Supplementary Material Available: Descriptions of the general procedures of the asymmetric hydrogenation and determination of the enantiomeric excesses of the products (2 pages). Ordering information is given on any current masthead page.

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Spiro Asymmetric Induction. 3. Synthesis of Optically Pure Syn or Anti α,β-Dihydroxy Esters by the Aldol Condensation of Chiral Glycolate Enolates†[1]

Summary: The diastereoselectivity of the aldol condensation of the chiral glycolate enolates **1** and **2** is metal-tunable, providing either syn or anti adducts **3–6**. Ethanolysis of these adducts then provides any stereoisomer of the α,β-dihydroxy esters **7–10** in optically pure form.

Sir: Polyhydroxylated carbon compounds are often important biological substances, exemplified by the carbohydrates. As rare or unnatural target molecules of this type become more important,[2] synthetic methods for their assembly become more desirable. As part of a program aimed at the de novo total synthesis of carbohydrates[3] as well as other highly oxygenated natural products, we report a stereoselective route to optically pure α,β-dihydroxy esters based on the aldol condensation of chiral glycolate enolates of **1** and **2**.[4-6] A retrosynthetic analysis of the carbohydrate problem then reduces to iterative aldol condensations, as outlined in Scheme I.[7] In this paper, we report that any one of the four possible stereoisomers of an α,β-hydroxy ester may be prepared in a rational manner.

We have recently reported a route to *S* or *R* α-hydroxy esters based on the highly diastereoselective alkylation of chiral glycolate enolates **1** and **2**, providing 100% optically pure materials after hydrolysis of the dioxolanones and recycling of the chiral auxilliary.[1a] Aldol condensations of these same enolates have been found to be extremely facially selective. The enolate of **1** reacts with various aldehydes to give products **3** and **4**, which result from attack on the *si* face of the enolate, producing the 2*S* stereochemistry (Table I).[8] No 2*R* products resulting from attack on the *re* face were detected. In a similar fashion, enolate **2** affords complete diastereofacial selectivity, providing the 2*R* stereochemistry in adducts **5** and **6** as a result of *re* face attack on the enolate. Again, no contamination with adducts resulting from *si* face attack were detected. Hence, the chiral enolates of **1** and **2** provide a highly enantioselective entry into either the 2*R* or 2*S* manifolds.

Examination of Table I shows that aldol diastereoselectivity may often be controlled to a large extent by selection of an appropriate enolate counterion. In general, lithium and magnesium counterions provide the anti aldol adducts **3** or **5**. This selectivity is consistent with previous work on the aldol condensations of cyclic *E* enolates.[9] In

† Dedicated to Professor Ernest L. Eliel on the occasion of his 65th birthday.

(1) For earlier papers, see: (a) Pearson, W. H.; Cheng, M.-C. *J. Org. Chem.* **1986**, *51*, 3746–3748. (b) Pearson, W. H.; Cheng, M.-C. *Ibid.* **1987**, *52*, 1353.

(2) Sharon, N. *Complex Carbohydrates: Their Chemistry, Biosynthesis and Function*; Addison-Wesley: Reading, MA, 1975. Candy, D. *Biological Function of Carbohydrates*; Wiley: New York, 1980. Kennedy, J. F.; White, C. A. *Bioactive Carbohydrates*; Ellis Horwood, Ltd.: Chichester, West Sussex, 1983.

(3) Jones, J. K. N.; Szarek, W. A. In *The Total Synthesis of Natural Products*; ApSimon, J.; Ed.; Wiley-Interscience: New York, 1973; Vol. 1, Chapter 1. Zamojski, A.; Grynkiewicz, G. In *The Total Synthesis of Natural Products*; ApSimon, J.; Ed.; Wiley-Interscience: New York, 1984; Vol. 6, Chapter 4, pp 141–235. McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. J. *Carbohydr. Chem.* **1984**, *3*, 671.

(4) (a) For the only other aldol condensations of a chiral glycolate enolate, see: d'Angelo, J.; Pages, O.; Maddaluno, J.; Dumas, F.; Revial, G. *Tetrahedron Lett.* **1983**, *25*, 5869. (b) For aldol condensations of an achiral glycolate enolate in the presence of a chiral additive, see: Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753. For aldol condensations of achiral glycolate enolates, see: (c) Touzin, A. M. *Tetrahedron Lett.* **1975**, 1477. (d) Takai, K.; Heathcock, C. H. *J. Org. Chem.* **1985** *50*, 3247. (e) Gray, B. D.; White, J. D. *J. Chem. Soc., Chem. Commun.* **1985**, 20. (f) Koreeda, M.; Luengo, J. I. *J. Org. Chem.* **1984**, 49, 2079 and references therein.

(5) For aldol condensations of higher α-hydroxy acid derivatives (i.e., lactic, mandelic, etc.), see: (a) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095–2105, and earlier work cited therein. (b) Heathcock, C. H.; Pirrung, M. C.; Young, S. D.; Hagen, J. P.; Jarvi, E. T.; Badertscher, U.; Marki, H.-P.; Montgomery, S. H. *J. Am. Chem. Soc.* **1984**, *106*, 8161–8174, and earlier work cited therein. (c) Heathcock, C. H.; Montgomery, S. H. *Tetrahedron Lett.* **1985**, *26*, 1001–1004. (d) Schultz, A. G.; Yee, Y. K. *J. Org. Chem.* **1976**, *41*, 4044–4045. (e) Seebach, D.; Coquoz, M. *Chimia* **1985**, *39*, 20–22. (f) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313–1324, and references to earlier work by Seebach and others cited therein.

(6) Conceptually related approaches to carbohydrates or related polyoxygenated compounds have been published, which rely on formation of the carbon–carbon bond of a vicinal diol by nucleophilic addition of an α-oxyanion or equivalent (other than an α-alkoxy enolate) to an aldehyde. For leading references, see: (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, 108, 7060–7067. (b) Roush, W. R.; Michaelides, M. R. *Tetrahedron Lett.* **1986**, *27*, 3353–3356. (c) Roush, W. R.; Harris, D. J.; Lesur, B. M. *Ibid.* **1983**, *24*, 2227–2230. (d) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1983**, *48*, 3489. (e) McGarvey, G. J.; Kimura, M. *Ibid.* **1982**, *47*, 5420–5422. (f) Hoffmann, R. W.; Metternich, R. *Liebigs Ann. Chem.* **1985**, 2246–2460. (g) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139–142. (h) Koreeda, M.; Tanaka, Y. *Ibid.* **1987**, *28*, 143–146.

(7) Heathcock[5c] has examined such an approach to racemic carbohydrates based on the aldol condensation of lactate enolates. For a related approach, see: (a) David, S.; Lepine, M.-C.; Aranda, G.; Vass, G. *J. Chem. Soc., Chem. Commun.* **1976**, 747. (b) David, S.; Lepine, M.-C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1262.

(8) All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, and elemental analysis or high resolution MS. **General procedure for the aldol condensation**: LDA (1.2–1.5 equiv, generated from *n*-BuLi/hexane and diisopropylamine) in dry THF (0.5 mL/mmol) was cooled to −78 °C. A solution of the desired dioxolanone **1** or **2** (1 equiv) in THF (0.3 mL/mmol) was added dropwise. After stirring for 10–20 min, 1 equiv of another metal source ($MgBr_2$ or Cp_2ZrCl_2) was added if desired. After stirring 30 min, the aldehyde (1.5–2.0 equiv) was added. Reaction was usually complete within 30–60 min (TLC analysis). Aqueous workup (ether/saturated sodium bicarbonate) followed by drying ($MgSO_4$), evaporation, and flash chromatography gave the pure isomeric aldol adducts. In all cases, only two isomers were obtained. These could be separated by radial chromatography (1 mm thick silica gel) with 5–10% ethyl acetate hexane or by semipreparative HPLC (Rainin Dynamax silica gel column) with 15% ethyl acetate/hexane. **General procedure for dioxolanone ethanolysis**: Anhydrous hydrochloric acid was bubbled through a solution of dioxolanone **3–6** in absolute ethanol (4 mL/mmol) at a moderate rate for ca. 2 min at room temperature. The solution was then refluxed for 2 h, cooled, poured into saturated sodium bicarbonate, and extracted twice with ethyl acetate. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography over silica gel with ca. 40% ethyl acetate/hexane provided the pure α,β-dihydroxy esters **7–10**.

(9) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 111–211. (c) Mukaiyama, T *Org. React. (N.Y.)* **1982**, *28*, 203.

0022-3263/87/1952-3176$01.50/0

Scheme I

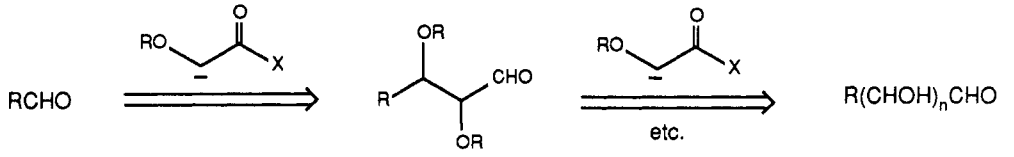
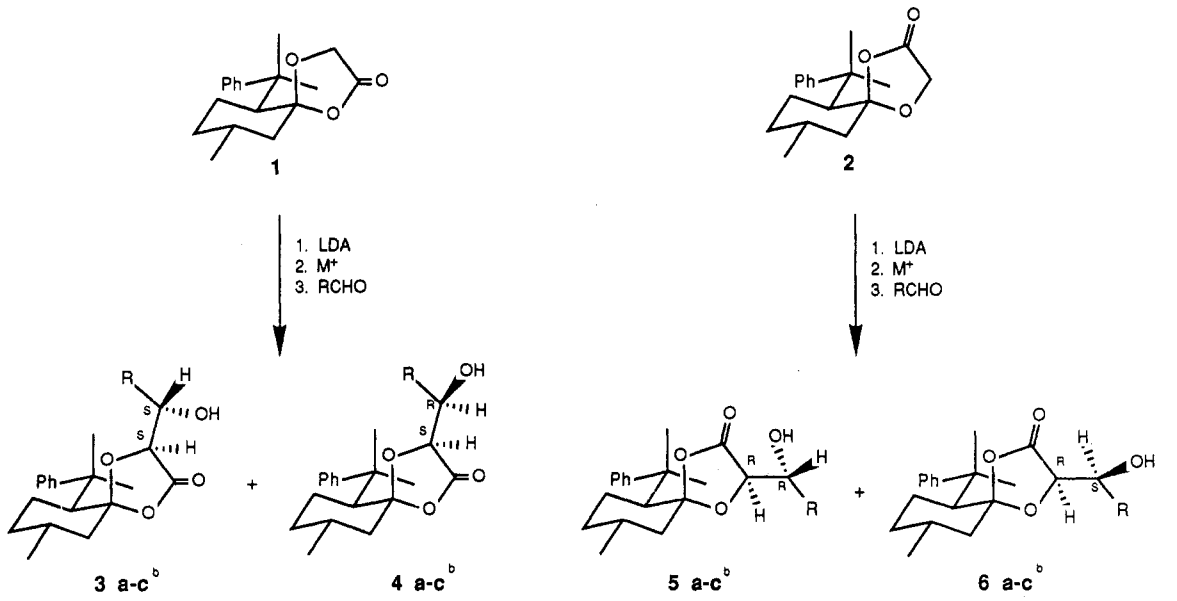


Table I. Aldol Condensations of Chiral Glycolate Enolates of 1 and 2[a]



dioxolanone	M^{+c}	RCHO	yield (%)[d]	ratio 3:4	ratio 5:6
1	Li^+	PhCHO	92	2.1:1.0	
1	Mg^{2+}	PhCHO	92	4.8:1.0	
1	Zr^{4+}	PhCHO	95	1.0:4.3	
1	Li^+	*n*-PrCHO	93	25.3:1.0	
1	Mg^{2+}	*n*-PrCHO	86	9.3:1.0	
1	Zr^{4+}	*n*-PrCHO	97	1.0:1.2	
1	Li^+	*i*-PrCHO	85	9.4:1.0	
1	Mg^{2+}	*i*-PrCHO	86	2.7:1.0	
1	Zr^{4+}	*i*-PrCHO	91	1.0:3.1	
2	Li^+	PhCHO	99		2.1:1.0
2	Mg^{2+}	PhCHO	89		3.0:1.0
2	Zr^{4+}	PhCHO	91		1.0:4.7
2	Li^+	*n*-PrCHO	96		7.0:1.0
2	Mg^{2+}	*n*-PrCHO	92		2.8:1.0
2	Zr^{4+}	*n*-PrCHO	91		1.0:1.7
2	Li^+	*i*-PrCHO	86		26.2:1.0
2	Mg^{2+}	*i*-PrCHO	89		8.0:1.0
2	Zr^{4+}	*i*-PrCHO	89		1.0:5.0

[a] All reactions were carried out in THF (ca. 0.1 M) at −78 °C. [b] **a**, R = Ph; **b**, R = n-C_3H_7; **c**, R = i-C_3H_7. [c] For $M^+ = Li^+$, no extra metal added. For $M^+ = Mg^{2+}$, $MgBr_2$ (1 equiv) was added. For $M^+ = Zr^{4+}$, Cp_2ZrCl_2 (1 equiv) was added. [d] Isolated, purified yields.

order to provide access to the syn series (i.e. **4** or **6**), we have found that zirconium enolates are useful, in accord with the work of Evans[10] and Yamamoto.[11] Attempts to increase the aldol diastereoselectivity using other metals and solvents have not been fruitful.[12]

Ethanolysis of the purified adducts **3–6** proceeded efficiently with refluxing ethanolic HCl to provide the optically pure[13] dihydroxy esters **7–10** without epimerization (Table II). The chiral auxilliary was recovered in 92–99% yield.

Conversion of the dihydroxy esters **7a–c** and **8a–c** to their acetonides **11** and **12** (2,2-dimethoxypropane, acetone,

(10) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975–3978. For a discussion of the transition state, see ref 9a.

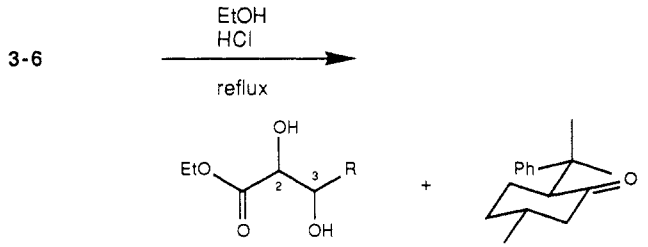
(11) Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1980**, *21*, 4607–4610.

(12) For example, ratios of **3a**:**4a** were as follows: LDA/pentane (1.9:1); LDA/(i-PrO)$_3$TiCl/THF (1.6:1); LDA/Et_2AlCl/THF (1.0:1); NaN(SiMe$_3$)$_2$/DME (2.5:1).

(13) Although optical purity was not directly determined on **7–10**, it may safely be assumed on the basis of the following facts: Dioxolanones **3–6** were all diastereomerically pure by chromatographic and spectroscopic means (^1H and ^{13}C NMR, capillary GC, HPLC). Their enantiomeric purity was judged by spectral and chromatographic analyses of Mosher's ester[14] derivatives, which are consistent with the known optical purity of pulegone (used in the preparation of 8-phenylmenthone). Most significantly, hydrolysis of **3–6** proceeded with no epimerization of the α,β-dihydroxy esters. Finally, our previous experience[1a] with these hydrolysis conditions has demonstrated the lack of racemization of the hydroxy esters.

(14) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Table II. Ethanolysis of Dioxolanones 3-6

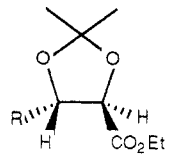


7-10

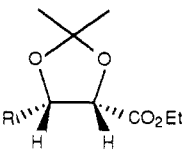
dioxolanone	R	yield (%)[a]	product[b]	stereochemistry
3a	Ph	93	**7a**	2*S*,3*S*
3b	*n*-Pr	92	**7b**	2*S*,3*S*
3c	*i*-Pr	87	**7c**	2*S*,3*S*
4a	Ph	93	**8a**	2*S*,3*R*
4b	*n*-Pr	92	**8b**	2*S*,3*R*
4c	*i*-Pr	81	**8c**	2*S*,3*R*
5a	Ph	95	**9a**	2*R*,3*R*
5b	*n*-Pr	88	**9b**	2*R*,3*R*
5c	*i*-Pr	88	**9c**	2*R*,3*R*
6a	Ph	95	**10a**	2*R*,3*S*
6b	*n*-Pr	84	**10b**	2*R*,3*S*
6c	*i*-Pr	81	**10c**	2*R*,3*S*

[a] Isolated, purified yield. [b] Apparently, none of these dihydroxy esters are known to optically pure form. See ref 16-18 for racemates or related acids.

p-TsOH, room temperature), proved useful for verification of their relative stereochemistry.[15] Cis acetonides **12** derived from the anti dihydroxy esters **7** showed a positive NOE enhancement between the ring protons, whereas the trans dioxolanes **11** showed no enhancement.



11



12

In summary, *any of the four possible stereoisomers of simple α,β-dihydroxy esters may be prepared in optically pure form* by selection of an appropriate chiral glycolate enolate and metal counterion. This ability to stereorationally assemble polyoxygenated carbon chains should be of considerable utility. Our investigations into this realm will be reported in due course, as will our studies on the incorporation of other heteroatoms.

Acknowledgment. We thank the Dreyfus Foundation (Award for Newly Appointed Faculty in Chemistry, 1984-9) and the National Institutes of Health for the generous support of this research.

(15) Touzin[4c] has prepared acetonides **11** and **12** where R = Ph for the purpose of determining relative stereochemistry. The cis or trans stereochemistry was related to the chemical shift of the OCH_2CH_3 protons on the ester. Since no basis for this assignment was given, we felt NOE studies were in order. Indeed, Touzin's assignments are correct: in all cases, the NMR correlation was consistent with the NOE data.

(16) For racemic *syn*- and *anti*-ethyl 2,3-dihydroxy-3-phenylpropanoate, see ref 4c. For all four stereoisomers of 2,3-dihydroxy-3-phenylpropanoic acid in optically pure form, see: Collet, A. *Bull. Soc. Chem. Fr.* **1975**, 215-219.

(17) For racemic *syn*- and *anti*-ethyl 2,3-dihydroxyhexanoic acid, see: (a) Mori, N.; Omura, S.; Tsuzuki, Y. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 2199-2201. (b) English, J., Jr.; Heywood, D. L. *J. Am. Chem. Soc.* **1955**, *77*, 4661-4664.

(18) For racemic *anti*-2,3-dihydroxy-4-methylpentanoic acid, see: Dalby, S.; Kenner, G. W.; Sheppard, R. C. *J. Chem. Soc.* **1960**, 968-973.

Registry No. **1**, 104196-76-1; **2**, 104264-82-6; **3a**, 108666-21-3; **3b**, 108666-22-4; **3c**, 108666-23-5; **4a**, 108739-49-7; **4b**, 108739-50-0; **4c**, 108739-51-1; **5a**, 108739-52-2; **5b**, 108739-53-3; **5c**, 108739-54-4; **6a**, 108739-55-5; **6b**, 108739-56-6; **6c**, 108739-57-7; **7a**, 108741-11-3; **7b**, 108666-24-6; **7c**, 108666-25-7; **8a**, 108741-12-4; **8b**, 108666-26-8; **8c**, 108693-47-6; **9a**, 108741-13-5; **9b**, 108666-27-9; **9c**, 108666-28-0; **10a**, 108741-14-6; **10b**, 108666-29-1; **10c**, 108666-30-4; PhCHO, 100-52-7; *n*-PrCHO, 123-72-8; *i*-PrCHO, 78-84-2.

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Photochemistry of the Amide System: Furancarboxanilide†

Summary: An investigation of the synthetically useful phototransformation of furan-2-carboxanilide derivatives (**1a**, R = H, and **1b**, R = CH_3) in protic and aprotic solvents is reported. *Unusually large vicinal coupling constants (18-19 Hz) in trans compounds* ***2a*** *and* ***2b*** are shown by an X-ray analysis on **2b** to be mainly due to the presence of unusually short C-C single bonds (1.498 (4) Å).

Sir: During the last 5 years furan and its derivatives have received a resurgence of interest in several areas of organic chemistry.[1-5] Application of an enamide photocyclization for the synthesis of novel heteroaromatic systems, as well as our interest in carbonyl transposition such as lactams to β-keto amines,[6] directed our attention to the photocyclization of the little known furan-2-carboxanilide (**1a**) and *N*-methylfuran-2-carboxanilide (**1b**).[7,8] This paper delineates the phototransformation products of these substances.

† This paper is dedicated to Professor Joseph F. Bunnett on the occasion of his 65th birthday.

(1) Furan-terminated cationic cyclizations, see: (a) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1985**, *50*, 3988. (b) Tanis, S. P.; Chaung, Y. H.; Head, D. B. *Tetrahedron Lett.* **1985**, *26*, 6147. (c) Tanis, S. P.; Herrinton, P. M.; Dixon, L. A. *Ibid.* **1985**, *26*, 5347. (d) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572.

(2) Furan in intramolecular Diels-Alder reactions, see: (a) Grootaert, W. M.; De Clercq, P. J. *Tetrahedron Lett.* **1986**, *27*, 2573. (b) Van Royen, L. A.; Mijngheer, R.; De Clercq, P. J. *Bull. Soc Chim. Belg.* **1984**, *93*, 1019 and references cited therein. (c) Sternbach, D. D.; Rossana, D. M. *J. Am. Chem. Soc.* **1982**, *104*, 5833.

(3) Furan carbonyl photoaddition, see: (a) Schreiber, S. L.; Satake, K. *Tetrahedron Lett.* **1986**, *27*, 2575. (b) Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1983**, *105*, 6723. (c) Schreiber, S. L.; Satake, K. *Ibid.* **1984**, *106*, 4186.

(4) (a) Schreiber, S. L.; Hoveyda, A. H.; Wu, H. J. *J. Am. Chem. Soc.* **1983**, *105*, 660. (b) Zamojski, A.; Kozluk, T. *Tetrahedron* **1983**, *39*, 805.

(5) Furans as intermediates for the synthesis of oxygenated natural products, see: Martin, S. F.; Guinn, D. E. *Tetrahedron Lett.* **1984**, *25*, 5607.

(6) (a) One of us (Y.K.) has also previously shown that this enamide photocyclization provides a facile entry into a novel fused aromatic system, see: Kanaoka, Y.; San-nohe, K. *Tetrahedron Lett.* **1980**, *20*, 3893. (b) Furancarboxanilides derived from dihydrodibenzazepine and diphenylamine on irradiation with a 450-W, medium-pressure mercury lamp (Vycor) in a mixture of benzene and methanol (9:1) for 24 h gave photo-Fries rearrangement products. Unpublished results of the Arizona group. (c) The importance of lactams to β-keto amines can be visualized in the conversion of readily accessible δ-lactams to 3-substituted piperidine derivatives, required in our laboratories in connection with another synthetic project.

(7) Kanaoka, Y.; Itoh, K. *Synthesis* **1971**, 36.

(8) For an excellent review on enamide photocyclization, see: Ninomiya, I.; Naito, T. *Heterocycles* **1981**, *15*, 1433.

0022-3263/87/1952-3178$01.50/0