samples at 80 K. The C–C band at 1558 cm^{-1} represents the initial all-trans pigment while that at 1575 cm^{-1} almost certainly arises from the short-wavelength M-type intermediate absorbing at ca. 380 nm. The results agree with previously determined correlation between λ_{max} and C=C stretching frequency and expected temperature dependence of M formation.[12]

On combination of the 6-cis and 2,6-dicis isomers of **2–4** with bacterioopsin, a broad absorption is noted with a λ_{max} of 450–460 nm with a shoulder at 510 nm. Extraction of the pigment with methylene chloride yields the respective 6-cis or 2,6-dicis isomer. These pigments are rapidly (~5 min) destroyed by hydroxylamine or *all-trans*-retinal. On irradiation, the absorption shifts to 487 nm, increases in intensity, and is identical with that of the all-trans pigments. Only the respective all-trans isomer is obtained when these irradiated pigments are extracted with methylene chloride. These results indicate that an unstable associate of the 6-*cis*- and 2,6-*dicis*-**2–4** retinals and bacterioopsin is formed, possibly allowed by the lack of the cyclohexyl ring and thus the greater flexibility of the chromophore.

The above experiments demonstrate that these acyclic chromophores can form pigments with bacterioopsin which show light-induced absorption and pH changes. As these retinal derivatives lack both a cyclohexyl ring and the fifth C=C, neither of these structural elements are evidently essential for these functions of the pigment. A similar but more restrictive conclusion has been proposed for the 5,6-ethylene bond by our studies of the 5,6-dihydroretinal pigments.[13] These results are consistent with isomerization and charge separation being the primary event[14] and indicate that the proton pumping and photocycling are dependent on the polyene chain portion of the retinal chromophore.

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Synthetic Studies on the Avermectins: Substituent Effects on Intramolecular Diels–Alder Reactions of *N*-Furfurylacrylamides and Further Reactions of the Cycloadducts

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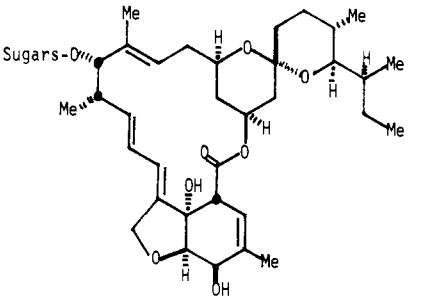
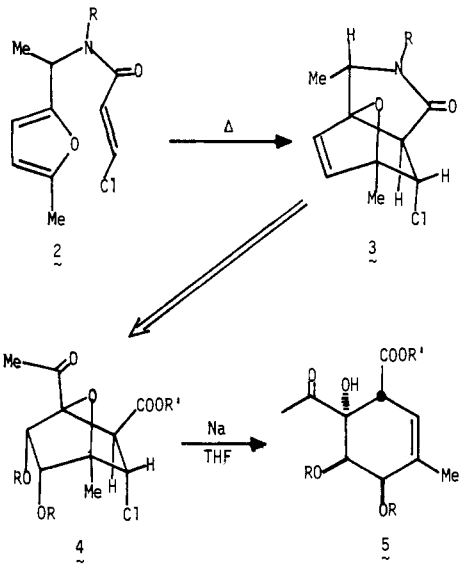
The avermectins[1] and milbemycins[2] are a recently discovered class of pentacyclic lactones having potent biological activity. Those compounds with a dihydroxyhexahydrobenzofuran unit have greater insecticidal activity than those with a tetrasubstituted-benzene unit,[3] with ivermectin (**1**) being the best broad-spectrum



1

antiparasitic agent. Although two excellent syntheses of milbemycin β_3 have been published[4] as well as routes to the top part of the molecule and attached sugars,[5] essentially no work has appeared on preparing properly substituted polyhydroxytetrahydrobenzoic acids for conversion into the bottom part of the avermectins. We now describe a process in which the intramolecular Diels–Alder adducts of *N*-furfuryl-β-chloroacrylamides can be reductively eliminated to give hydroxylated tetrahydrobenzoates as a model for the bottom part of the avermectins.

Our approach to the bottom half of **1** has two key constructive steps: an intramolecular cycloaddition of an *N*-furfuryl-β-chloroacrylamide **2** to give **3** and the reductive elimination of the chloro ether **4**, derived from **3**, to give **5**. The internal Diels–Alder



2 **3** **4** **5**

reactions of furans is a quite useful process, with tertiary *N*-furfurylacrylamides giving the adducts in high yield.[6–8] We have found that a methyl group on the connecting chain greatly accelerates the Diels–Alder reaction, affording one diastereomer in pure form.

The *N*-furfurylacrylamides **8a–h** were prepared from the corresponding 2-acetylfurans or furaldehydes **6a** by a simple

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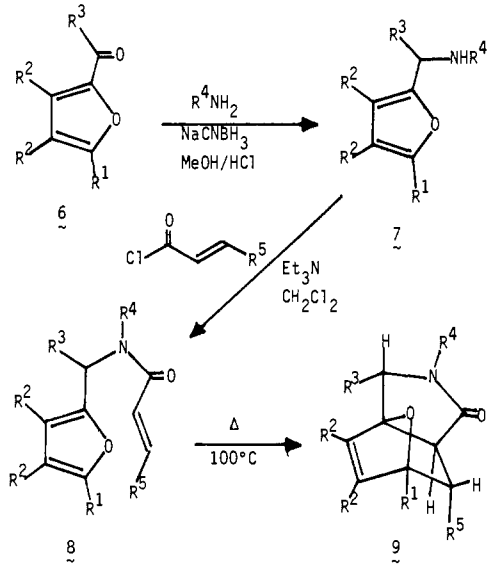
Table I. Intramolecular Diels–Alder Reaction of **8** to give **9** (110 °C/Toluene)

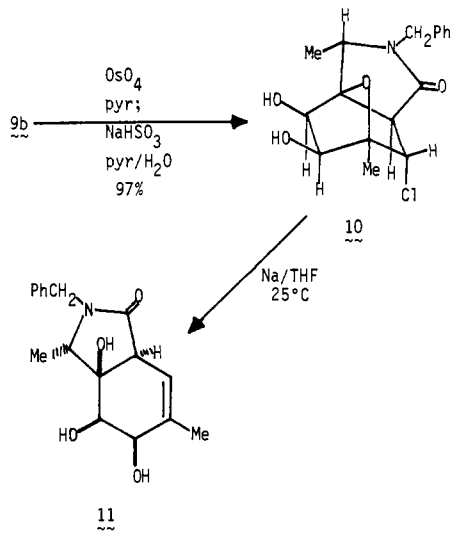
compd	R_1	R_2	R_3	R_4	R_5	time, h	yield, %	diaster ratio[a]
a	Me	H	Me	*o*-HOC_6H_4	Cl	12	74	5:1
b	Me	H	Me	CH_2Ph	Cl	1.1[b]	100	>95:<5
c	Me	H	Me	CH_2Ph	H	1	100	>95:<5
d	H	H	Me	CH_2Ph	Cl	1	100	>95:<5
e	Me	H	H	CH_2Ph	Cl	8	67	
f	Me	OMe	Me	CH_2Ph	Cl	<10 min [c]	100	1:1
g	Me	H	Me	H	Cl	48[d]	0	
h	Me	H	Me	Ac	Cl	4[e]	100	>95:<5

[a] The ratio of endo R^3 vs. exo R^3. In the cases listed >95:<5, none of the opposite isomer could be seen by high-field ^1H NMR. [b] This reaction could also be run at 25 °C, proceeding in 65% yield in 6 days. [c] This reaction was complete in 12 h at 25 °C, also providing a 1:1 diastereomeric mixture of **9f**. [d] Starting material was recovered unchanged. [e] This reaction was carried out at 153 °C by heating **8g** in acetic anhydride for 4 h effecting both acetylation and cyclization.

two-step route (reductive amination and acylation) in good overall yields.[9] The cyclization of these amides **8** to give the cycloadducts **9** was easily effected (Table I). A comparison of the rate of cyclization of **8e** with those of **8b–d** demonstrates the accelerative effect of a methyl group on the connecting chain. This substituent effect does not eliminate the need for a tertiary amide, as seen by Parker,[6] since **9g** cannot be prepared from **8g** by this route. However, this cyclization could be carried out on the imide formed in situ by acetylation of **8g** with acetic anhydride at 153 °C, giving **9h** in quantitative yield. Treatment of **9h** with ethanolic HCl gave **9g** in 77% yield. When **9g** was heated in toluene for 2 h, it reverted completely back to **8g**, thus indicating a strong (>3 kcal) thermodynamic bias against cyclization in the secondary amide case. The methyl group in the pyrrolidone ring was shown to be endo (trans to the oxygen bridge) by single-crystal X-ray analysis.[10] Finally the 3,4-dimethoxyfuran **8f** [prepared from 3,4-dimethoxyfuran[11] in four steps: methylation (*n*-BuLi, MeI) and acetylation (*n*-BuLi, Ac_2O), followed by reductive amination and acylation] cyclized quantitatively to **9f** under extremely mild

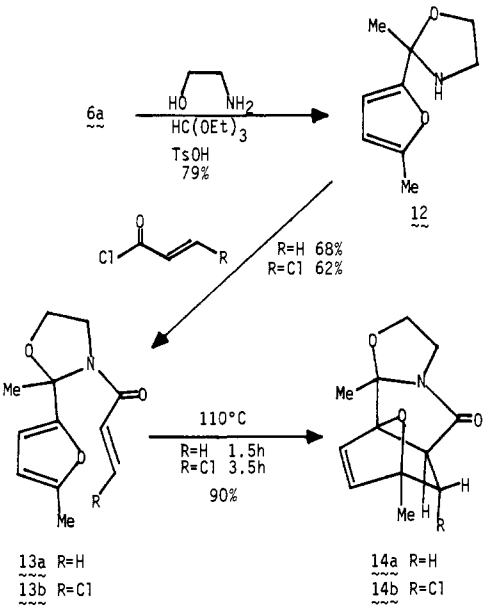


conditions (100 °C for ~5 min or 25 °C for 12 h). In this case the product **9f** was formed as a 1:1 mixture of diastereomers since the normally favored endo isomer now suffers strong steric interaction with the adjacent methoxy group. We have not determined the reasons for the acceleration and diastereospecificity due to the methyl group on the connecting chain, although it is



probably a case of the Thorpe–Ingold effect.[13] Force-field calculations[14] indicate that the two diastereomers differ in energy by ~1.2 kcal/mol, favoring the endo isomer. Thus the diastereoselectivity must be due to a kinetic preference for the endo as well as a thermodynamic one.[15]

Hydroxylation of **9b** under the usual conditions proceeded in



(9) The reductive amination of 2-acetyl-3,4-dimethoxy-5-methylfuran (**6f**) was quite slow (2 weeks) presumably due to the conjugation of the 3-methoxy group with the acetyl carbonyl which thereby significantly lowers its reactivity.

(10) The details of the crystal structure will be published elsewhere. We thank Professor C. E. Strouse for his assistance in determining this structure.

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(13) A similar, though much weaker, effect has been observed in the cyclization of substituted 2-(4-pentenyl)furans. Sternbach, D. D.; Rossana, D. M. *Tetrahedron Lett.* **1982**, 303.

(14) These calculations were carried out by using Still's modification of the Allinger MM2 program. We thank Professor Still for his assistance.

97% yield to give **10**. Although the newly introduced hydroxyl groups have the incorrect stereochemistry (cis to the oxygen bridge rather than trans), we decided to use this molecule to test the reductive elimination procedure necessary for the preparation of the β,γ-unsaturated ester in the real system (**4** → **5**). It was gratifying to observe that treatment of **10** with sodium in THF at 25 °C effected clean reductive elimination to afford the olefinic triol **11** in 78% yield. We believe this to be the first report of an opening of a furan cycloadduct to give an oxygenated non-aromatic product.

Although the N-unsubstituted lactam **9g** could be cleaved by Mukaiyama's procedure[7] (N-nitrosation, followed by reaction with hydroxide ion, and mild acid hydrolysis), an oxidation is still required to produce the desired acetyl group, as in **5**. The overall sequence could be significantly shortened as follows. Reaction of 2-acetyl-5-methylfuran **6a** with 2-aminoethanol produced in 79% yield the aminal **12**, which could be acylated with acryloyl chloride or β-chloroacryloyl chloride to give **13a,b** in 68% and 62% yield, respectively. Cyclization of **13a,b** at 110 °C for 1.5 and 3.5 h, respectively, gave a 90% yield of **14a,b**, each as a single diastereomer, most likely the α-methyl compound shown. Therefore disubstitution at the benzylic center also increases the rate of cyclization vs. the unsubstituted case.

The conversion of compounds such as **9** and **14** into intermediates, e.g., **5**, for the synthesis of the avermectins is currently under investigation.

Acknowledgment. We thank the Agricultural Research Division of the American Cyanamid Co. for financial support and helpful discussions.

(15) Chromatography of **9a** gave a fraction that was an approximately 1:1 mixture of diastereomers. Heating this mixture at 100 °C caused a very slow isomerization of the exo to the endo isomer (presumably via retro-Diels–Alder followed by cyclization) which did not proceed to the 5:1 ratio even after several days. This is additional evidence for a kinetic preference for the endo isomer.

Additions and Corrections

Polymer Films on Electrodes. 14. Spectral Sensitization of n-Type SnO_2 and Voltammetry at Electrodes Modified with Nafion Films Containing $Ru(bpy)_3^{2+}$ [*J. Am. Chem. Soc.* **1984**, *106*, 7371–7380]. MAHADEVAIYER KRISHNAN, XUN ZHANG, and ALLEN J. BARD*

Figures 8 and 9 were transposed in printing. They should appear as follows:

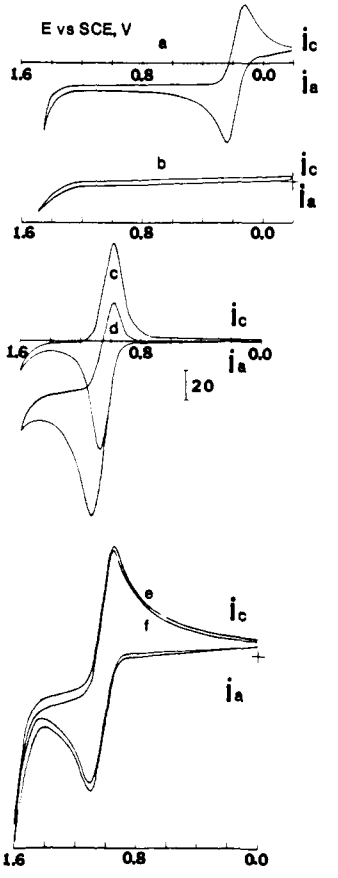

Figure 8. Cyclic voltammetry in 0.1 KCl at 10 mV/s: (a) SnO_2 electrode in 1 mM $K_4Fe(CN)_6$; (b) SnO_2/NAF (d = 0.4 μm) in 1 mM $K_4Fe(CN)_6$; (c) SnO_2/NAF, $Ru(bpy)_3^{2+}$ in base electrolyte (d = 0.3 μm); (d) same electrode as (c) with 1 mM $K_4Fe(CN)_6$ added to the solution; (e) SnO_2/NAF, $Ru(bpy)_3^{2+}$ thick film electrode in base electrolyte; (f) same electrode with 1 mM $K_4Fe(CN)_6$ added to the solution.

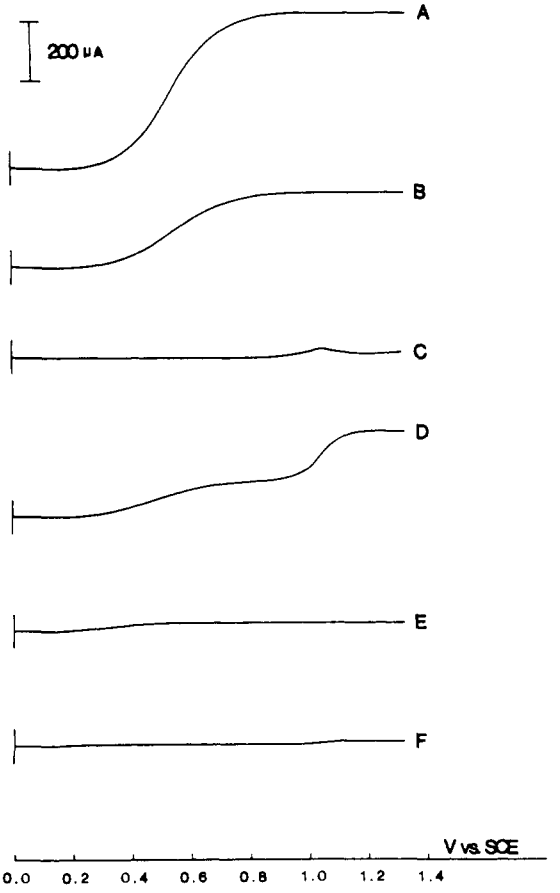

Figure 9. Voltammetry at GC RDE in 0.1 M Na_2SO_4 at scan rate 5 mV/s and rotation rate 1000 rpm: (A) bare GC RDE with 1 mM hydroquinone; (B) GC/NAF (d = ~0.3 μm) with 1 mM hydroquinone; (C) GC/NAF, $Ru(bpy)_3^{2+}$ (d = ~0.3 μm) in base electrolyte alone; (D) GC/NAF, $Ru(bpy)_3^{2+}$ (d = ~0.3 μm) with 1 mM hydroquinone; (E) GC/NAF (d = ~3 μm) with 1 mM hydroquinone; (F) GC/NAF, $Ru(bpy)_3^{2+}$ (d = ~3 μm) with 1 mM hydroquinone.