concentration was treated with a 20% solution of KOH (6.172 mL, 22.045 mmol) in dioxane/water (1:1, 150 mL). After the reaction mixture was stirred for 12 h, it was passed through Dowex 50W-X4. The filtrate (pH ~2.5) was evaporated to dryness and treated with trifluoroacetic anhydride (11 mL, 66.135 mmol) followed by methanol (20 mL) under the conditions described for the preparation of compound **17SS** to give crude β-hydroxy acid **17RR**, which was purified by silica gel chromatography; yield 1.550 g (8.81 mmol, as an oil, 40% overall from **17SR**). Spectroscopic data were identical with those of compound **17SS**.

**Methyl 2(*R*)-hydroxy-3(*S*)-ethyl-*N*-(benzyloxy)-succinamate (18RS)** was prepared in 91% yield from **17RS** by the water-soluble carbodiimide procedure described earlier: mp 104–105 °C (recrystallized from ethyl acetate–hexanes); IR ($CHCl_3$) 34008, 1740, 1680 $cm^{-1}$; $^1H$ NMR (90 MHz) $\delta$ 0.93 (t, 3 H, $J$ = 7.5 Hz), 1.70 (m, 2 H), 2.46 (br m, 1 H), 3.75 (s, 3 H), 4.26 (d, 1 H, $J$ = 5.5 Hz), 4.87 (s, 2 H), 7.42 (s, 5 H), 8.90 (br, NH); mass spectrum (CI with $CH_4$), $m/e$ 282 (M + 1). Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.76; N, 4.98. Found: C, 59.61; H, 6.76; N, 4.91.

**Methyl 2(*R*)-hydroxy-3(*R*)-ethyl-*N*-(benzyloxy)-succinamate (18RR)** was obtained from **17RR** in 91% crude and 84% recrystallized yield by the usual carbodiimide coupling procedure: mp 95–96 °C (recrystallized from ether–hexanes); $[\alpha]^{20}_D$ +6.1° ($c$ 0.97, $CH_3OH$); IR ($CHCl_3$) 3090, 1730, 1685 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 0.90 (t, 3 H, $J$ = 7.5 Hz), 1.53 (m, 1 H), 1.76 (m, 1 H), 2.46 (m, 1 H), 3.78 (s, 3 H), 4.33 (br s, 1 H), 4.90 (s, 2 H), 7.40 (br d, 5 H). Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.79; H, 6.76; N, 4.98. Found: C, 59.54; H, 6.88; N, 5.18.

Similarly prepared was **18SS** in 85% yield from **17SS**: mp 94–95 °C; $[\alpha]^{20}_D$ –5.5° ($c$ = 1.2, $CH_3OH$). Spectroscopic data were identical with those reported for the mirror image **18RR**.

**Synthesis of β-lactams 19SS and 19SR** was accomplished by the treatment of **18RS** and **18RR**, respectively, with DEAD/TPP as described for the preparation of **7**. Thus, **1-(benzyloxy)-3(*S*)-ethyl-4(*S*)-carbomethoxy-2-azetidinone (19SS)** was obtained: 75% yield; mp 71–72 °C; $[\alpha]^{20}_D$ –2.8° ($c$ 3.5, $CH_3OH$); IR ($CHCl_3$) 1780, 1745 $cm^{-1}$; $^1H$ NMR (300 MH) $\delta$ 0.99 (t, 3 H, $J$ = 7.5 Hz), 1.45–1.63 (m, 2 H), 3.08 (m, apparent q, 1 H), 3.78 (s, 3 H), 4.24 (d, 1 H, $J$ = 6 Hz), 5.09 (dd, apparent distorted q, 2 H), 7.32–7.48 (m, 5 H); mass spectrum (CI with $CH_4$), $m/e$ 264 (M + 1). Anal. Calcd for $C_{14}H_{17}O_4$: C, 63.88; H, 6.46; N, 5.32. Found: C, 63.87; H, 6.48; N, 5.32.

**1-(Benzyloxy)-3(*R*)-ethyl-4(*S*)-carbomethoxy-2-azetidinone (19SR)** was also obtained as an oil in 75% yield from **18RR**: $[\alpha]^{20}_D$ +5.6° ($c$ 4.4, $CH_3OH$); IR (neat) 1780, 1750 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 0.98 (t, 3 H, $J$ = 7.5), 1.60–1.83 (m, 2 H), 2.89 (m, 1 H), 3.76 (s, 3 H), 3.80 (d, 1 H, $J$ = 2.4 Hz), 5.05 (dd, apparent distorted q, 2 H), 7.32–7.48 (m, 5 H); mass spectrum (CI with $CH_4$), $m/e$ 264 (M + 1).

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**Registry No. 2aR**, 83540-94-7; **2aS**, 66212-45-1; **2bS**, 83540-95-8; **2bR**, 83540-96-9; **2cR**, 83477-76-3; **2dR**, 83477-74-1; **3R**, 636-61-3;

dl-5, 83477-75-2; 5R, 83541-02-0; 6aS, 83477-77-4; 6bS, 83477-78-5; 6cR, 83477-79-6; 6dR, 83477-80-9; 7a, 83477-82-1; 7b, 83477-83-2; 7d, 83477-81-0; 11, 83477-84-3; 12, 83477-85-4; 14R (R = Pr-i), 83540-97-0; 14S (R = Pr-i), 83541-68-8; 15RS (R = Pr-i), 83477-86-5; 15RR (R = Pr-i), 83477-87-6; 15SR (R = Pr-i), 83477-88-7; 15RR (R = Et), 83477-89-8; 15RS (R = Et), 83477-90-1; 15SS (R = Pr-i), 83478-00-6; 16RS, 83540-98-1; 16SR, 83540-99-2; 16SS, 83541-00-8; 17RS, 83477-91-2; 17SR, 83477-92-3; 17SS, 83477-94-5; 17RR, 83477-95-6; 18RS, 83477-96-7; 18RR, 83477-97-8; 18SS, 83486-41-3; 19SS, 83477-98-9; 19SR, 83541-01-9; 20SS, 83477-93-4; i, 83477-99-0; L-malic acid, 97-67-6; O-benzylhydroxylamine hydrochloride, 2687-43-6; diethyl D-malate, 7554-28-1; dl-malic acid, 617-48-1.

# Dichlorodicyanoquinone Oxidations in the Indole Area. Synthesis of Crenatine

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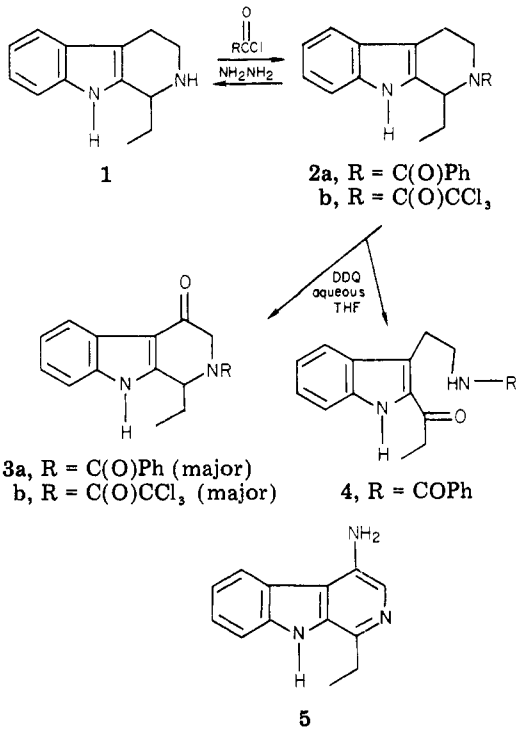
The influence of temperature on the reaction of dichlorodicyanoquinone (DDQ) with 1,2,3,4-tetrahydro-β-carbolines has been explored. The DDQ oxidation of amide **2a**, when performed at room temperature, gave **3a** (3-acylindole)/**4** (2-acylindole) in a ratio of ca. 1:1, while this was increased to 2:1 at 0 °C and to ca. 5:1 at −78 °C. This method for preparation of 4-oxo-β-carbolines has been employed for synthesis of the β-carboline alkaloid crenatine (**11**). In addition, treatment of the 4-oxotetrahydro-β-carboline (**3b**) with hydrazine gave 1-ethyl-4-amino-β-carboline (**12**) which should provide access to a series of 4-substituted β-carbolines.

Previously, we have demonstrated that a carbonyl group located at the 3-position of β-carbolines was important for binding to the benzodiazepine (Valium) receptor(s).[1-4] It has, therefore, become of interest to develop access to other substituted β-carbolines, including the 4-oxo derivatives. In this vein, both selenium dioxide ($SeO_2$)[5] and dichlorodicyanoquinone (DDQ)[6a] have been recently employed for the preparation of 3-acylindoles.[6b] Several alkaloids such as borrecapine[7a] and aristotelinone[7b] contain the 3-acylindole functionality; moreover, others contain functional groups which can be formally derived from 3-acylindoles such as crenatine[8,9] (**11**), 1-methoxycanthin-6-one,[10] and 4-hydroxy-β-carboline-1-carboxaldehyde, which was found recently to be a potent xanthine oxidase inhibitor.[11] Both $SeO_2$[5] and DDQ[6] offer excellent entries into these biologically important molecules, and we report recent work on DDQ oxidations of tetrahydro-β-carbolines which have resulted in the synthesis of the alkaloid crenatine (**11**).

Scheme I




Oikawa and Yonemitsu reported in 1977 that DDQ could be employed to oxidize 2,3-disubstituted indoles[6a,12] and tetrahydrocarbazoles to the corresponding carbonyl compounds. Use of this technology in our hands has permitted the conversion of 1,2,3,4-tetrahydro-β-carbolines into 3-acylindoles with remarkable ease; yields of this process were as high as 77% and reached a maximum when the oxidations were carried out at low temperature. The key

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