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Studies Directed at a Synthesis of the Morphine Alkaloids.[1] Regiocontrol in Robinson-Type Annelations of 2-(Hydroxymethyl)-4-oxo-3-piperidinecarboxylic Acid γ-Lactones

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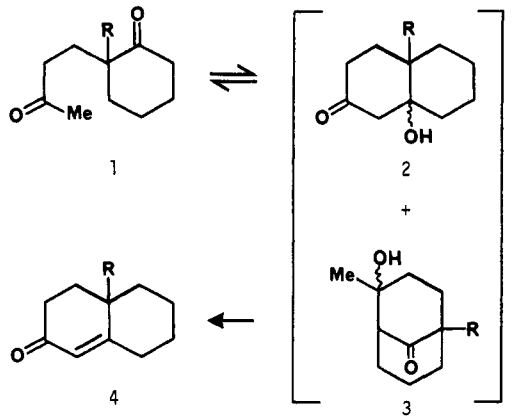
Conjugate reduction of **5a** with $NaBH_4$ in THF–pyridine, followed by sequential addition of excess benzaldehyde and ethanolic hydrochloric acid, gives keto lactone **6a**, uncontaminated with lactonic alcohol **7a**. Annelation of **6a** with (2-methoxyphenoxy)methyl vinyl ketone (**8c**) gives bicyclic aldol **9a**. $A^{(1,3)}$ strain prevents rearrangement and dehydration of **9a** to the desired Robinson-type annelation product **12a**. Cleavage of the urethane group in **9a** gives **9c**, and this $A^{(1,3)}$-strain-relieved derivative was successfully converted to enone **12c** via the fused-ring aldol **11c**. The photoconversion of **12f** to **13** demonstrates remote control of stereochemistry at C(9) in the morphine ring system by aryl vinyl ether photocyclization.

The Robinson annelation provides a convenient strategy for conversion of cyclohexanones to octalones and related fused-ring systems.[2] Generally, methyl vinyl ketone is used as the annelation reagent to give a 1,5-diketone, from which base-induced aldol cyclization–dehydration affords the octalone (e.g., 1 → 4). Cyclization can occur to give



1 2 + 3 4

not only the desired fused-ring aldol **2**, but also the bicyclic aldol **3**; in fact, **3** is generally the kinetic cyclization product.[3] The Robinson annelation is successful when there is an equilibration among **1**, **2**, and **3** because aldol **2** is susceptible to base-induced dehydration, while **3** (requiring a bridgehead enolate) is not.

An examination of the factors that govern reversibility during 1,5-dicarbonyl cyclization has been limited to carbocyclic systems.[3,4] The Robinson-type annelation of 4-oxopiperidine derivatives has been investigated in connection with studies directed at a synthesis of the morphine alkaloids.[1] In this paper, we report the annelation of 2-(hydroxymethyl)-4-oxo-3-piperidinecarboxylic acid γ-lactones of type **6** with (aryloxy)methyl vinyl ketone **8c** to give enone **12c** and comment on the factors that control the interconvertibility of intermediate aldols **9** and **11**. The conversion of **12f** to a "tetracyclic" morphine ring analogue,[5] **13**, in which we demonstrate remote stereochemical control during aryl vinyl ether photocyclization, also is presented.

Preparation of the Annelation Substrate and Annelation Reagent. Procedures for preparation of **5b** and **5c** have been previously reported.[6] The synthesis of **5a** follows the literature method[6] and is detailed in the Experimental Section. Selective reduction of the olefinic bond in **5a–5c** provided a challenge because of the dense, potentially reactive functionality attached to the olefinic carbon atoms. In fact, catalytic hydrogenation (palladium on carbon or platinum oxide) or dissolving metal reduction (Li/NH_3) results in extensive ketone reduction without reaction with the olefinic bond. Similar results are ob-

(1) For an earlier report, see: Schultz, A. G.; Lucci, R. D.; Napier, J. J.; Kinoshita, H.; Ravichandran, R.; Shannon, P.; Yee, Y. K. *J. Org. Chem.* **1985**, *50*, 217.

(2) (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 3. (b) Gawley, R. E. *Synthesis* **1976**, 777.

(3) (a) Johnson, W. S.; Korst, J. J.; Clemens, R. A.; Dutta, J. *J. Am. Chem. Soc.* **1960**, *82*, 614. (b) Spencer, T. A.; Neel, H. S.; Ward, D. C.; Williamson, K. C. *J. Org. Chem.* **1966**, *31*, 434. (c) Muskopf, J. W.; Coates, R. M. *J. Org. Chem.* **1985**, *50*, 69.

(4) (a) Lacey, R. N. *J. Chem. Soc.* **1960**, 1639. (b) Nagel, A. A., Ph.D. Thesis, University of Pittsburgh, 1971. (c) Danishefsky, S.; Cain, P.; Nagel, A. *J. Am. Chem. Soc.* **1975**, *97*, 380.

(5) Schultz, A. G.; Lucci, R. D. *J. Chem. Soc., Chem. Commun.* **1976**, 925.

(6) Schultz, A. G.; Shannon, P. J.; Tobin, P. S. *J. Org. Chem.* **1979**, *44*, 291.

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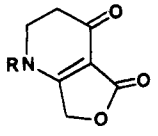
tained with sodium borohydride[7] or sodium cyanoborohydride[8] in protic solvents.

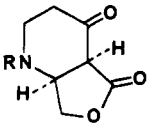
Reduction with $NaBH_4$ in THF proved more promising. At room temperature, ketone reduction predominates, but as the reaction temperature is lowered, an increasing proportion of conjugate reduction is observed. Reduction of **5b** in THF at −15 °C, followed by aqueous acid workup, gives two diastereoisomeric alcohols **7b**. These alcohols could be converted to the desired keto lactone **6b** by oxidation with Me_2SO–trifluoroacetic anhydride reagent[9] in ~30% overall yield from **5**.

It is generally recognized that ketone reductions with $NaBH_4$ are proton or Lewis acid catalyzed.[10] We reasoned that in aprotic solvents, conjugate reduction of **5b** should give an intermediate ketone enolate, which would be resistant to further reduction by $NaBH_4$ until aqueous acid is added in the workup step. Rapid reduction of the resulting keto lactone **6b** by residual $NaBH_4$ (or BH_3 generated by reaction of $NaBH_4$ with acid)[11] would give alcohols **7b**.

In accord with this supposition, ketone reduction can be suppressed by the addition of benzaldehyde before the aqueous acid workup step. Thus, reduction of **5a** with



5a, R = CO_2CH_2Ph
b, R = CO_2Me
c, R = Me



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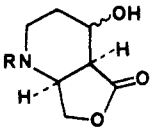

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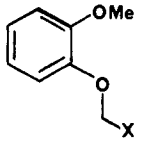


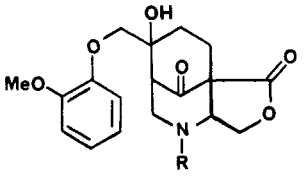
8a, X = CHO
b, X = CHOHCH=CH_2
c, X = COCH=CH_2

$NaBH_4$ in THF–pyridine (10:1) at −15 °C, followed by sequential addition of excess benzaldehyde and ethanolic hydrochloric acid, gives the desired keto lactone **6a**. Remaining benzaldehyde and benzyl alcohol are removed by extraction of **6a** into cold aqueous sodium carbonate; acidification gives crystalline keto lactone **6a** (mp 109–110 °C) in 75% yield.

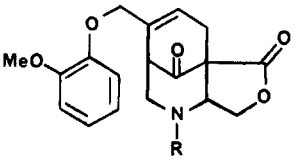
While we have not studied the generality of this conjugate reduction methodology, we suggest that it may be useful with systems related to **5a**, in which a relatively stable enolate is generated during the conjugate reduction step. However, we have not been able to convert the basic enamide **5c** to **6c** using the benzaldehyde quench.

The annelation reagent **8c** is prepared by adaptation of a related procedure.[1] Aldehyde **8a** reacts with vinylmagnesium bromide to give the relatively stable allylic alcohol **8b**. Jones oxidation of **8b** gives the sensitive methyl vinyl ketone derivative **8c** in 50–70% yield. Generally, **8c** is prepared, distilled, and used immediately in annelation studies.

Annelation of 6a and 6b with (2-Methoxyphenoxy)methyl Vinyl Ketone (8c). When the annelation of keto lactone **6b** with **8c** is performed with potassium *tert*-butoxide in benzene–*tert*-butyl alcohol solution, bicyclic aldol **9b** is formed as the major reaction product.



9a, R = CO_2CH_2Ph
b, R = CO_2Me
c, R = H



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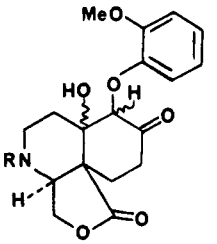
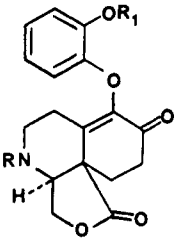
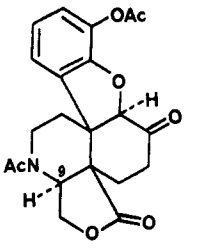
Dehydration of **9b** with methanesulfonyl chloride in pyridine gives the olefin **10b**. We have not observed the production of either fused-ring aldol **11b** or aryloxy enone



11a, R = CO_2CH_2Ph
b, R = CO_2Me
c, R = H



12a, R = CO_2CH_2Ph; R_1 = Me
b, R = CO_2Me; R_1 = Me
c, R = H; R_1 = Me
d, R = Ac; R_1 = Me
e, R = Ac; R_1 = H
f, R = R_1 = Ac



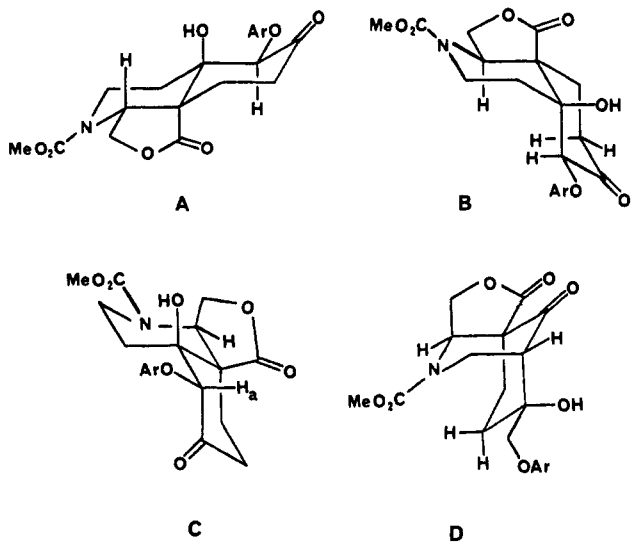
13

12b in condensations of **6b** with **8c**, and we have not been able to convert **9b** into **12b** under a variety of standard reaction conditions.[3] Similar results were obtained in annelation studies with **6a** to give **9a** in 80% isolated yield (see Experimental Section).

We believe that the inability to convert **9b** into **12b** is, in large part, a result of allylic or $A^{(1,3)}$ strain[12] that would be present in aldol **11b**. Structures A–C represent possible diastereoisomers of **11b**. Structure D is a stereorepresentation of aldol **9b**. A and B experience $A^{(1,3)}$ strain as a result of interactions between the planar urethane group and the adjacent equatorial lactone methylene unit. This strain is relieved in C, but severe eclipsing interactions are present and C does not possess the favored trans diaxial relationship between H_a and the OH group. Thus, diastereoisomers A-C appear to be of higher energy than aldol D and presumably they are not formed to a significant extent under the usual aldol equilibrating conditions.[5]

The N-unsubstituted bicyclic aldol **9c** provided a test of the importance of $A^{(1,3)}$ strain. Hydrogenolysis of **9a**

(7) Schultz, A. G.; Godfrey, J. D. *J. Am. Chem. Soc.* **1980**, *45*, 2040.
(8) Hutchins, R. O.; Natale, N. R. *Org. Prep. Proced. Int.* **1979**, *11*, 201.
(9) Swern, D. *J. Org. Chem.* **1976**, *41*, 3329.
(10) (a) Brown, H. C.; Mead, E. J.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1955**, *77*, 6209. (b) Brown, H. C.; Ichikawa, K. *J. Am. Soc.* **1961**, *83*, 4372. (c) Wigfield, D. C.; Gowland, F. W. *J. Org. Chem.* **1977**, *42*, 1108. (d) Ritchie, C. D.; Pratt, A. L. *J. Am. Chem. Soc.* **1964**, *86*, 1571.
(11) Marshall, J. A.; Johnson, W. S. *J. Org. Chem.* **1963**, *28*, 421.
(12) (a) Paulsen, H.; Todt, K. *Chem. Ber.* **1967**, *100*, 3385. (b) Buchi, G.; Bould, S. J.; Naf, F. *J. Am. Chem. Soc.* **1971**, *93*, 2492. (c) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.



gives the secondary amine **9c**, which smoothly converts to the desired crystalline aryloxy enone **12c** on treatment with pyrrolidine and *p*-toluenesulfonic acid in refluxing benzene solution. In one experiment, fused-ring aldol **11c** could be isolated and characterized.[13]

Photocyclization of Aryloxy Enone 12f. The photochemistry of **12a–12c** and related systems[1] is complicated by competing photoreactions which seem to be a result of the *o*-methoxy substituent. Substitution of an acetoxy group for the methoxy group was found to facilitate photocyclization of aryloxy enones.[1] Conversion of **12c** to **12d** by N-acetylation, followed by methyl ether cleavage with BBr_3 in CH_2Cl_2, and acetylation of the resulting phenol **12e** (not characterized) gives the desired aryloxy enone **12f**.[14] As anticipated, photocyclization of **12f** gives benzodihydrofuran **13** (89% yield) as a single, crystalline (mp 229–231 °C) diastereoisomer.[15] Thus, a means to remotely control stereochemistry at C(9) in the morphine ring system by aryl vinyl ether photocyclization has been realized.

Experimental Section[16]

Methyl 1,4,5,6-Tetrahydro-1-[(benzyloxy)carbonyl]-2-methyl-4-oxo-3-pyridinecarboxylate. Potassium (11.55 g, 0.296 mol) was added to dry 2-methyl-2-propanol (250 mL) and heated at reflux temperature for 5 h. After cooling to room temperature, methyl 1,4,5,6-tetrahydro-2-methyl-4-oxo-3-pyridinecarboxylate[17] (45.5 g, 0.269 mol) was added. Dimethylformamide (60 mL) was added and the mixture was stirred at room temperature for 3.5 h and then cooled to 0 °C, after which benzyl chloroformate (46.0 mL of 95% composition, 0.296 mol) was added over 0.5 h. After stirring at room temperature for 1 h, the mixture was concentrated, diluted with water and 1 N HCl, and extracted with a mixture of dichloromethane and ether (1:2.5). The organic phase was washed with brine, dried, and concentrated to give an oil. Chromatography (SiO_2, hexane–ethyl acetate, 2:1) followed by crystallization (ether) gave methyl 1,4,5,6-tetrahydro-1-[(benzyloxy)carbonyl]-2-methyl-4-oxo-3-pyridinecarboxylate (64.9 g, 80%, mp 57–58 °C). IR ($CHCl_3$) 5.76–5.85, 6.01 and 6.31 μm; ^1H NMR δ 7.4 (5 H, s), 5.27 (2 H, s), 4.13 (2 H, t), 3.80 (3 H, s), 2.52 (2 H, t), and 2.35 (3 H, s).

Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65. Found: C, 63.23; H, 5.63.

Methyl 1,4,5,6-Tetrahydro-1-[(benzyloxy)carbonyl]-2-(bromomethyl)-4-oxo-3-pyridinecarboxylate. A suspension of 15.15 g (50 mmol) of methyl 1,4,5,6-tetrahydro-1-[(benzyloxy)carbonyl]-2-methyl-4-oxo-3-pyridinecarboxylate, *N*-bromosuccinimide (10.7 g, 60 mmol), and pyridine (0.70 mL, 9 mmol) in benzene (50 mL) was heated to 80–85 °C and irradiated with a 275-W sunlamp for 0.5 h. After cooling, the reaction mixture was dissolved in chloroform and washed with 1% sodium bisulfite and brine. Drying and evaporation of solvent gave 19.0 g of bromide of sufficient purity for subsequent reactions. ^1H NMR ($CDCl_3$) δ 7.4 (5 H, s), 5.3 (2 H, s), 4.7 (2 H, s), 4.15 (2 H, t), 3.85 (3 H, s), and 2.6 (2 H, t).

Methyl 1,4,5,6-Tetrahydro-2-(acetoxymethyl)-1-[(benzyloxy)carbonyl]-4-oxo-3-pyridinecarboxylate. A solution of methyl 1,4,5,6-tetrahydro-1-[(benzyloxy)carbonyl]-2-bromomethyl-4-oxo-3-pyridinecarboxylate (prepared from 15.2 g, 50 mmol, of its precursor) and potassium acetate (9.8 g, 100 mmol) in DMF (50 mL) was stirred at room temperature for 13 h. After solvent was removed at reduced pressure, the mixture was diluted with water and extracted with dichloromethane. The combined organic extracts were dried, concentrated to an oil, and chromatographed (SiO_2, ethyl acetate–hexane, 1:1) to give the acetate (15.2 g, 84%). Recrystallization of a portion from ethyl acetate gave an analytical sample (mp 84–85 °C). IR ($CHCl_3$) 5.75, 5.97 and 6.27 μm; ^1H NMR ($CDCl_3$) δ 7.4 (5 H, s), 5.27 (2 H, s), 5.09 (2 H, s), 4.15 (2 H, t), 3.82 (3 H, s), 2.60 (2 H, t), and 1.93 (3 H, s).

Anal. Calcd for $C_{18}H_{19}NO_7$: C, 59.83; H, 5.31. Found: C, 59.99; H, 5.32.

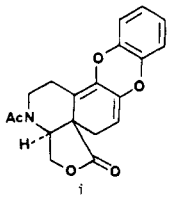
1,4,5,6-Tetrahydro-1-[(benzyloxy)carbonyl]-2-(hydroxymethyl)-4-oxo-3-pyridinecarboxylic Acid γ-Lactone (5a). A solution of methyl 1,4,5,6-tetrahydro-2-(acetoxymethyl)-1-[(benzyloxy)carbonyl]-4-oxo-3-pyridinecarboxylate (14.4 g, 40 mmol) and *p*-toluenesulfonic acid (1.32 g, 7.0 mmol) in MeOH (240 mL) was heated at reflux temperature for 6.5 h. The resulting mixture was cooled to 0 °C and after 12 h the precipitated solid was removed by filtration to give 5.3 g of **5a**. The filtrate was concentrated, dichloromethane was added, and the resulting solution was washed with aqueous $NaHCO_3$, dried, concentrated, and crystallized from methanol to give an additional 2.7 g of lactone **5a** (8.0 g, 70%, mp 160.5–162 °C). IR (KBr) 5.68, 5.75, 6.01 and 6.29 μm; ^1H NMR ($CDCl_3$) δ 7.45 (5 H, s), 5.34 (2 H, s), 5.24 (2 H, s), 4.28 (2 H, t), and 2.65 (2 H, t); electron impact mass spectrum, *m/e* 287 (M^+).

Anal. Calcd for $C_{15}H_{13}NO_5$: C, 62.71; H, 4.56. Found: C, 62.61; H, 4.52.

1-[(Benzyloxy)carbonyl]-2-(hydroxymethyl)-4-oxo-3-piperidinecarboxylic Acid γ-Lactone (6a). To a suspension of **5a** (8.60 g, 30 mmol) in 130 mL of THF–pyridine (10:1) was added finely powdered sodium borohydride (1.38 g, 36 mmol) at −15 °C. The mixture was stirred for 0.5 h at −15 °C. Benzaldehyde (24.0 mL, 0.24 mol) was added and stirring was continued for 10 min at room temperature. After cooling to −78 °C, a solution of

(13) Becker and co-workers report that Michael addition of 1-acetyl-2-benzyl-3-(carbomethoxy)-4-piperidone to methyl vinyl ketone gives 1-(carbomethoxy)-2-benzyl-3-aza-3-acetyl-6-hydroxy-6-methylbicyclo-[3.3.1]nonan-9-one, which can be rearranged to 1-benzyl-2-acetyl-9-(carbomethoxy)-10-hydroxydecahydro-6-isoquinolone. However, in contrast to **11b**, the 1-benzyl and 9-carbomethoxy groups are trans-related and $A^{(1,3)}$ strain need not be present in the ring-fused aldol. See: Becker, H. G. O.; Fratz, U.; Klose, G.; Heller, K. *J. Prakt. Chem.* **1965**, *29*, 142 and references cited therein.

(14) The procedure developed for conversion of **12d** into **12f** (see Experimental Section) is considered to have been optimized. Using modified reaction conditions, a major byproduct appeared to be the cyclization product i.



(15) The assignment of isoquinolone ring junction stereochemistry in **13** rests on a combination of ^1H NMR spectral correlations within a series of cis-fused derivatives. See: Schultz, A. G.; Lucci, R. D.; Fu, W. Y.; Berger, M. H.; Erhardt, J.; Hagmann, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 2150.

(16) For details relevant to instrumentation, solvent purification, and other experimental techniques, see ref 1.

(17) Becker, H. G. O. *J. Prakt. Chem.* **1961**, *12*, 294.

concentrated HCl (18 mL) and ethanol (32 mL) was added at −78 °C, and the mixture was stirred for 5 min, warmed to room temperature, and then heated at reflux temperature for 15 min. Water was added, and the resulting solution was extracted with dichloromethane. The combined organic extracts were dried and concentrated to an oil, which was diluted with ether–dichloromethane (4:1) and extracted with cold 1 N sodium carbonate solution (4 × 75 mL). The aqueous basic solution was immediately washed with ether–dichloromethane (4:1) and acidified with cold 6 N HCl. The aqueous acid solution was extracted with dichloromethane, and the combined organic extracts were dried and concentrated to give a paste (7.5 g), which crystallized from ethyl acetate to give **6a** (6.37 g, 75%, mp 109–110 °C). IR ($CHCl_3$) 5.63, 5.83, and 5.97 μm; ^1H NMR ($CDCl_3$) δ 7.40 (5 H, s), 5.22 (3 H, s and m), 4.60–4.20 (3 H, m), 3.75–3.15 (2 H, m), and 2.75–2.35 (2 H, m); electron impact mass spectrum, *m/e* 289 (M^+).

Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.22. Found: C, 62.46; H, 5.42.

3-Hydroxy-4-(2-methoxyphenoxy)but-1-ene (8b). To a suspension of Mg turnings (7.20 g, 0.30 g atom) in THF (300 mL) was added a 15 mL portion of a solution of vinyl bromide (32.0 mL, 0.45 mol) in THF (50 mL). The rest of the vinyl bromide solution was added over 1 h at 10–15 °C with stirring. After 2 h, a solution of **8a**[1] (29.40 g, 0.18 mol) in THF (150 mL) was added, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was poured onto a mixture of ice and 6 N HCl (50 mL) and then extracted with ether–hexane (1:1). The combined organic layers were washed with saturated $NaHCO_3$ and brine, then dried and evaporated to give **8b** as a yellow oil. Chromatography on a Waters Prep 500 (hexane–ethyl acetate, 2:1) afforded **8b** (23.8 g, 70%). The phenyl urethane derivative displayed a melting point of 116 °C (ethyl acetate–hexane). IR ($CHCl_3$) 2.90 and 6.29 μm; ^1H NMR ($CDCl_3$) δ 7.93 (4 H, s), 6.20–5.20 (3 H, m), 4.45 (1 H, m), 4.0 (2 H, d), 3.83 (3 H, s), and 3.15 (1 H, d).

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11. Found: C, 69.01; H, 6.32.

(2-Methoxyphenoxy)methyl Vinyl Ketone (8c). To a solution of **8b** (5.83 g, 30 mmol) in acetone (100 mL) cooled to 0 °C, was added Jones reagent (30 mL) over 2 min. The mixture was stirred at 0 °C for 5 min, after which isopropanol (5 mL) was added. The mixture was diluted with water and extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$, water, and brine, then dried, concentrated, and distilled in a Kugelrohr apparatus to give **8c** (3.4 g, 59%, 97–105 °C, 0.1 mmHg). IR ($CHCl_3$) 5.88, 6.15, and 6.27 μm; ^1H NMR ($CDCl_3$) δ 7.0–6.5 (5 H, m), 5.88 (1 H, dd), 4.82 (2 H, s), and 3.90 (3 H, s). **8c**, thus prepared, was immediately used in annelation studies.

Aldol 9a. To a mixture of potassium *tert*-butoxide (0.33 g, 3 mmol), benzene (30 mL), and 2-methyl-2-propanol (7.5 mL) was added finely powdered **6a** (4.36 g, 15 mmol) followed by a solution of **8c** (3.4 g, 17.7 mmol) in benzene (10 mL). The mixture was stirred at room temperature for 2 h, after which dilute hydrochloric acid was added. The solution was washed with chloroform, and the combined organic extracts were dried and concentrated to give a paste (8.4 g), which was chromatographed (SiO_2, hexane–ethyl acetate, 1:1) to give **9a** (5.73 g 79.5%). IR ($CHCl_3$) 2.86, 5.60, 5.81, and 5.88 μm; ^1H NMR ($CDCl_3$) δ 7.38 (5 H, s), 6.95 (4 H, m), 5.5–5.0 (3 H, m), 4.8–4.3 (4 H, m), 3.85 and 3.82 (5 H, 2 s), 3.65 (1 H, m), 2.95 (1 H, br s), and 2.8–1.75 (4 H, m).

Aldol 9c. A mixture of **9a** (5.73 g, 11.9 mmol), acetic acid (80 mL), and 5% palladium on carbon (1.2 g) was hydrogenated at 1 atm for 3 h. The mixture was filtered and concentrated, and residual acetic acid was evaporated under vacuum (0.2 mmHg). To the resulting paste was added saturated $NaHCO_3$ solution, and after extraction with dichloromethane, the combined organic extracts were dried and concentrated. The resulting paste was crystallized from ethyl acetate–methanol to give **9c** (3.2 g, 77.5%, mp 140–141 °C). IR ($CHCl_3$) 2.86, 3.03, 5.63, 5.85, and 6.29 μm; ^1H NMR ($CDCl_3$) δ 6.95 (4 H, s), 4.4–3.95 (4 H, m), 3.85 (3 H, s), 3.7–3.0 (3 H, m), 2.9–2.5 (3 H, m), 2.5–1.7 (4 H, m); electron impact mass spectrum, *m/e* (relative intensity) 347 (64) M^+, 224 (100), 210 (57), 124 (94).

Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09. Found: C, 62.48; H, 6.20.

Enone 12c and Aldol 11c. A mixture of **9c** (2.70 g, 7.8 mmol), *p*-toluenesulfonic acid (0.11 g, 0.58 mmol), and pyrrolidine (1.66 g, 23.4 mmol) in benzene (40 mL) was heated at reflux temperature with a Dean-Stark apparatus containing 4 Å molecular sieves for 5.5 h. A solution of acetic acid–water–sodium acetate (2:2:1, 5 mL) was added, and the mixture was heated at reflux temperature for 20 min. The mixture was concentrated, diluted with saturated $NaHCO_3$ solution, and extracted with chloroform. The combined chloroform extracts were dried and concentrated to give a foam (3.0 g), which was chromatographed (SiO_2, ethyl acetate–ethanol, 20:1) to give 2.07 g of a solid. Recrystallization from ethyl acetate gave **12c** (1.83 g, 71%, mp 180–183 °C). IR ($CHCl_3$) 5.65 and 5.90 μm; ^1H NMR ($CDCl_3$) δ 6.85 (4 H, m), 4.50 (1 H, dd, J = 10 Hz, 3.5 Hz), 4.10 (1 H, d, J = 10 Hz), 3.9 (3 H, s), 3.4 (1 H, d, J = 3.5 Hz), 3.2–1.80 (9 H, m); electron impact mass spectrum, *m/e* (relative intensity) 329 (100) M^+, 206 (54).

Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81. Found: C, 65.43; H, 5.94.

Further elution with ethyl acetate–ethanol (10:1) gave aldol **11c** (0.11 g, 4%, analytical sample from methanol, mp 190–191 °C). IR ($CHCl_3$) 2.92, 5.68, 5.76, and 6.27 μm; ^1H NMR ($CDCl_3$) δ 7.4–6.8 (4 H, m), 4.92 (1 H, s), 4.8–4.0 (3 H, m), 3.88 (3 H, s), 3.7–2.6 (5 H, m), 2.6–1.8 (4 H, m), and 1.6–1.0 (1 H, m); electron impact mass spectrum, *m/e* (relative intensity) 347 (88), 192 (100).

Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09. Found: C, 62.06; H, 6.24.

Enone 12d. A mixture of **12c** (1.74 g, 5.3 mmol), dichloromethane (75 mL), saturated $NaHCO_3$ solution (150 mL), and acetyl chloride (8.35 g, 0.106 mol) was stirred at 0 °C for 15 min and then at room temperature for 0.5 h. The two-phase reaction mixture was separated, and the aqueous phase was extracted with dichloromethane. The combined organic extracts were dried, evaporated, and crystallized to give **12d** (1.90 g, 97%, mp 180–181 °C). IR ($CHCl_3$) 5.67, 5.90 and 6.08 μm; ^1H NMR ($CDCl_3$) δ 6.95–6.5 (4 H, m), 4.95–4.1 (3 H, m), 3.92 (3 H, s), 3.8–3.0 (2 H, m), 3.0–2.3 (6 H, m), 2.15 (3 H, s); electron impact mass spectrum, *m/e* 371 (M^+, 100%).

Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70. Found: C, 64.53; H, 5.68.

Enone 12f. To a solution of **12d** (6.50 g, 17.5 mmol) in dichloromethane (200 mL) was added boron tribromide (22.5 g, 90 mmol) in dichloromethane (50 mL) at −78 °C. The mixture was stirred at −78 °C for 5 min, warmed to room temperature over 10 min, and poured cautiously into a well-stirred saturated $NaHCO_3$ solution (300 mL). The resulting solution was made slightly acidic with 1 N HCl and extracted with dichloromethane. The combined organic extracts were dried and concentrated to give **12e** as a foam (6.0 g). The foam was dissolved in acetic anhydride (75 mL) and pyridine (25 mL) and stirred at room temperature for 4.5 h. The mixture was concentrated and the residue was diluted with water and extracted with dichloromethane. The extract was dried and concentrated to a foam (6.5 g). Chromatography on a Waters Prep 500 (SiO_2, ethyl acetate) gave **12f** (4.79 g, 68%). An analytical sample was prepared by crystallization from ethyl acetate (mp 147–150 °C). IR ($CHCl_3$) 5.68, 5.71, 5.92, 6.08, and 6.27 μm; ^1H NMR ($CDCl_3$) δ 7.2–6.7 (4 H, m), 5.0–4.2 (3 H, m), 4.1–3.0 (2 H, m), 3.0–2.1 (6 H, m), 2.32 (3 H, s), and 2.12 (3 H, s); electron impact mass spectrum *m/e* 399 (M^+), 357 (100%).

Anal. Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30. Found: C, 63.07; H, 5.30.

Irradiation of Enone 12f. A benzene–methanol–acetic acid (1:1:1, 67 mL) solution of **12f** (798 mg, 2 mmol) in a 25-mm Pyrex test tube containing a magnetic stirring bar was degassed with argon for 0.5 h. After irradiation for 4 h, the solution was concentrated, diluted with dichloromethane, and washed with aqueous sodium bicarbonate. The dichloromethane solution was dried and concentrated to give a paste, which crystallized from methanol to give **13** (0.714 g, 89%, mp 229–231 °C). IR ($CHCl_3$) 5.65, 5.78, and 6.06 μm; ^1H NMR ($CDCl_3$) δ 7.2–6.9 (3 H, m), 5.68 (1 H, t), 4.48 (1 H, s), 4.75–3.9 (2 H, m), 3.9–3.4 (2 H, m), 2.9–2.1 (5 H, m), 2.30 (3 H, s), 2.02 (3 H, s), and 2.0–1.7 (1 H, m); electron impact mass spectrum, *m/e* 399 (M^+), 357, 315, metastable peak at 277.9 (357→315).

Anal. Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30. Found: C, 62.99; H, 5.40.

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Registry No. **5a**, 98689-06-6; **6a**, 98689-07-7; **8a**, 18167-91-4; **8b**, 98689-08-8; **8c**, 93758-01-1; **9a**, 98689-09-9; **9c**, 98689-10-2; **11c**, 98689-12-4; **12c**, 98689-11-3; **12d**, 98689-13-5; **12e**, 98689-15-7; **12f**, 98689-14-6; methyl 1,4,5,6-tetrahydro-1-[(benzyloxy)carbonyl]-2-methyl-4-oxo-3-pyridinecarboxylate, 98689-03-3; methyl 1,4,5,6-tetrahydro-2-methyl-4-oxo-3-pyridinecarboxylate, 68185-61-5; methyl 1,4,5,6-tetrahydro-1-[(benzyloxy)carbonyl]-2-(bromomethyl)-4-oxo-3-pyridinecarboxylate, 98689-04-4; methyl 1,4,5,6-tetrahydro-2-(acetoxymethyl)-1-[(benzyloxy)carbonyl]-4-oxo-3-pyridinecarboxylate, 98689-05-5; vinyl bromide, 593-60-2.

Enantioselective Synthesis of Seven Pyrrolizidine Diols from a Single Precursor

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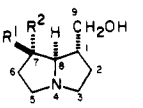
The enantioselective synthesis of seven pyrrolizidine diols has been accomplished from a single, readily available intermediate. The key step of this general scheme involves an acetoxy-directed acyliminium ion–ketene dithioacetal cationic cyclization to give the optically active 1-azabicyclo[3.3.0]octane **14**, from which the pyrrolizidines **1–7** were prepared. The pyrrolizidine diols in the 7*S* series were obtained by adjusting the oxidation level and stereochemistry in the B ring of the key intermediate. Inversion of the C-7 alcohol group, followed by adjustment of oxidation level and stereochemistry in the B ring, afforded the corresponding pyrrolizidines in the 7*R* series.

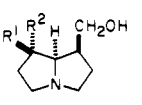
Introduction

The challenging structures and diverse biological activity of pyrrolizidine alkaloids[1] have stimulated a great deal of interest in their synthesis. The ideal general synthetic route to the pyrrolizidines would be stereo- and enantioselective, operationally simple, efficient, and flexible enough to allow different groups and oxidation levels to be introduced at C-1, C-2, C-7, and C-8. Since the first synthesis of (+)-retronecine (**6**) by Geissman and Waiss in 1962,[2a] many new routes to racemic pyrrolizidines have been published,[2] but enantioselective syntheses have been a relatively recent development.[3] Prompted by that fact and by "an obvious deficiency ... of good synthetic routes to 1,2-dehydropyrrolizidines ...",[4] we set out to develop a practical synthesis of either enantiomer of any common pyrrolizidine diol (**1–8**) as part of a larger project directed at macrocyclic bislactones such as monocrotaline (**9**).



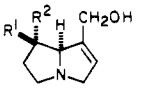
R^1 = H, R^2 = OH (+)-Hastanecine, **1**

R^1 = OH, R^2 = H (−)-Turneforcidine, **2**



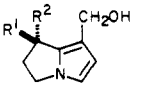
(−)-Dihydroxheliotridane, **3**

(−)-Platynecine, **4**



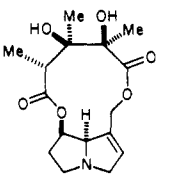
R^1 = H, R^2 = OH (+)-Heliotridine, **5**

R^1 = OH, R^2 = H (+)-Retronecine, **6**



(+)-Dehydroheliotridine, **7**

(−)-Dehydroretronecine, **8**



Monocrotaline, **9**

Preliminary Cyclization Studies

The general plan was to use an optically active alcohol group in an A-ring precursor as a control element to establish the correct absolute stereochemistry at the ring juncture via an acyliminium ion cyclization.[5] Toward that end, we have reported a new cationic cyclization terminator, the ketene dithioacetal group, that efficiently mediates the required five-membered ring formation in this cyclization.

After these model studies verified that the pyrrolizidine skeleton could be constructured in this manner, the synthesis of the more highly oxygenated derivatives **1–8** was undertaken. Of several optically active potential pyrrolizidine diol precursors, the first tested was **13**. This intermediate drew our attention because of its potentially easy accessibility and because the diol protecting group completely blocks one face of the imide ring. Concern about removal of the superfluous oxygen group at C-6 (pyrrolizidine numbering) was deferred until cyclization stereoselectivity was established. Thus, 2,3-*O*-cyclo-

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