

A synthesis of moenocinol from isoprenoid precursors

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Abstract - A synthesis of 5 based on synthons 3,6,7 is summarized.

INTRODUCTION

The antibiotic Moenomycin A (1) ¹ is the main constituent of the commercial product flavomycin ^R which is employed in animal nutrition. ² 1 is an efficient inhibitor of the biosynthesis of the peptidoglycans of bacterial cell-walls by interacting with the enzyme(s) ³ that catalyze the transfer of the disaccharide-oligopeptide unit from the disaccharide-(oligopeptide)-pyrophosphoryl-undecaprenol intermediate to the growing linear peptidoglycan chain. ⁴ From degradation ⁵ and biochemical studies ⁶, it was concluded that only units E,F,G,H, and I of 1 are essential for full biological (in vitro) activity. Unit I which is linked to the 2-position of D-phosphoglycerate is a unique C₂₅ lipid alcohol called moenocinol. ⁷ On mild acid hydrolysis the allyl ether bond is selectively cleaved and moenocinol (5) is liberated from the rest of the molecule. ^{1,2} Three isoprene units can easily be identified in 5 whereas the central C₁₀ part (C-5 through C-22) does not obey the isoprene rule in an obvious way.

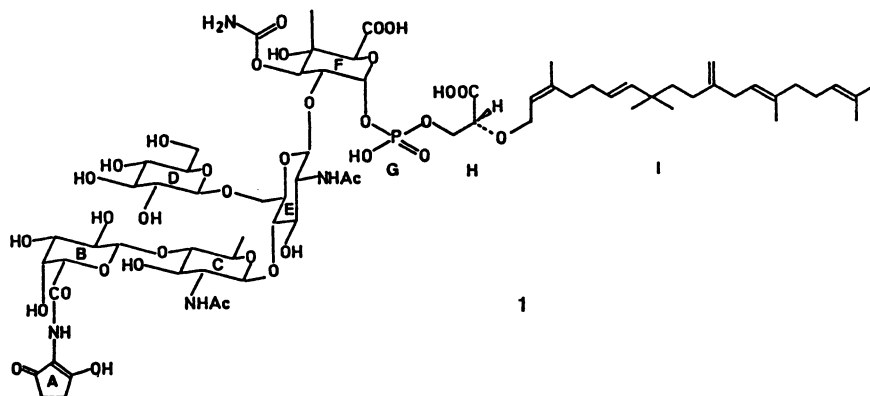


Figure 1

RETROSYNTHETIC ANALYSIS (Figure 2)

Because of its unique structure 5 has stimulated considerable synthetic efforts. All previous syntheses of 5 ⁹⁻¹³ (with one exception ¹⁴) were based on disconnections between C-11 and C-12 and between C-6 and C-7 leading to geraniol (3) and (via synthon 4) to nerol (2) as precursors of the trisubstituted olefinic parts. One of the major problems to be dealt with was the C-C bond formation between C-11 and C-12 by reaction of some vinyl anion equivalent with a geranyl halide. ⁹⁻¹³

Our approach to 5 is unique in that it uses isoprenoid precursors exclusively. ¹⁵ Disconnection of 5 at the C-4 - C-5 and the C-11 - C-12 bonds gives two isoprenoid synthons (3 and 7). We realized that reconnection (in the retrosynthetic sense) of the B-unit at C-5 and C-11 also leads to an isoprenoid synthon (of type 6). Thujic acid (9) and kharahanaenone (10) have this carbon skeleton which is biogenetically formed by anti-Markovnikov cyclization of geranyl pyrophosphate (see 8).

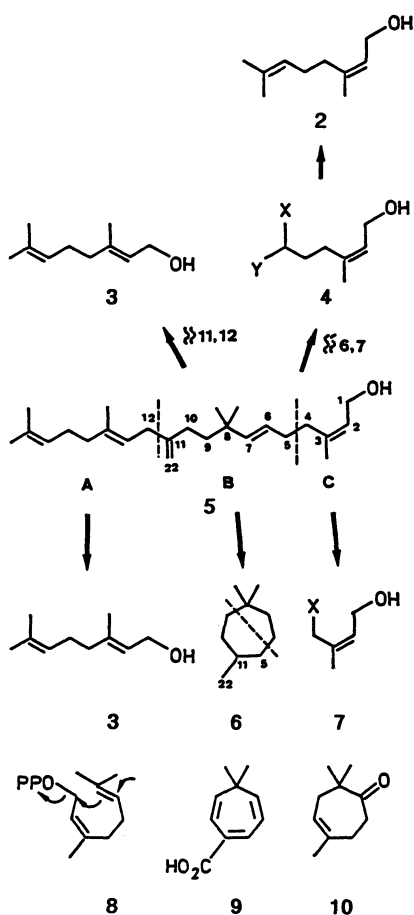


Figure 2

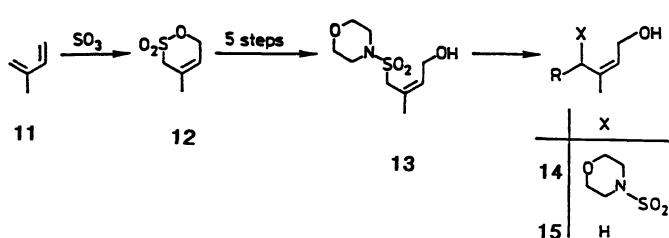


Figure 3

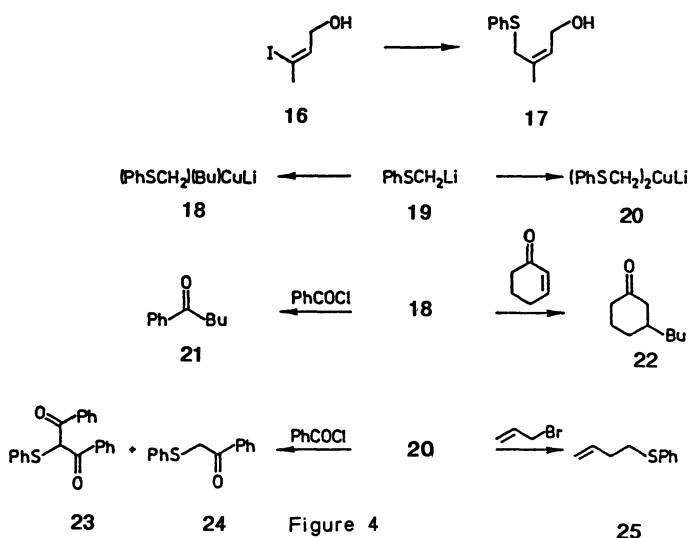


Figure 4

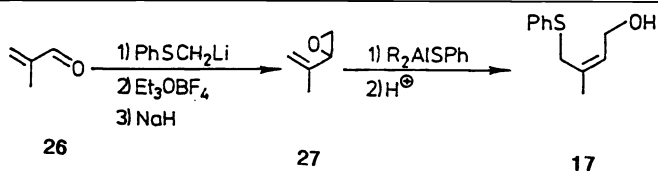


Figure 5

SYNTHESIS OF UNIT C

A synthetic equivalent of synthon 7 has recently been introduced by Moiseenkov *et al.*¹⁶ (Fig.3). The sultone 12 was converted in 5 steps into the sulfonamide 13 the dilithium salt of which was selectively alkylated to give 14. Reductive removal of the sulfonamide group to give 15 was performed with Na/NH₃ in the presence of a crown ether. Although this procedure works well the synthesis of 13 is multistep and rather time-consuming.¹⁸ We tried, therefore, to develop an alternative. A simple solution seemed to be the alkylation of 16¹⁹ with a cuprate 20 derived from phenylthiomethyl lithium (19)²¹ to give 17 (Fig. 4). This plan failed since 20 did not show the desired properties. Although the reactivity pattern of 20 is still not completely understood it seems that the PhSCH₂ ligand behaves like the sulphonyl-stabilized carbanion ligands in the mixed homocuprates described by Johnson and Dhanoa²² and is transferred reluctantly and only to very reactive electrophiles. In the reactions of the mixed homocuprate 18 with benzoyl chloride and with cyclohexenone only the products of butyl transfer were observed (see Fig. 4). The symmetrical homocuprate 20 reacted with allyl bromide to give 25 in 71% yield. Reaction of 20 with 0.5 equiv. of benzoyl chloride produced a 1:2 mixture of 23 and 24 whereas treatment of 20 with 1 equiv. of benzoyl chloride afforded 23 exclusively. From the reaction of 20 with cyclohexenone we were unable to detect any addition product (1,4 or 1,2).²⁵

In another attempt to arrive at a synthetic equivalent of synthon 7 (Fig. 5) it was tried to make use of recent work of Takaya and coworkers²³ who have reported that vinyl oxiranes react with diethylaluminium benzenethiolate in benzene at room temperature to afford mainly

Table 1. Reactions of Some Vinyl Oxiranes with Dialkylaluminium Benzenethiolate in Benzene at 20°C

		$\text{R}^1 \text{---} \text{C}(\text{Oxirane}) \text{---} \text{R}^2 \xrightarrow[2) \text{H}^\oplus]{1) \text{R}_2\text{AlSPh}}$					
R ¹	R ²	yields (%)				Ref.	
1	H CH ₃	90	2			a	
2	H C ₅ H ₁₁	86	4			a	
3	CH ₃ CH ₃	81	13			a	
4	H CH ₃	49	11	8.6			
5	CH ₃ H	26	38	3.5			
6	H H	-	62	4	5		

a) A. Yasuda, M. Takahashi, and H. Takaya, *Tetrahedron Lett.* **25**, 2413 (1981)

(Z)-4-phenylthio-2-butene-1-ol derivatives in good yields (see entries 1-3 in Table 1). The vinyl oxiranes are easily accessible using the Johnson-Coates procedure²⁴ (see Fig. 5). We found²⁵ that the Takaya method is not of general applicability since the stereoselectivity appears to depend very much on the substituents present at the vinyl oxirane unit. In the case which is relevant in the present context (entry 5 in Table 1) the ratio of the Z- and E-isomers was 1:1.5, and the parent vinyl oxirane itself gave only (E)-4-phenylthio-2-buten-1-ol along with some side-products (entry 6 in Table 1).²⁶

In 1984 Moiseenkov et al.²⁹ reported that isoprene and phenylsulfinyl chloride (28) react under high-pressure conditions to give 30 in 75% yield (possibly via 29). Acetolysis of 30 furnished acetoxy sulfoxide 31. This appears to be the method of choice for the synthesis of (Z)-prenyl alcohol units. In applying the Moiseenkov method in moenocinol synthetic studies, we found that care has to be taken in handling 31. It is unstable and rearranges even at 20°C to give the E-isomer 33. The isomerization presumably involves two[2,3]sigmatropic rearrangements³⁰ as indicated in Fig. 6. Reduction of both 31 and 33 provided 17 and 32, respectively.²⁵

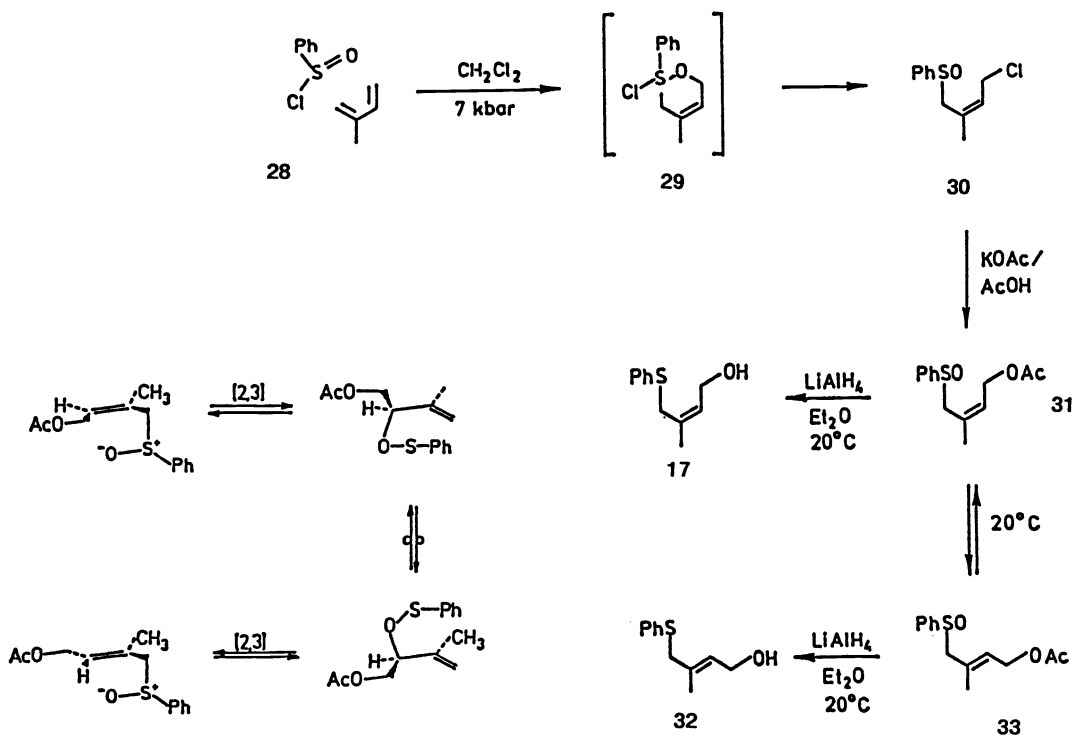


Figure 6

FRAGMENTATION BEHAVIOUR OF 2-TOSYLOXYMETHYL CYCLIC KETONES

For the synthesis of **37** which has the carbon skeleton of the A-B unit of moenocinol (**5**) we envisaged an alkylation of β -keto ester **35** (a synthetic equivalent of synthon **6**) with geranyl chloride to give **36**, conversion of **36** into keto tosylate **38**, and finally, a Grob fragmentation of **38** (Fig. 7). 2-Mesyloxymethyl- and 2-tosyloxymethyl-cyclopentanones, respectively, on reaction with OH^- and CH_3O^- undergo this ring-cleaving fragmentation in high yield (see entries 1 and 2 in Table 2). In related six-membered compounds the fragmentation reaction occurs only to a minor extent (entries 3-5 in Table 2). Unfortunately, conversion of **38** to the desired C_{20} moenocinol intermediate **37** under the fragmentation conditions failed. Rather than **37**, there were obtained **40**, **41**, formed from anion **39** by C- and O-alkylation, respectively, along with **43**, the formation of which can be explained by a homo-Favorskii mechanism as indicated in formula **42**.³¹ In a model experiment 2-methyl-2-tosyloxymethyl-cycloheptanone (**45**) was subjected to the CH_3O^- treatment (0.3 m CH_3ONa in CH_3OH , 24h at 95°C). GC-MS revealed the formation of four main reaction products (Fig. 9): the intramolecular C- and O-alkylation products **49** and **50**, respectively, the direct substitution product **48**, and 2-methylcycloheptanone (**51**) which is (ironically) formed by an unwanted retro-aldol fragmentation (ratio of **48**, **49**, **50**, **51**: 1:2.4:1.6:2.5, total yield: 96%). The unsaturated ester **47** could not be detected.³¹

What are the factors that determine the different reactivity of 2-tosyloxymethylcycloanones depending on ring-size as evident from the results collected in Table 2? In terms of Fig. 10 two mechanistic possibilities can be considered:

a) The rate of formation of **53** or **54** from **52** is product-determining. In the case of **52** ($n=1$) reaction $52 \rightarrow 53$ would then have to be faster than $52 \rightarrow 54$, whereas in the case of **52** ($n=2$ and $n=3$) $52 \rightarrow 54$ would be faster than $52 \rightarrow 53$.

b) Preequilibria are maintained between **52** and **53** and **54**, respectively, and the second step is slow. In this case the relative energy contents of transition states **55**, **56**, and **57** would determine the product ratio of **58**, **59**, and **60**.

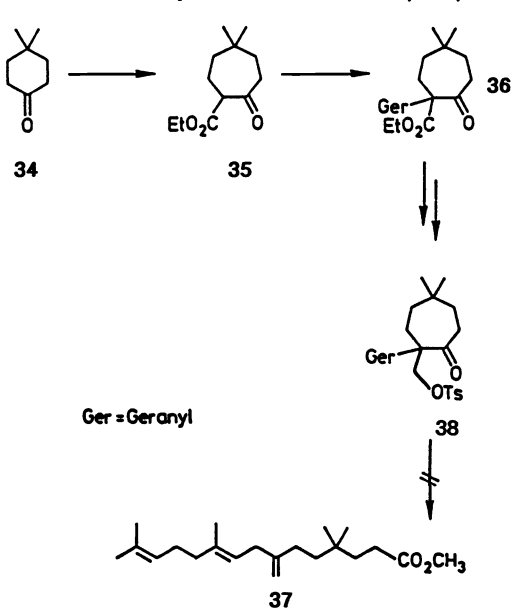


Figure 7

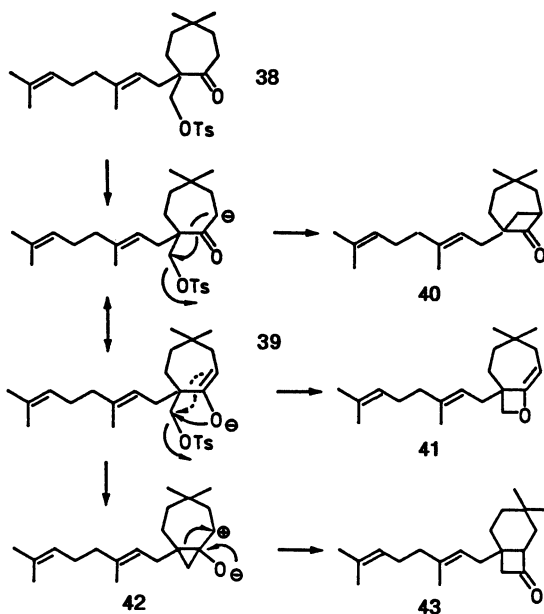


Figure 8

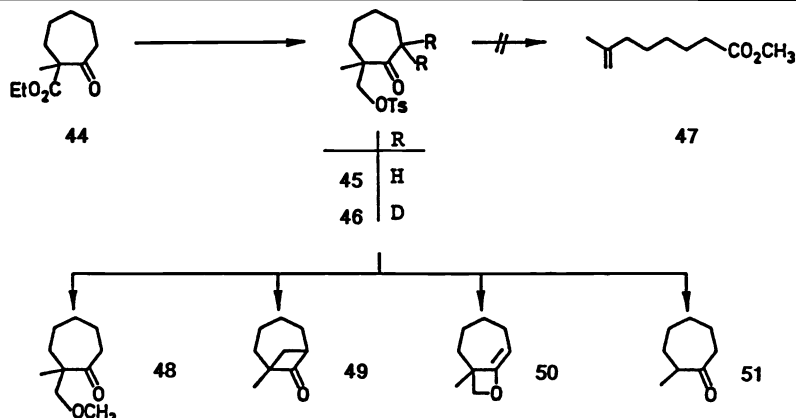


Figure 9

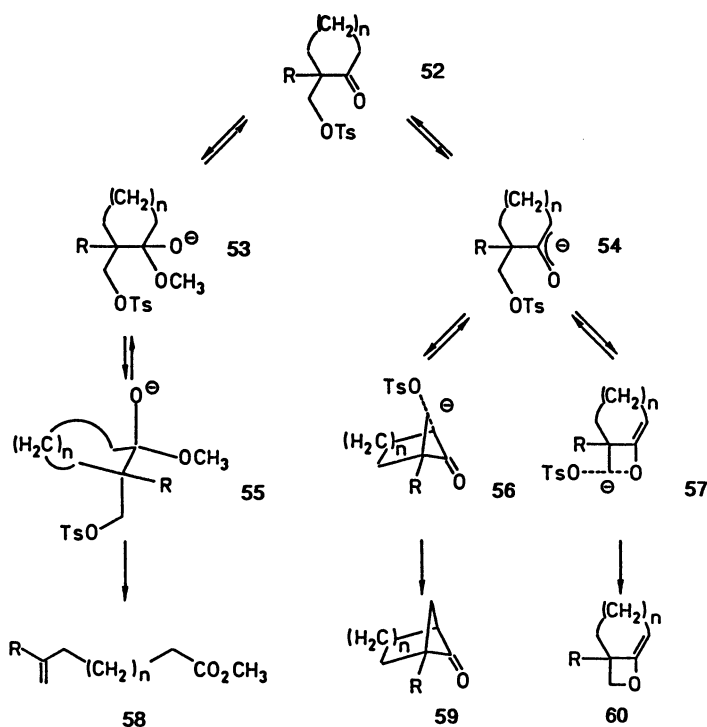

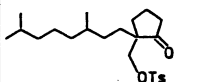




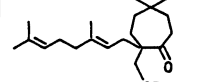


Figure 10

Table 2. Reactions of Some 2-Tosyloxymethyl (2-Mesyloxymethyl) Cyclohexanones with Nucleophiles/Bases.

	Nucleophile/ Base	Fragmentation §	C-Alkylation ¶	O-Alkylation §	Ref.
1	 HO ⁻	82	-	-	a
2	 CH ₃ O ⁻	61	-	-	b
3	 HO ⁻	5	78	-	c
4	 HO ⁻	1	90	-	c
5	 HO ⁻	3	89	-	c
6	 H ₃ CO ⁻	-	31	20	d
7	 H ₃ CO ⁻	-	39	35	b









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





d) E. Adams, U. Heinz, and P. Welzel, unpublished.

Table 3. Relative Rates of Reduction of Some Cyclic Ketones by Sodium Borohydride in Isopropanol at 25°C.

							
84.4 ^{a)}	1.2	1048.0 ^{a)}	59.0	13.0	1.0	17.8	1.5

^{a)} From H.C. Brown and K. Ichikawa, *Tetrahedron* **1**, 221 (1957)

Table 4. Relative Rates of Trimethylsilyl Enol Ether Formation ^{a)} of Some Cyclic Ketones at -78°C.

					
2.0	0.47	1.0	1.25	1.43	1.14

^{a)} Procedure as described by E.J. Corey and A.W. Gross, *Tetrahedron Lett.* **25**, 495 (1985)

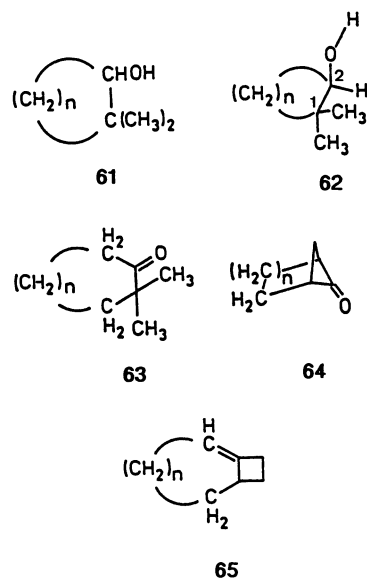


Figure 11

With the aim of discriminating between these two possibilities the effect of ring-size of 2,2-disubstituted cyclanones upon the reduction rate with sodium borohydride in 2-propanol (as a measure of the reactivity with nucleophiles) and the rate of silyl enol ether formation (kinetic acidity) was investigated. In both cases relative rates have been determined. The results are summarized in Tables 3 and 4.^{25,33}

In the reduction with NaBH₄ (see Table 3) 2,2-disubstitution leads to a marked rate reduction, but the reactivity order is the same as published by Brown and Ishikawa³⁴ for the unsubstituted cyclanones: cyclohexanone > cyclopentanone > cycloheptanone.^{35,36} For silyl enol ether formation the following reactivity order was determined (Table 4): 2,2-dimethylcyclopentanone > 2,2-dimethylcycloheptanone > 2,2-dimethylcyclohexanone. At least in the cycloheptanone series the rate of trimethylsilyl enol ether formation is not very much influenced by 2,2-disubstitution as compared with the parent ketone. The results collected in Tables 3 and 4 seem to rule out a correlation between reaction mode of 2-tosyloxymethyl cyclic ketones with RO⁻ nucleophiles/bases and the reactivity of the corresponding 2,2-dimethylcyclanones both with nucleophiles (NaBH₄) and bases (silyl enol ether formation).

In the case of **45** it has been substantiated that anion **54** (n=3) is formed in a preequilibrium step. Treatment of **45** with CD₃ONa/CD₃OD at 4°C led to complete hydrogen-deuterium exchange at the free α-position (determined by 400 MHz ¹H NMR). **45** was completely stable under these conditions; the formation of **48-50** was not observable. Although our experimental results are still incomplete it seems quite obvious that it is the relative energy contents of transition states **55**, **56**, and **57**, which determines the product ratio of **58**, **59**, and **60**. A number of force field calculations with some model compounds have been carried out by Prof. W. Roth, Ruhr Universität Bochum, in order to estimate the relative stabilities of the respective transition states. We wish to thank Prof. Roth for kindly allowing us to use these results for the present discussion. First the steric energy difference between the minimum conformation of **61** and conformation **62** with the torsional angle (H₃C-)C₁-C₂(-OH)=180° was calculated. The energy differences are rather small and do not vary much depending on the ring size. Since the geometry of the transition states **56** and **57** for C- and O-alkylation are unknown the increase in steric energy in going from **63** to **64** and **65** was calculated. The absolute values of these calculated energy differences are certainly of no significance but the differences between them ($\Delta\Delta E$) clearly show that the steric energy in going from **63** to **64** and **65**, respectively, increases considerably with decreasing ring size. One has, of course, to worry whether the ketones **63** are really good models for the corresponding enolates **54**. Since it has been shown that the kinetic acidity does not vary very much with ring size (see Table 4) the change in steric energy in going from the ketone to the enolate is obviously rather similar in the five-, the six- and the seven-membered series.

Experimentally it was established that in the 6-membered series (52, n=2) fragmentation competes (to some extent) with C-alkylation (see Table 2, entries 3, and 5). In this series transition states **55** and **56** should be rather close in energy.¹ In the 5-membered series with a (calculated) higher activation energy of about 5-8 kcal mol⁻¹ for C- and O-alkylation as compared to the 6-membered series one would, therefore, expect only fragmentation to occur,

whereas in the 7-membered series the energy content of 56 and 57 was calculated to be by about 8-9 kcal mol⁻¹ lower as compared to the six-membered series. Exclusive C- and O-alkylation would be expected in this case. This is in nice agreement with the experimental results (Table 2).

SYNTHESIS OF UNIT A-B

When it turned out that the fragmentation route towards to the A-B unit of 5 would fail recourse was made to Torii's sulfenylating β -keto ester cleavage.³⁷ Reaction of 35 with 2-(morpholiniothio)-benzthiazole (66) in benzene solution (8h at 80°C and 14.5 h at 60°C) led to the formation of 67 (63%),¹⁸ whereas in methanol solution cleavage product 68 was formed in 77% yield.¹⁵ Generation of the more stabilized ester enolate from 68 and alkylation with geranyl chloride furnished 71 in 85% yield.¹⁵

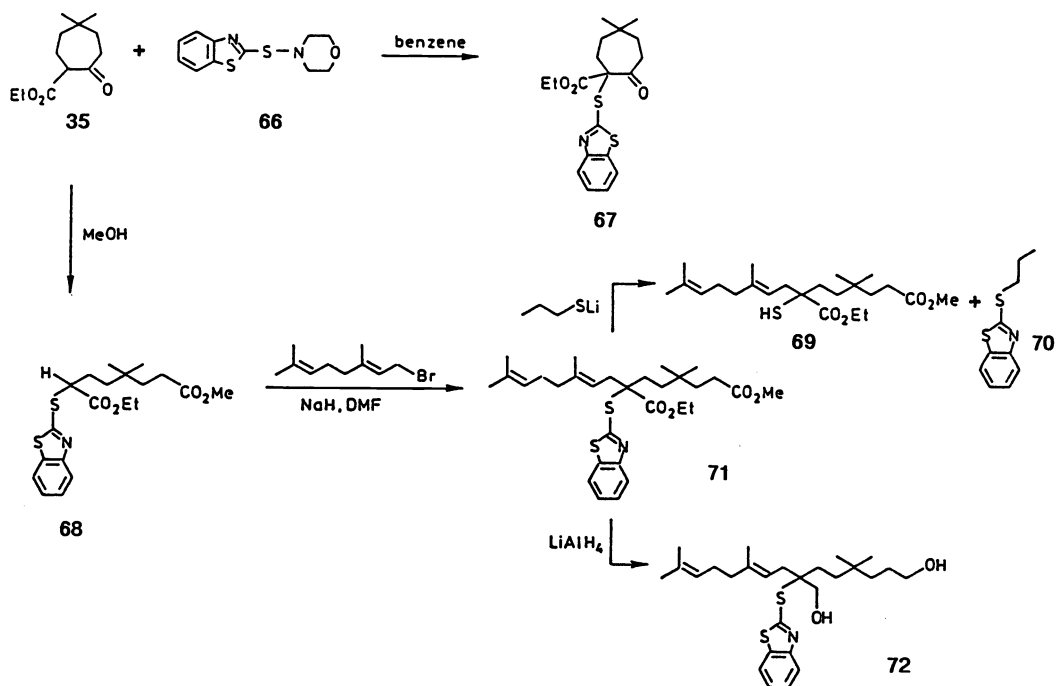


Figure 12

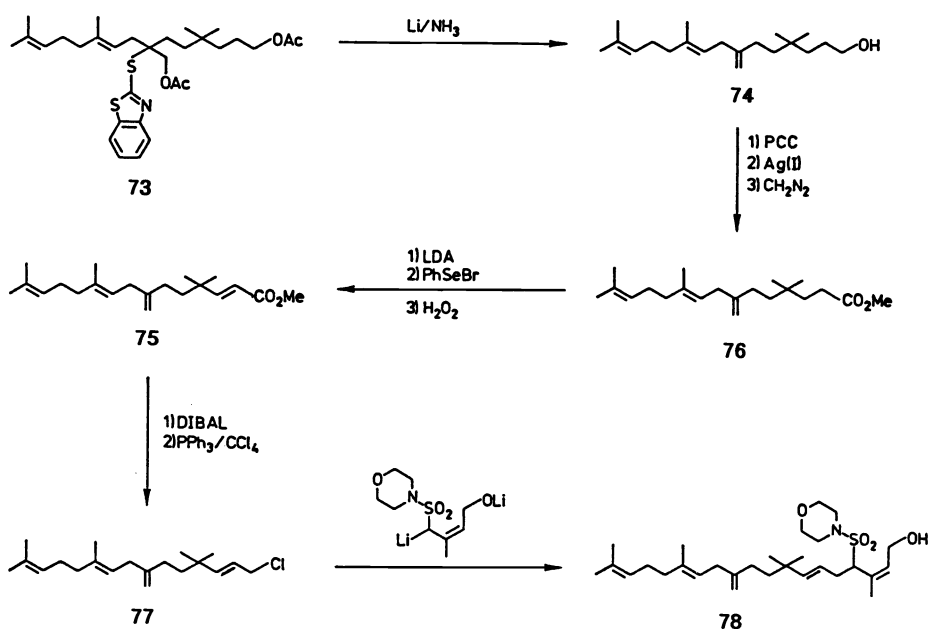


Figure 13

COMPLETION OF THE SYNTHESIS

In order to protect the C-1 carboxylic acid function it was tried to cleave the methyl ester group of **71** selectively using the lithium propylmercaptide method ³⁸ (Fig.12). This reagent added, however, preferentially to the C-N double bond of the thiazole ring to give **69** and **70** which were isolated in 40 and 54% yield, respectively.¹⁸ On the other hand, reduction with LiAlH₄ worked as desired (although less efficiently in terms of the overall synthetic economy) and provided **72** (76%). Acetylation of **72** to give **73** and subsequent reductive elimination ¹² with lithium in liquid ammonia, followed by ester hydrolysis gave **74** in 76% yield. Conversion of **74** into **77** was accomplished as summarized in Fig. 13. Finally, reaction of **77** with the dilithium salt of **13** to give **78** followed by reductive desulfonylation ¹⁷ provided **5**.¹⁵

Acknowledgements We are very grateful to Professors W.R.Roth, Bochum (force field calculations), F.G.Klärner, Bochum (high-pressure experiments), and A.Krief, Namur (synthesis of 2,2-dimethylcyclohexanones) for their help and advice. Financial support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the Hoechst AG, and the Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen (graduate studentship to U.H.) is kindly acknowledged.

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