followed by reductive workup and separation of the diastereomeric lactones by flash chromatography gave as a major product lactone **11**. Deprotection afforded the desired (*R*)-(−)-pantolactone, identical in all respects with an authentic sample of chiral **12**.

In conclusion, we have demonstrated the ability of remote, acyclic chirality to control the stereochemical course of the glycolate Claisen rearrangement. We note that the terminal vinylic products obtained from rearrangement of glycolates **2** are not accessible in chiral form from internal asymmetric transfer using chiral allylic alcohols.[17] We are examining other auxiliary substituents in order to elucidate the nature and scope of stereochemical induction by homoallylic chirality in the glycolate system.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (AI-19632) for their support of this work. High-field NMR spectra were obtained at the N.I.H. Research Resource facility (RR-01317) in this department. We thank Professor Kathlyn A. Parker for her assistance with the molecular mechanics calculations.

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Acyclic Stereocontrol in Catalyzed Intramolecular Diels–Alder Cyclizations of 4-Methyl-2,8,10-undecatrienals

Summary: A 4-methyl substituent has been found to exert profound diastereocontrol on the Diels–Alder cyclization of 2,8,10-undecatrienals in the presence of ethylaluminum dichloride, giving trans-fused 5-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-4-carboxaldehydes with the methyl group equatorially disposed, consistent with a product-like transition state with the tether in a chair and the developing cyclohexene ring in a boat conformation.

Sir: The Diels–Alder reaction has long been recognized as a favored strategy for the synthesis of six-membered rings, often with a high degree of stereochemical control.[1] In recent years the intramolecular Diels–Alder reaction has proven equally valuable as a route to polycyclic systems.[2] Although the intramolecular version of the reaction can be limited by the nature of the "tether" connecting the diene and dienophile, numerous applications have nonetheless been reported.[2,3] Among these are examples where the tether bears a substituent and thus possesses a chiral center. In such cases mixtures of diastereoisomeric products may be formed.[4] Pursuant to work on the synthesis of chlorothricolide[5] and kijanolide,[6] we were interested in developing the Diels–Alder strategy illustrated in Figure 1. We previously found that conjugated aldehydes undergo Lewis acid catalyzed Diels–Alder cyclizations to

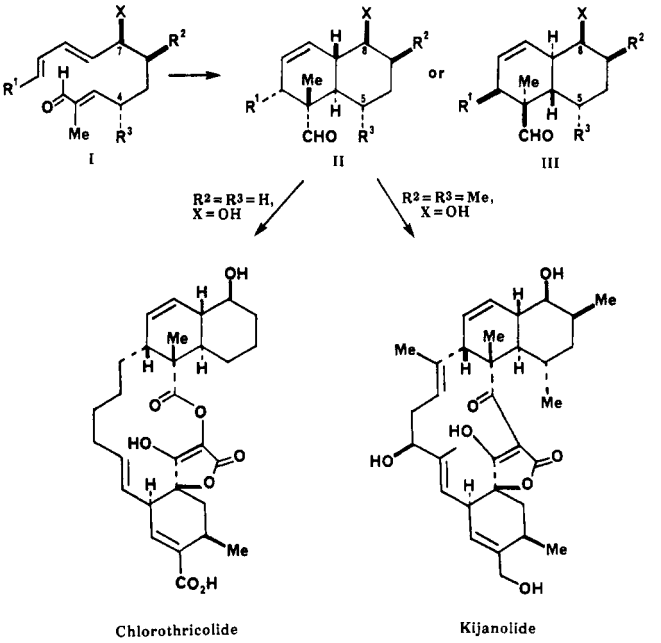
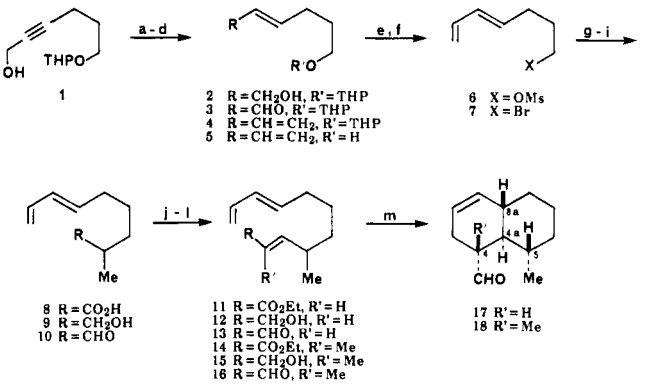


Figure 1. Diastereoselectivity in the intramolecular Diels–Alder approach to the hydronaphthalene segment of macrocyclic antitumor antibiotics.

Chart I. Series A Compounds[a]



[a] (a) Red-Al, Et_2O; (b) PDC, DMF; (c) $Ph_3P{=}CH_2$, THF; (d) MeOH, Dowex H^+; (e) MsCl, Et_3N, CH_2Cl_2; (f) THF, LiBr; (g) $CH_3CH{=}C(OLi)_2$, THF, HMPA; (h) $LiAlH_4$, Et_2O; (i) PDC, CH_2Cl_2; (j) $Ph_3P{=}C(R)CO_2Et$; (k) DIBAH, Et_2O; (l) MnO_2, CH_2Cl_2; (m) $EtAlCl_2$, CH_2Cl_2, −78 to −23 °C; R′ = H, 1 h; R′ = Me, 24 h.

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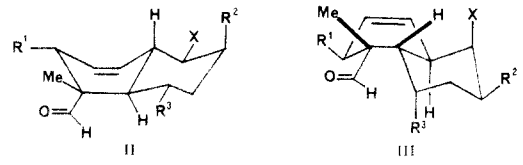


II III

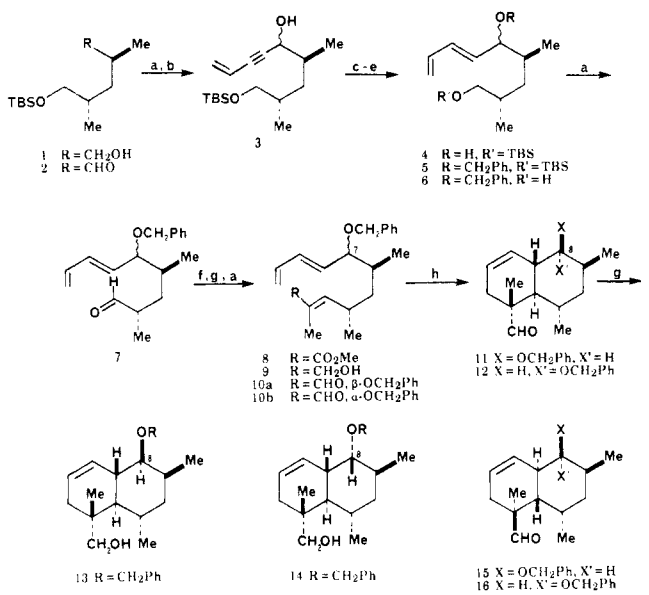
Series	Energies II	Energies III
a $R^1 = R^3 = Me$, $R^2 = X = H$	23.44 kcal	28.15 kcal
b $R^1 = R^2 = R^3 = Me$, $X = OMe$	31.84 kcal	37.16 kcal

Figure 2. Diastereomeric transition-state models for Diels–Alder cyclization of enal diene I with a chair tether.

trans-fused hydronaphthalenes in excellent yields under extremely mild reaction conditions.[7] In the course of those studies we noted that a (*tert*-butyldimethylsilyl)oxy (OTBS) substituent at C-7 exhibited high diastereocontrol to give essentially one of the two a priori possible trans-fused racemic cyclization products. For reasons still unclear, the OTBS grouping strongly prefers the axial orientation in the cyclization product. Methoxy, benzyloxy, or methoxymethyl groups at C-7 showed no such preference.[7,8] With the aim of extending this approach to more complex natural products such as kijanimycin, we wished to evaluate the directing effect of a 4-methyl substituent on the stereochemistry of the cyclization. The question may be stated as follows: In a precursor such as I ($R^2 = R^3 = Me$) will high endo selectivity still be observed and, if so, will R^3 direct cyclization to diastereoisomer II rather than III? Should the answer be yes, an attractive route to the hydronaphthalene subunits of kijanolide[6] and related natural product aglycones[9] would be at hand.

As a first step toward answering this question we prepared the 4-methyl-2,8,10-undecatrienal **A13** from the alkynol **A1** by the sequence detailed in Chart I. As expected, both stereochemically important steps, reduction of propargylic alcohol **A1** with Red-Al[10] and condensation of aldehyde **A10** with ethyl triphenylphosphorylidene acetate proceeded with virtually complete trans stereochemistry. The *trans,trans*-trienal **A13** cyclized readily upon exposure to ethylaluminum dichloride in methylene chloride at −78 to −23 °C. After 1 h, hydronaphthalene aldehyde **A17** of >95% purity could be isolated in 82% yield after chromatography.[11] In analogous fashion, the 2-methyl homologue **A14** was prepared through condensation of aldehyde **A10** with ethyl α-(triphenylphosphorylidene)propionate. Once again, only the trans conjugated ester could be detected. Cyclization of the 2,4-dimethyl-2,8,10-undecatrienal **A16** in methylene chloride with ethylaluminum dichloride at −78 to −23 °C, proved noticeably slower than for **A13**, requiring 24 h for completion. In this case, hydronaphthalene **A18** of >95% purity was isolated in 78% yield.[11] The structures of cycloadducts **A17** and **A18** were readily deduced from their high-field ^1H NMR spectra. In both products the ring fusion proton at H-4a showed strong axial coupling to its neighbors H-8a, H-5, and, for **A17**, H-4.[12] Thus the C-4

Chart II. Series B Compounds[a,b]



[a] (a) $(COCl)_2$, Me_2SO, CH_2Cl_2, −60 °C; Et_3N, −25 °C; (b) CH_2=CHC≡CLi, THF, −78 °C; (c) Red-Al, Et_2O, 0 to 25 °C; (d) *n*-BuLi, THF, HMPA, $PhCH_2Br$, −78 to 25 °C; (e) Bu_4NF, THF, 25 °C; (f) Ph_3P=C(Me)CO_2Me, CH_2Cl_2, 0 to 25 °C; (g) *i*-Bu_2AlH, Et_2O, −78 °C; (h) $EtAlCl_2$, CH_2Cl_2, ~0.1 M, −78 to −23 °C. [b] TBS = *t*-$BuMe_2Si$

methyl grouping in **A13** and **A16** strongly directs cyclizations in favor of type II vs. type III diastereoisomeric products (see Figure 1).

Before embarking upon the more difficult synthesis of a potential kijanolide precursor such as I ($R^2 = R^3 = Me$), we attempted to estimate the relative energetics of cyclizations leading to II and III with the aid of molecular modeling.[13,14] We were particularly concerned with the unknown directing effect of R^2, as this grouping could be forced to assume an axial orientation in the transition state leading to the desired product (e.g., II, $R^2 = R^3 = Me$).

The structures pictured in Figure 2 were employed in our modeling studies.[14] It was found that a C-3 alkyl substituent, R^1, effectively prevents the cyclohexene ring from assuming a chair conformation during energy minimization. The "a series" was used to approximate the formation of **A18** and the "b series" was used for **B11**. Calculations on the boat–chair diastereoisomers II and III showed a clear preference for the former in both the a and b series. The related boat–twist-boat conformers of II and III gave appreciably higher energy values, even in the case of IIb.[15] Calculations on the C-8 α-epimer of IIb and IIIb (cf. **B12**) showed exactly the same ordering of diastereo and conformational preferences. The transition state represented by IIb (with an axial X = OMe substituent) was 4 kcal lower in energy than the diastereoisomer IIIb

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(11) Analysis was effected by means of glass capillary gas chromatography and high-field ^1H NMR spectra.

(12) The analysis was made through a 2D *J*-resolved experiment which showed $J_{H_{4a},H_4} = J_{H_{4a},H_5} = J_{H_{4a},H_{8a}} = 10.4$ Hz for aldehyde **A14**. The cis relationship of the C-1 formyl and C-4 methyl was also verified by NOE difference spectra.

(13) Molecular modeling was carried out with the Still Model program employing the Allinger MM2 force field.

(14) The assumption of a late transition state was made in accord with recent ab initio calculations (Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1984**, *25*, 4609). Although II and III (Figure 2) may differ from the actual transition-state geometry, the calculated energies may still reflect the relative transition-state energies as both products are formed via the same pathway.

(15) Energies for twist-boat conformers corresponding to IIa and IIIa ($R^1 = R^3 = Me$, $R^2 = X = H$) were calculated as 29.87 and 32.35 kcal, while the more substituted analogues (b series; $R^1 = R^2 = R^3 = Me$, X = OMe) gave values of 39.67 and 41.43 kcal, respectively.

(with an equatorial X = OMe substituent). The boat–twist-boat conformers of these α-methoxy epimers were 7 and 10 kcal higher in energy, respectively. Based on these findings, neither an axial R^2 = Me nor an axial X = alkoxy substituent would be expected to compromise the equatorial preference of the R^3 = Me substituent in cyclizations leading to kijanolide-type structures II.

To test this stereochemical prediction we prepared the 1:1 mixture of C-7 epimeric benzyl ether enal dienes **B10** from the mono TBS derivative **B1** of (±)-2,4-dimethyl-1,5-pentanediol[16] (Chart II). Treatment of the 1:1 mixture **B10** with ethylaluminum dichloride at −78 to −23 °C produced an inseparable 1:1 mixture of products in 70% chromatographed yield. Reduction of this mixture with DIBAH afforded a separable 1:1 mixture of alcohols **B13** and **B14**. The C-8 carbinyl proton of the former appeared as a doublet of doublets at 3.22 ppm with J = 10 and 5 Hz whereas the corresponding proton of the latter gave rise to an unresolved envelope at 3.35 ppm in full accord with the structure assignments. Had the diastereomeric pair **B15** and **B16** been produced, the axial carbinyl proton of the latter would have expectedly given rise to a pattern showing two diaxial couplings.

In principle, the undesired C-8 epimer **B14** could be inverted via benzyl ether cleavage, oxidation–reduction. However, the foregoing results indicate that an acyclic precursor with the correct configuration at C-7 (e.g., **B10a**) should afford the desired bicyclic aldehyde diastereoisomer **B11** directly. Work along these lines is currently in progress.

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Supplementary Material Available: Spectral data for compounds in Charts I and II (9 pages). Ordering information is given on any current masthead page.

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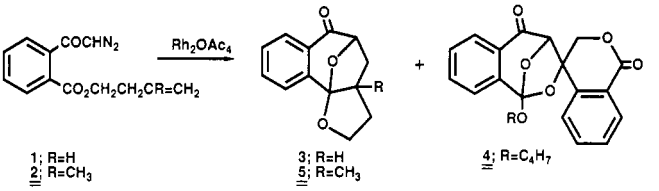
Tandem Cyclization–Cycloaddition Reactions of α-Diazoacetophenone Derivatives†

Summary: Treatment of *o*-alkyl-2-enoxycarbonyl-α-diazoacetophenones with rhodium acetate results in an initial cyclization to give a six-ring carbonyl ylide which undergoes a subsequent intramolecular dipolar cycloaddition with the neighboring double bond.

Sir: The reaction of carbenes with heteroatoms bearing a lone pair of electrons to give ylides has been known for some time.[1] Nestled in this area are some examples of carbenes undergoing reaction with carbonyl groups to give carbonyl ylides.[2–8] In recent years there has been a growing interest in the potential use of carbonyl ylides as 1,3-dipoles for total synthesis.[9–11] Their dipolar cycloaddition to olefinic, acetylenic, and hetero multiple bonded dipolarophiles has been well demonstrated.[12] The intramolecular trapping of carbonyl ylides by multiple bonds represents a useful method for the synthesis of some novel carbocyclic ring systems.[10–15] An attractive feature of this reaction is the opportunity to control the stereochemistry of the product at several centers. In this communication we present results which show that cyclic six-membered ring carbonyl ylides, produced from *o*-alkyl-2-enoxycarbonyl-α-diazoacetophenones, undergo intramolecular cycloaddition with a C–C double bond suitably located within the molecule. The resulting product represents a multiply functionalized rigid bicyclic system which is capable of subsequent synthetic elaboration.

The synthesis of α-diazoacetophenone **1** consisted of treating phthalic anhydride with 1-buten-4-ol followed by conversion of the resulting acid to the diazoketone in the usual fashion. Treatment of **1** with a catalytic quantity of rhodium(II) acetate at 25 °C in benzene afforded cyclohepta[1,2-*b*]furanone **3** in 87% yield (NMR ($CDCl_3$,360 MHz) δ 1.15–1.25 (m, 1 H), 1.55–1.68 (m, 3 H), 1.96–2.67 (m, 1 H), 3.90 (dt, 1 H, J = 8.3 and 5.7 Hz), 4.17 (dt, 1 H, J = 8.3 and 6.8 Hz), 4.79 (dd, 1 H, J = 7.4 and 2.0 Hz), and 6.90–8.14 (m, 4 H). In addition to cycloadduct **3**, a 10% yield of spiroisochromanedione **4** was also obtained.



This material could be prepared in larger quantities by adding a sample of 1*H*-2-benzopyran-1,4(3*H*)-dione (**6**) to the initial reaction mixture. This would suggest that **6** is formed from **1** by a competitive hydrolysis and is followed by a cycloaddition reaction with **9** across the carbonyl group to produce **4**.

The NMR spectrum of cycloadduct **3** was a bit complicated since a number of overlapping peaks were present. In order to simplify the spectrum, the reaction of **2** with rhodium diacetate was carried out. The cyclization–cycloaddition sequence proceeded quite smoothly producing

† Dedicated to Howard E. Zimmerman on the occasion of his 60th birthday.

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