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A Thero and Cram Selective Aldol-Lactonization Reaction and Its Application to the Synthesis of Prelog Djerassi Lactonic Acid

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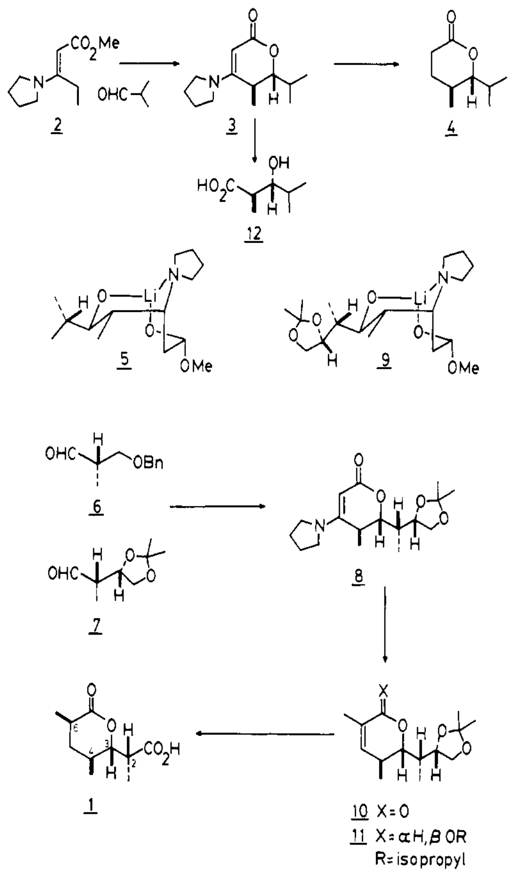
The title compound (**1**) has been a keystone in the chemistry of macrolide antibiotics since its isolation by Prelog and Djerassi during degradation studies of narbomycin and methymycin, respectively.[1] Synthetic interest in this substance intensified after its detailed structure was illuminated and its stereochemical arrangement was found to constitute part of the backbone of a number of biologically important antibiotics.[2] The majority of these efforts have secured the stereochemistry present in **1** by means of rings which were ultimately transformed into the synthetic target.[3] Our own plan for the crafting of **1** and related systems stemmed from the notion that a threo-selective aldol-lactonization reaction which also exhibited "Cram" behavior could be used to prepare the three contiguous chiral centers at C_2, C_3, and C_4—the fourth center being secured in a subsequent process.[4]

The published behavior of enolates derived from conjugated vinylamine–carbonyl systems prompted us to examine the LDA (1.05 equiv, 1 M in THF) generated (−78 °C, 20 min) enolate of the crotonate system **2** (1.0 equiv) with isobutyraldehyde (1.05 equiv, 1 M in THF, −78 °C, 5 min, 22 °C, 30 min).[5] This reaction afforded a single lactonic product, **3**, in over 95% yield after chromatography. Compound **3** was converted by standard means into the lactone **4**.[6] The ^{1}H NMR spectra of both **3** and **4** showed a trans relationship between the methyl and isopropyl groups, indicating that the aldol-lactonization reaction had proceeded with greater than 95% threo selectivity.[7] The stereoselectivity exhibited in the formation of **3** can be rationalized by assuming a pericyclic transition state as depicted in structure **5** where the substituents occupy only equatorial positions.[8]

Scheme I



We next turned our attention to the Cram selectivity problem by examining the reaction of aldehydes **6**[9] and **7**[10] with the enolate **2**. The aldehyde **6** in combination with the enolate **2** gave a mixture of lactonic products which proved to have a ratio of 2.5:1 Cram to anti-Cram stereochemistry at the C_2 methyl group.[11] However, the aldehyde **7**, on reaction with the enolate **2**, afforded a mixture of lactones (92% yield after filtration chromatography) in which the Cram product dominated to the extent of 9:1. Stereochemically pure **8** was obtained by recrystallization of this mixture from benzene/hexane, mp 153–153.5 °C.

As a definitive proof of structure for **8**, we embarked on its conversion into the lactonic acid **1**. Lithium (3 equiv) in liquid ammonia (0.125 M containing THF and *tert*-butyl alcohol, 0.8 equiv), reduction of **8** (1 equiv) at −78 °C for 5 min (excess lithium destroyed with isoprene) followed by vacuum removal of the ammonia at −40 °C, subsequent cooling of the reaction residue to −78 °C, and addition of methyl iodide (50 equiv) afforded after 2 h at −40 °C the corresponding methylated aminolactone. This substance (1 equiv) dissolved in toluene (0.5 M) was treated with *m*-chloroperbenzoic acid (1.5 equiv) at 0 °C and then stirred at 22 °C for 24 h. Addition of triethylamine (5 equiv) to the reaction mixture followed by heating at 100 °C for 30 min, standard workup, and filtration chromatography gave the crystalline unsaturated lactone **10**, mp 97.5–98 °C in 70% yield from **8**.

The correct stereochemistry at C_6 was secured by first reducing the unsaturated lactone (1 equiv) dissolved in THF (0.2 M) at −78 °C for 20 min with diisobutylaluminum hydride (1.15 equiv

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(1) (a) Anliker, R.; Dvornik, D.; Gubler, K.; Heusser, H.; Prelog, V. *Helv. Chim. Acta* **1956**, *39*, 1785. (b) Djerassi, C.; Zderic, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 2907, 6390.

(2) Lactone **1** has been isolated as a degradation product of neomethymycin by: Djerassi, C.; Halpern, O. J. *J. Am. Chem. Soc.* **1957**, *79*, 2022, 3926; In addition, **1** has been obtained from picromycin by: Anliker, R.; Gubler, K. *Helv. Chim. Acta* **1957**, *40*, 119. Brockman, H.; Oster, R. *Chem. Ber.* **1957**, *90*, 605. The detailed stereochemical features of **1** were determined by: Rickards, R. W.; Smith, R. M. *Tetrahedron Lett.* **1970**, 1025.

(3) Syntheses of racemic **1** have been reported by (a) Masamune, S.; Kim, C. U.; Wilson, K. E.; Spessard, G. O.; Georghiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* **1975**, *97*, 3512. (b) White, J. D.; Fukuyama, Y. *Ibid.* **1979**, *101*, 226. (c) Stork, G.; Nair, V. *Ibid.* **1979**, *101*, 1315. Syntheses of optically active **1** have been reported by: (a) Grieco, P. A.; Ohfune, Y.; Yokoyama, Y.; Owens, W. *Ibid.* **1979**, *101*, 4749. (b) Nakano, A.; Takimoto, S.; Inanaga, J.; Katsuki, T.; Ouchida, S.; Inoue, K.; Aiga, M.; Okukado, N.; Yamaguchi, M. *Chem. Lett.* **1979**, 1019. (c) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 497. (d) Jarosz, S.; Fraser-Reid, B. *Tetrahedron Lett.* **1981**, *22*, 2533. Syntheses of **1** from acyclic precursors have been reported by: (a) Hirama, M.; Garvey, D. S.; Lu, L. D.-L.; Masamune, S. *Ibid.* **1979**, 3937. (b) Bartlett, P. A.; Adams, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 337. (c) Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557.

(4) Just prior to completion of this work, we were informed by Professor S. Danishefsky that he was completing a synthesis of **1** using a Diels–Alder reaction in a strategy similar to our own. We congratulate Professor Danishefsky on his synthetic effort.

(5) (a) Vinick, F. L.; Gschwend, H. W. *Tetrahedron Lett.* **1978**, 315. (b) Dugger, R. W.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1181.

(6) The reaction sequence used (i) 1 N HCl–THF (1:5), 0.2 M, 48 h, 30 °C; (ii) 15% by weight PtO_2, 95% EtOH, 1.0 M, H_2 (1900 psi), 20 h, 22 °C; (iii) MsCl (2.0 equiv), C_5H_5N, 0.25 M, 8 h, 60 °C; (iv) 15% by weight Rh·Al_2O_3, 95% EtOH, 0.6 M, H_2 (1000 psi), 2 h, 22 °C.

(7) All new compounds gave satisfactory physical data; ^{1}H and ^{13}C spectra were recorded on a Bruker WH-400 spectrometer.

(8) (a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920. (b) Dubois, J. E.; Fort, J. F. *Tetrahedron* **1972**, *28*, 1653, 1665. (c) Dubois, J. E.; Fellman, P. *C. R. Hebd. Seances Acad. Sci.* **1972**, *274*, 1307. (d) Dubois, J. E.; Fellman, P. *Tetrahedron Lett.* **1975**, 1225. (e) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. (f) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(9) Aldehyde **6** was obtained from its corresponding ester by LAH reduction followed by PCC oxidation. A preparation of the racemic ester is described by: Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505.

(10) The aldehyde **7** was obtained from its corresponding racemic alcohol by PCC oxidation. The preparation of this alcohol is described by: Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 2643.

(11) (a) Cram D. J.; Elhafez, F. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Cram, D. J.; Wilson, D. R. *Ibid.* **1963**, *85*, 1245. (c) Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1981**, 2895 and references cited therein.

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in hexane) followed by warming the reaction to 0 °C for 1 h. The resulting anomeric mixture of lactols (1.0 equiv) dissolved in benzene (0.1 M) was then converted into the lactolide **11** (90% yield from **10**, greater than 95% anomerically pure, axial) by treatment at 22 °C with a mixture of isopropyl alcohol (10.0 equiv) and PPTSA (0.2 equiv).[12] Hydrogenation of **11** (1.0 equiv) in THF solution (0.3 M) using 15% by weight of Rh·Al_2O_3 at 1900 psi for 22 h afforded the saturated lactolide greater than 95% stereochemically pure.[13] The conversion of this material into the target lactonic acid **1** was accomplished by sequential treatment of it (1.0 equiv) with 75% acetic acid (0.1 M, stirring for 18 h at 22 °C), sodium metaperiodate (6.5 equiv, stirring for 1 h at 0 °C), and then chromium trioxide (0.2 equiv, stirring for 3 h at 0 °C). Standard workup followed by chromatography and crystallization gave pure Prelog Djerassi lactonic acid, mp 115–115.5 °C, in 65% yield from **11**. This material proved identical with a sample of racemic **1**.[14]

In addition to employing the enolate **2** as a four-carbon unit, we were interested in its utility as a two-carbon synthon: to this end, we examined degradation reactions of the adduct **3**. Treatment of **3** (1.0 equiv) in a 5:1 mixture of THF and water (0.1 M) containing H_5IO_6 (5.5 equiv) for 48 h at 22 °C gave an excellent yield of the hydroxy acid **12**, thereby suggesting new avenues of use for this type of enolate system. The possibility of realizing enantioselective aldol reactions using chiral amine derivatives of **2** is currently under investigation.

Acknowledgment. M.A.P. gratefully acknowledges receipt of a Sherman-Clarke fellowship from the University of Rochester.

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(12) For a discussion of the anomeric effect, see: (a) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *27*, 527. (b) Zefirov, N. S.; Shekhtman, N. M. *Russ. Chem. Rev.* **1971**, *40*, 315.

(13) Hydrogenation of a methoxy analogue of this type of lactolide has been reported in ref 3d. We thank Professor Danishefsky for suggesting the isopropyl residue at the anomeric center since its greater axial population enhances the stereochemical outcome of lactolide reduction.

(14) We thank Professor S. Masamune for a generous sample of racemic **1**.

Lewis Acid Catalyzed Cyclocondensations of Functionalized Dienes with Aldehydes

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The reactions of highly "nucleophilic" derivatives of 1,3-butadiene with "electrophilic" olefins and acetylenes have been helpful in the total synthesis of a wide variety of natural products.[1] We now report on the cyclocondensations of such dienes with aldehydes. It is already clear that the potentialities of this reaction are substantial and far-reaching.

Our orienting goal in this investigation was a projected total synthesis of the important hypocholestemic natural product compactin (**1**).[2] The viability of the retrosynthetic dissection implied in Figure 1 remains to be demonstrated. However, the analysis has already had heuristic value in stimulating new synthetic strategies directed toward the potential subunits **2**[3] and **3**. Herein thought focus on the latter system. The though was that **3** might be derived from **4**. Compound **4** was envisioned as arising from precursor **4′** which was seen to be the formal cycloadduct of **5** and **6**.

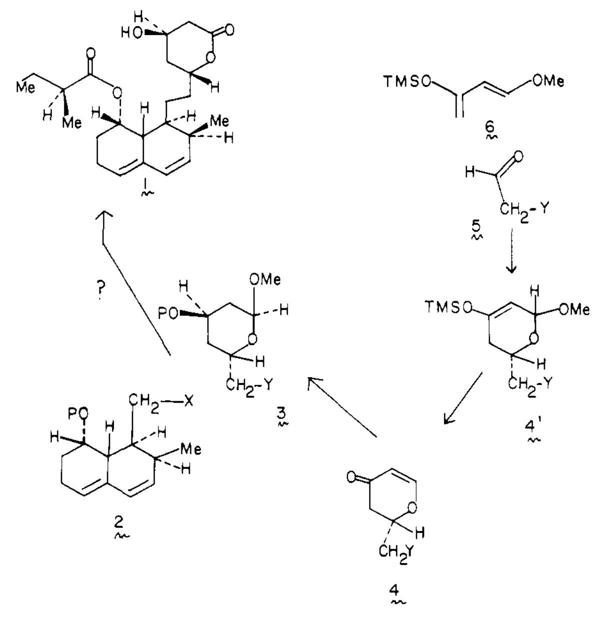
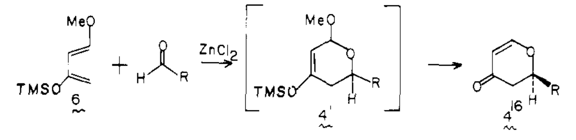


Figure 1.

Table I



entry[17]	*R*	yield of **4**, %
a	CH_2OCH_2Ph	87
b	CH_2SPh	70
c	CHNHCbz	80
d	Ph[18]	65
e	*p*-NO_2Ph	58
f	*o*-OCH_3Ph	58
g	CH_3[19]	17
h	CH_2CH_3[18]	48
i	$CH(CH_3)_2$	43
j	$CH_2CH(CH_3)_2$	37

In this communication we describe (i) the "cycloaddition"[4] of siloxy dienes with aldehydes via Lewis acid catalysis, (ii) the use of this process in the stereoslective synthesis of the pyranone portion of compactin, and (iii) the development of a fully synthetic general route to hexose systems and modified hexose systems. The latter are important components in a variety of antibiotics[5] and antitumor agents.[6]

The ability of a carbonyl group, in principle, to function as a "heterodienophile" in an apparent[4] Diels–Alder reaction with conjugated dienes has been previously recognized. The bulk of these reports have involved particularly reactive carbonyl groups such as glyoxalate[7,8] or mesoxalate.[9] More recently, there have

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(1) Danishefsky, S. *Acc. Chem. Res.* submitted for publication.

(2) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin trans. 1* **1976**, 1165. For a recent synthesis of (+)-compactin: Wang, Nai-Y.; Hsu, Chi-Tung; Shih, Charles J. *J. Am. Chem. Soc.* **1981**, *103*, 6538.

(3) For new chemistry directed toward systems of the type **2**, see: Danishefsky, S.; Funk, R. L.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 6889.

(4) We emphasize that at this juncture the term cycloaddition has structural rather than mechanistic implications. The issue of mechanism will be dealt with separately. For the moment we note that in the cases involving zinc chloride catalysis, no intermediates on the way to type **4** products have been detected. In the boron trifluoride cases, possible intermediates have been detected.

(5) Rinehard, K. L., Jr.; Suami, T. "Aminocyclitol Antibiotics"; American Chemical Society: Washington, DC, 1980; Am. Chem. Soc. Sym. Ser. No. 125.

(6) Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley: New Yok, 1979; Vol. 1.

(7) Shavrygina, O. A.; Makin, S. M. *Khim-Farm. Zh.* **1969**, *3*, 17.

(8) Jurczak, J.; Zamojski, A. *Tetrahedron* **1972**, *28*, 1505. David, S.; Eustache, J. *J. Chem. Soc. Perkin Trans.* 1 **1979**, 2230.

(9) Konowal, A.; Jurczak, J.; Zamojski, A. *Rocz. Chem.* **1968**, *42*, 2045.

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