NITROGEN PROTECTING GROUPS IN THE ESTER ENOLATE CLAISEN REARRANGEMENT OF AMINO ESTERS

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SYNTHESIS OF A FURANOMYCIN DERIVATIVE

Thesis by
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In Partial Fulfillment of the Requirements
for the Degree of
Master of Science

California Institute of Technology
Pasadena, California

1984

(Submitted December 16, 1983)

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The ester enolate Claisen rearrangement, first reported by Ireland and co-workers,[1] has become a valuable tool for the stereoselective construction of carbon-carbon bonds. Earlier procedures[2-5] for the aliphatic Claisen rearrangement suffered from various shortcomings--high reaction temperatures, acidic reaction media, low yields, and use of one of the reaction partners in considerable excess. In contrast, the enolate Claisen rearrangement proceeds at much lower temperatures under mild reaction conditions, making it compatible with complex or acid-sensitive functionality.[6]

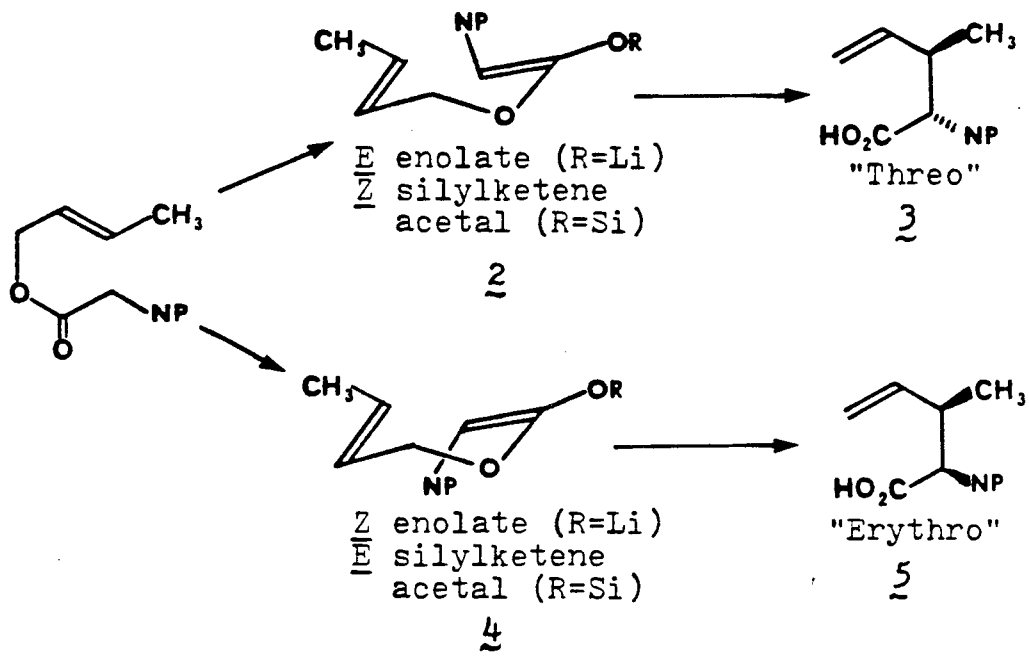
A heteroatom substituent at the alpha position of the ester substrate provides an interesting and useful variation of the enolate Claisen rearrangement. Investigations in this area have been undertaken in these laboratories[7] and by Bartlett,[8] who recently published results of rearrangements of some nitrogen and oxygen substituted ester enolates. Thus, allyl glycinate and lactate enolate derivatives undergo facile rearrangement to give α-amino and α-hydroxy acids, respectively.

Of particular concern in these rearrangements is the C_2-C_3 relative stereochemistry of the products, which, for a given allylic double bond geometry in

the starting ester, is determined both by the nature of the transition state (boatlike or chairlike) and by the enolate geometry. Since the Claisen rearrangement of acyclic substrates is known favor a chairlike transition state,[13-17] the single variable affecting product stereochemistry is the enolate geometry (Scheme 1).

Scheme 1

Chairlike transition state (favored)



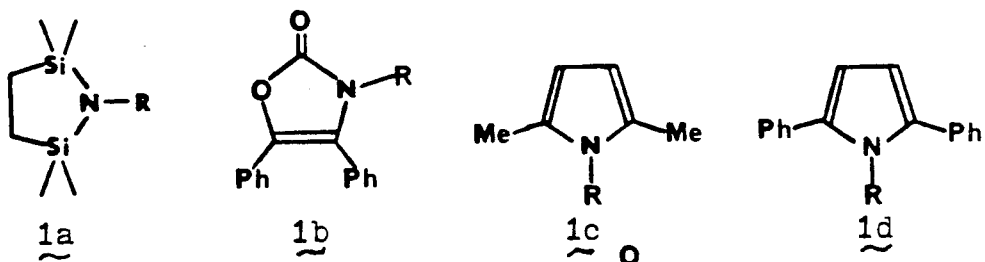
The synthetic utility of the reaction would clearly be maximum if both enolate geometries were easily accessible in a highly stereoselective fashion. As observed by both us and Bartlett, a very important factor affecting enolization geometry in the nitrogen substituted esters is the nature of the nitrogen

protecting group; several have been evaluated in this respect. The use of "carbonyl type" (amide or carbamate) protecting groups such as t-butoxycarbonyl (Boc), benzyl carbamoyl (CBz), or benzoyl invariably leads predominantly or exclusively to the E enolate, thus giving threo product. Bartlett proposed metal chelation between the nitrogen and the ester carbonyl oxygen to account for this selectivity. This explanation is quite reasonable in the above cases, but inconsistencies arise in others. For example, phthalyl protected esters also give high E selectivity, even though the nitrogen lacks both a partial negative charge and a readily-available lone pair of electrons. In contrast, dibenzyl protected ester, in which the nitrogen lone pair is readily available for complexation, shows a slight (1.4:1) selectivity favoring the Z enolate. Furthermore, if the system is made more highly dissociating by the addition of hexamethylphosphric triamide (HMPA), thus rendering intramolecular complexation less important, the stereoselectivity reverses to 2.2:1 favoring the E enolate. In addition, rearrangements of unprotected lactate esters generally show poor stereoselectivity, even though the lactate oxygen bears a full negative charge and should therefore be extensively associated with metal cations. It appears that Bartlett's explanation is incomplete, and that other factors must be taken into consideration.

For example, metal complexation between the ester carbonyl oxygen and the protecting group carbonyl oxygen would also lead to the E enolate; although this chelate is seven-membered, it should still be expected to play a part. Another possible mode of complexation would involve the nitrogen and the ester oxygen; this might explain the enolization geometry of the dibenzyl protected ester. Another factor which must be considered is steric bulk, although it is not immediately clear which direction that influence would take.

In any case, there is a clear need for a nitrogen protecting group which will allow access to the Z enolate in a highly selective manner. Four new protecting groups have been evaluated with respect to their influence on enolization geometry: 2,2,5,5-tetramethyl-2,5-disilapyrrolidine ("Stabase", 1a),[19] 4,5-diphenyl-4-oxazolin-2-one ("Ox", 1b),[20] 2,5-dimethylpyrrole ("DMP", 1c),[21] and 2,5-diphenylpyrrole ("DPP", 1d).[22] (Fig. 1). The results of these experiments

Fig. 1



1a 1b 1c 1d

In model compounds, R = $-CH_2\overset{O}{\overset{\|}{C}}OCH_2CH{=}CHCH_3$ (TRANS)

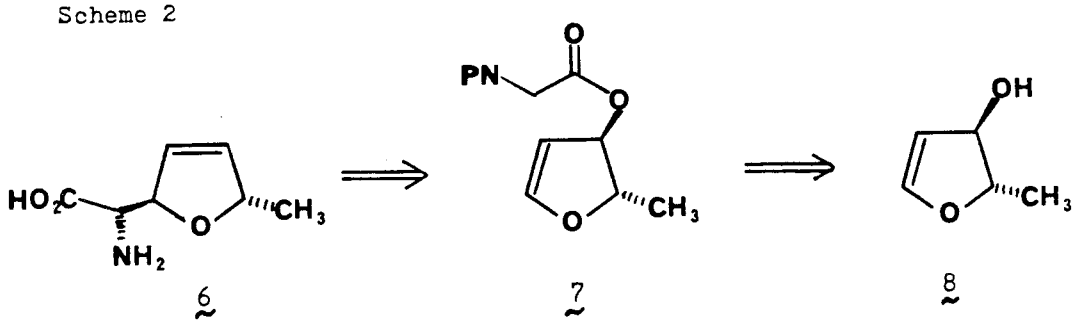
will be discussed shortly.

In the course of these studies, a unique and very pronounced rearrangement rate retardation was discovered in the silylketene acetals containing pyrroles as protecting groups; efforts to elucidate the origin of this effect will also be discussed.

Finally, we wished to apply the knowledge of stereochemical control gained in these experiments to a synthesis of the natural product (+)-furanomycin (6). This novel α-amino acid, isolated from a Streptomyces culture by Katagiri,[10] exhibits isoleucine antagonism[9,10] and antiphage activity against T-even coliphages.[10] Furanomycin has been synthesized twice, first by Masamune[11] via a route which presumably gave a mixture of epimers at the α-center, and later by Joullie,[12] who utilized a resolution process to obtain the proper epimer at this center. Bartlett has recently prepared related systems by a route similar to ours.[35]

The essence of our approach to furanomycin is illustrated in Scheme 2. In this process, the beta

Scheme 2



6 7 8

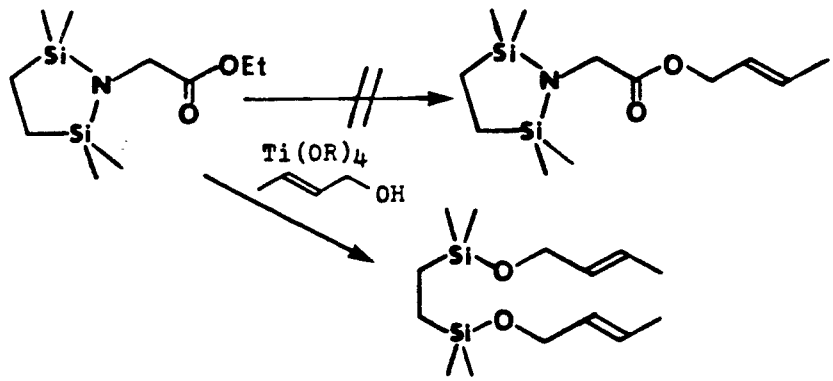
configuration at C-4 in the glycal ester precursor 7 is transferred to the C-2 center (furanomycin numbering) in the product. Concurrently, the configuration of the α center in the product is determined by the enolate geometry, which in turn is controlled by the protecting group on nitrogen, and by the nature of the transition state, which has been shown to be boat-like in the case of furanoid glycal silylketene acetals.[6,18,36] Fortunately, the required S configuration at the α center in 6 is obtained through the more easily obtainable E enolate. The required glycal 8 is derived from a sugar, as will be described later.

Results and Discussion

A. Rearrangement of "Stabase" Protected Amino Esters.

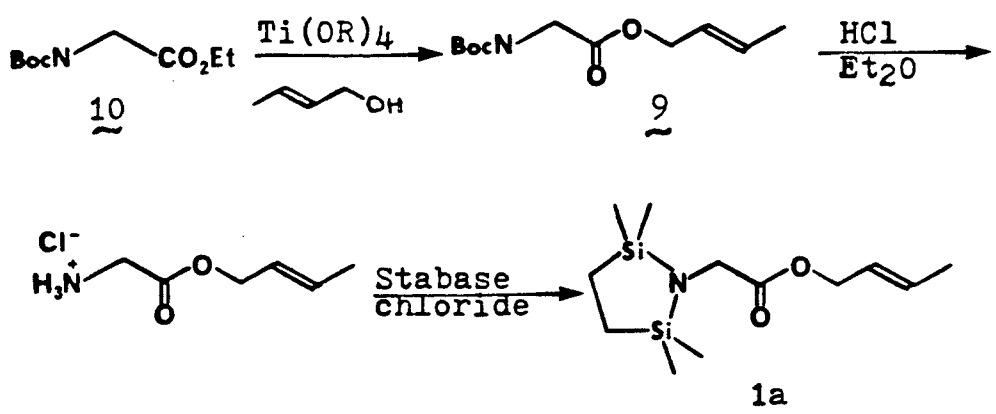
Synthesis of the model compound trans-crotyl stabase-glycinate (1a) proved to be more difficult than anticipated. An attempt to prepare the crotyl ester from the known[19] ethyl ester by titanium mediated transesterification[23] failed (Scheme 3), as did all

Scheme 3



attempts to prepare the free acid. Ester 1a was finally prepared by the sequence shown in Scheme 4. Thus, Boc-ethyl ester 10, prepared by the method of Moroder et al,[24] was transesterified with crotyl alcohol containing a catalytic amount of titanium tetraisopropoxide

Scheme 4



to give 9 (95%). Removal of the Boc group with ethereal hydrogen chloride followed by reaction with 1,1,4,4-tetramethyl-1,4-dichlorodisilethylene[19] (Stabase chloride) in the presence of triethylamine gave the model ester 1a in 74% overall yield.

Rearrangement of 1a under the standard enolate Claisen conditions[1] gave a mixture of diastereomers with little stereoselectivity, the erythro isomer being preferred over the threo by about 1.4:1. Enolization in the presence of HMPA gave a similar product ratio, and the use of bases other than LDA had little or no effect on the stereoselectivity.

Aside from the almost nonexistent stereochemical bias conferred by the stabase group, this group also proved to be inferior because of its extreme instability. Some of the stabase adducts prepared were unstable to neutral aqueous workup; few would withstand chromatography. This instability, which has also been noted by other researchers,[21,25] is apparently due to the weakness of the silicon-nitrogen bond (ca. 77 kcal/mol)[26] as compared to the silicon-oxygen bond (108 kcal/mol). (See Scheme 3, for example.)

B. Rearrangement of "Ox" Protected Amino Esters.

The crystalline model ester 1b was prepared in 82% yield from lithium crotoxide and the acid chloride of the known[20] ox-protected glycine. Rearrangement of

this ester under standard conditions gave exclusively *threo* product, as proven by hydrogenation of the double bond, deprotection, and comparison with authentic isoleucine (*erythro* configuration) and allo-isoleucine (*threo* configuration). Not surprisingly, then, the "Ox" group biases enolization geometry in the same direction (*E*) as the other "carbonyl type" protecting groups used previously. Although this stereochemical influence may arise from metal chelation involving the "Ox" carbonyl and ester carbonyl oxygens, it should be noted that enolization in the presence of HMPA does not affect the outcome.

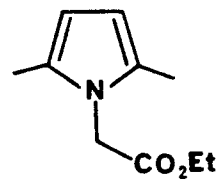
The great advantage of the "Ox" group lies in its physical and chemical properties. Physically, these derivatives are fluorescent and usually crystalline; chemically, they are quite stable to a variety of reagents. Removal is accomplished by one of three methods-reduction with sodium in ammonia, oxidation with m-chloroperoxybenzoic acid, or catalytic hydrogenolysis.

C. Rearrangement of Pyrrole Protected Amino Esters.

At this point we felt it likely that enolization geometry in the above cases was being steered by lithium ion complexation involving either the nitrogen itself or the oxygen of an adjacent carbonyl. We therefore turned our attention to pyrroles, which, by virtue of

aromatic delocalization of the nitrogen lone pair, contain no important complexing functionality.

The pyrroles were prepared by the Paal-Knorr synthesis from an amine and a 1,4-diketo compound. Thus, reaction of ethyl glycinate hydrochloride with 2,5-hexanedione in acetic acid containing one equivalent of sodium acetate afforded the pyrrole ester 11 as a colorless oil (after distillation) in 91% yield.



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The model ester 1c was prepared in 92% yield from the ethyl ester by titanium catalyzed transesterification using a large excess of crotyl alcohol. Interestingly, this reaction required about four days at 80° C for completion, as contrasted with overnight conversion of ethyl Boc-glycinate. This relative sluggishness is probably due to complexation of the titanium with the pyrrole ring, resulting in partial deactivation of the catalyst.

The dimethylpyrrole derivatives are moderately stable to most organic reagents; deprotection is effected by refluxing with ethanolic "hydroxylamine hemihydrochloride" in a method originally used to prepare 1,4-diketones.[27] Unfortunately, all dimethylpyrrole

derivatives prepared were remarkably air-sensitive, turning red or black during workups despite reasonable efforts to minimize exposure to air. This oxidation process apparently begins with a 1,4 addition of singlet oxygen across the pyrrole nucleus. The resulting unstable internal peroxide then decomposes via several pathways, resulting in polymeric material and a mixture of products.

The Paal-Knorr reaction was also utilized to prepare 2,5-diphenylpyrrylacetic acid. Unfortunately, the requisite diketone, 1,4-diphenyl-1,4-butanedione, was not readily available and proved to be somewhat difficult to prepare in reasonable yield. Attemped selective reduction of dibenzoylethylene[28] with a variety of reducing agents (H_2-Pt/C, H_2-Rh/C, Zn-HOAc,[29] Zn-EtOH, Li-NH_3,[30] HCl-ferrocene[31]) gave either none of the desired product or a complex mixture. The zinc-zinc chloride reagent described by Toda and Iida[32] worked reasonably well (65%) once on a small scale, but gave a mess when the reaction was scaled up. The required diketone was finally synthesized reasonably cleanly but only in moderate yield (52%) by copper (II) promoted coupling of the lithium enolate of acetophenone as described by Saegusa et al.[33]

Condensation of the diketone with glycine in refluxing acetic acid afforded the diphenylpyrrole

protected glycine in 80% recrystallized yield. Formation of the acid chloride (oxalyl chloride-DMF) followed by reaction with lithium crotoxide gave the model ester 1d in 99% chromatographed yield. In contrast to the dimethylpyrroles, the diphenylpyrroles were all quite air-stable.

Also prepared was the unsubstituted pyrrole ester, crotyl (1-pyrryl)acetate (1e). Because the required succindialdehyde was not readily available, it was prepared *in situ* by acid catalyzed hydrolysis of 2,5-dimethoxytetrahydrofuran. Thus, crotyl glycinate (prepared by acid deprotection of the Boc derivative) reacted with 2,5-dimethoxytetrahydrofuran in refluxing acetic acid to give ester 1e in 38% overall yield. Like the dimethylpyrroles, this ester was air-sensitive, although apparently not to the same degree.

The pyrrole esters 1c-1e were subjected to the standard enolate Claisen conditions. In all cases only starting material was recovered.

This surprising result clearly indicated a problem with either (a) enolization and trapping, or (b) rearrangement of the silylketene acetal. In order to distinguish between these possibilities, the diphenylpyrrole ester 1d was subjected to the standard enolization-trapping conditions. In this experiment, the normal trapping reagent, chlorotrimethylsilane, was replaced by t-butyldimethylsilyl chloride because

of the greater chemical stability of t-butyldimethylsilylketene acetals over the trimethylsilyl derivatives. Following a neutral aqueous workup, a quantitative crude yield of the silylketene acetal 2d was isolated, thus showing that the problem lay in the thermal stability of the acetal, not in its formation. The 500 MHz ^{1}H NMR spectrum of 2d showed no hint of more than one stereoisomer; enolization apparently occurred with complete stereoselectivity.

This silylketene acetal, unlike any previously known, was stable for weeks at room temperature; indeed, even in refluxing THF (67° C), rearrangement was incomplete after several hours. Rearrangement did occur at 100° and was complete after one hour, affording an 84% crude yield of a single diastereomer. Catalytic hydrogenation of the isolated double bond gave the pyrrole-protected isoleucine analog. Attempted removal of the pyrrole ring by a variety of methods (high pressure catalytic hydrogenolysis, Birch reduction, treatment with hydroxylamine hemihydrochloride in refluxing ethanol) failed, necessitating an alternative procedure for stereochemical assignment.

Authentic diphenylpyrrole derivatives of isoleucine and allo-isoleucine were prepared by reacting the amino acids with dibenzoylethane as previously described. Comparison of these samples with the hydrogenated Claisen product proved the latter to possess

the threo configuration (3, Scheme 1), thus indicating the geometry of the precursor silylketene acetal to be Z.

The silyl trapped enolates of pyrrole esters 1c and 1e were also found to rearrange at elevated temperatures; in both cases, an hour at 100° was required for complete reaction. Both gave a diastereomeric mixture of products.

The product mixture from the dimethylpyrrole ester 1c was hydrogenated and then deprotected with ethanolic hydroxylamine hemihydrochloride. This reaction gave a black, water soluble tar which contained the free amino acids. The ratio of isomers was about 4:1; NMR comparison with the authentic amino acids showed the major Claisen product to be threo. This assignment was confirmed by comparison of authentic dimethylpyrrole derivatives of isoleucine and allo-isoleucine with the hydrogenated Claisen product, as in the diphenylpyrrole case.

Similar treatment of the unsubstituted pyrrole ester 1e afforded a 1.2:1 mixture of diastereomers, again favoring the threo configuration.

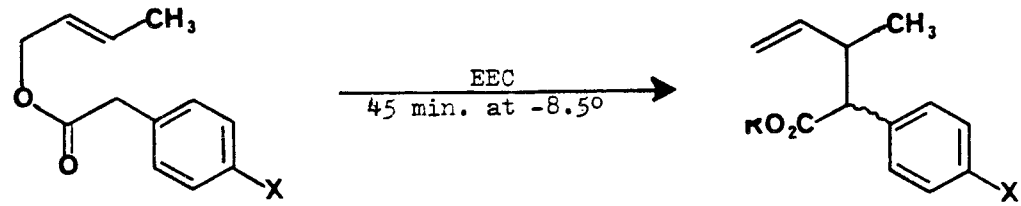
The results of these experiments suggest that steric factors, rather than lithium complexation, are controlling enolization geometry in these cases. If the previously discussed lithium complexation mechanism was operative here, one would expect the diphenylpyrrole

ester to give the lowest stereoselectivity; i.e., complexation should become less important with increasing bulk around the pyrrole nucleus. Instead, the opposite trend is observed: greater bulk leads to greater stereoselection. If this trend is simply due to a sterically-induced conformational preference in the ester substrate, this would indicate an "anti Cram" conformation; i.e., one in which the carbonyl oxygen is "smaller" than the ester oxygen.

Of equal or greater interest was the anomalous thermal stability of the pyrrole silylketene acetals. Steric hinderance is clearly not responsible for this effect, since equally bulky esters (e.g. "Stabase" esters) rearrange normally. The electronic influence of a π-donor in the 1-position of the ester should certainly be appraised. Carpenter and Burrows have recently published theoretical studies on the qualitative effects of π-donor and π-acceptor substituents on the rates of aliphatic Claisen rearrangements.[34] Their studies indicate that a π-donor in the 1-position of a Claisen substrate should increase the rate of rearrangement, a prediction clearly at odds with our results.

In order to clarify these electronic effects, we undertook a rearrangement kinetics study on esters 12a-c (Scheme 5), which were prepared by standard methods. These esters were enolized and trapped as usual, and the resulting silylketene acetals allowed to rearrange

Scheme 5



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(a) X= H
(b) X= -OCH3
(c) X= -N(CH3)2
(d) X= -NO2

13 R=H
14 R=CH3

for 45 minutes at -8.5°. Following this, the reaction mixtures were quickly recooled to -78°, quenched with acidic methanol, and worked up as usual. Ratios of starting materials to products were determined gravimetrically, and the rate constants were calculated. To our surprise, the strongest π-donor, p-dimethylaminophenyl, proved to be rate accelerating relative to the unsubstituted phenyl (k_{rel} = 4.1). The rate differences, while experimentally significant, are nonetheless quite small; all esters rearranged at rates comparable to other non-pyrrole esters studied previously. Nitrophenyl ester 12d was also rearranged under standard conditions; however, this reaction was not clean. The difficulty appears to arise from site ambiguity during enolate trapping; i.e., silylation can occur on either the ester oxygen or the nitro group oxygen. The latter product presumably reverts to starting material on hydrolysis. Because of this problem, a rearrangement rate constant was not rigorously determined for the

p-nitrophenyl ester. Rearrangement did appear to be slightly slower than with the p-methoxyphenyl ester; again, the difference was quite small.

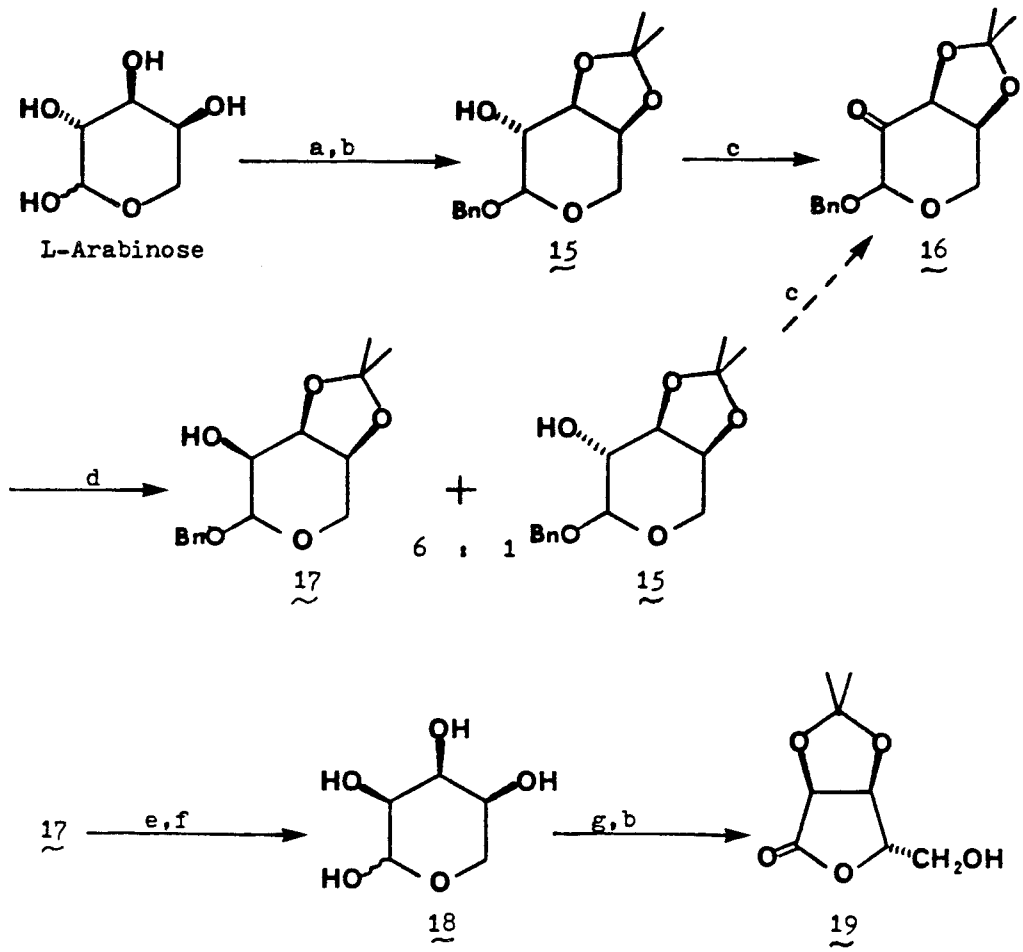
The results of these experiments clearly indicate that π-donation is not responsible for the abnormally high rearrangement activation barriers of pyrrole substituted silylketene acetals. At this time we are at a loss to explain the bizzare behavior of these systems.[44]

D. Synthesis of Furanomycin Derivatives.

The furanoid glycal piece required for the enolate Claisen rearrangement was prepared as shown in Scheme 6. Readily available L-arabinose was converted to the 3,4-acetonide benzyl glycoside (15) in 87% overall yield. Inversion of the C-2 hydroxyl was accomplished by Swern oxidation to the ketone 16 followed by DIBAl reduction, which gave a 6:1 mixture of C-2 epimers 17 and 15, respectively, in 91% overall yield. Beta epimer 17 was readily obtained in pure form by a single recrystallization from cyclohexane.

Hydrogenolysis of the benzyl group proceeded smoothly in quantitative yield, thus circumventing the need for the harsher, lower-yielding Birch debenzylation. Problems had been anticipated at this step; previous results from this laboratory have shown similar molecules to be unaffected by hydrogenolysis conditions.[37]

Scheme 6

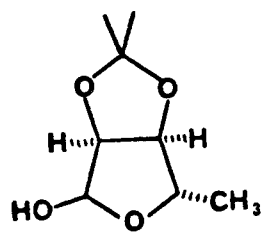


It was proposed that this lack of reactivity was due to poisoning of the catalyst by sulfurous impurities carried over from the Swern oxidation. If this is indeed the case, the cyclohexane recrystallization apparently removed these offending substances.

Hydrolysis of the acetonide group furnished L-ribose (18), which was oxidized with bromine water in the presence of $CaCO_3$ to the calcium salt of L-ribonic acid. Treatment of the crude salt with acidic acetone

containing dimethoxypropane gave the kinetically favored five membered lactone 19 (53% from ribose 3,4-acetonide). Prolonged reaction times led to decreased yields owing to formation of a thermodynamically favorable delta-lactone.

Lactone 19 reacted smoothly with either CCl_4-tris(dimethylamino)phosphine or, better, oxalyl chloride-DMF to afford a virtually quantitative yield of the chloro compound. Conversion to the iodide (KI, refluxing 2-butanone) followed by tri-n-butylstannane reduction gave the dehalogenated methyl lactone in 84% overall yield. Dibal reduction of the lactone provided lactol 20 in 88% yield.



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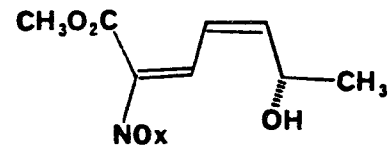
Established methodology[39] was utilized to prepare glycal 8. Thus, conversion of lactol 20 to the chloro derivative (CCl_4-tris(dimethylamino)phosphine) followed by lithium-ammonia reduction afforded a 9:1 mixture of glycal 8 and the des-chloro derivative. The glycal was easily separated from the minor byproduct by flash chromatography, although the byproduct did not interfere in the subsequent steps.

For the "acidic part" of the ester enolate Claisen substrate, ox-protected glycine was chosen. The "Ox" group was selected over Boc because its greater stability allowed the preparation of the acid chloride, whereas all attempts to prepare Boc-glycyl chloride either failed or gave very low yields. Anderson[7] has used the acyl imidazolide of Boc-glycine to prepare enantio-furanomycin via a route analogous to the one used here, but the yields were dismal (6%). It was believed that incomplete esterification and/or ketene formation were at least partially responsible for the low yield. The use of a better acylating agent (e.g. an acid chloride) should serve to diminish or eliminate these problems.

Ox-glycyl chloride reacted with the lithium alkoxide of glycal 8 at -78° to give the highly sensitive glycal ester 7 (Scheme 2), which was not isolated or even warmed to room temperature, but directly subjected to the standard enolate Claisen conditions. Diazomethane treatment of the acidic products followed by chromatographic separation afforded three compounds--the methyl ester of the desired ox-furanomycin 6, methyl ox-glycinate, and a third material which was tentatively identified as the hydroxy diene ester 21. The proportion of this latter product, which is formed by a base catalyzed beta elimination process from the desired product, could be minimized by using slightly



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less than one equivalent of base in the enolization process and by acidifying the mixture immediately after warming to room temperature.

Production of the ox-glycine byproduct proved to be impossible to supress. With the idea that incomplete esterification was generating this material, we tried using longer reaction times during esterification; the results were sporadic and unpromising. Another possible origin of the byproduct was fragmentation of the glycal ester caused by traces of acid in the acid chloride. We attempted to eliminate this contingency by adding the acid chloride to an excess of the glycal alkoxide with the hope that the excess alkoxide would scavenge traces of acid; no improvement was noted. Positive evidence for this fragmentation could arise from detection of the other fragmentation product--2-methylfuran. Unfortunately, this furan is too volatile to make its isolation from the reaction mixture feasible.

In accordance with the Murphy doctrine, the last step of the synthesis, deprotection of ox-furanomycin, did not work. Of the three deblocking methods described in the literature,[20] only Birch removal is compatible

with the double bond present in the molecule. This method failed in numerous attempts. Interestingly, a dibenzyl protected cis furanomycin analog had also previously been found to resist deprotection under Birch conditions.[40] Whether these failures reflect some aspect peculiar to the furanomycins or are totally coincidental is as yet unknown.

EXPERIMENTAL SECTION

(E)-2-Butenyl (4,5-diphenyl-2-oxo-4-oxazolinyl)-acetate (1b).

To 0.852 g (2.88 mmol) of Ox-glycine[20] in 15 ml of dry benzene was added 0.74 ml (8.6 mmol) of oxalyl chloride and one drop of DMF. The mixture was stirred for 3 hours at room temperature, then solvent and excess oxalyl chloride were removed under reduced pressure to give the acid chloride as a pale yellow solid.

To a cold (-78°), stirred solution of 0.5 ml (6 mmol) of trans-crotyl alcohol in 10 ml of dry THF was added 1.2 ml (3.2 mmol) of a 2.63 M solution of n-butyllithium in hexane. A solution of the acid chloride prepared above in 15 ml of THF was then added via cannula, and the resulting mixture was stirred for 10 min. at -78° before being warmed to room temperature. Aqueous workup followed by chromatography on silica with 25% ethyl acetate-petroleum ether afforded 0.829 g (82%) of the desired ester: mp 103-104°; Rf 0.21 (25% ethyl acetate-petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.69 (d, 3H, J=6 Hz), 4.17 (s, 2H), 4.49 (d, 2H, J=6 Hz), 5.6 (m, 2H), 7.3 (m, 10H). An analytical sample was prepared by two recrystallizations from ethyl acetate-petroleum ether. Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.20; H, 5.48; N, 3.97.

threo-2-(4,5-Diphenyl-2-oxo-4-oxazolinyl)-3-methyl-4-pentenoic acid (3b).

To a cold (-78°), stirred solution of 0.42 ml (2.98 mmol) of diisopropylamine in 7.0 ml of dry THF was added 0.90 ml (2.4 mmol) of a 2.63 M solution of n-butyllithium in hexane. The mixture was warmed to 0°, stirred at that temperature for 5 min., and re-cooled to -78°. To this was slowly added a solution of 0.692 g (1.98 mmol) of ester 1b in 15 ml of dry THF, and the resulting mixture was stirred for 10 min. at -78°. Chlorotrimethylsilane (10 mmol) was then added in the form of 1.7 ml of the supernatant centrifugate from a 3:1 (v:v) mixture of TMSCl and triethylamine. The mixture was stirred for 1 hour at -78°, then warmed to room temperature and stirred overnight. Aqueous workup afforded 0.415 g (60%) of white crystalline product 3b: mp 212-214.5°; ^{1}H NMR ($CDCl_3$) δ 0.99 (d, 3H, J=7 Hz), 3.3 (m, 1H), 3.88 (d, 1H, J=10 Hz), 5.1 (m, 2H), 5.5 (m, 1H), 6.2 (br s, 1H), 7.23 (s, 4H), 7.4 (m, 6H). An analytical sample was prepared by recrystallization. Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.23; H, 5.33; N, 3.99. Diazomethane treatment of the acid gave the methyl ester: Rf 0.25 (20% ethyl acetate-petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.03 (d, 3H, J=7 Hz), 3.3 (m, 1H), 3.69 (s, 3H), 3.95 (d, 1H, J=10 Hz), 5.0 (m, 2H), 5.6 (m, 1H), 7.18 (s, 4H), 7.4 (m, 6H).

allo-Isoleucine

In a small bomb tube was placed 45 mg of 10% palladium on carbon moistened with 0.4 ml of 1 N HCl. To this was added a solution of 0.126 g of 3b in 6.5 ml of ethanol. This mixture was shaken overnight under 50 psig of hydrogen, then filtered through diatomaceous earth. Removal of the solvent under reduced pressure left a white solid, which was dissolved in 2.0 ml of absolute ethanol. To this was added 25 ml of ether. This mixture was allowed to stand overnight at -6°, whereupon it deposited white crystals of the amino acid hydrochloride: ^{1}H NMR (D_2O + DSS internal standard) δ 0.9 (m, 6H), 1.4 (m, 2H), 2.1 (m, 1H), 5.03 (d, 1H, J=4 Hz). NMR comparison of this Claisen-derived product with authentic isoleucine and a Sigma mixture of isoleucine and allo-isoleucine left no doubt as to the threo stereochemistry of the Claisen product (corresponding to allo-isoleucine). A mixture of the reaction product with authentic isoleucine gave two distinct downfield doublets in the NMR spectrum and an overall spectrum identical to that obtained from the Sigma mixture of diastereomers.

Ethyl 2,5-dimethyl-1-pyrrylacetate (11).

A solution of 2.4 ml (20 mmol) of 2,5-hexanedione, 5.71 g (40.9 mmol) of ethyl glycinate hydrochloride, and 2.00 g (24.4 mmol) of sodium acetate in 35 ml of

acetic acid was heated under argon at 55° for 2 hours, then cooled and poured into 150 ml of icewater. The product was extracted with dichloromethane and this solution was washed (saturated $NaHCO_3$), dried ($MgSO_4$), and evaporated under reduced pressure to give a brown oil. Evaporative distillation (110°, 0.004 mmHg) afforded 3.36 g (91%) of the dimethylpyrrole ester: IR (neat) 3120, 3000, 1750, 1525, 1410, 1305, 1210, 1190, 1020, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, J=7 Hz), 2.15 (s, 6H), 4.18 (q, 2H, J=7 Hz), 4.44 (s, 2H), 5.78 (s, 2H). An analytical sample was prepared by multiple evaporative distillations. Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.30; H, 8.38; N, 7.76.

(E)-2-Butenyl 2,5-dimethyl-1-pyrrylacetate (1c).

A mixture of 2.68 g (14.8 mmol) of ethyl ester 11, 60 ml of trans-crotyl alcohol, and ca. 1 ml of titanium tetraisopropoxide was heated at 80° with stirring under argon for 4 days, after which time the excess crotyl alcohol was removed under reduced pressure. Aqueous acidic workup followed by evaporative distillation afforded 2.84 g (92%) of the model ester: ^1H NMR ($CDCl_3$) δ 1.70 (d, 3H, J=5 Hz), 2.14 (s, 6H), 4.44 (s, 2H), 4.55 (d, 2H, J=5 Hz), 5.7 (m, 2H), 5.77 (s, 2H). Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.39; H, 8.29; N, 6.84.

(E)-2-Butenyl 2,5-diphenyl-1-pyrrylacetate (1d).

To a suspension of 1.14 g (4.11 mmol) of diphenylpyrrole acetic acid[22] in 30 ml of dry benzene was added 1.06 ml (12.3 mmol) of oxalyl chloride and 2 drops of DMF. After the mixture was stirred for 1 hour, the volatiles were removed under vacuum. The resulting solid was dissolved in 15 ml of dry THF and this solution was cannulated into a cold (-78°), stirred solution of lithium crotoxide, prepared at -78° from 1.7 ml (20 mmol) of trans-crotyl alcohol and 3 equivalents of n-butyllithium in 20 ml of THF. The mixture was warmed to room temperature, and aqueous workup followed by chromatography with 8% ethyl acetate-petroleum ether afforded 1.34 g (99%) of ester 1d: Rf 0.29 (10% ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$) δ 1.68 (d, 3H, J=5 Hz), 4.43 (d, 2H, J=6 Hz), 4.54 (s, 2H), 5.6 (m, 2H), 6.28 (s, 2H), 7.4 (br s, 10H). Anal. Calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.32. Found: C, 79.69; H, 6.31; N, 4.18.

(E)-2-Butenyl t-butoxycarbonylaminoacetate (9).

A mixture of 7.92 g (39.0 mmol) of ethyl Boc-glycinate,[24] 50 ml of trans-crotyl alcohol, and ca. 1 ml of titanium tetraisopropoxide was heated at 80° overnight. Excess crotyl alcohol was then removed under aspirator pressure, and the residue was stirred vigorously with 100 ml of ether and 25 ml of 2N HCl to effect

hydrolysis of the titanium species. Standard workup followed by evaporative distillation (70°, 0.05 mmHg) afforded 7.79 g (87%) of the ester: Rf 0.16 (10% ethyl acetate-petroleum ether); IR (neat) 3400, 2980, 1750, 1510, 1170, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.71 (d, 3H, J=6 Hz), 3.84 (d, 2H, J=6 Hz), 4.54 (d, 2H, J=6 Hz), 5.4 (br s, 1H), 5.7 (m, 2H). Anal. Calcd. for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.73; H, 8.47; N, 5.99.

(E)-2-Butenyl 1-pyrrylacetate (1e).

Dry hydrogen chloride was passed through a stirred solution of 1.97 g (8.60 mmol) of crotyl Boc-glycinate (9) in 30 ml of dry ether. After 30 min., white crystals were deposited from the solution; after 90 min. the gas flow was discontinued and the solvent removed under an argon purge.

To the white residue of crotyl glycinate hydrochloride was added 0.71 g (8.7 mmol) of sodium acetate, 1.1 ml (8.5 mmol) of 2,5-dimethoxytetrahydrofuran, and 25 ml of acetic acid. The mixture was heated at 60° under argon with exclusion of light for 3 hours, then cooled to room temperature and poured into water. Extractive workup afforded a brown oil, which was chromatographed on 200 g of silica with 10% ethyl acetate-petroleum ether to give 0.58 g (38%) of pyrrole ester 1e: Evaporative distillation 70° (0.6 mmHg);

Rf 0.29 (15% ethyl acetate-hexane); IR ($CDCl_3$) 3050, 2950, 1750, 1500, 1295, 1200, 1090, 1070, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (d, 3H, J=6 Hz), 4.59 (d, 2H, J=6 Hz), 4.61 (s, 2H), 5.7 (m, 2H), 6.2 (m, 2H), 6.7 (m, 2H). Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.11; H, 7.25; N, 7.94.

General procedure for the rearrangement of pyrrole esters: threo-3-Methyl-2-(2,5-diphenyl-1-pyrryl)-4-pentenoic acid (3d).

A solution of lithium diisopropylamide in 10 ml of THF was prepared as usual from 0.48 ml (3.4 mmol) of diisopropylamine and 1.00 ml (2.54 mmol) of a 2.54 M solution of n-butyllithium in hexane. To this solution at -78° was added via cannula 0.560 g (1.69 mmol) of ester 1d in 10 ml of THF. Twenty minutes was allowed for enolization, then a solution of 1.0 g (6.6 mmol) of t-butyldimethylsilyl chloride in 2 ml of THF was added. The resulting mixture was warmed to room temperature and stirred for 30 min., then volatiles were removed under vacuum. The residual oil was heated at 100° for 40-60 min.; rearrangement progress was followed by TLC. Aqueous workup afforded 0.472 g (84%) of the acid 3d: ^1H NMR ($CDCl_3$) δ 0.49 (d, 3H, J=7 Hz), 2.5 (m, 1H), 4.65 (d, 1H, J=10 Hz), 4.81 (d, 2H, J=3 Hz), 5.5 (m, 1H), 6.21 (s, 2H), 7.4 (m, 10H). An analytical sample was prepared by esterification with diazomethane, followed by chromatography on silica (8% ethyl acetate-

petroleum ether) and evaporative distillation (120°, 0.01 mmHg). Anal. Calcd. for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 80.03; H, 6.75; N, 4.11.

3-Methyl-2-(2,5-dimethyl-1-pyrryl)-4-pentenoic acid (3c, 5c).

By the procedure described for the rearrangement of diphenylpyrrole ester 1d, 0.934 g (4.51 mmol) of dimethylpyrrole ester 1c was converted to 0.700 g (75%) of a diastereomeric mixture of the corresponding acids: ^{1}H NMR ($CDCl_3$) δ 0.77, 1.22 (d, 3H, J=7 Hz), 2.25 (s, 6H), 3.2 (m, 1H), 4.32, 4.39 (d, 1H, J=11 Hz), 5.1 (m, 2H), 5.76 (s, 2H), 5.8 (m, 1H), 8.5 (br s, 1H). Diazomethane treatment followed by chromatography on silica (10% ethyl acetate-petroleum ether) and evaporative distillation (50°, 0.005 mmHg) afforded the methyl esters: Rf 0.47 (20% ethyl acetate-hexane). Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.65; H, 8.68; N, 6.35.

3-Methyl-2-(1-pyrryl)-4-pentenoic acid (3e, 5e).

By the procedure described for the rearrangement of ester 1d, 0.195 g (1.09 mmol) of ester 1e yielded, after diazomethane treatment and chromatography, 53.0 mg (25%) of the methyl esters: Evaporative distillation 50° (0.09 mmHg); Rf 0.30 (10% ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$) δ 0.82, 1.04 (d, 3H, J=7 Hz), 3.0 (m, 1H), 3.63, 3.68 (s, 3H), 4.21, 4.28

(d, 1H, J=10 Hz), 5.1 (m, 2H), 5.5 (m, 1H), 6.1 (m, 2H), 6.7 (m, 2H).

Methyl 3-methyl-2-(2,5-dimethyl-1-pyrryl)pentanoate (22c)

To a mixture of 0.66 g (3.2 mmol) of acids 3c and 5c and ca. 100 mg of 10% platinum on carbon was was added 20 ml of ethyl acetate. The flask was back-flushed several times with argon, then with hydrogen. The mixture was stirred vigorously overnight under 1 atmosphere of hydrogen, then filtered through diatomaceous earth. Diazomethane treatment followed by chromatography on silica (8% ethyl acetate-petroleum ether) provided 55.9 mg (29%) of a diastereomeric mixture of the hydrogenated esters: Rf 0.34 (10% ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$) δ 0.61 (d, J=7 Hz), 1.0 (m), 2.4 (m), (total 9H), 2.22 (s, 6H), 3.69 (s, 3H), 4.29 (d, 1H, J=11 Hz), 5.76 (s, 2H). Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.85; H, 9.45; N, 6.39.

Methyl 3-methyl-2-(2,5-dimethyl-1-pyrryl)pentanoate (erythro)

The Paal-Knorr reaction between 111 mg (0.85 mmol) of isoleucine and 0.10 ml (0.85 mmol) of 2,5-hexanedione was conducted in a manner similar to that described for the preparation of ester 11. Chromatography on silica with 8% ethyl acetate-petroleum ether provided 80.9 mg (43%) of the erythro ester: Evaporative

distillation 50° (0.001 mmHg); Rf 0.34 (10% ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$) δ 0.8 (m), 1.04 (d, J=6 Hz), 2.5 (m), (total 9H), 2.21 (s, 6H), 3.68 (s, 3H), 4.26 (d, 1H, J=12 Hz), 5.74 (s, 2H). Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.04; H, 9.55; N, 6.28.

Similarly, the Sigma-supplied mixture of isoleucine and allo-isoleucine was converted in 89% yield to the diastereomeric mixture of pyrroles. The NMR spectrum of this mixture was identical to that obtained from a mixture of the Claisen-derived product and the isoleucine derivative; thus, the major Claisen product (formed in about a 4:1 ratio over the minor product) was again threo (corresponding to allo-isoleucine).

allo-Isoleucine: Removal of the dimethylpyrrole moiety.

A mixture of 0.65 g (3.11 mmol) of the hydrogenated Claisen product, 0.76 g (11 mmol) of hydroxylamine hydrochloride, 3.8 ml (6.7 mmol) of 10% KOH solution, and 10 ml of ethanol was refluxed under argon for 2 days and then cooled to room temperature. Enough 10% KOH solution was added to bring the solution to pH 11, and the solvent was removed under reduced pressure. Remaining volatiles (eg NH_2OH) were removed by placing the residue under high vacuum.

The residue was then slurried in ethanol, and

enough conc. HCl was added to bring the solution to pH 1. This was heated to boiling and filtered into 150 ml of stirred ether. This caused the separation of a black oil, which was water-soluble and refused to crystallize. However, the ^{1}H NMR spectrum of this material (D_2O solution) did show the amino acid to be present. Furthermore, addition of genuine isoleucine hydrochloride caused a new set of NMR signals to appear in the diagnostic regions δ 1.0 and 4.1, indicating that the major Claisen product was threo, corresponding to allo-isoleucine.

Methyl 3-methyl-2-(2,5-diphenyl-1-pyrryl)pentanoate (22d).

A mixture of 15.5 mg (0.047 mmol) of 3d, 7 mg of 10% platinum on carbon, and 6.5 ml of ethyl acetate was stirred overnight under 1 atmosphere of hydrogen, then filtered through diatomaceous earth. Removal of the solvent under reduced pressure provided a quantitative yield of the hydrogenated product: ^{1}H NMR ($CDCl_3$) δ 0.38 (d, 3H, J=7 Hz), 0.61 (d, 3H, J=7 Hz), 1.0 (m, 2H), 1.8 (m, 1H), 4.52 (d, 1H, J=10 Hz), 6.17 (s, 2H), 7.3 (br s, 10H), 8.5 (br s, 1H). Diazomethane treatment followed by chromatography on silica (10% ethyl acetate-petroleum ether) afforded the methyl ester: Evaporative distillation 120° (0.01 mmHg); Rf 0.26 (10% ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$) δ 0.36

(d, J=7 Hz), 0.59 (d, J=6 Hz), 0.6 (m), 1.4 (m), 1.8 (m), (total 9H), 3.68 (s, 3H), 4.53 (d, 1H, J=11 Hz), 6.19 (s, 2H), 7.4 (br s, 10H). Anal. Calcd. for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.47; H, 7.23; N, 4.07.

Methyl 3-methyl-2-(2,5-diphenyl-1-pyrryl)pentanoate (erythro) (22d).

A mixture of 79.6 mg (0.607 mmol) of isoleucine and 121 mg (0.508 mmol) of 1,4-diphenyl-1,4-butanedione in 2.0 ml of acetic acid was refluxed under argon for 2 hours. Aqueous workup was followed by diazomethane treatment and chromatography on silica (10% ethyl acetate-petroleum ether) to afford 35.3 mg (20%) of the methyl ester: ^{1}H NMR ($CDCl_3$) δ 0.6 (m), 1.7 (m), 3.73 (s), 4.43 (d, J=10 Hz), 6.18 (s), 7.4 (br s); clearly different from the spectrum of the hydrogenated, methylated Claisen product.

(E)-2-Butenyl phenylacetate (12a).

To stirred solution of 5.00 g (36.7 mmol) of phenylacetic acid in 100 ml of dry benzene was added 6.3 ml (73 mmol) of oxalyl chloride and 2 drops of DMF. The mixture was stirred for 3 hours at room temperature and the volatiles were then removed under reduced pressure. Addition of 75 ml of dry ether provided a clear solution of the acid chloride.

A solution of lithium crotoxide was procured by

addition of butyllithium (1.3 M in hexane) to a cold (-78°) solution of 4.7 ml (55 mmol) of trans-crotyl alcohol and a small crystal of 1,10-phenanthroline in 200 ml of dry ether until a faint red color persisted. Into this was cannulated the solution of the acid chloride prepared above, and the resulting mixture was allowed to warm to room temperature. Aqueous workup followed by evaporative distillation (150°, 1 mmHg) afforded 5.58 g (80%) of ester 12a: Rf 0.44 (20% ethyl acetate-hexane); IR ($CDCl_3$) 3030, 2950, 1730, 1250, 1150, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (d, 3H, J=6 Hz), 3.60 (s, 2H), 4.50 (d, 2H, J=6 Hz), 5.7 (m, 2H), 7.28 (br s, 5H). Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.55; H, 7.46.

(E)-2-Butenyl (4-methoxyphenyl)acetate (12b).

By a procedure similar to that described for the preparation of ester 12a, 1.56 g (9.36 mmol) of para-methoxyphenylacetic acid provided 1.44 g (70%) of crotyl ester 12b: Evaporative distillation 90° (0.05 mmHg); Rf 0.20 (10% ethyl acetate-hexane); IR ($CDCl_3$) 3010, 2930, 1730, 1620, 1510, 1450, 1250, 1160, 1040, 970; ^1H NMR ($CDCl_3$) δ 1.69 (d, 3H, J=6 Hz), 3.54 (s, 2H), 3.77 (s, 3H), 4.50 (d, 2H, J=6 Hz), 5.6 (m, 2H), 6.84 (d, 2H, J=9 Hz), 7.20 (d, 2H, J=9 Hz). Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.94; H, 7.37.

(E)-2-Butenyl (4-nitrophenyl)acetate (12d).

A mixture of 2.12 g (11.7 mmol) of p-nitrophenylacetic acid and 1.7 ml (23 mmol) of thionyl chloride was heated at 75° for 50 min.; subsequent removal of volatiles under reduced pressure left the acid chloride as an orange solid. This was dissolved in 10 ml of dichloromethane and added to a cold (0°), stirred solution of 1.5 ml (18 mmol) of crotyl alcohol and 1.1 ml (14 mmol) of pyridine in 20 ml of dichloromethane. This mixture was stirred for 2 hours at room temperature. Aqueous workup followed by chromatography on 200 g of silica with 15% ethyl acetate-petroleum ether afforded 2.26 g (82%) of nitrophenyl ester 12d: Rf 0.26 (20% ethyl acetate-hexane); IR ($CDCl_3$) 3025, 2960, 1740, 1610, 1530, 1350, 1170, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (d, 3H, J=6 Hz), 3.72 (s, 2H), 4.48 (d, 2H, J=6 Hz), 5.6 (m, 2H), 7.42 (d, 2H, J=9 Hz), 8.17 (d, 2H, J=8 Hz).

(E)-2-Butenyl (4-aminophenyl)acetate (12f).

To a solution of 0.299 g (1.27 mmol) of nitro ester 12d in 15 ml of acetic acid was added 4.5 g (69 mmol) of zinc dust and a small amount (ca 10 mg) of copper (II) acetate. The mixture was stirred for 2 hours, filtered, and poured into icewater. This mixture was made mildly alkaline by addition of $NaHCO_3$ until no further gas evolution was observed. Extractive

workup followed by chromatography on 30 g of silica with 30% ethyl acetate-petroleum ether afforded 0.251 g (96%) of the aminophenyl ester: Rf 0.16 (30% ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$) δ 1.67 (d, 3H, J=6 Hz), 3.50 (s, 2H), 3.6 (br s, 2H), 4.46 (d, 2H, J=5 Hz), 5.6 (m, 2H), 6.56 (d, 2H, J=9 Hz), 7.02 (d, 2H, J=9 Hz).

(E)-2-Butenyl (4-dimethylaminophenyl)acetate (12c).

According to the methylation procedure described by Borch,[41] 0.248 g (1.21 mmol) of amino ester 12f, 1.0 ml of 12.3 M aqueous formaldehyde, and 230 mg (3.66 mmol) of sodium cyanoborohydride afforded, after chromatography on 30 g of silica with 10% ethyl acetate in petroleum ether, 0.211 g (75%) of dimethylaminophenyl ester 12c: Evaporative distillation 100° (0.05 mmHg); Rf 0.15 (15% ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$) δ 1.66 (d, 3H, J=6 Hz), 2.92 (s, 6H), 3.48 (s, 2H), 4.46 (d, 2H, J=6Hz), 5.6 (m, 2H), 6.64 (d, 2H, J=9 Hz), 7.11 (d, 2H, J=9 Hz). Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.12; H, 8.33; N, 5.92.

Rearrangement kinetics of esters 12a-12c: General procedure.

A solution of 1.1 eq of LDA was prepared as usual from 1.1 eq of n-butyllithium and 1.5 eq of diisopropylamine in 5.0 ml of THF. To this solution was added, via cannula at -78°, 1.0 eq (typically 0.8 mmol) of

the ester dissolved in 2.0 ml of THF. Following a 10 min. enolization period, 2 eq of chlorotrimethylsilane (as the supernatant centrifugate from a 3:1 v:v mixture of TMSCl and triethylamine) was syringed in. Ten minutes was allowed for trapping, then the mixture was quickly warmed to -8.5° in a bath maintained at that temperature by a refrigeration unit. Exactly 45 min. later, the mixture was re-cooled to -78°, quenched by the addition of 1.0 ml of acidic methanol (CH_3OH containing enough conc. aqueous HCl to give 2 N HCl), and warmed to room temperature. Partitioning of the organic product between ether and aqueous alkali effectively separated the diastereomeric mixture of product acids from starting material; hence a gravimetric determination of the ratio was possible. With the reasonable assumption that the rearrangement followed unimolecular kinetics, the rate constant was calculated using the equation $k = -(1/t)\ln(S/S_o)$, where t is elapsed time, S is the weight of remaining starting material, and S_o is the initial weight of starting material.

3-Methyl-2-phenyl-4-pentenoic acid (13a).

By the procedure described above, 157 mg (0.827 mmol) of ester 12a gave 101.6 mg (0.534 mmol) of unrearranged starting material and 55.1 mg (0.290 mmol) of a diastereomeric mixture of product acids 13a; thus $k = 1.6 \times 10^{-4}$ sec^{-1} (at -8.5°). For acids 13a:

^{1}H NMR ($CDCl_3$) δ 0.78, 1.14 (d, 3H, J=6 Hz), 2.9 (m, 1H), 3.30, 3.33 (d, 1H, J=10 Hz), 4.8 (m, 2H), 5.5 (m, 1H), 7.28 (br s, 5H), 11.3 (br s, 1H). An analytical sample was prepared by diazomethane treatment of the acid, followed by chromatography and evaporative distillation (60°, 0.01 mmHg) of the methyl ester 14a. Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.29; H, 7.93.

3-Methyl-2-(4-methoxyphenyl)-4-pentenoic acid (13b).

By the procedure described above, 180 mg (0.816 mmol) of ester 12b gave 86.4 mg (0.392 mmol) of the starting material and 95.1 mg (0.432 mmol) of a diastereomeric mixture of product acids 13b; thus k = 2.7×10^{-4} sec^{-1} (at -8.5°). For acids 13b: ^{1}H NMR ($CDCl_3$) δ 0.78, 1.13 (d, 3H, J=7 Hz), 2.9 (m, 1H), 3.25, 3.27 (d, 1H, J=10 Hz), 3.72 (s, 3H), 4.8 (m, 2H), 5.4 (m, 1H), 6.76 (d, 2H, J=9 Hz), 7.16 (d, 2H, J=9 Hz), 11.3 (br s, 1H). An analytical sample was prepared by diazomethane treatment of the acid, followed by chromatography and evaporative distillation of the ester 14b: IR ($CDCl_3$) 3085, 2950, 2845, 1725, 1615, 1510, 1460, 1435, 1250, 1185, 1065, 830 cm^{-1}. Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.70, H, 7.71.

3-Methyl-2-(4-dimethylaminophenyl)-4-pentenoic acid (13c).

According to the procedure described above, 183 mg (0.785 mmol) of ester 12c gave back 31.1 mg (0.133 mmol) of starting material, thus $k = 6.6 \times 10^{-4}$ sec^{-1}. Because the rearranged product is an amino acid, its recovery from the reaction mixture was difficult and incomplete. Diazomethane treatment followed by chromatography (10% ethyl acetate-petroleum ether) and evaporative distillation (70°, 0.05 mmHg) gave the methyl esters 14c: Rf 0.22 (10% ethyl acetate-hexane); ^1H NMR ($CDCl_3$) δ 0.80, 1.09 (d, 3H, J=7 Hz), 2.89 (s, 6H), 3.21, 3.24 (d, 1H, J=10 Hz), 3.60 (s, 3H), 4.8 (m, 2H), 5.5 (m, 1H), 6.60 (d, 2H, J=9 Hz), 7.10 (d, 2H, J=9 Hz). Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.69; H, 8.41; N, 5.52.

3-Methyl-2-(4-nitrophenyl)-4-pentenoic acid (13d).

For the reason mentioned in the text, the rate constant for rearrangement of this ester was not determined; however, the ester was rearranged under the standard conditions. The rate of this rearrangement appeared by TLC to be comparable to, although slightly slower than, the rate of rearrangement of p-methoxyphenyl ester 12b. Thus, 225 mg (0.955 mmol) of ester 12d afforded, after diazomethane treatment and chromatography with 10% ethyl acetate-petroleum ether, 110 mg

(0.443 mmol, 46%) of a diastereomeric mixture of esters 14d: Rf 0.21 (10% ethyl acetate-hexane); IR ($CDCl_3$) 3100, 3000, 1735, 1610, 1525, 1440, 1350, 1210, 1175, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82, 1.14 (d, 3H, J=7 Hz), 2.9 (m, 1H), 3.49 (d, 1H, J=10 Hz), 3.65, 3.71 (s, 3H), 4.8 (m, 2H), 5.5 (m, 1H), 7.5 (m, 2H), 8.2 (m, 2H).

3(R)-Hydroxy-2(S)-methyl-2,3-dihydrofuran (8).

To a cold (-78°), stirred solution of 1.005 g (5.770 mmol) of lactol 20[43] and 0.61 ml (6.3 mmol) of carbon tetrachloride in 120 ml of dry THF was added 1.11 ml (6.11 mmol) of tris(dimethylamino)phosphine. The clear solution was stirred for 30 min. at -78° and then warmed to room temperature.

Approximately 125 ml of ammonia (previously dried by passage through a KOH tower) was condensed onto 9.4 cm (58 mmol) of lithium wire. The deep blue solution was stirred for 30 min. at ammonia reflux, then cooled to -78°. To this was added via cannula the chloride solution prepared above, and the resulting mixture was allowed to warm to ammonia reflux. After 30 min., about 1 g of anhydrous $MgSO_4$ and enough dry ammonium chloride to discharge the blue color was added, and the ammonia was allowed to evaporate. Dry ether was occasionally added to the mixture to maintain the volume at ca. 75 ml. When the ammonia had all escaped, the mixture was filtered and the solvent

removed under atmospheric pressure through a short Vigreux column. Because of the volatility of the glycal, little or no product was obtained if the solvent was removed under reduced pressure on a rotary evaporator. Flash chromatography of the product with 70% ether-pentane, again with atmospheric-pressure solvent removal, afforded about 0.48 g (80%) of the glycal: Evaporative distillation 40° (20 mmHg); Rf 0.18 (50% ether-hexane); ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 3H, J=7 Hz), 1.50 (d, 1H, J=8 Hz), 4.4 (m, 2H), 5.10 (dd, 1H), 6.50 (d, 1H, J=3 Hz).

"Ox" derivative of (+)-Furanomycin (23)

By the oxalyl chloride-DMF method described previously, 1.00 g (3.39 mmol) of ox-glycine was converted to the acid chloride. The light yellow solid was placed under high vacuum overnight to remove all volatile material.

To a cold (-78°), stirred solution of ca. 0.48 g (4.8 mmol) of glycal 8 and a small crystal of 1,10-phenanthroline in 7.0 ml of dry THF was slowly added n-butyllithium (2.64 M in hexane) until a faint pink color persisted. The acid chloride prepared above was dissolved in 7.0 ml of THF and added to the glycal anion solution over a period of 15 min. This solution was stirred at -78° for 90 min. and then cannulated into a cold (-78°), stirred solution of 1.0 eq of LDA

in 17 ml of THF. After 10 min., 2 eq of chlorotrimethylsilane was added as 1.2 ml of the supernatant centrifugate from a 3:1 v:v mixture of TMSCl and triethylamine. Ten minutes was allowed for trapping, then the mixture was warmed to room temperature and stirred for 30 min. Aqueous workup afforded 0.876 g of yellow solid, which contained the desired product accompanied by ox-glycine, solvent, and a small amount of the beta-eliminated acid 21.

The product was chromatographed on silica with 20% acetic acid-toluene. Although the mixture resolved well on TLC in this solvent, column separation was very poor even when the silica was grossly underloaded (ca. 500-1000:1 w:w silica:product). Mixed fractions were always obtained; these were repeatedly re-chromatographed. The end result of all this was about 0.36 g of ox-furanomycin; the actual weight was uncertain because the product tenaciously retained solvent. Large amounts of ethyl acetate, THF, toluene, and other solvents were routinely observed in the NMR spectrum even after the product stood overnight or longer under high vacuum. Integration of the product and solvent peaks gave a corrected yield of 27% of 23: $[\alpha]_D$ +36.9° (c=0.07016, $CHCl_3$); IR ($CHCl_3$) 3500, 3020, 3000, 1760, 1450, 1375, 1095, 1070, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, 3H, J=7 Hz); 3.84 (d, 1H, J=9 Hz), 4.5 (m, 1H, C<u>H</u>CH_3); 5.5 (dd, 1H, OC<u>H</u>),

5.6 (dd, 1H); 5.9 (dd, 1H), 7.2 (d, 10H), 10.5 (br s, 1H). An analytical sample was prepared by diazomethane treatment followed by evaporative distillation (180°, 0.01 mmHg) of the methyl ester: Rf 0.24 (30% ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$) δ 1.20 (d, 3H, J=6 Hz), 3.74 (s, 3H), 3.98 (d, 1H, J=10 Hz), 4.6 (m, 1H), 5.4 (m, 1H), 5.8 (m, 1H), 6.1 (m, 1H), 7.4 (d, 10 H). Anal. Calcd. for $C_{23}H_{21}NO_5$: C, 70.58; H, 5.41; N, 3.58. Found: C, 70.66; H, 5.59; N, 3.53.

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43. This lactol was prepared by a method analogous to that used by B. Fitzsimmons and R. Anderson in these laboratories. For experimental details, see ref. 7 and 37.

44. It has recently been found that allyl esters of 2-indoleacetic acid undergo the enolate Claisen reaction normally, whereas esters of 3-indole-acetic acid give none of the desired product. This phenomenon is probably closely related to the "pyrrole anomaly".

45. Boiling points are uncorrected. Melting points were determined using a Hoover melting point apparatus and are uncorrected. All temperatures reported are in degrees Celsius. Infrared (IR) spectra were recorded on a Perkin-Elmer 1310 infrared spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian EM-390, Jeol FX-90Q, or Brucker WM-500 specrometers.

^1H chemical shifts are reported in delta values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Optical rotations were measured in 1 dm cells of 1 ml capacity using a Jasco DIP-181 polarimeter.

Analytical thin-layer chromatography (TLC) was conducted on precoated TLC plates, silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck and Co. Darmstadt, Germany. Silica gel columns for chromatography utilized E. Merck "Silica Gel 60", 70-230 mesh ASTM. "Flash" chromatography was conducted according to the method of Still.[42]

"Dry" solvents were distilled shortly before use from an appropriate drying agent. Ether and tetrahydrofuran (THF) were distilled under dry argon from sodium-benzophenone ketyl. Benzene was distilled from calcium hydride. Hexamethylphosphoric triamide (HMPA) was distilled at ca. 1.0 mmHg from calcium hydride. Triethylamine was distilled under argon from sodium-benzophenone ketyl. Diisopropylamine and hexamethyldisilazane were distilled before use from calcium hydride.

Other reagents were purified as follows: oxalyl chloride and chlorotrimethylsilane (TMSCl) were stirred with calcium hydride overnight and then distilled under argon; tris(dimethylamino)-

phosphine (TDAP) was distilled under ca. 20 mmHg of argon before use; thionyl chloride was distilled from linseed oil; dimethylformamide (DMF) was distilled from calcium hydride at reduced pressure. Ammonium chloride was dried at 75° under vacuum (1 mmHg) over phosphorous pentoxide for at least 12 hours.

All other reactants and solvents were "Reagent Grade" unless otherwise specified. "Ether" refers to anhydrous diethyl ether which is supplied by Mallinckrodt and Baker. "Petroleum ether" refers to the Analyzed Reagent grade hydrocarbon fraction, bp 35-60°, which is supplied by J. T. Baker Co., Phillipsburg, N.J., and was not further purified.

Reactions were run under an argon atmosphere arranged with a mercury bubbler such that the system could be alternately evacuated and backflushed with argon, leaving the system under a slight positive pressure of argon.

Syringes and reaction flasks were dried in an oven at 120-140° for at least 12 hours, and were cooled in a desiccator over anhydrous calcium sulfate prior to use.

Elemental combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan.