AN ABSTRACT OF THE THESIS OF

Paul Robert Johnson for the degree of Master of Science in Chemistry presented on November 18, 1982.

Title: Condensation of Crotonic and Tiglic Acids with Aldehydes and Ketones

Abstract approved: Redacted for Privacy

Dr. James D. White

3,3-Dimethoxy-2,2-dimethylpropionaldehyde was prepared from isobutyraldehyde and formaldehyde in four steps. Heptanal, benzaldehyde, isobutyraldehyde, 3,3-dimethoxy-2,2-dimethylpropionaldehyde, acetone, and cyclopentanone were each condensed with the dianions of crotonic acid and tiglic acid at -78°C, 25°C, and 65°C, and the proportions of the α and γ condensation products were determined. The results indicated that the proportions of α and γ condensation products are dependent on the steric size of the aldehyde or ketone, on the presence of a methyl substituent at the α carbon of the acid, on the reaction temperature, and on the duration of the reaction. A mechanism, which involves reversible formation of the α product and recombination to the γ product is proposed. A required precursor to boromycin, 7,7-dimethoxy-5-hydroxy-2,6,6-trimethylheptanoic acid lactone was prepared by condensing 3,3-dimethoxy-2,2-dimethylpropionaldehyde with the dianion of tiglic acid to give 7,7-dimethoxy-5-hydroxy-2,6,6-trimethyl-2-heptenoic acid. This acid was hydrogenated and lactonized to give the corresponding δ-lactone.

Condensation of Crotonic and Tiglic Acids with Aldehydes and Ketones

by

Paul Robert Johnson

A THESIS

submitted to

Oregon State University

in partial fulfillment of
the requirements for the
degree of

Master of Science

Completed November 18, 1982

Commencement June 1983

APPROVED:

Redacted for Privacy

Professor of Chemistry, in charge of major

Redacted for Privacy

Head of Department of Chemistry

Redacted for Privacy

Dean of Graduate School

Date thesis is presented November 18, 1982

Typed by Karen L. Johnson for Paul Robert Johnson

For Guy Dority,

my mentor and friend

ACKNOWLEDGEMENTS

I would like to thank the postdocs and graduate students with whom I spent many hours both in and out of lab, for the knowledge and experience they shared with me and for the patience they exerted in answering my numerous questions. In particular, I would like to acknowledge Drs. Mitchell Avery, Giorgio Caravatti, J.P. Carter, Wesley KM Chong, Satish Choudhry, and Alan Whittle. I also wish to thank Professor James D. White for his guidance and encouragement; my wife, parents, and in-laws for their emotional support; and Rodger Kohnert for his work in running the Nuclear Magnetic Resonance and Mass Spectrometers. Finally, I wish to acknowledge the National Institute of Health and the N.L. Tartar Foundation for their financial support of this project.

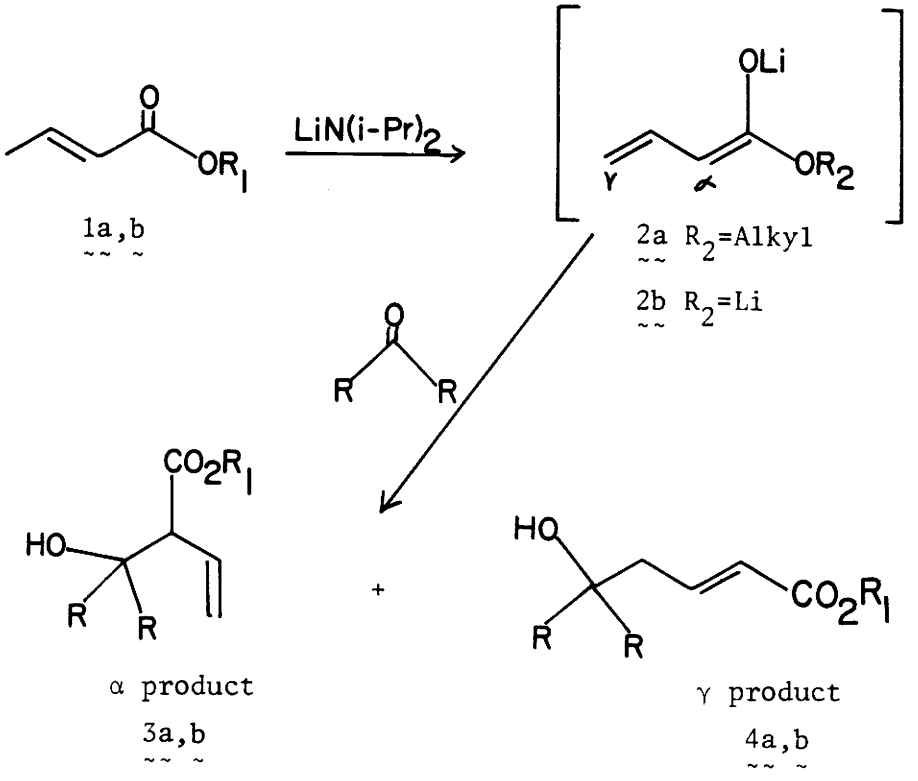
TABLE OF CONTENTS

LIST OF TABLES

CONDENSATION OF CROTONIC AND TIGLIC ACIDS WITH ALDEHYDES AND KETONES

I. INTRODUCTION

The aldol condensation of an aldehyde or ketone with the enolate anion 2a of an α,β-unsaturated ester 1a can lead to two isomeric products. One possible product 3a is derived from electrophilic attack on the ester at the carbon α to the carbonyl (C-2), and the other product 4a results from attack at the carbon γ to the carbonyl (C-4) (Scheme 1).[1] A similar situation is found with α,β-unsaturated acids 1b, in which the carboxylate-enolate dianion 2b can give α or γ substitution products 3b and 4b, respectively.



1a,b

2a R_2=Alkyl

2b R_2=Li

α product

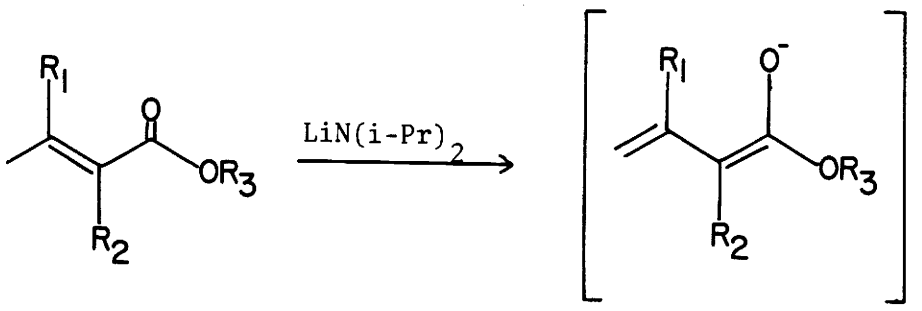
3a,b

γ product

4a,b

a, R_1=Alkyl; b, R_1=H

Scheme 1



5, $R_1=R_2=R_3=H$

6, $R_1=R_3=H$, $R_2=CH_3$

7, $R_1=CH_3$, $R_2=H$, $R_3=H$

11, $R_1=R_2=H$, $R_3=Et$

12, $R_1=H$, $R_2=CH_3$, $R_3=Et$

13, $R_1=CH_3$, $R_2=H$, $R_3=Et$

8, $R_1=R_2=H$, $R_3=Li$

9, $R_1=H$, $R_2=CH_3$, $R_3=Li$

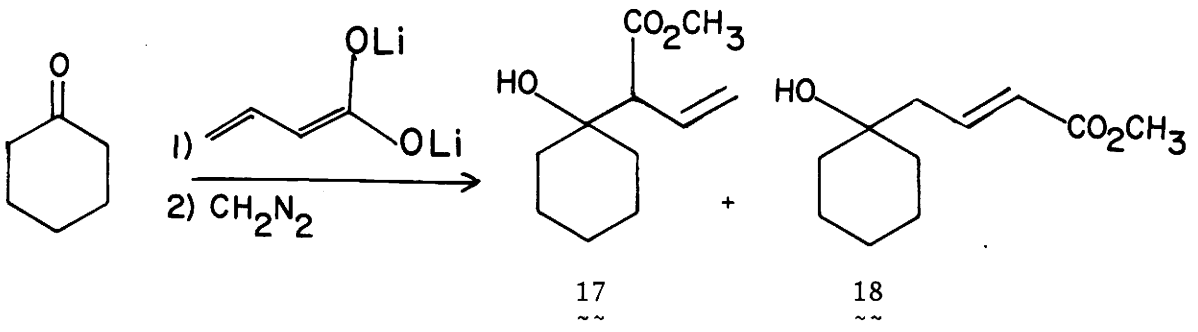
10, $R_1=CH_3$, $R_2=H$, $R_3=Li$

14, $R_1=R_2=H$, $R_3=Et$

15, $R_1=H$, $R_2=CH_3$, $R_3=Et$

16, $R_1=CH_3$, $R_2=H$, $R_3=Et$

The dianions of crotonic (5), tiglic (6), and senecioic acids (7), and the monoanions (enolates) of their respective esters 11, 12, 13, have been studied by several research groups with the purpose of maximizing the yield of the γ product. In 1972, Watanabe et al published the first example of such a reaction.[2] In their study, they showed that γ condensation products were obtained from the reaction of crotonic acid with several different ketones when the acid was treated with 2.2 molar equivalents of lithium naphthalenide and diethylamine in tetrahydrofuran at 40-50°C. The E,γ hydroxy acid 4b was the sole product. No observance of the isomeric α product was reported by these authors.



17 18

Scheme 2

Pfeffer et al published in 1973 that they had repeated Watanabe's work and had indeed found α product 3b (Scheme 2).[3] They proposed that the discrepancy was due to the method used for esterification of the acid for characterization. Watanabe had esterified his acidic product by refluxing the acid in methanol with a catalytic amount of p-toluenesulfonic acid. Pfeffer showed that, while the γ product 4b is esterified quite readily, the α product 3b is very slow to esterify, probably due to the hindered nature of the acid. Thus, under Watanabe's conditions, the α substituted acid was perhaps lost in a basic extraction during workup of the ester. Pfeffer therefore suggested the use of diazomethane for esterification and, when the condensation of crotonic acid dianion with cyclohexanone was repeated using diazomethane to esterify the acid, a 2:3 ratio of α to γ products (17 and 18 respectively) was obtained. The two authors did concur that the γ product had not undergone geometrical isomerization of the double bond.

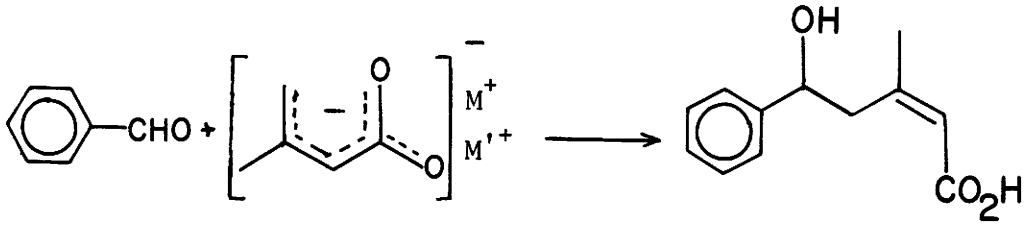
Cardillo et al in 1973 studied the effects of various metal counterions to the dianion of senecioic acid and its isomer, 3-methyl-3-butenoic acid, on the α to γ ratio when they were condensed with benzaldehyde.[4] Combinations of lithium, sodium, potassium, dibutylaluminum, and tributyl tin were tried. The results are tabulated below (Table 1). In order to help solubilize the salts, hexamethylphosphoramide (HMPA) was added to the sodium-lithium, potassium-lithium, and potassium-potassium mixtures.

Table 1. Ratio of α/γ Condensation Products from Senecioic Acid with Benzaldehyde

M - M'	% of α	% of γ	% overall yield
$Li-SnBu_3$	100	0	58
$AlBu_2-Li$	67	33	55
Li-Li	54	46	61
Na-Li	35	65	80
K-Li	22	78	46
K-K	0	100	40

In explaining these results, Cardillo stated that a strongly electropositive cation should favor a free dianionic species, whereas a weakly electropositive cation should favor a more covalent species. The results shown in Table 1 demonstrate that increasing ionic character of the organometallic bond leads to a greater proportion of C-4 attack and thus γ product. Several structures were considered

for the metalated dianion, the "U" species 10a being proposed as the thermodynamically more stable structure. This structure explains why only the cis isomer was observed for the C-4 alkylated products (Scheme 3).

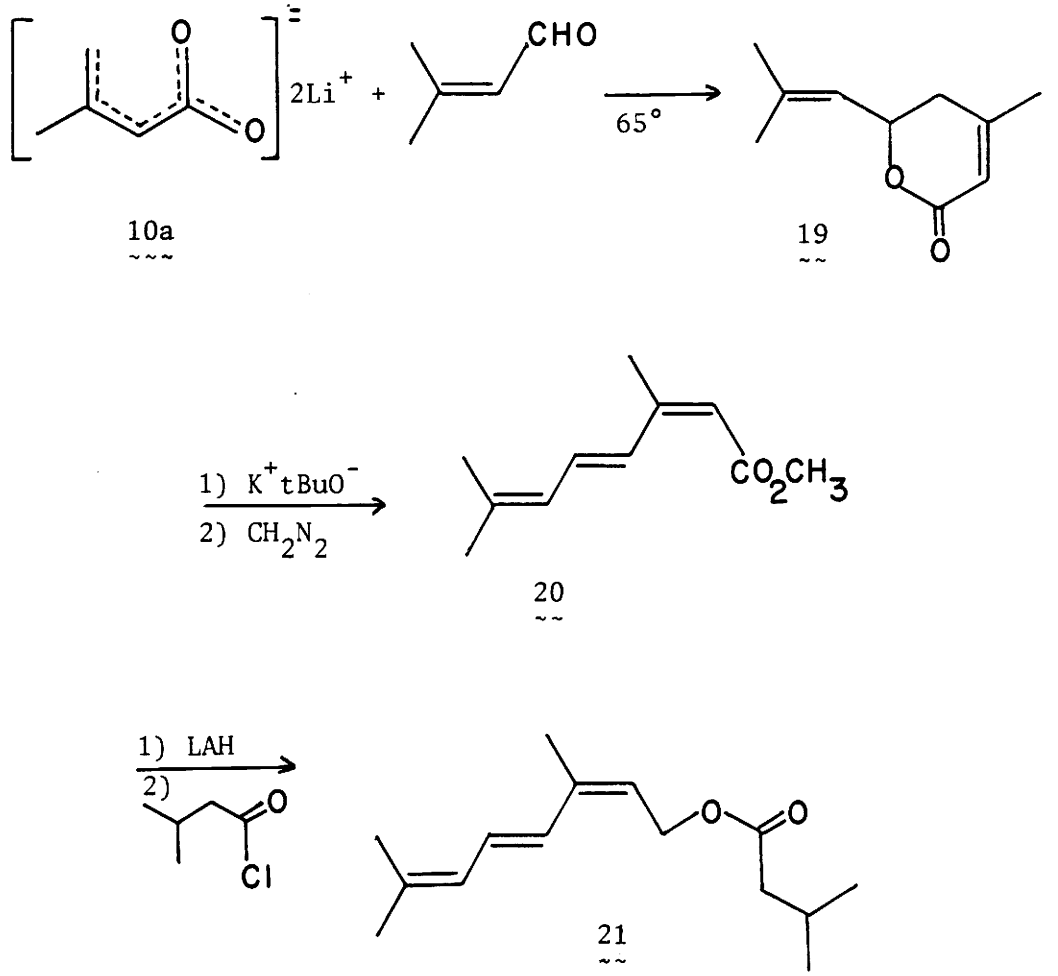


10a

Scheme 3

In a later paper, Cardillo used this methodology in a stereospecific synthesis of dehydroneryl isovalerate, where a senecioic acid dianion (10a) condensation provided a method for addition of an intact isoprene unit.[5] In this report, he showed that there was a definite temperature dependence of the α to γ product ratio. Only the α isomer was obtained when the reaction was kept at -78°C but, upon heating the reaction to reflux in tetrahydrofuran, only the γ product, which is converted quantitatively into the corresponding lactone 19, was found. This observation suggested that the condensation is reversible at higher temperature and that the γ product is more stable. This product was further transformed by treatment with potassium t-butoxide followed by diazomethane to

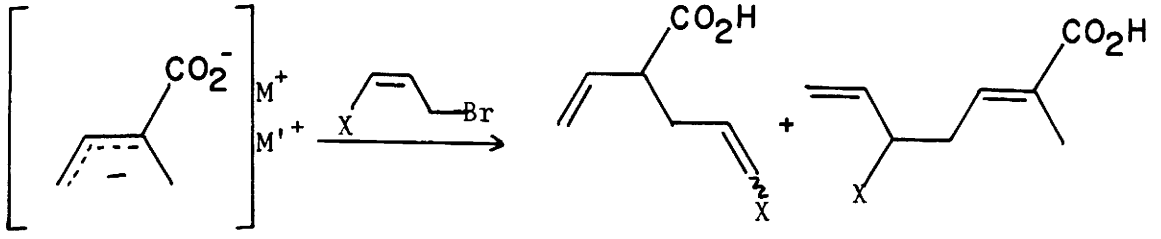
form the desired terpenoid 20. Elaboration gave dehydroneryl isovalerate (21) (Scheme 4).



Scheme 4

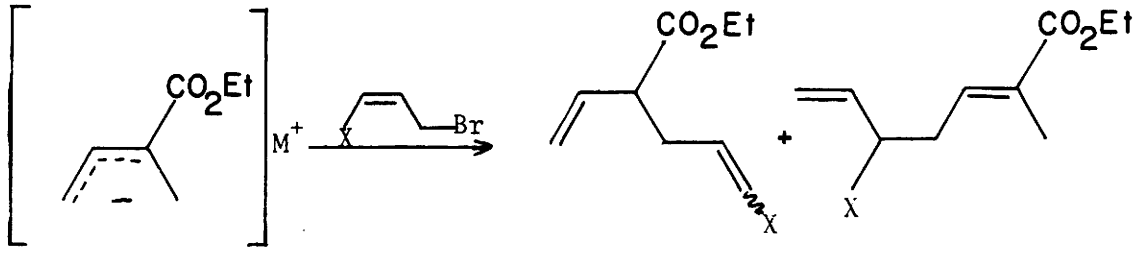
Katzenellenbogen and Crumrine, in their study of the γ-alkylation of α,β-unsaturated acid dianions and the corresponding ester anions, reacted (E) and (Z)-3-methyl-2-hexenoic, crotonic, senecioic, tiglic, and angelic acid dianions with a variety of allyl halides,

using lithium or copper as the cation (Scheme 5).[6] Although their study did not involve the aldol reaction, it did point out some important facts concerning the acid dienolates. First, the addition of cuprous iodide to the lithium dianion of the acid 9 resulted in a marked increase in the proportion of γ product, whereas no significant increase was observed in the corresponding ester anion 15. While it is not clear how a copper(I) counterion is able to effect such a dramatic reversal from α to γ product, in the case of 9b, it was shown that products from α alkylation are derived from direct (S_N2) displacement of halide, whereas γ products arise from transposition of the allylic unit (S_N2'). Second, crotonic, tiglic, and most notably angelic acid (the Z isomer of tiglic acid), all



9

M^+ = Li	% α	% γ
a) M'^+ = Li	100	0
b) M'^+ = Cu	4	96

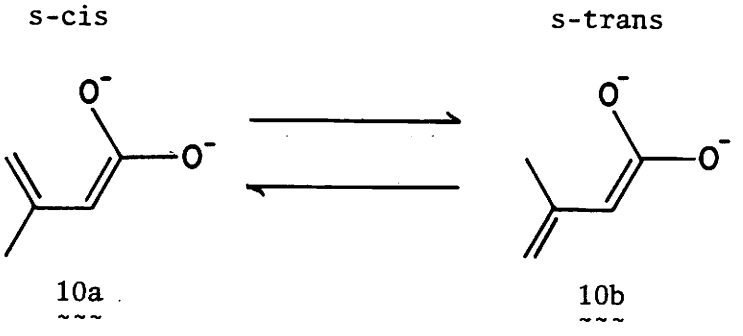


15

	% α	% γ
a) M^+ = Li	95	5
b) M^+ = Cu	95	5

Scheme 5 (X=D)

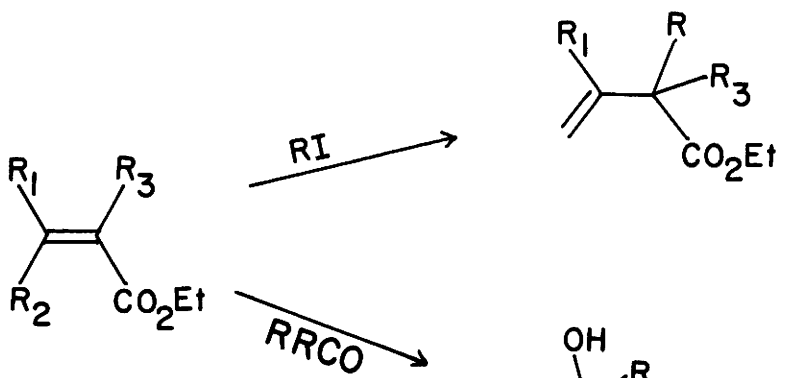
gave γ products with the E configuration. With senecioic acid, a 1:1 mixture of E:Z isomers was obtained. This seems to conflict with Cardillo's work in which he obtained only the Z isomer from senecioic acid. The 1:1 mixture of geometrical isomers obtained by γ alkylation of senecioic acid could only arise from equilibration of the s-cis 10a and s-trans 10b forms of the dianion. The interconvertibility of the s-cis and s-trans isomers is best supported by the fact that the dianions of tiglic acid and angelic acid gave only the product of tiglic configuration.



10a 10b

Ikekawa et al observed a distinct difference between the ratios of α to γ products of α,β-unsaturated esters when they were reacted with alkyl halides as opposed to carbonyl electrophiles.[7] There was also a marked increase in the γ product if the dienolate possessed an α methyl group. In their study, a series of alkyl halides and carbonyl electrophiles was reacted with ethyl senecioate (13), ethyl tiglate (12), and ethyl 2-methyl senecioate (22) (Scheme 6). Typical reaction conditions involved addition of the ester to a solution of lithium diisopropylamide in tetrahydrofuran-hexamethylphosphoramide at -78°C, followed by addition of 1.2 equivalents of

the electrophile at -78°C. Only α attack was observed with an alkyl halide but with carbonyl compounds, ethyl senecioate gave entirely α product whereas ethyl tiglate and ethyl 2-methyl senecioate gave only γ product.



12, $R_1=R_3=CH_3$, $R_2=H$

13, $R_1=R_2=CH_3$, $R_3=H$

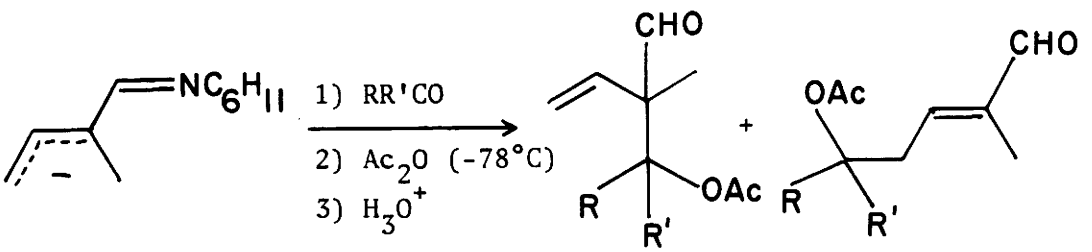
22, $R_1=R_2=R_3=CH_3$

Scheme 6

In a study by Casinos and Mestres on a series of different aldehydes and ketones with the dianions of senecioic acid and crotonic acid, it was found that the ratio of α to γ products was dependent not only on the structure of the acid and the temperature, but also on the structure of the carbonyl electrophile.[8] It was also shown that the α product can rearrange to the γ product when subjected to lithium diethylamide in tetrahydrofuran and warmed to 50°C. These authors felt that their results indicate that the

α isomer is the kinetic product and that upon warming, a slow isomerization through retroaddition and recombination to the more stable γ product takes place.

More recent research in this field has involved other α,β-unsaturated carbonyl derivatives, as in the work of Vedejs et al.[9] They studied the reaction of carbonyl electrophiles with the anion of the aldimine of tigaldehyde (Scheme 7) and found, as have others,[4,8] that the addition of hexamethylphosphoramide to the reaction mixture greatly enhances the yield of the γ product, presumably by increasing the ionic character of the allylic anion. Using a series of electrophiles, they also confirmed that increasing the steric size of the electrophile favors the γ product.

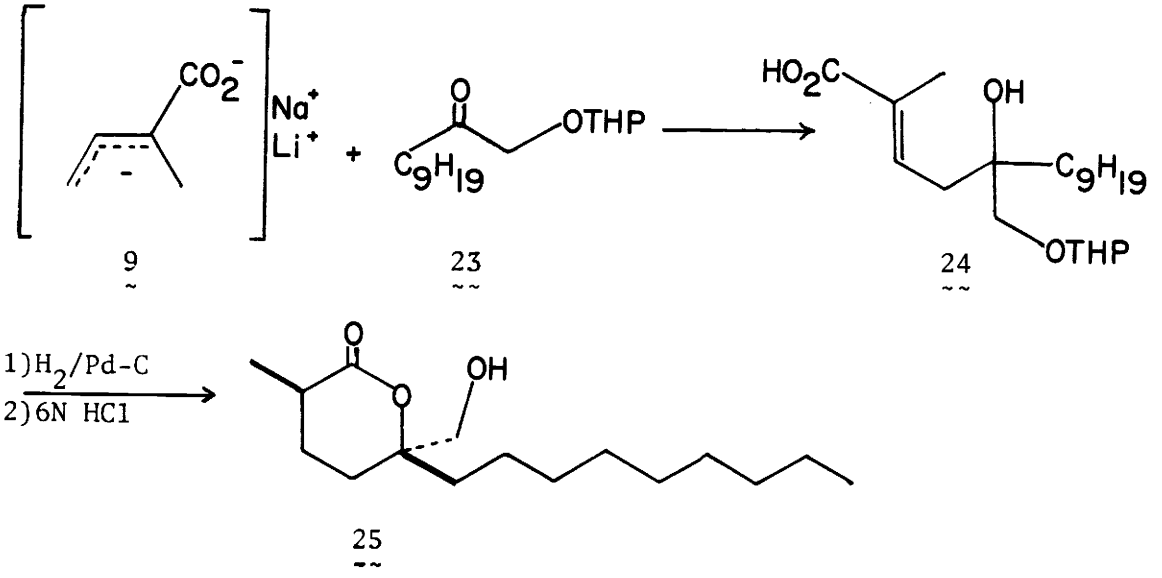


Scheme 7

Snieckus et al carried out a study similar to Katzenellenbogen's, using the lithium and copper dienolates of crotonic and senecioic amides as contrasted with the acids.[10] These authors claimed that the amides afforded greater regio- and stereoselectivity compared to the corresponding acid dienolates, but otherwise the results of the two groups are in close accord.

Much of the impetus for investigation of the reactions discussed above has revolved around the synthesis of terpenes, in which the unsaturated acid or derivative thereof is used as a synthon for the isoprenoid unit.[11,12] Since only the γ isomer is useful in this regard, most efforts have been directed towards finding ways to control the regioselectivity and to maximize the yield of the γ product.

Most recently, Cardillo in his continuing research in this field, has used the γ condensation product of tiglic acid to produce the δ-lactone moiety of a marine algal antibiotic malyngolide (25).[13] In this example, he used the lithium-sodium dianion of tiglic acid with the ketone 23 to give a 68% yield of the γ product 24. The double bond of 24 was then reduced and the hydroxy acid lactonized to (±)malyngolide (Scheme 8).

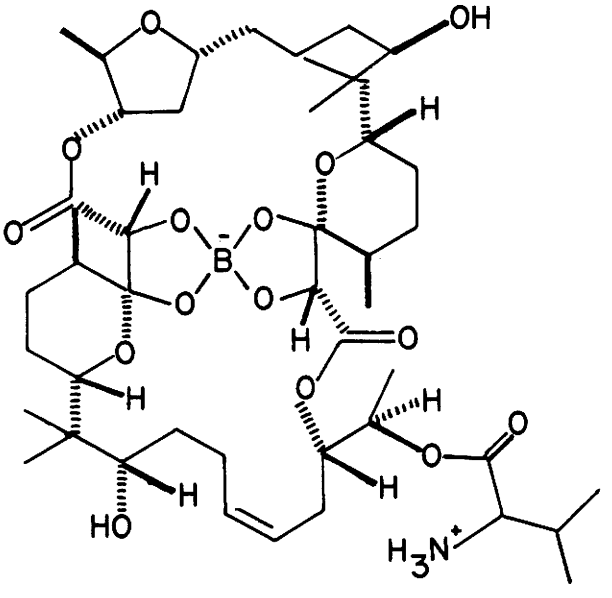


9 23 24

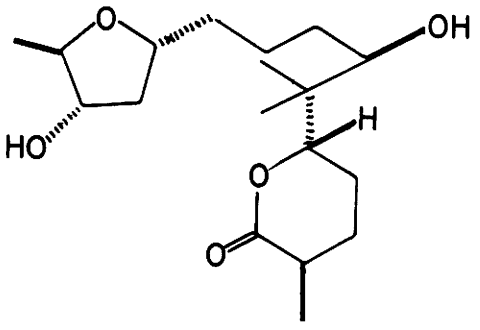
25

Scheme 8

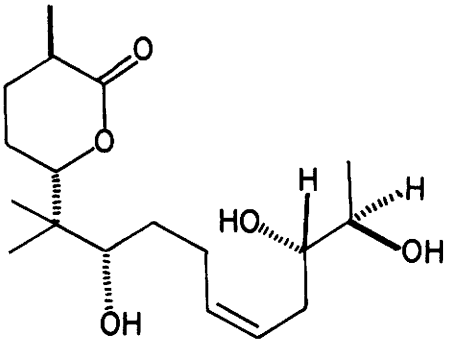
Our own interest in this process was stimulated by the need to synthesize a segment of the boromycin molecule. Boromycin (26) is an antibiotic of Streptomyces antibioticus. It was shown by Avery and White that boromycin can be degraded into two lactones by successive treatment with aqueous sodium hydroxide and then hydrochloric acid.[14] The two fragments so generated, the so-called "northern" 27 and "southern" 28 lactones, result from a retro-Claisen scission of the glycolate moieties which arise by cleavage of the macrolide linkages of 26.



26

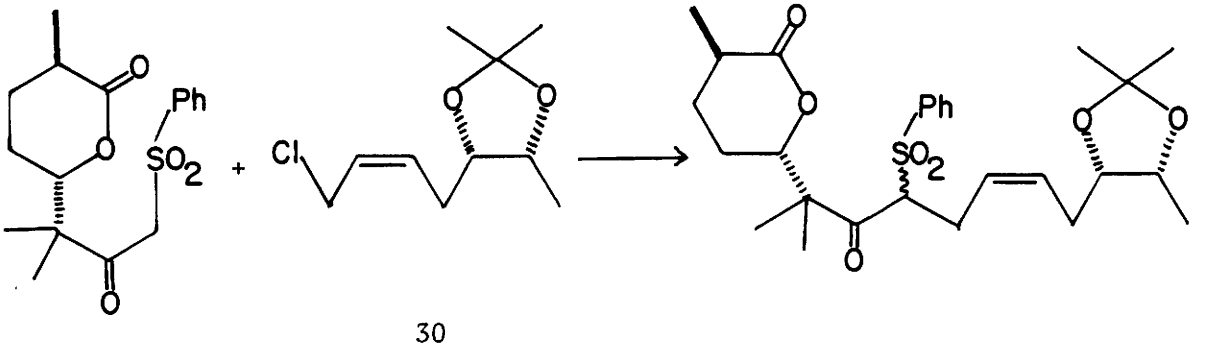


27



28

One approach to the synthesis of boromycin involves the construction of the northern and southern segments followed by coupling to give the macrocycle. Our strategy for the synthesis of the northern and southern halves follows a convergent route, whereby the anion of ketosulfone 29 would be alkylated with 30 (Scheme 9) to give, after reductive removal of the sulfonyl group, the southern lactone 28. The northern lactone 27 could then be prepared via similar methodology or directly from the southern half 28. The

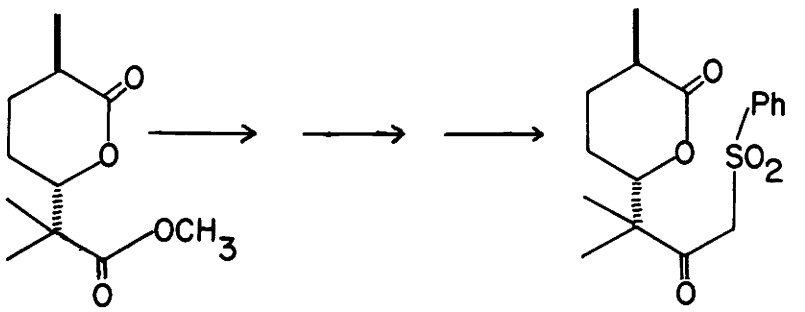


29

30

Scheme 9

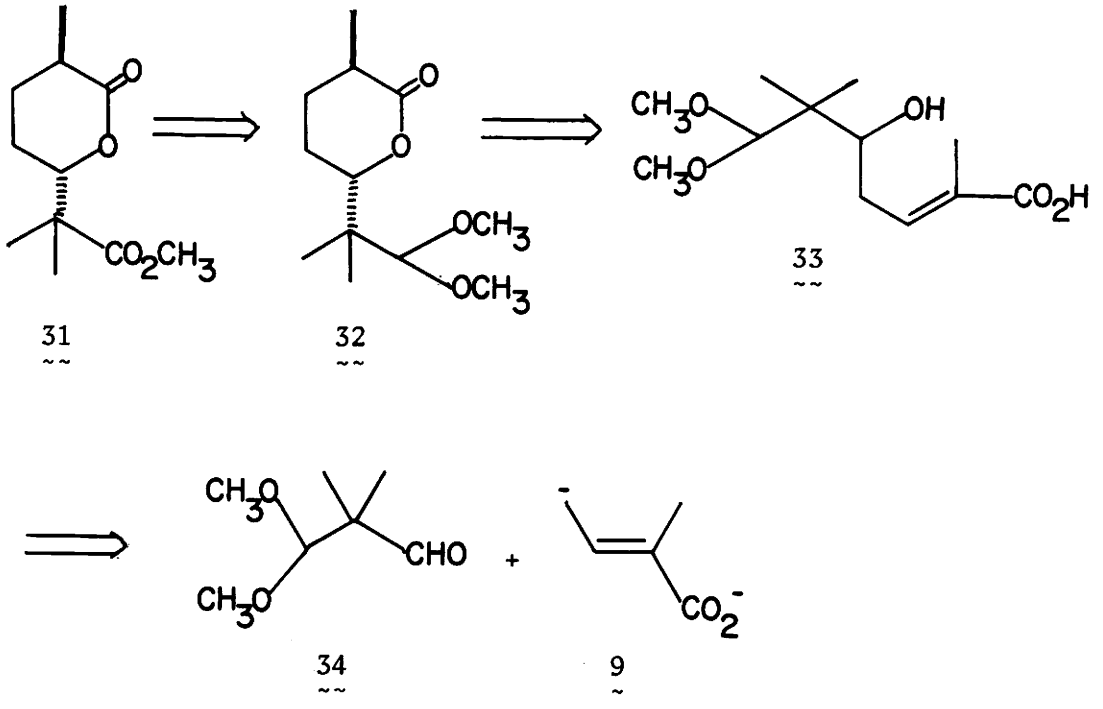
sulfone 29 is obtained from the δ-lactone ester 31 via several steps (Scheme 10), and this substance thus becomes a pivotal intermediate in the boromycin strategy. It was envisioned that a tiglate



31 29

Scheme 10

dianion condensation with the aldehyde 34 could be developed into an efficient route to 31 (Scheme 11) via the hydroxy acid 33 and the lactone 32. In addition to a general study of the condensation of dianions of tiglic and crotonic acids with aldehydes and ketones, with the aim of clarifying those factors which influence the α:γ ratio, this work has focussed on the specific application of the reaction to the synthesis of 32.



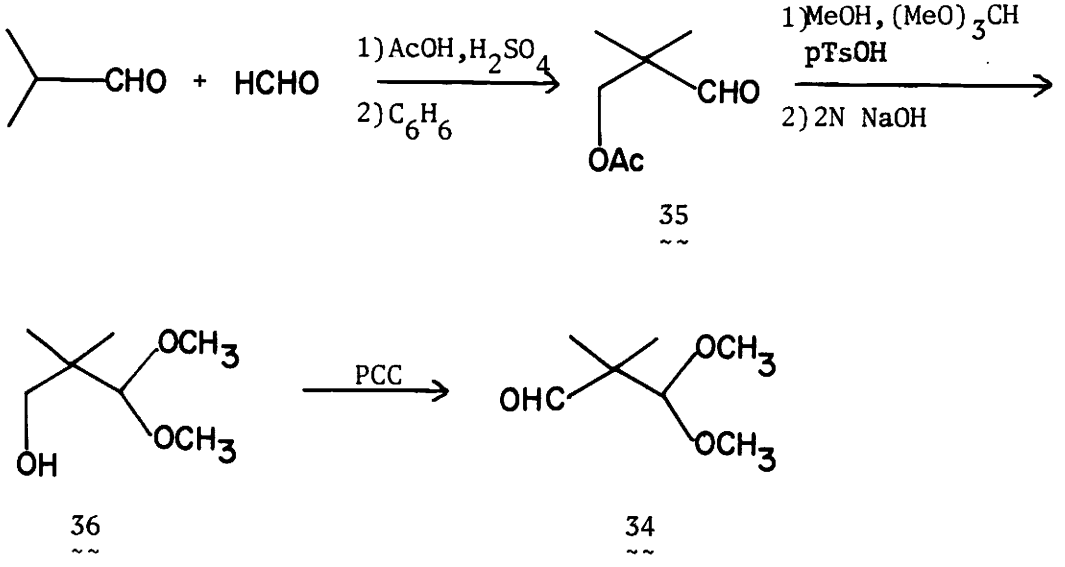
31 32 33

34 9

Scheme 11

II. Condensation Studies with Crotonate and Tiglate Dianions

Since aldehyde 34 was to be the starting point for a synthesis of boromycin and, hence, a key substrate for condensation studies, our first objective was a synthesis of this compound. This was most easily and efficiently accomplished by the route shown in Scheme 12.



35 36 34

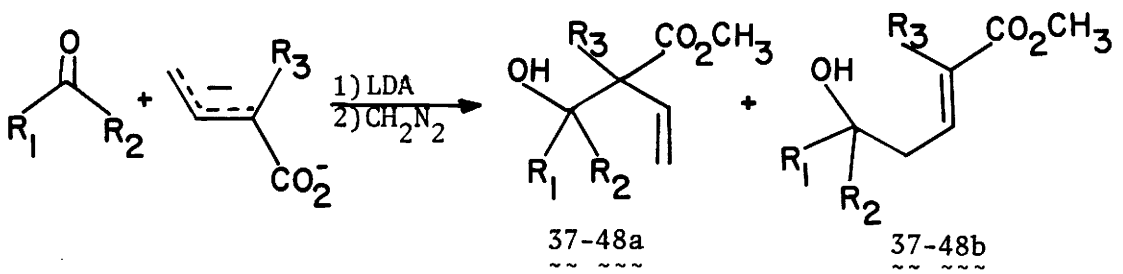
Scheme 12

Isobutyraldehyde was condensed with 37% aqueous formaldehyde in glacial acetic acid containing a catalytic amount of sulfuric acid. Water was removed from the system as a benzene azeotrope by reflux under a Dean-Stark condenser to give 3-acetoxy-2,2-dimethylpropionaldehyde (35). Formation of the dimethyl acetal of 35 and

cleavage of the acetate was done in a two-step process using trimethyl orthoformate in methanol with p-toluenesulfonic acid as catalyst, followed by hydrolysis of the ester with 2N sodium hydroxide. This protocol directly gave the acetal 36. The primary alcohol was then oxidized with pyridinium chlorochromate to furnish 3,3-dimethoxy-2,2-dimethylpropionaldehyde (34) in 68% yield from isobutyraldehyde.

Previous studies of the condensation of α,β-unsaturated acid dianions with carbonyl electrophiles suggested that several factors, including the steric bulk of the carbonyl electrophile, the reaction temperature, the counterion, and the use of hexamethylphosphoramide as cosolvent, can influence the proportion of α to γ condensation products.[4,8,9] In our work, we were particularly interested in the effect which increasing steric size of the carbonyl compound and additional substitution at the α carbon of the unsaturated acid would have on the α:γ product ratio, and also in the effect of reaction temperature on the ratio with a given carbonyl compound and acid. Since the previous studies involved reagent combinations which did not address these questions consistently, and especially since the earlier work had not been systematic with respect to reaction time or temperature, we wished to standardize the reaction conditions in order to enable us to better understand the effect of each variable on the product ratio. A series of four aldehydes and two ketones were selected for this purpose, with increasing steric hindrance around the carbonyl moiety: heptanal, benzaldehyde, isobutyraldehyde, 3,3-dimethoxy-2,2-dimethylpropionaldehyde (34), acetone, and cyclopentanone. Crotonic (5) and tiglic acids (6) were

chosen as the unsaturated acid components, primarily to determine whether an α methyl group in the carboxylic acid would have a significant effect on the α to γ ratio. Each combination of acid and aldehyde or ketone was reacted under identical conditions at three different temperatures: -78°C, room temperature, and at the reflux temperature of tetrahydrofuran (65°C) (Scheme 13). The products obtained from these condensations are given in Table 2.



Scheme 13

Table 2. Products from Condensation of Crotonic and Tiglic Acids with Aldehydes and Ketones

Product	R_1	R_2	R_3
37a	C_6H_{13}	H	H
37b	C_6H_{13}	H	H
38a	C_6H_{13}	H	CH_3
38b	C_6H_{13}	H	CH_3
39a	C_6H_5	H	H
39b	C_6H_5	H	H
40a	C_6H_5	H	CH_3
40b	C_6H_5	H	CH_3

Table 2, Continued:

Product	R_1	R_2	R_3
41a	$(CH_3)_2CH$	H	H
41b	$(CH_3)_2CH$	H	H
42a	$(CH_3)_2CH$	H	CH_3
42b	$(CH_3)_2CH$	H	CH_3
43a	$(CH_3O)_2CHC(CH_3)_2$	H	H
43b	$(CH_3O)_2CHC(CH_3)_2$	H	H
44a	$(CH_3O)_2CHC(CH_3)_2$	H	CH_3
44b	$(CH_3O)_2CHC(CH_3)_2$	H	CH_3
45a	CH_3	CH_3	H
45b	CH_3	CH_3	H
46a	CH_3	CH_3	CH_3
46b	CH_3	CH_3	CH_3
47a	$-(CH_2)_4-$		H
47b	$-(CH_2)_4-$		H
48a	$-(CH_2)_4-$		CH_3
48b	$-(CH_2)_4-$		CH_3

The crotonate and tiglate dianions were prepared by addition of the acid, as a solution in tetrahydrofuran, to a solution of 2.2 equivalents of lithium diisopropylamide in tetrahydrofuran at -78°C. Formation of the dianion was indicated by a bright yellow colored solution. The aldehyde or ketone was then added as a solution in tetrahydrofuran to the dianion at -78°C and the mixture was stirred at the specified temperature for six hours. Workup involved

quenching the reaction with a mixture of saturated aqueous ammonium chloride and ether, washing the ethereal layer with saturated aqueous sodium bicarbonate, and acidifying the combined aqueous layer with 3N hydrochloric acid. The acidic products were extracted with ether and esterified with diazomethane. After removal of the solvent and any volatile byproducts, the NMR spectrum of the mixture was recorded without further purification. Separation of the α and γ mixture was achieved on silica, using either medium pressure liquid chromatography or flash chromatography. Characterization of the purified products was performed on both the hydroxy esters themselves and their 3,5-dinitrobenzoate derivatives.

The products of condensation at the α carbon of the acid all have in common the terminal, vinylic methylene group, observed in the NMR spectrum as a multiplet at δ5.0-5.2, and a vinylic proton, found at δ6.2. This latter signal is a multiplet in the crotonic acid series and a doublet of doublets, with coupling constants of 7 and 16 Hz due to cis and trans coupling respectively with the terminal methylene, in the tiglic acid series. The γ condensation products have in common the allylic methylene group, observed at δ2.3, and the vinylic proton, seen as a triplet at δ6.85. By comparing the integration of the β vinylic proton of the α product with the β vinylic proton of the γ product, and also the terminal vinylic methylene of the α product with the allylic methylene of the γ isomer, it was possible to obtain independent determinations of the α/γ ratios for each case. These are given in Table 3.

Table 3. Ratio of α to γ Products from Condensation of Crotonic and Tiglic Acid with Aldehydes and Ketones

Carbonyl Compound	Acid	Reaction Temp (°C)	α:γ Ratio
$C_6H_{13}CHO$	5	-78	(a)
$C_6H_{13}CHO$	5	25	100:0
$C_6H_{13}CHO$	5	65	1:1
$C_6H_{13}CHO$	6	-78	20:1
$C_6H_{13}CHO$	6	25	15:1
$C_6H_{13}CHO$	6	65	1:5
C_6H_5CHO	5	-78	(a)
C_6H_5CHO	5	25	100:0
C_6H_5CHO	5	65	1:1
C_6H_5CHO	6	-78	100:0
C_6H_5CHO	6	25	15:1
C_6H_5CHO	6	65	0:100
$(CH_3)_2CHCHO$	5	-78	20:1
$(CH_3)_2CHCHO$	5	25	4:1
$(CH_3)_2CHCHO$	5	65	1:4
$(CH_3)_2CHCHO$	6	-78	3:1
$(CH_3)_2CHCHO$	6	25	1:3
$(CH_3)_2CHCHO$	6	65	0:100
$(CH_3O)_2CHC(CH_3)_2CHO$	5	-78	3:1
$(CH_3O)_2CHC(CH_3)_2CHO$	5	25	3:2
$(CH_3O)_2CHC(CH_3)_2CHO$	5	65	1:20
$(CH_3O)_2CHC(CH_3)_2CHO$	6	-78	1:1
$(CH_3O)_2CHC(CH_3)_2CHO$	6	25	2:5
$(CH_3O)_2CHC(CH_3)_2CHO$	6	65	0:100

Table 3, Continued:

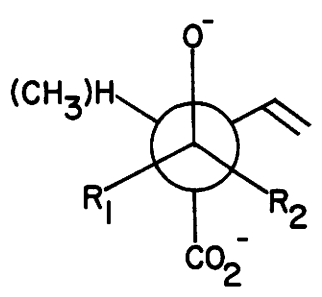
Carbonyl Compound	Acid	Reaction Temp (°C)	α:γ Ratio
$(CH_3)_2CO$	5	-78	20:1
$(CH_3)_2CO$	5	25	2:1
$(CH_3)_2CO$	5	65	1:2
$(CH_3)_2CO$	6	-78	10:1
$(CH_3)_2CO$	6	25	1:2
$(CH_3)_2CO$	6	65	1:11
$(CH_2)_4CO$	5	-78	6:1
$(CH_2)_4CO$	5	25	5:2
$(CH_2)_4CO$	5	65	0:100
$(CH_2)_4CO$	6	-78	100:0
$(CH_2)_4CO$	6	25	1:1
$(CH_2)_4CO$	6	65	0:100

(a) not determined

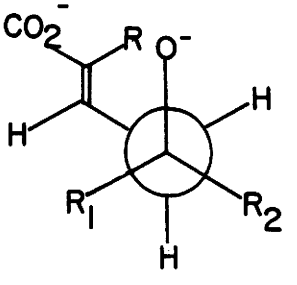
Three general trends are evident from the data in the Table. First, there is a shift from α to γ product with increasing steric bulk of the carbonyl electrophile. Second, there is a greater tendency to form γ product with tiglic acid than with crotonic acid. Third, higher temperature favors the γ product for a given acid and electrophile. These features of the reaction are discussed explicitly below.

It can be seen from the Table that the more highly branched aldehydes yield a greater percentage of γ product. A likely explanation for this result is that formation of the α isomer is

affected adversely by increasing the steric size of the aldehyde. Conformational analysis (Figure 1) of the α and γ products indicate that gauche interactions involving the R groups and the vinyl and carboxylate groups in the α product are substantial, whereas no such interactions occur in the γ product (where the R groups can be positioned between two hydrogens of the adjacent methylene). Steric factors should therefore make the α product less stable as the carbonyl component in the reaction increases in size.



α product



γ product

Figure 1

The greater proportion of γ product with tiglic acid, as opposed to crotonic acid, can again by explained by steric effects, since there is greater steric hindrance in the α product derived from tiglic acid, which has an α methyl group, as opposed to the α product from crotonic acid, which has a hydrogen atom at this site. This effect is brought out more noticeably in the difference in α:γ product ratios between the unhindered aldehydes, where only a relatively small change occurs, and the more hindered aldehydes and ketones, where a complete reversal of the α:γ ratio is observed going from the crotonic to the tiglic series.

The effect of temperature on the reaction is consistent with a pathway which becomes reversible at elevated temperature, and which leads to the γ isomer as the thermodynamic product. This is in accord with the results of Casinos and Mestres, who demonstrated that a similar reaction is indeed reversible.[8] That the α isomer is the kinetic product is unsurprising, given the fact that alkylation of α,β-unsaturated ester enolates occurs most rapidly at the α position.[6] Thus, increasing reaction temperature permits reversal of the kinetic pathway to α product, resulting in thermodynamic control of the reaction and a preponderance of the sterically less congested γ isomer.

A comparison of our work with the studies of Vedejs and Mestres shows similarities both in the α:γ product ratios obtained and in the trends observed under different reaction conditions (Table 4). For instance, it can be seen from Table 4 that there is general agreement that the γ isomer is favored at elevated temperature or when the carbonyl compound is a ketone. It can also be seen, by noting the difference in α:γ ratios from reactions run at the same temperature but for different reaction times, that the reaction time is an important factor in determining the α to γ ratio. Longer reaction times clearly afford a greater amount of γ product, which again is consistent with reversibility of the reaction path to α isomer.

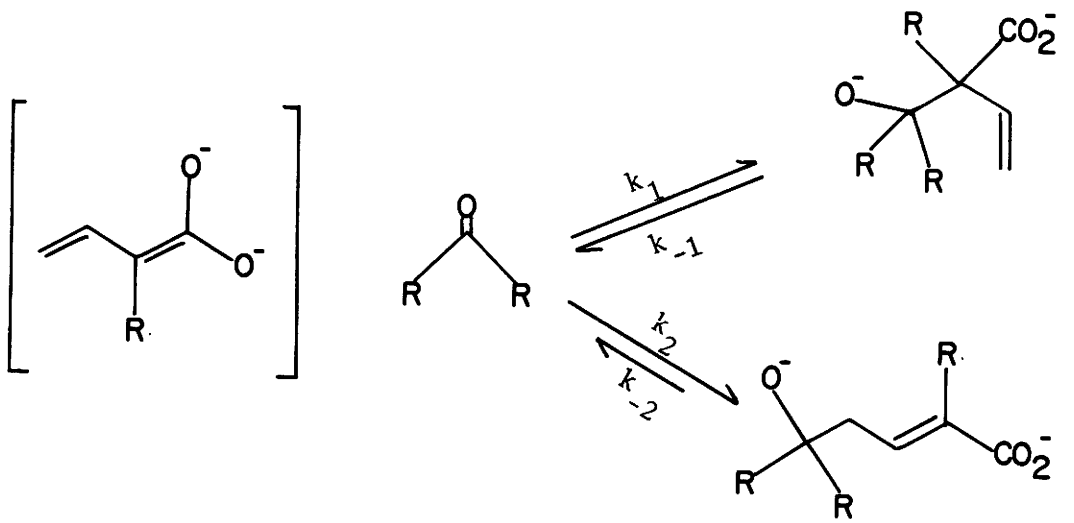
Table 4. Comparison of Studies on α to γ Ratios

Carbonyl Compound	Acid	Temp (°C)	Time (h)	α:γ Ratio	Ref
C_6H_5CHO	5	25	6	100:0	this work
C_6H_5CHO	5	45	2	7:3	8
C_6H_5CHO	5	65	(a)	1:1	this work
$(CH_2)_5CO$	5	-70	0.1	9:1	8
$(CH_2)_4CO$	5	-70	6	6:1	this work
$(CH_2)_5CO$	5	45	2	6:4	8
$(CH_2)_5CO$	5	45	10	1:9	8
$(CH_2)_4CO$	5	65	(a)	0:100	this work
C_6H_5CHO	6	25	6	15:1	this work
C_6H_5CHO	6	25	12	2:1	9
$C_6H_{13}CHO$	6	25	6	15:1	this work
C_2H_5CHO	6	25	14	2:1	9
C_2H_5CHO	6	65	2	1:3	9
$C_6H_{13}CHO$	6	65	(a)	1:5	this work

(a) 3 h at 25°C, then 3 h at 65°C

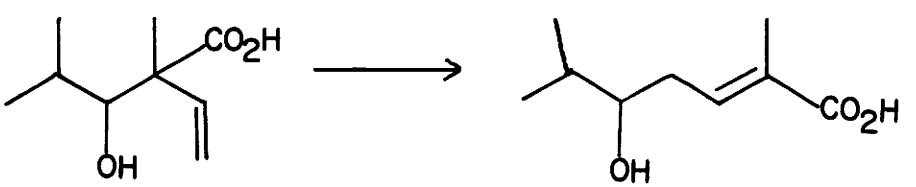
A plausible mechanism which can rationalize all of the data is shown in Scheme 14. Arguments already outlined, as well as the reaction time-dependent data in Table 4, support the contention that the α isomer is the kinetic product, while the γ isomer is the thermodynamic product.[13] At low temperature (-78°C), $k_1 >> k_{-1}$ and also $k_1 > k_2$, but at elevated temperature, $k_1 \cong k_{-1}$, so that the reaction pathway can be diverted to γ isomer. Here, $k_2 >> k_{-2}$, and there

is very little impetus for the γ product to undergo the retro-aldol condensation. The fact that, under certain conditions,



Scheme 14

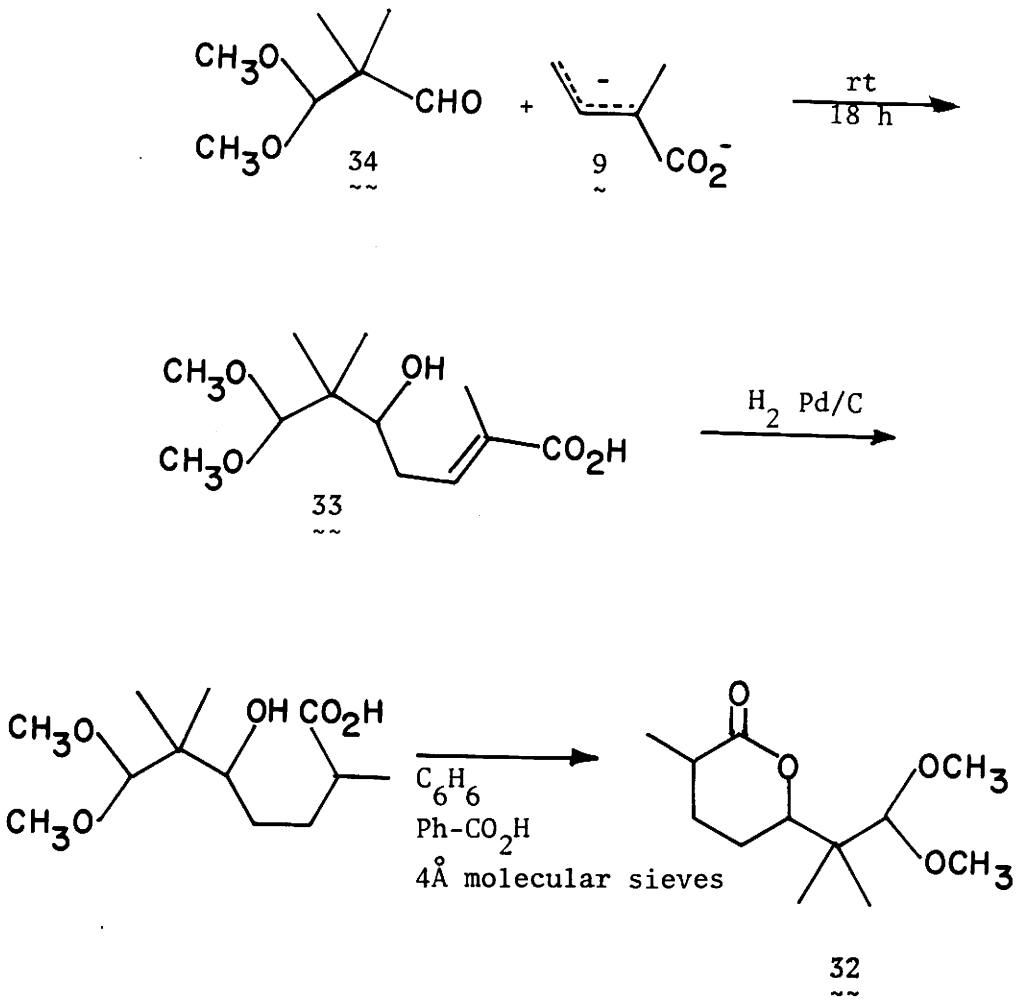
this reaction is reversible, and that the α product can be equilibrated to the γ, has been shown by Mestres and ourselves. The purified α product from the condensation of isobutyraldehyde with tiglic acid was subjected to 2.2 equivalents of lithium diisopropylamide at 25°C for 12 hours to give a mixture of 49 and 50 in the ratio of 1:10 respectively.



49 50

The above mechanism could also explain why hexamethylphosphoramide, or a more electropositive counterion such as sodium or potassium, causes a shift in the ratio towards the γ product. Increased dissociation of the alkoxide intermediate from the α condensation pathway, which would result from removal of the counterions (as with hexamethylphosphoramide) or from increased ionic character of the metal alkoxide bond (as with sodium and potassium), would cause k_{-1} to increase, and hence more of the γ product would be formed.

Having established the conditions necessary to maximize the proportion of γ product in the condensation of tiglate dianion with aldehyde 34, synthesis of lactone 32 required for boromycin was easily accomplished. The aldehyde 34, in tetrahydrofuran, was added to a solution of the dianion of tiglic acid at -78°C and the reaction was allowed to proceed at room temperature for 18 hours. Under these conditions, the hydroxy acid 33 was the sole product. The double bond of 33 was hydrogenated over palladium-on-carbon at one atmosphere, and the saturated acid was then lactonized by refluxing in benzene, with benzoic acid as catalyst, to give the lactone acetal 32 in 74% yield from 34 (Scheme 15).



Scheme 15

In conclusion, it has been shown that the principal factors which control α versus γ attack of a carbonyl electrophile on the dianion of an α,β-unsaturated acid are: (1) the steric size of the carbonyl compound, (2) substitution at the α carbon of the acid, (3) the reaction temperature, and (4) the reaction time. The kinetically favored product from this aldol condensation is the α isomer. However, at temperatures above -78°C, the retro reaction can take place at an appreciable rate, resulting in formation of the

thermodynamically more stable γ isomer. The synthetic utility of the condensation of an aldehyde or ketone with an α,β-unsaturated acid for the preparation of δ-lactones has been demonstrated by the facile synthesis of a key intermediate required for the synthesis of the antibiotic boromycin.

III. EXPERIMENTAL

General

Melting points were obtained on a Büchi melting-point apparatus and are uncorrected. Infrared spectra (IR) were obtained with a Perkin-Elmer 727B infrared spectrometer. Ultraviolet spectra (UV) were obtained on a Varian-Cary 210 Ultraviolet/Visible Spectrophotometer. Nuclear magnetic resonance spectra (NMR) were obtained with either a Varian EM-360A, HA-100, or FT-80A and are reported in δ units with tetramethylsilane (TMS) as the internal standard; the abbreviations s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, bs=broad singlet, etc. are used throughout. Mass spectra (MS) were obtained with either a Varian MAT CH-7 or a Finnigan 4500 spectrometer at an ionization potential of 70 eV. Exact mass determinations were performed on a CEC-110C spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by MicAnal, Tucson, Arizona. Column chromatography was performed using neutral silica gel 60 230-400 mesh ASTM. Analytical thin layer chromatography (TLC) plates were obtained from Analtech. Medium pressure liquid chromatography (MPLC) was performed using an FMI solvent pump. High pressure liquid chromatography (HPLC) was performed using a Waters M45 solvent pump with a Waters U6K injector and a Waters semipreparative silica column. The detector used for both high pressure and medium pressure liquid chromatography was an Isco UV detector Model 1850 at a wavelength of 260 nm. Dry tetrahydrofuran (THF) was obtained by distillation over sodium and benzophenone. All organic solutions were dried over magnesium sulfate

and filtered through a sintered glass funnel prior to rotary evaporation at water aspirator pressure. Residual solvent was removed under vacuum, usually at less than 0.2 Torr. All reactions were routinely carried out under an inert atmosphere of argon or nitrogen. All glassware was dried in an oven at 150°C.

3,3-Dimethoxy-2,2-dimethylpropanol (36)[16]

3-Acetoxy-2,2-dimethylpropanol (35) (20 g, 139 mmol), prepared by condensation of isobutyraldehyde with formaldehyde,[15] was dissolved in methanol (100 mL). Trimethyl orthoformate (30 mL) and p-toluenesulfonic acid (1 g) were added, and the solution was stirred at room temperature for 24 h. A saturated solution of sodium chloride (100 mL) was added, and the solution was extracted with ether (3 x 100 mL). The ethereal extract was dried and solvents were removed in vacuo to yield 18.6 g (90%) of 36: b.p.$_{14}$ 85°C (lit. b.p.$_{13}$ 81°C); IR (neat) 3450, 1480, 1190, 1100, 1070 cm^{-1}; NMR ($CDCl_3$) δ 4.05 (s, 1H), 3.55 (s, 6H), 3.45 (s, 2H), 0.95 (s, 6H); MS m/e (rel. int.) 145 (84), 131 (100, M^+-OH).

3,3-Dimethoxy-2,2-dimethylpropionaldehyde (34)

To a slurry of pyridinium chlorochromate (21.8 g, 101 mmol) in dry methylene chloride (200 mL) at 0°C was added slowly a solution of 33 (10 g, 67.5 mmol) in methylene chloride (50 mL). After the mixture was stirred for 8 h at 25°C, water (100 mL) and ether (100 mL) were added, and the mixture was stirred vigorously. The layers were

separated and the organic layer was washed with water (50 mL). The combined aqueous layer was extracted with ether (3 x 50 mL). The organic layer was dried, and then poured through a 3 cm x 50 cm column filled with 50 g of Florisil. The column was eluted with ether. Solvents were removed in vacuo to yield 9.63 g (97%) of 34: IR (neat) 1730, 1080 cm^{-1}; NMR ($CDCl_3$) δ 9.6 (s, 1H), 4.3 (s, 1H), 3.6 (s, 6H), 1.1 (s, 6H); MS m/e (rel. int.), calcd for $C_7H_{13}O_3$: 145.086, found 145.086 (23, M^+-H), 131 (100), 115 (40).

General Procedure for Addition of Crotonic and Tiglic Acids to Aldehydes and Ketones

Lithium diisopropylamide (2.2 eq) was prepared by addition of n-butyllithium (1.5M in hexane, 2.2 eq) to a solution of diisopropylamine (2.2 eq) in 5 mL of dry tetrahydrofuran at -78°C. The solution was stirred for 0.5 h at 0°C, then recooled to -78°C. The acid (1 eq) in 5 mL of dry tetrahydrofuran was added slowly to the lithium diisopropylamide solution and stirred at 25°C for 1 h, then recooled to -78°C. The aldehyde or ketone (1 eq) in 5 mL of dry tetrahydrofuran was added slowly to the yellow solution of the dianion, and the mixture was stirred at the required temperature for 6 h. The solution was poured into a mixture of saturated ammonium chloride (10 mL) and ether (10 mL), shaken, and the layers were separated. The ethereal layer was extracted with saturated sodium bicarbonate (3 x 10 mL), and the combined aqueous layer was acidified with 3M hydrochloric acid. The acidified aqueous solution was extracted with ether (3 x 20 mL),

and the combined ethereal layer was dried. Solvent was removed in vacuo to give an oil. The oil was dissolved in ether (10 mL), and an ethereal solution of diazomethane was added until the yellow color of the diazomethane persisted. Solvents were removed in vacuo to yield the esters as oils. After purification, the esters were characterized as their 3,5-dinitrobenzoate derivatives, prepared by dissolving the esters in 2 to 3 mL of pyridine and adding 2 eq of 3,5-dinitrobenzoyl chloride. After stirring the mixture for 12 h, ether (2 mL) and 3M hydrochloric acid (2 mL) were added, and the layers were separated. The organic layer was washed with water and then with saturated sodium bicarbonate solution. The ethereal solution was dried and the solvent was removed in vacuo. Purification was achieved on silica by flash chromatography (20% ethyl acetate in hexane).[17] Removal of solvent in vacuo gave the 3,5-dinitrobenzoates as either a solid or an oil. The solids were recrystallized from ethanol, while the oils were purified by high pressure liquid chromatography (20% ethyl acetate in hexane).

Methyl 3-Hydroxy-2-vinylnonanoate (37a) and Methyl 5-Hydroxy-2-undecenoate (37b)

a) Crotonic acid (86.0 mg, 1 mmol) was condensed with heptanal (110.0 mg, 0.96 mmol) at 25°C. Standard workup and esterification gave 90 mg (43.8%) of 37a.

b) Crotonic acid (86.0 mg, 1 mmol) was condensed with heptanal (112.0 mg, 0.98 mmol) at 25°C for 3 h, then at 65°C for 3 h.

Standard workup and esterification gave 78 mg (37%) of a mixture of 37a and 37b in a ratio of 1:1. Separation was achieved by MPLC (ether/hexane, 1/1).

37a: IR (neat) 3525, 1735, 1640, 1430, 1190, 1160 cm^{-1}; NMR ($CDCl_3$) δ 5.6-6.1 (m, 1H), 5.05-5.35 (m, 2H), 3.7 (m, 1H), 3.71 (s, 3H), 3.09 (m, 1H), 1.15-1.7 (m, 10H), 0.9 (t, 3H, J=5); MS m/e (rel. int.) 197 (11.89, M^+-OH), 100 (20.68).

3,5-Dinitrobenzoate. MS, calcd for $C_{19}H_{24}N_2O_8$: m/e 408.153, found 408.154.

37b: IR (neat) 3490, 1725, 1660, 1435, 1270 cm^{-1}; NMR ($CDCl_3$) δ 6.92 (dt, 1H, J=15,7), 5.85 (d, 1H, J=15), 3.7 (m, 1H), 3.71 (s, 3H), 2.35 (dd, 2H, J=7,7), 1.15-1.7 (m, 10H), 0.9 (t, 3H, J=5); MS m/e (rel. int.) 197 (15.84, M^+-OH), 100 (100).

3,5-Dinitrobenzoate. Anal. Calcd for $C_{19}H_{24}N_2O_8$: C, 55.88%; H, 5.92%; N, 6.86%. Found: C, 55.86%; H, 5.75%; N, 6.72%.

Methyl 3-Hydroxy-2-methyl-2-vinylnonanoate (38a) and Methyl 5-Hydroxy-2-methyl-2-undecenoate (38b)

a) Tiglic acid (0.5 g, 5 mmol) was condensed with heptanal (0.569 g, 5 mmol) at -78°C. Standard workup and esterification gave 0.753 g (62%) of a mixture of 38a and 38b in a ratio of 20:1, respectively. Separation was achieved by MPLC (ether/hexane, 1/1).

b) Tiglic acid (0.50 g, 5 mmol) was condensed with heptanal (0.56 g, 4.9 mmol) at 25°C. Standard workup and esterification gave 0.76 g (66%) of 38a and 38b in a ratio of 16:1, respectively.

Separation was achieved by MPLC (ether/hexane, 1/1).

c) Tiglic acid (0.50 g, 5 mmol) was condensed with heptanal (0.56 g, 4.9 mmol) at 25°C for 3 h, then at 65°C for 3 h. Standard workup and esterification gave 0.43 g (38%) of a mixture of 38a and 38b in a ratio of 5:1, respectively. Separation was achieved by MPLC (ether/hexane, 1/1).

38a: IR (neat) 3550, 1730, 1640, 1460, 1240 cm^{-1}; NMR ($CDCl_3$) δ 6.3-5.8 (m, 1H), 5.4-5.1 (m, 2H), 3.8 (m, 1H), 3.7 (s, 3H), 1.5-1.2 (m, 13H), 0.9 (t, 3H, J=5); MS m/e (rel. int.) 229 (7.4, M^++H), 211 (35.5), 114 (100).

3,5-Dinitrobenzoate. Anal. Calcd for $C_{20}H_{26}N_2O_8$: C, 56.87%; H, 6.20%; N, 6.63%. Found: C, 56.88%; H, 6.19%; N, 6.47%.

38b: IR (neat) 3470, 1715, 1645, 1435, 1280, 1070 cm^{-1}; NMR ($CDCl_3$) δ 6.8 (t, 1H, J=7), 3.75 (s, 3H), 3.7 (m, 1H), 2.4 (dd, 2H, J=7,7), 1.9 (s, 3H), 1.5-1.2 (m, 10H), 0.9 (t, 3H, J=5); MS m/e (rel. int.) 229 (6, M^++H), 211 (17), 151 (30), 114 (100).

3,5-Dinitrobenzoate, m.p. 52-54°C. Anal. Calcd for $C_{20}H_{26}N_2O_8$: C, 56.87%; H, 6.20%; N, 6.63%. Found: C, 56.98%; H, 6.29%; N, 6.60%.

Methyl 3-Hydroxy-3-phenyl-2-vinylpropionate (39a) and Methyl 5-Hydroxy-5-phenyl-2-pentenoate (39b)

a) Crotonic acid (0.086 g, 1 mmol) was condensed with benzaldehyde (0.104 g, 0.98 mmol) at 25°C. Standard workup and esterification gave 175 mg (86%) of 39a.

b) Crotonic acid (0.086 g, 1 mmol) was condensed with benzaldehyde (0.104 g, 0.98 mmol) at 25°C for 3 h, then at 64°C for 3 h. Standard workup and esterification gave 137 mg (65%) of a mixture of 39a and 39b in a 1:1 ratio. Separation was achieved by flash chromatography (ethyl acetate/methylene chloride/hexane, 1/2/4). Solvents were removed in vacuo and 39b was repurified by flash chromatography (5% acetone in chloroform).

39a: IR (neat) 3500, 1730, 1640, 1440, 1190, 1155 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (s, 5H), 6.0-5.5 (m, 1H), 5.2-5.0 (m, 2H), 4.9 (m, 1H), 3.6 (s, 3H), 3.5 (m, 1H); MS m/e (rel. int.) 107 (59), 100 (100).

3,5-Dinitrobenzoate. MS, calcd for $C_{19}H_{16}N_2O_8$: m/e 400.091, found 400.090.

39b: IR (neat) 3470, 1710, 1660, 1440, 1275, 1200, 1020 cm^{-1}; NMR ($CDCl_3$) δ 7.27 (s, 5H), 6.9 (dt, 1H, J=16,7), 5.82 (dt, 2H, J=16, 2), 4.75 (bt, 1H), 3.62 (s, 3H), 2.6 (dd, 2H, J=7,7); MS m/e (rel. int.) 189 (29, M^+-OH), 107 (100), 100 (69).

3,5-Dinitrobenzoate. Anal. Calcd for $C_{19}H_{16}N_2O_8$: C, 57.00%; H, 4.03%; N, 7.00%. Found: C, 57.39%; H, 4.33%; N, 6.67%.

Methyl 3-Hydroxy-2-methyl-3-phenyl-2-vinylpropionate (40a) and Methyl 5-Hydroxy-2-methyl-5-phenyl-2-pentenoate (40b)

a) Tiglic acid (0.50 g, 5 mmol) was condensed with benzaldehyde (0.53 g, 5 mmol) at -78°C. Standard workup and esterification gave 1.01 g (94%) of 40a.

b) Tiglic acid (0.50 g, 5 mmol) was condensed with benzaldehyde (0.53 g, 5 mmol) at 25°C. Standard workup and esterification gave 0.84 g (80%) of a mixture of 40a and 40b in a ratio of 13:1, respectively. Separation was achieved by flash chromatography (ethyl acetate/methylene chloride/hexane, 1/2/4), and 40b was then purified by flash chromatography (5% acetone in chloroform).

c) Tiglic acid (0.256 g, 2.56 mmol) was condensed with benzaldehyde (0.265 g, 2.5 mmol) at 25°C for 3 h, then at 65°C for 3 h. Standard workup and esterification gave 0.44 g (80%) of 40b. Purification was achieved by flash chromatography (5% acetone in chloroform).

40a: IR (neat) 3450, 1720, 1630, 1245 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (s, 5H), 5.85-6.45 (m, 1H), 4.95-5.4 (m, 4H), 3.75 (s, 3H), 1.3 (s, 3H); MS m/e (rel. int.) 221 (2.5, M^++H), 203 (100), 114 (49), 107 (19).

3,5-Dinitrobenzoate. Anal. Calcd for $C_{20}H_{18}N_2O_8$: C, 57.97%; H, 4.38%; N, 6.76%. Found: C, 57.86%; H, 4.40%; N, 6.58%.

40b: IR (neat) 3400, 1700, 1645, 1440, 1280 cm^{-1}; NMR ($CDCl_3$) δ 7.36 (s, 5H), 6.85 (tq, 1H, J=7,2), 4.8 (t, 1H, J=7), 3.7 (s, 3H), 2.6 (dd, 2H, J=7,7), 1.8 (bs, 3H); MS m/e (rel. int.) 221 (0.6, M^++H), 203 (56), 143 (87), 114 (100), 107 (71).

3,5-Dinitrobenzoate. MS, calcd for $C_{20}H_{18}N_2O_8$: m/e 414.106, found 414.104.

Methyl 3-Hydroxy-4-methyl-2-vinylpentanoate (41a) and Methyl 5-Hydroxy-6-methyl-2-heptenoate (41b)

a) Crotonic acid (0.085 g, 0.98 mmol) was condensed with isobutyraldehyde (0.067 g, 0.93 mmol) at -78°C. Standard workup and esterification gave 0.135 mg (80%) of a mixture of 41a and 41b in a ratio of $\geq$ 20:1, respectively. Separation was accomplished by flash chromatography (ethyl acetate/methylene chloride/hexane, 1/2/4).

b) Crotonic acid (0.086 g, 1 mmol) was condensed with isobutyraldehyde (0.071 g, 0.99 mmol) at 25°C. Standard workup and esterification yielded 110 mg (64%) of a mixture of 41a and 41b in a ratio of 4:1, respectively. Separation was accomplished by flash chromatography (ethyl acetate/methylene chloride/hexane, 1/2/4).

c) Crotonic acid (0.086 g, 1 mmol) was condensed with isobutyraldehyde (0.071 g, 0.99 mmol) at 25°C for 3 h, then at 65°C for 3 h. Standard workup and esterification gave 35 mg (20%) of a mixture of 41a and 41b in a ratio of 1:4, respectively. Separation was accomplished by flash chromatography (ethyl acetate/methylene chloride/hexane, 1/2/4).

41a: IR (neat) 3550, 1730, 1635, 1160 cm^{-1}; NMR ($CDCl_3$) δ 6.2-5.6 (m, 1H), 5.3-5.1 (m, 2H), 3.7 (s, 3H), 3.2 (dd, 1H, J=7,8), 2.67 (dd, 1H, J=7,8), 1.7 (m, 1H), 0.97 (d, 6H, J=7); MS m/e (rel. int.) 157 (8, M^++H), 141 (21), 100 (100).

3,5-Dinitrobenzoate. Anal. Calcd for $C_{16}H_{18}N_2O_8$: C, 52.46%; H, 4.95%; N, 7.65%. Found: C, 52.48%; H, 4.86%; N, 7.63%.

41b: UV (MeOH) λ_{max} = 211 nm (ε 11000); IR (neat) 3500, 1730, 1635, 1430, 1160 cm^{-1}; NMR ($CDCl_3$) δ 6.97 (dt, 1H, J=16,7), 5.87 (dt, 2H, J=16,2), 3.7 (s, 3H), 3.45 (dt, 1H, J=1,6), 2.4 (dd, 6H, J=7); MS m/e (rel. int.) 159 (2, M^++H), 141 (61), 100 (100).

3,5-Dinitrobenzoate, m.p. 74.5-75°C. Anal. Calcd for $C_{16}H_{18}N_2O_8$: C, 52.46%; H, 4.95%; N, 7.65%. Found: C, 52.42%; H, 4.82%; N, 7.38%.

Methyl 2,4-Dimethyl-3-hydroxy-2-vinylpentanoate (42a) and Methyl 2,6-Dimethyl-5-hydroxy-2-heptenoate (42b)

a) Tiglic acid (0.256 g, 2.56 mmol) was condensed with isobutyraldehyde (0.18 g, 2.5 mmol) at -78°C. Standard workup and esterification gave 0.286 g (61%) of a mixture of 42a and 42b in a ratio of 3:1, respectively. Separation was achieved by flash chromatography (ethyl acetate/methylene chloride/hexane, 1/2/4).

b) Tiglic acid (0.25 g, 2.5 mmol) was condensed with isobutyraldehyde (0.18 g, 2.5 mmol) at 25°C. Standard workup and esterification gave 0.297 g (65%) of a mixture of 42a and 42b in a ratio of 1:3, respectively. Separation was achieved by flash chromatography (ethyl acetate/methylene chloride/hexane, 1/2/4).

c) Tiglic acid (0.25 g, 2.5 mmol) was condensed with isobutyraldehyde (0.18 g, 2.5 mmol) at 25°C for 3 h, then at 65°C for 3 h. Standard workup and esterification gave 0.225 g (48%) of 42b.

42a: IR (neat) 3550, 1735, 1650, 1240, 1100, 1000 cm^{-1}; NMR ($CDCl_3$) δ 6.3-5.9 (m, 1H), 5.3-5.0 (m, 2H), 3.7 (s, 3H), 3.6 (d, 1H, J=7), 1.8 (m, 1H), 1.35 (s, 3H), 0.95 (d, 6H, J=7); MS m/e (rel. int.)

187 (13, M^++H), 169 (40), 114 (100).

3,5-Dinitrobenzoate. MS, calcd for $C_{17}H_{20}N_2O_8$: m/e 380.122 found 380.121

42b: UV (MeOH) λ_{max}=218 nm (ε 12100); IR (neat) 3540, 1720, 1650, 1280, 1100 cm^{-1}; NMR ($CDCl_3$) δ 6.78 (t, 1H, J=8), 3.68 (s, 3H), 3.48 (dt, 1H, J=4,1), 2.3 (dd, 2H, J=4,8), 1.8 (s, 3H), 1.75 (m, 1H, J=7,1), 2.3 (dd, 2H, J=4,8); MS m/e (rel. int.) 187 (30, M^++H), 169 (60), 114 (100).

3,5-Dinitrobenzoate, m.p. 86.5-87°C. Anal. Calcd for $C_{17}H_{20}N_2O_8$: C, 53.68%; H, 5.3%; N, 7.37%. Found: C, 53.36%; H, 5.20%; N, 7.02%.

Methyl 5,5-Dimethoxy-4,4-dimethyl-3-hydroxy-2-vinyl pentanoate (43a) and Methyl 7,7-Dimethoxy-6,6-dimethyl-5-hydroxy-2-heptenoate (43b)

a) Crotonic acid (0.086 g, 1 mmol) was condensed with 3,3-dimethoxy-2,2-dimethylpropionaldehyde (34) (0.146 g, 1 mmol) at -78°C. Standard workup and esterification gave 125 mg (55%) of a mixture of 43a and 43b in a ratio of 3:1, respectively. Separation was achieved by flash chromatography (ethyl acetate/ether/hexane, 1/2/3).

b) Crotonic acid (0.086 g, 1 mmol) was condensed with 34 (0.146 g, 1 mmol) at 25°C. Standard workup and esterification gave 0.143 g (54%) of a mixture of 43a and 43b in a ratio of 3:2, respectively. Separation was achieved by flash chromatography (ethyl acetate/ether/hexane, 1/2/3).

c) Crotonic acid (0.172 g, 2 mmol) was condensed with 34 (0.292 g, 2 mmol) at 25°C for 3 h, then at 65°C for 3 h. Standard workup and esterification gave 0.274 g (56%) of a mixture of 43a and 43b in a ratio of 1:20, respectively. Separation was achieved by flash chromatography (ethyl acetate/ether/hexane, 1/2/3).

43a: IR (neat) 3550, 1735, 1640, 1440, 1155, 1060 cm^{-1}; NMR ($CDCl_3$) δ 6.2-5.8 (m, 1H), 5.3-5.1 (m, 2H), 4.1 (s, 1H), 3.8 (d, 1H, J=6), 3.7 (s, 3H), 3.5 (s, 6H), 3.4 (m, 1H), 0.95 (s, 6H); MS m/e (rel. int.) 215 (8, M^+-OCH_3), 86 (98), 84 (100).

3,5-Dinitrobenzoate. MS, calcd for $C_{19}H_{24}N_2O_{10}$: m/e 440.143 found 440.139.

43b: IR (neat) 3525, 1725, 1660, 1270, 1100 cm^{-1}; NMR ($CDCl_3$) δ 7.1 (dt, 1H, J=15,7), 5.9 (d, 1H, J=15), 4.02 (s, 1H), 3.67 (s, 3H), 3.5 (s, 6H), 3.45 (t, 1H, J=7), 2.3 (dd, 2H, J=7,7), 0.90 (s, 3H), 0.86 (s, 3H); MS m/e (rel. int.) 215 (5, M^+-OCH_3), 100 (52), 86 (100).

3,5-Dinitrobenzoate. MS (M^+-OCH_3), calcd for $C_{18}H_{21}N_2O_9$: m/e 409.125 found 409.127.

Methyl 5,5-Dimethoxy-3-hydroxy-2,4,4-trimethyl-2-vinyl-pentanoate (44a) and Methyl 7,7-Dimethoxy-5-hydroxy-2,6,6-trimethyl-2-heptenoate (44b)

a) Tiglic acid (0.1 g, 1 mmol) was condensed with 34 (0.146 g, 1 mmol) at -78°C. Standard workup and esterification gave 0.198 g (80.5%) of a mixture of 44a and 44b in a ratio of 1:1. Separation was accomplished by MPLC (ethyl acetate/methylene chloride/hexane, 1/3/4).

b) Tiglic acid (0.1 g, 1 mmol) was condensed with 34 (0.146 g, 1 mmol) at 25°C. Standard workup and esterification gave 0.193 g (78%) of a mixture of 44a and 44b in a ratio of 2:5, respectively. Separation was achieved by MPLC (ethyl acetate/methylene chloride/hexane, 1/3/4).

c) Tiglic acid (0.2 g, 2 mmol) was condensed with 34 (0.292 g, 2 mmol) at 25°C for 3 h, then at 65°C for 3 h. Standard workup and esterification gave 50 mg (10%) of 44b.

44a: IR (neat) 3540, 1730, 1640, 1250, 1095, 1060 cm^{-1}; NMR ($CDCl_3$) δ 6.1 (dd, 1H, J=16,7), 5.2 (m, 2H), 4.15 (s, 1H), 3.95 (s, 1H), 3.65 (s, 3H), 3.5 (s, 6H), 1.4 (s, 1H), 1.0 (s, 3H), 0.9 (s, 3H); MS m/e (rel. int.) 229 (21, M^++H), 143 (92), 115 (100).

The 3,5-dinitrobenzoate would not form.

44b: IR (neat) 3530, 1710, 1645, 1260, 1060 cm^{-1}; NMR ($CDCl_3$) δ 6.9 (t, 1H, J=7), 4.05 (s, 1H), 3.8 (t, 1H, J=4), 3.7 (s, 3H), 3.5 (s, 6H), 2.25 (dd, 1H, J=7,4), 1.9 (s, 3H), 1.0 (s, 3H), 0.9 (s, 3H); MS m/e (rel. int.) 229 (7, M^++H), 115 (69), 86 (100).

3,5-Dinitrobenzoate. MS, calcd for $C_{20}H_{26}N_2O_{10}$: m/e 454.159, found 454.159.

Methyl 3-Hydroxy-3-methyl-2-vinylbutanoate (45a) and Methyl 5-Hydroxy-5-methyl-2-hexenoate (45b)

a) Crotonic acid (0.172 g, 2 mmol) was condensed with acetone (0.102 g, 1.75 mmol) at -78°C. Standard workup and esterification

gave 107 mg (77%) of a mixture of 45a and 45b in a ratio of 20:1, respectively. Separation was accomplished by flash chromatography (ethyl acetate/ether/hexane, 1/2/3).

b) Crotonic acid (0.172 g, 2 mmol) was condensed with acetone (0.108 g, 1.86 mmol) at 25°C. Standard workup and esterification gave 123.5 mg (46%) of a mixture of 45a and 45b in a ratio of 2:1, respectively. Separation was accomplished by flash chromatography (ethyl acetate/ether/hexane, 1/2/3).

c) Crotonic acid (0.172 g, 2 mmol) was condensed with acetone (0.108 g, 1.86 mmol) at 25°C for 3 h, then at 65°C for 3 h. Standard workup and esterification gave 0.122 g (45%) of a mixture of 45a and 45b in a ratio of 1:2, respectively. Separation was accomplished by flash chromatography (ethyl acetate/ether, hexane, 1/2/3).

45a: IR (neat) 3530, 1735, 1640, 1435, 1190 cm^{-1}; NMR ($CDCl_3$) δ 6.15-5.7 (m, 1H), 5.3-5.1 (m, 2H), 3.7 (s, 3H), 3.03 (d, 1H, J=8), 1.25 (s, 6H); MS m/e (rel. int.) 173 (7, M^++H), 155 (17), 129 (14), 100 (100).

3,5-Dinitrobenzoate. Anal. Calcd for $C_{15}H_{16}N_2O_8$: C, 51.14%; H, 4.58%; N, 7.95%. Found: C, 51.27%; H, 4.29%; N, 7.93%.

45b: IR (neat) 3500, 1725, 1660, 1435, 1270, 1190 cm^{-1}; NMR ($CDCl_3$) δ 6.95 (dt, 1H, J=16,8), 5.82 (dt, 2H, J=16,2), 3.7 (s, 3H), 2.35 (dd, 2H, J=2,8), 1.25 (s, 6H); MS m/e (rel. int.) 173 (5, M^++H), 155 (9), 100 (100).

The 3,5-dinitrobenzoate decomposed upon purification.

Methyl 2,3-Dimethyl-3-hydroxy-2-vinylbutanoate (46a) and Methyl 2,5-Dimethyl-5-hydroxy-2-hexenoate (46b)

a) Tiglic acid (0.20 g, 2 mmol) was condensed with acetone (0.10 g, 1.72 mmol) at -78°C. Standard workup and esterification gave 0.232 g (78%) of a mixture of 46a and 46b in a ratio of 10:1, respectively. Separation was achieved by flash chromatography (ether/hexane, 1/1).

b) Tiglic acid (0.20 g, 2 mmol) was condensed with acetone (0.114 g, 1.96 mmol) at 25°C. Standard workup and esterification gave 0.117 g (35%) of a mixture of 46a and 46b in a ratio of 1:2, respectively. Separation was accomplished by flash chromatography (ether/hexane, 1/1).

c) Tiglic acid (0.20 g, 2 mmol) was condensed with acetone (0.116 g, 2 mmol) at 25°C for 3 h, then at 65°C for 3 h. Standard workup and esterification gave 0.216 g (63%) of a mixture of 46a and 46b in a ratio of 1:11, respectively. Separation was accomplished by flash chromatography (ether/hexane, 1/1).

46a: IR (neat) 3540, 1710, 1640, 1260 cm^{-1}; NMR ($CDCl_3$) δ 6.2 (dd, 1H, J=10,16), 5.2 (dd, 1H, J=1,10), 5.1 (dd, 1H, J=1,16); MS m/e (rel. int.) 173 (6, M^++H), 155 (68), 114 (100).

3,5-Dinitrobenzoate. Anal. Calcd for $C_{16}H_{18}N_2O_8$: C, 52.46%; H, 4.95%; N, 7.65%. Found: C, 52.66%; H, 4.91%; N, 7.47%.

46b: IR (neat) 2500, 1710, 1645, 1250 cm^{-1}; NMR ($CDCl_3$) δ 6.84 (t, 1H, J=8), 3.76 (s, 3H), 2.4 (d, 2H, J=8), 1.9 (s, 3H), 1.3 (s, 6H); MS m/e (rel. int.) 173 (3, M^++H), 155 (100), 114 (91).

3,5-Dinitrobenzoate, m.p. 88-88.5°C. Anal. Calcd for $C_{16}H_{18}N_2O_8$: C, 52.46%; H, 4.95%; N, 7.65%. Found: C, 52.52%; H, 5.01%; N, 7.68%.

Methyl 3-Cyclopentyl-3-hydroxy-2-vinylpropionate (47a) and Methyl 5-Cyclopentyl-5-hydroxy-2-propenoate (47b)

a) Crotonic acid (0.172 g, 2 mmol) was condensed with cyclopentanone (0.168 g, 2 mmol) at -78°C. Standard workup and esterification gave 0.218 g (59%) of 47a.

b) Crotonic acid (0.172 g, 2 mmol) was condensed with cyclopentanone (0.166 g, 1.93 mmol) at 25°C. Standard workup and esterification gave 0.222 g (62%) of a mixture of 47a and 47b in a ratio of 2.5:1, respectively. Separation was achieved by flash chromatography (ether/hexane, 1/1).

c) Crotonic acid (0.172 g, 2 mmol) was condensed with cyclopentanone (0.158 g, 1.88 mmol) at 25°C for 3 h, then at 65°C for 3 h. Standard workup and esterification gave 0.146 g (42%) of 47b.

47a: IR (neat) 3550, 1730, 1640, 1435, 1195, 1160, 990 cm^{-1}; NMR ($CDCl_3$) δ 6.2-5.8 (m, 1H), 5.25-5.05 (m, 2H), 3.7 (s, 3H), 3.1 (d, 1H, J=8), 1.85-1.5 (m, 8H); MS m/e (rel. int.) 185 (6, M^++H), 135 (35), 107 (100), 101 (99).

3,5-Dinitrobenzoate. Anal. Calcd for $C_{17}H_{18}N_2O_8$: C, 53.97%; H, 4.80%; N, 7.40%. Found: C, 54.10%; H, 4.81%; N, 7.45%.

47b: IR (neat) 3500, 1720, 1655, 1435, 1270, 1190, 970 cm^{-1}; NMR ($CDCl_3$) δ 7.0 (dt, 1H, J=15,8), 5.85 (dt, 1H, J=15,1), 3.63 (s, 3H), 2.4 (dd, 2H, J=8,1), 1.7-1.5 (m, 8H); MS m/e (rel. int.)

100 (100), 85 (73).

3,5-Dinitrobenzoate, m.p. 83-83.5°C. Anal. Calcd for $C_{17}H_{18}N_2O_8$: C, 53.98%; H, 4.80%; N, 7.30%. Found: C, 53.92%; H, 4.80%; N, 7.30%.

Methyl 3-Cyclopentyl-3-hydroxy-2-methyl-2-vinylpropanoate (48a) and Methyl 5-Cyclopentyl-5-hydroxy-2-methyl-2-pentenoate (48b)

a) Tiglic acid (0.257 g, 2.57 mmol) was condensed with cyclopentanone (0.21 g, 2.5 mmol) at -78°C. Standard workup and esterification gave 0.476 g (96%) of 48a.

b) Tiglic acid (0.2 g, 2 mmol) was condensed with cyclopentanone (0.165 g, 1.96 mmol) at 25°C. Standard workup and esterification gave 0.185 g (48%) of a mixture of 48a and 48b in a ratio of 2:1, respectively.

c) Tiglic acid (0.2 g, 2 mmol) was condensed with cyclopentanone (0.165 g, 1.93 mmol) at 25°C for 3 h, then at 65°C for 3 h. Standard workup and esterification gave 0.148 g (40%) of 48b.

48a: IR (neat) 3550, 1730, 1640, 1250, 1110 cm^{-1}; NMR ($CDCl_3$) δ 6.1 (dd, 1H, J=10,16), 5.2 (dd, 1H, J=1,10), 5.1 (dd, 1H, J=1,16), 3.66 (s, 3H), 1.85-1.45 (m, 8H), 1.36 (s, 3H); MS m/e (rel. int.) 145 (5), 114 (100), 82 (60).

3,5-Dinitrobenzoate. MS, calcd for $C_{18}H_{20}N_2O_8$: m/e 392.122, found 392.120.

48b: IR (neat) 3500, 1710, 1645, 1260 cm^{-1}; NMR ($CDCl_3$) δ 6.84 (t, 1H, J=8), 3.72 (s, 3H), 2.5 (d, 2H, J=8), 1.88 (s, 3H), 1.8-1.6 (m, 8H); MS m/e (rel. int.) 181 (37), 114 (100).

3,5-Dinitrobenzoate, m.p. 97°C. Anal. Calcd for $C_{18}H_{20}N_2O_8$: C, 55.10%; H, 5.14%; N, 7.14%. Found: C, 54.94%; H, 5.01%; N, 7.58%.

Conversion of 2,4-Dimethyl-3-hydroxy-2-vinylpentanoic Acid (49) to 2,6-Dimethyl-5-hydroxy-2-heptenoic Acid (50)

Acids 49 and 50 (0.207 g) were prepared as before in a ratio of 3:1, respectively. The mixture of acids, in tetrahydrofuran (5 mL), was added slowly to a solution of lithium diisopropylamide in tetrahydrofuran (5 mL), at -78°C. The solution was stirred at 25°C for 18 h. Workup gave 0.10 g (48%) of a mixture of 49 and 50 in a ratio of 1:10, respectively.

7,7-Dimethoxy-5-hydroxy-2,6,6-trimethyl-heptanoic Acid δ-Lactone (32)

Tiglic acid (1.3 g, 13 mmol) in 20 mL of tetrahydrofuran was added to a solution of lithium diisopropylamide (28.5 mmol) in tetrahydrofuran (20 mL), prepared from diisopropylamine (3.0 g, 29.6 mmol) and n-butyllithium (1.5M in hexane, 19 mL, 28.5 mmol), at -78°C. The solution was stirred at 25°C for 1 h and recooled to -78°C. Aldehyde 34 (1.7 g, 12 mmol) in tetrahydrofuran (20 mL) was added slowly. The solution was stirred at 25°C for 18 h, then poured into a mixture of a saturated solution of ammonium chloride (20 mL) and ether (20 mL), and shaken. The layers were separated and the organic layer was extracted with a saturated solution of sodium bicarbonate (3 x 10 mL). The aqueous layer was acidified with 3M hydrochloric acid and extracted with ether (3 x 30 mL). The ether extract was dried and solvents were

removed in vacuo to give 2.6 g (88%) of the unsaturated acid 33 as an oil. This material was dissolved in methanol (200 mL) and stirred for 24 h under one atmosphere of hydrogen with 5% palladium on carbon (0.26 g) as catalyst. The solution was filtered through Celite, and solvents were removed in vacuo to give 2.4 g (91%) of the saturated acid as an oil. This was dissolved in benzene (200 mL), and benzoic acid (12 mg) was added. The solution was refluxed for 24 h under a dropping funnel containing 4Å molecular sieves. After removal of solvent in vacuo, the oil was purified by chromatography (40% ethyl acetate in hexane) to give 1.96 g (85%) of the lactone acetal 32.

32: IR (neat) 1740, 1460, 1380, 1180, 1080 cm^{-1}; NMR ($CDCl_3$) δ 4.34 (m, 1H), 4.24,4.22 (2s, 0.5H, 0.5H), 3.52,3.50,4.99 (3s, 1.5H, 3H, 1.5H), 2.7-1.5 (m, 5H), 1.30,1.22 (2d, 1.5H, 1.5H), 0.94,0.92 (2s, 1.5H, 1.5H), 0.84 (s, 3H); MS m/e (rel. int.), calcd for $C_{11}H_{19}O_3$: 199.133, found 199.133 (100, M^+-OCH_3), 113 (88).

IV. BIBLIOGRAPHY

1. D.A. Evans, G.C. Andrews, and B. Buckwalter, J. Amer. Chem. Soc., 96, 5560 (1974).

2. K. Suga, S. Watanabe, and T. Fujita, Aust. J. Chem., 25, 2393 (1972).

3. P. Pfeffer, L. Silbert, and E. Kensel, Tetrahedron Lett., 1163 (1973).

4. G. Cainelli, G. Cardillo, M. Contento, G. Trapani, and A. Umani Ronchi, J. Chem. Soc. Perkin Trans. I, 400 (1973), and references therein.

5. G. Cardillo, M. Orena, and S. Sandri, Tetrahedron, 32, 107 (1976).

6. J. Katzenellenbogen and A. Crumrine, J. Amer. Chem. Soc., 98, 4925 (1976).

7. A. Kajikawa, M. Morisaki, and N. Ikekawa, Tetrahedron Lett., 4135 (1975).

8. I. Casinos and R. Mestres, J. Chem. Soc. Perkin Trans. I, 1651 (1978), and references therein.

9. E. Vedejs and D.M. Gapinski, Tetrahedron Lett., 4913 (1981).

10. M. Majewski, G.B. Mpango, M.T. Thomas, A. Wu, and V. Snieckus, J. Org. Chem., 46, 2029 (1981).

11. B.S. Pitzele, J.S. Baran, and D.H. Steinman, Tetrahedron, 32, 1347 (1976).

12. P.L. Creger, Ann. Rep. Med. Chem., 12, 278 (1977).

13. G. Cardillo, M. Orena, G. Porzi, and S. Sandri, J. Org. Chem., 46, 2437 (1981).

14. M.A. Avery and J.D. White, Tetrahedron Lett., 3123 (1981).

15. S. Hattori and M. Tokizawa, Japan Pat. 70, 21687 (Chem. Abstr. 73, 87460d, 1970).

16. E. Späth and L. Pattan-Raschik, Monatsh. Chem., 79, 455 (1948).

17. α Condensation products which arose from aldehydes with crotonic and tiglic acids were a mixture of erythro and threo isomers.