708 *J. Org. Chem.* **1987**, *52*, 708-710

A New Protocol for the Diastereoselective Formation of Lactones from either Achiral or Chiral Vinylogous Urethanes

Summary: The condensations of vinylogous urethanes, with or without a chiral auxiliary, and a variety of acid chlorides are described. Treatment of these acylated products with either L-Selectride or organometallic reagents leads, with high diastereoselectivity, to lactone products.

Sir: We have described several threo-selective aldol-lactonization reactions using lithium enolates of vinylogous urethanes.[1] Some limitations for these reactions have been encountered, including good, but not optimal, threo selectivity with certain aldehydes, poor chemical yields and diastereoselectivity with ketones, and less than exemplary threo and enantiomeric selectivity when chiral auxillaries were employed as part of the enolate. Circumvention of these problems by modifying reaction conditions proved fruitless. Evans[2] and later Yamaguchi[3] have described acylations of amide enolates with acid chlorides. Further, the resulting β-keto amides were observed to undergo diastereoselective reactions, primarily reduction with hydride reagents. In view of these reports, we set out to acylate some vinylogous urethanes at their C-4 positions, under the assumption that addition of nucleophiles to the ketonic residue of such species could be diastereoselective and therefore highly useful.

Reaction of the vinylogous urethane enolate, **1**, with isobutyryl chloride was examined first because the aldol reaction of **1** with isobutyraldehyde was known to form the lactone **2** in a 20:1 ratio of threo:erythro isomers, respectively (90% yield).[4] Deprotonation of the vinylogous urethane **3** with lithium diisopropylamide (LDA/THF/-78 °C/0.5 M) generated the highly twisted enolate system **1**[5] which on reaction with isobutyryl chloride (added 1 M in THF/5 h/-78 °C) gave the C-4 acylated vinylogous urethane **4** in 85% yield, after chromatography.[6] Reduction of the ketonic residue of **4** with L-Selectride (Aldrich) (THF/-20 °C/2 h) afforded lactone **2**. In this instance, however, **2** was formed as its threo isomer only—no trace of the erythro lactone could be detected.[7] We found subsequently that both the acylation and the reduction reactions can be sequentially carried out in the same flask (-78 °C, acylation; -20 °C, reduction) without sacrifice of either yield or purity.

We then turned our attention to an examination of those acid chlorides whose aldehyde analogues had exhibited modest diastereoselectivity in reaction with **1**. The diastereoselectivity and chemical yields of these reaction pairs are compared in Table I, which reveals that the acylation of enolate **1** by acid chlorides followed by in situ L-Selectride reduction affords superior threo selectivity for the lactonic products formed.

Because the above reactions are the chemical equivalent of condensations between **1** and aldehydes, it occurred to us that a modification of this protocol might result in development of a diastereoselective chemical equivalent for ketone condensations—a transformation of significant synthetic potential.[8] To this end, methyllithium (-20 °C/2 h) was reacted with **4** to afford a single lactone product, **5**, in 90% yield. In order to determine the stereoselection of methyllithium addition, we added the reagent to compound **6** (obtained from **1** and benzoyl chloride) and again obtained a single lactone product, **7**. Degradation of **7** with periodic acid (22 °C/THF/H_2O) followed by treatment of the crude reaction product with diazomethane gave the methyl ester **8**. This material, along with its corresponding C-3 epimer **9**, has been described, and the spectrum of **8**, obtained by degradation of **7**, was found to be identical with that reported.[9]

Table I

RCHO or RCOCl, R =	aldol		acylation–reduction	
	threo:erythro	yield, %	threo:erythro	yield, %
CH_3	9.5:1	71	99:1[a]	82
$CH_3(CH_2)_2$	10:1	74	99:1[a]	82
$CH_3(CH_2)_3$	11:1	80	99:1[a]	86
$(CH_3)_3$	7.5:1	81	99:1[a]	68
C_6H_5	7:1	84	99:1[a]	90

[a] In the examples indicated the erythro isomer is not detected, however, its value is given as 1% since the limit of its detection is 1% by NMR.

The limits of stereoselection for alkyllithium addition reactions to C-4 acylated vinylogous urethanes were next examined. Methyllithium was added (-20 °C/22 h) to compound **10** (**1** and propionyl chloride) to afford a single lactone, **11** in 92% yield. Conversely, addition of either ethyllithium or ethylmagnesium bromide to **12** (**1** and acetyl chloride) gave a 7:1 mixture of the lactones **13** and **11**, respectively. When the steric bulk of the nucleophile was increased (e.g., *n*-butyllithium instead of ethyllithium), the reaction of **12** again became highly diastereoselective in that lactone **14** was obtained with only a small amount (ca. 5%) of its C-5 epimer detectable in the crude reaction mixture. Other combinations of C-4 acylated vinylogous urethanes and organolithium or -magnesium reagents have been examined, and almost without exception these reactions proceeded in excellent chemical yields and with high diastereoselectivity.[10]

One of the most frustrating aspects of the chemistry of enolates like **1** was our inability to develop a chiral auxiliary for these anions that afforded threo aldol products. Monosubstituted pyrrolidine-derived analogues of **1** led to mixtures of both threo and erythro aldol products and gave poor enantiomeric excess (ee) values. On the other hand, chiral 2,5-dimethylpyrrolidine-derived analogues of **1** gave outstanding ee values for thier aldol reactions, but all of these condensation products possessed only erythro stereochemistry.[11] These observations provoked us to attempt reaction of the dimethylpyrrolidine-substituted enolate **15** with isobutyryl chloride. We were disappointed to find, in marked contrast to the enolate **1**, that **15** condensed with the acid chloride at both its C-2 and C-4

---

(1) Schlessinger, R. H.; Poss, M. A.; Richardson, S. *J. Am. Chem. Soc.* **1986**, *108*, 3112 and references cited therein.

(2) Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154.

(3) (a) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 6015. (b) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 4643. (c) Nakata, T.; Nagao, S.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6465.

(4) Schlessinger, R. H.; Poss, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 357.

(5) Adams, A. D.; Schlessinger, R. H.; Tata, J. R.; Venit, J. J. *J. Org. Chem.* **1986**, *51*, 3068.

(6) Satisfactory spectral and physical data were obtained for all new compounds.

(7) Analyses of threo/erythro ratios were done by ^1H NMR (300 MHz).

(8) The corresponding condensations between enolate 1 and a variety of ketones have been examined. These reactions occur in yields of 30% to 50% with diastereoselectivity ratios of 2:1 to 6:1.

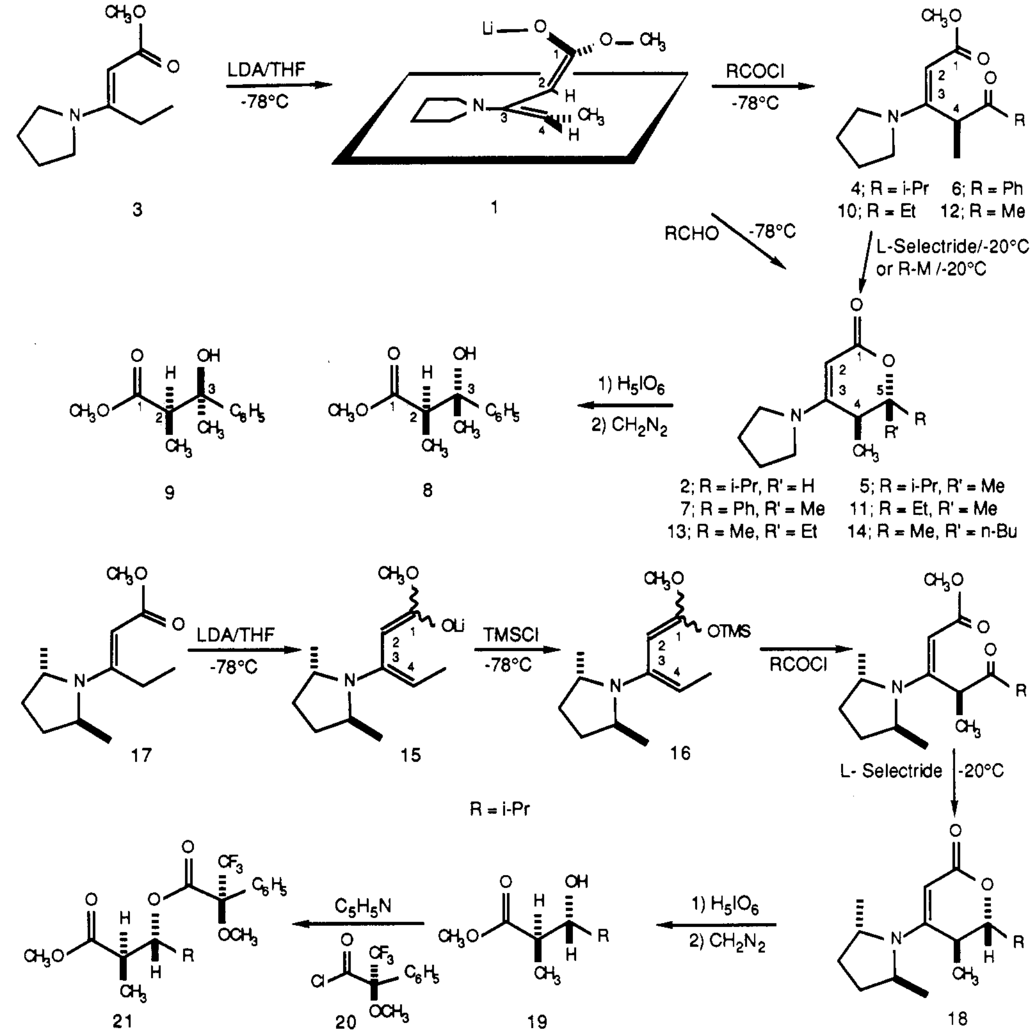
(9) Wooten, J. B.; Houminer, Y. *J. Org. Chem.* **1982**, *47*, 5102. The addition of methyllithium to a β-keto amide, which establishes a precedence for this reaction, has been described in ref 2.

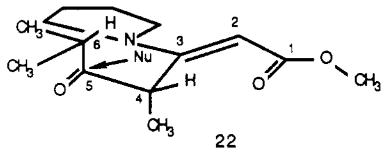
(10) The exception was vinylmagnesium bromide, which gave very poor (2:1) ratios in most cases.

(11) Schlessinger, R. H.; Iwanowicz, E. J.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 3070.

0022-3263/87/1952-0708$01.50/0

Scheme I





22

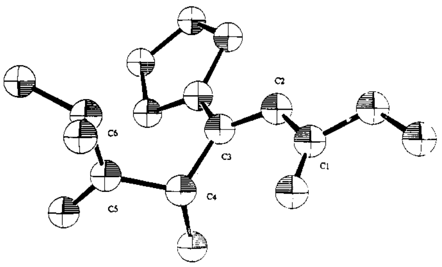


Figure 1

positions.[12] This difficulty was eschewed by conversion of **15** into its trimethylsilyl-derived ketene acetal analogue **16** which condensed with acid chlorides only at its C-4 position.[13] Typically, the vinylogous urethane **17** was deprotonated with LDA (1 M/THF/−78 °C) and then reacted with trimethylsilyl chloride (1.1 equiv −78 °C). To the intermediate ketene acetal enamine, **16**, was added isobutyryl chloride (1.1 equiv) followed by stirring (−20 °C/4 h). Lastly, the reaction was treated with L-Selectride (−20 °C/2 h) to afford the threo lactone **18** in 89% yield.[14]

The enantiomeric purity of **18** was evaluated by periodic acid degradation of it (22 °C/THF/H_2O) and the crude reaction product, without purification, was treated with diazomethane to afford the ester **19**.[15] The secondary hydroxyl group of **19** was then esterified with the acid chloride **20** to give compound **21**.[16] Careful ^1H NMR examination (400 MHz) of **21** indicated an ee value for it of 94%. Butyryl chloride and benzoyl chloride also have been reacted with **16** and the acylation products reduced in situ with L-Selectride. The ee values for these reactions were 94% and 97%, respectively. This one-flask procedure provides us with a much needed optical induction method in the threo manifold.

The diastereoselectivity observed for the reaction of L-Selectride and nucleophiles with the C-4 acylated vi-

---

[12] The geometry of enolate **15** has not been as rigorously examined as that of **1**, and hence, the structure assigned to **15** should be viewed as tentative.

[13] The trimethylsilyl-derived ketene acetal enamine analogues of both **1** and **15** have been examined in this group from both spectroscopic and synthetic viewpoints. For an example of their utility in spectroscopic studies, see ref 5.

[14] The erythro analogue of **18** was prepared, for purposes of comparison with the threo form, by condensation of **15** with isobutyraldehyde. For a protocol describing similar reactions, see ref 11.

[15] Meyers, A. L.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309. The ester **19** reported in this paper is the 2*S*,3*S* isomer.

[16] Mosher, H. S.; Dale, J. A.; Dull, D. L. *J. Org. Chem.* **1969**, *34*, 2543.

nylogous urethanes deserves some comment. Single-crystal X-ray analysis of 4, mp 87–89 °C, confirmed the minimum energy conformation suggested by molecular models for this material to be that depicted by structure 22 (Scheme I, Figure 1). Assuming some correlation between the conformation of 4 in solution and in the condensed phase, it becomes clear that nucleophilic attack can reasonably occur only via the vector indicated in 22. This vector requirement seems insensitive to the steric bulk carried at C-6, since changing from methyl to *tert*-butyl does not influence diastereoselectivity. The same effect holds for those acylated products derived from the vinylogous urethane 17, where in these cases the absolute configuration of the lactone products is determined in the acylation step. Applications of these convenient and effective threo-selective processess to problems of total synthesis are currently being examined.

Acknowledgment. We gratefully acknowledge financial support from the NIH and the Merck Corp. We also acknowledge Dr. Alan D. Adams and Mr. Edwin J. Iwanowicz for valuable help and discussion during the course of this work.

Supplementary Material Available: X-ray crystallographic data for 4 and experimental data for 2, 5, 18, and 4 (10 pages). Ordering information is given on any current masthead page.

---

[17] Sherman Clarke Fellow.

Richard Schlessinger,* James R. Tata[17]
Department of Chemistry
University of Rochester
Rochester, New York 14627

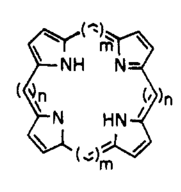
James P. Springer*
Merck, Sharp, and Dohme Research Laboratories
Rahway, New Jersey 07065

Received October 22, 1986

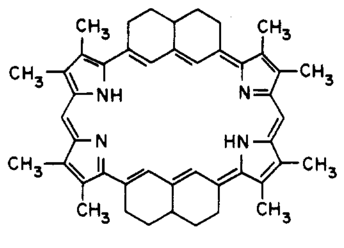
Synthesis of a [1,5,1,5]Platyrin, a 26 π-Electron Tetrapyrrolic Annulene

Summary: The synthesis of the strongly diatropic, highly reactive tetraazaannulene 2 is reported.

Sir: Expansion of the azaannulene, porphyrin, by inserting odd numbers of carbon alternatively between the pyrrolic rings, 1, gives rise to a family of coplanar porphyrin vinylogues, to which we have given the name "platyrins".[1] Like the porphyrins, the platyrins are conjugated azaannulenes containing $(4n + 2)$ π-electrons. The synthesis of the first member of this new series, a [1,3,1,3]platyrin, has been reported by us.[2] We now report the synthesis of the next member, the [1,5,1,5]platyrin, 2.

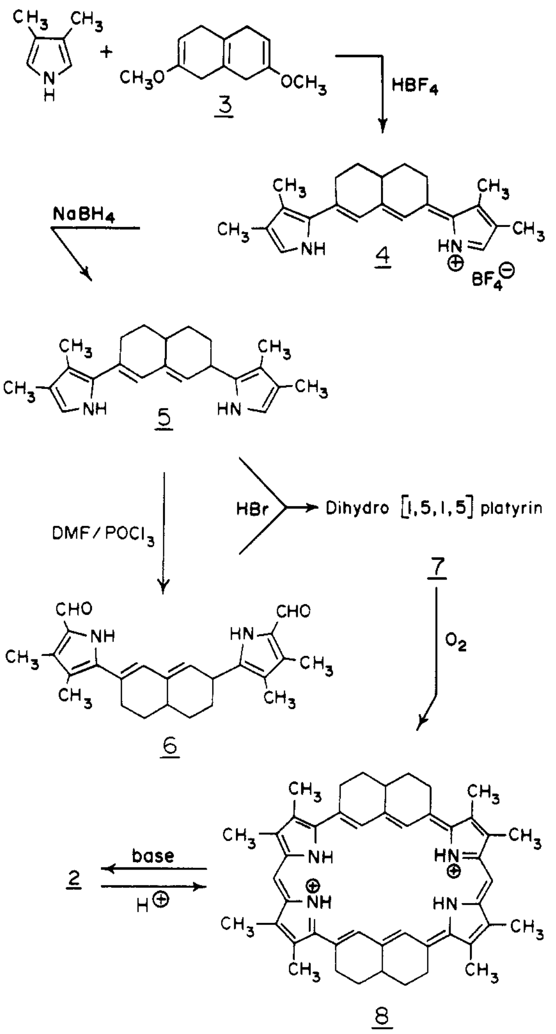


1



2

Acid-catalyzed condensation (HBF_4/C_2H_5OH) of 3,4-dimethylpyrrole with 2,7-dimethoxy-1,4,5,8-tetrahydronaphthalene (3),[3] gave a 97% yield of the green pentamethine salt 4 [mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 11.73 (br, 2 H, N*H*), 7.20 (m, 2 H, pyrrole-C*H*), 6.74 (s, 2 H, vinyl-C*H*), 3.2–1.4 (m, 9 H, -C*H*$_2$-), 2.18 (s, 6 H, C*H*$_3$), 1.85 (s, 6 H, C*H*$_3$); vis λ_{max} ($HCCl_3$) 658 nm; mass spectrum, *m/z* (relative intensity) 318 (24, M – HBF_4), 94 (100)]. Partial reduction of 4 ($NaBH_4$ in CH_3CN) afforded a near quantitative yield of 5, a pale yellow, oxygen-sensitive oil [^{1}H NMR ($DCCl_3$) δ 7.66 (br, 1 H, N*H*), 7.44 (br, 1 H, N*H*), 6.35 (d, 2 H, pyrrole-C*H*), 6.10 (s, 1 H, pyrrole-C*H*), 5.42 (d, 1 H, vinyl-C*H*), 3.58 (br, 1 H, -C*H*-), 2.7–1.1 (m, 9 H, -C*H*$_2$-), 2.13 (s, 3 H, C*H*$_3$), 2.02 (s, 9 H, C*H*$_3$)]. Reaction of 5 with dimethylformamide and phosphorus oxychloride gave a 71% yield of the bis-formylated product 6 [^{1}H NMR ($DCCl_3$) δ 9.60 (br, 2 H, N*H*), 9.30 (s, 1 H, C*H*O), 9.25 (s,



---

[1] To fill the need for a simple name, we have coined the word "platyrin", a word derived from the Greek "πλατυς" (platys) meaning "wide or broad" and the suffix "-rin" from the ending of porphy*rin*, hence, a wide or broad porphyrin. A bracket indicating the number of methine carbons may be prefixed to the name, e.g., a porphyrin would also be a [1,1,1,1]platyrin, 1.

[2] Berger, R. A.; LeGoff, E. *Tetrahedron Lett.* 1978, 4225.

[3] Tolmachev, A. I.; Solminskii, Yu. L.; Kiprianov, A. I. *Dokl. Akad. Nauk. SSR* 1967, *177,* 869. Radlick, R. *J. Org. Chem.* 1965, *30,* 3208. Weinstein, B.; Fenselau, A. N. *J. Org. Chem.* 1965, *30,* 3209. Marshall, J.; Andersen, N. *J. Org. Chem.* 1965, *30,* 1293.

0022-3263/87/1952-0710$01.50/0