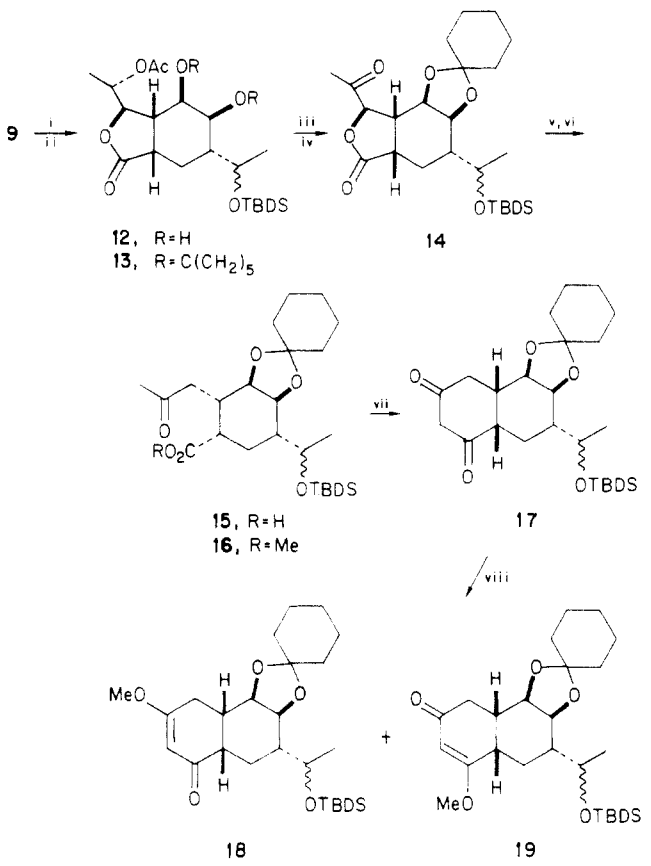
Scheme II[a]

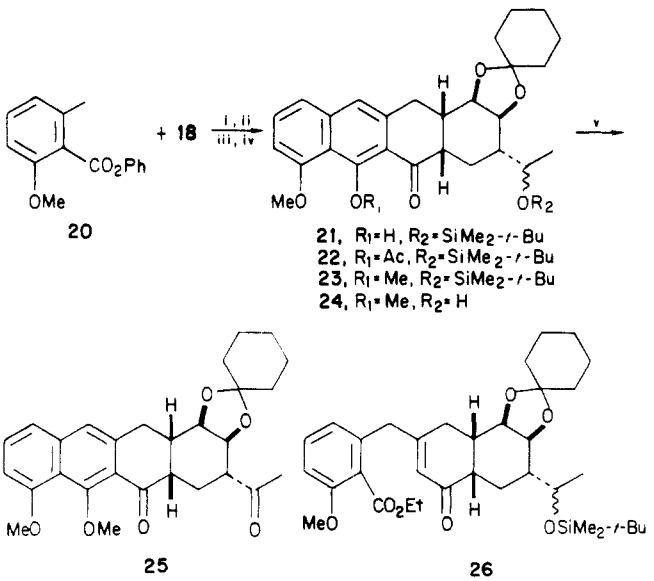


[a] (i) OsO_4 (catalyst), *N*-methylmorpholine *N*-oxide (3.3 equiv), THF/H_2O (3:1), 25 °C, 3 days; (ii) $(MeO)_2C(CH_2)_5$ (25 equiv), camphorsulfonic acid (catalyst), 25 °C, 4 h, 65% from **10**; (iii) K_2CO_3, MeOH, 25 °C, 2 h; (iv) PCC (5 equiv), CH_2Cl_2, 25 °C, 10 h, 61% from **13**; (v) SmI_2 (2 equiv), $FeCl_3$ (catalyst) THF, 25 °C, 0.25 h; (vi) CH_2N_2, Et_2O, 25 °C, 10 min, 84% from **14**; (vii) *t*-BuOK (3.3 equiv), C_6H_6, 25 °C, 20 min; (viii) CH_2N_2, Et_2O, 0 °C, 10 min, 89% from **16**.

in the presence of ferric chloride proved to be a highly effective reagent for this transformation and, after treatment of the reduction product with diazomethane, keto ester **16** was acquired in excellent yield. The latter underwent a smooth, intramolecular Claisen condensation[12] to dione **17**, which, upon methylation, afforded the enol ether **18** (ν 1645, 1610 cm^{-1}), accompanied by its readily separated isomer **19** (2.5:1, respectively).[13]

Assembly of the tetracyclic skeleton of **1** was carried out via the Staunton–Weinreb protocol.[14] Thus, the *o*-toluate anion from **20**[15] was condensed with **18** in the presence of anhydrous cerium trichloride to afford the intensely fluorescent naphthacenone **21** ($\lambda_{max}^{CHCl_3}$ 269, 398 nm), which was characterized as both its acetate **22** and dimethyl ether **23** (Scheme III). Finally, in order to converge the epimeric pair of silyl ethers at a single substance, **23** was transformed to alcohol **24**, and the latter was oxidized to ketone **25** ($\lambda_{max}^{CHCl_3}$ 264, 341 nm). A detailed examination of the reaction of **18** with **20** has revealed new insights into the mechanism of this interesting annulation,[16]

Scheme III[a]



[a] (i) $LiN(i\text{-}Pr)_2$, $CeCl_3$ (2.5 equiv), THF, −78 °C → 26 °C, 0.5 h, 62%; (ii) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 25 °C, 3 h; (iii) Me_2SO_4, K_2CO_3, Me_2CO, Δ, 8 h; (iv) *n*-Bu_4NF, THF, 25 °C, 6 h; (v) PCC, CH_2Cl_2, 25 °C, 3 h, 70% from **21**.

including the fact that **26** is not an intermediate en route to **21**. These details, together with further transformations of **25**, will be reported subsequently.

Acknowledgment. This work was supported by the National Science Foundation through Grant CHE-8101223. Funds for the purchase of a Bruker AM 400 NMR spectrometer were provided by the National Science Foundation through Grant CHE-8216190.

Supplementary Material Available: ^1H NMR data for **13** and the cyclohexylidene ketal of the diol derived from hydroxylation of **11** and a 2D-COSY spectrum of the latter that establish the configurations of **9–11** (2 pages). Ordering information is given on any current masthead page.

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Auxiliary-Directed Diastereoselectivity in the Claisen Rearrangement of Glycolate Esters

Summary: Examples are presented in which the stereochemical course of the Claisen rearrangement of allylic glycolates is controlled by a chiral substituent appended to the glycolate hydroxyl (eq 1).

Sir: Recent studies[1,2] have focused on synthetic and mechanistic aspects of the highly diastereoselective enolate Claisen rearrangment[3] of acyclic α-alkoxy esters. Herein

(12) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 4597.
(13) Muhle, H.; Tamm, C. *Helv. Chim. Acta* **1962**, *45*, 1475.
(14) Staunton, J.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1053. Dodd, J. H.; Starrett, J. E.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 1811.
(15) Hauser, F. M.; Pogany, S. A. *Synthesis* **1980**, 814.
(16) Dodd, J. M.; Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4045 and references cited.
(17) On leave from Salem College, Winston-Salem, NC.

(1) (a) Kallmerten, J.; Gould, T. J. *Tetrahedron Lett.* **1983**, 5177. (b) Kallmerten, J.; Gould, T. J. *J. Org. Chem.* **1985**, *50*, 1128.
(2) (a) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221. (b) Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, 729. (c) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941.
(3) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

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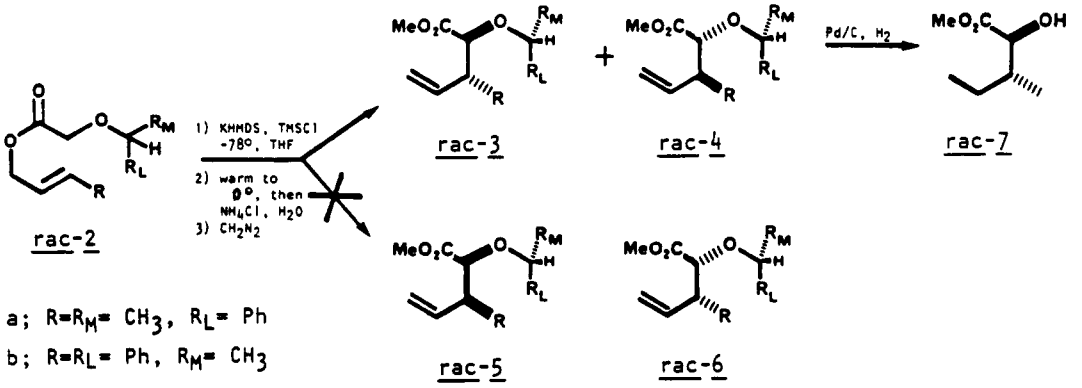
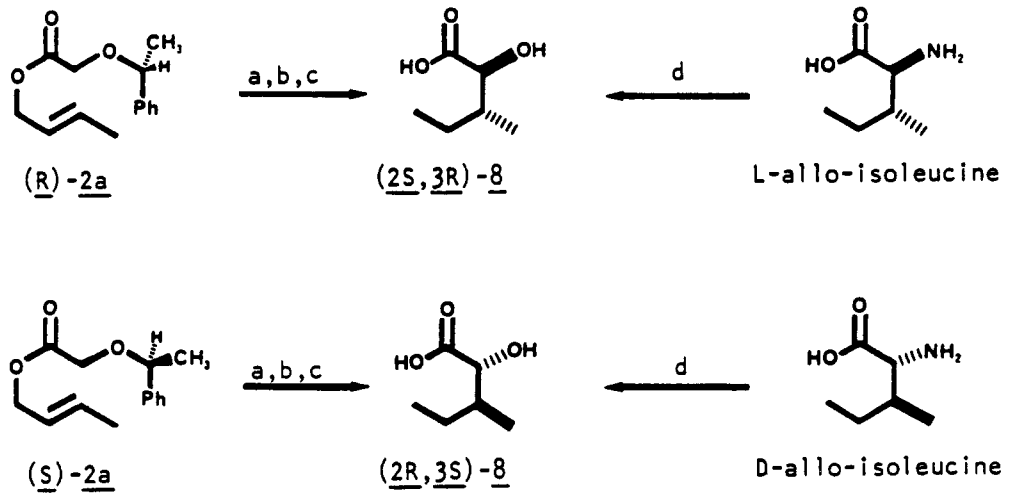
Scheme I



Scheme II[a]



[a] (a) KHMDS, Me_3SiCl, −78–0 °C, then CH_2N_2; (b) KOH, MeOH; (c) H_2, Pd–C, MeOH; (d) $NaNO_2$, AcOH, aqueous HCl.

we demonstrate the unique potential of allylic glycolates to undergo auxiliary-directed Claisen rearrangement, where the stereochemical course of the reaction is controlled by a chiral substituent appended to the glycolate hydroxyl (eq 1). Asymmetric transfer within the cyclic framework

(1)

1

of [2,3]- and [3,3]-sigmatropic reactions is well established and has contributed to the widespread application of these processes as effective and reliable procedures for stereorational homologation of allylic systems.[4] In contrast, the stereochemical consequences of chirality *outside* the pericyclic arena on the outcome of the Claisen and related rearrangements remain largely unexplored.[5,6] Asymmetric induction by external chirality offers unique synthetic advantages, since the stereodirecting center is retained in the rearrangement product; directing chirality *within* the pericyclic framework is necessarily lost to rehybridization during the sigmatropic event.

A critical requirement for asymmetric induction in the Claisen rearrangement of glycolate systems such as **1** is a favored stereodifferentiating transition-state conformation in which the external auxiliary directs the facial selectivity of addition to the enolate π-system. A recent report describing the diastereoselective aldol addition of chiral glycolates to carbonyl electrophiles[7] and the close similarity between the six-center transition states proposed to account for diastereoselectivity[8] in the aldol condensation and acyclic Claisen rearrangement suggested to us that the potential for auxiliary-directed selectivity in the latter reaction was high. In order to assess this potential, we have prepared the racemic phenethyl-protected glycolates **2**. Four diastereomeric products can result from enolate Claisen rearrangement of these substrates as shown in Scheme I (all structures in this scheme are racemic; for clarity, only one set of enantiomers is shown). Rearrangement of ester *rac*-**2a**[9] gave two major products in a

(4) (a) Hill, R. K. *Asymmetric Synthesis*; Morrison, J. D.; Ed.; Academic: New York, 1984; Vol. 3; Chapter 8. (b) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (c) Ziegler, F. E. *Acc. Chem. Res.* **1977** *10*, 227. (d) Bennett, G. B. *Synthesis* **1977**, 589.

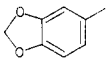
(5) Examples of stereochemical induction by "external" chirality have been reported for Claisen rearrangements of sterically biased cyclic substrates: (a) Kurth, M. J.; Decker, O. H. W. *Tetrahedron Lett.* **1983**, 4535. (b) Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 443; (c) Mikami, K.; Fujimoto, K.; Kasuga, T.; Nakai, T. *Tetrahedron Lett.* **1984**, 6011. (d) Chillous, S. E.; Hart, D. J.; Hutchinson, D. K. *J. Org. Chem.* **1982**, *47*, 5418. (e) Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 2198. (f) Church, R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1118. (g) Morrow, D. F.; Culbertson, T. P.; Hofer, R. M. *J. Org. Chem.* **1967**, *32*, 361. (h) For additional examples see ref 4a and references therein.

(6) The ability of external acyclic chirality to influence the diastereoselectivity of the Claisen rearrangement has recently been demonstrated: (a) Kurth, M. J.; Yu, C.-M. *Tetrahedron Lett.* **1984**, 5003. (b) Cha, J. K.; Lewis, S. C. *Tetrahedron Lett.* **1984**, 5263. (c) Hatakeyama, S.; Saijo, K.; Takano, S. *Tetrahedron Lett.* **1985**, 865.

(7) d'Angelo, J.; Pages, O.; Maddaluno, J.; Dumas, F.; Revial, G. *Tetrahedron Lett.* **1983**, 5869.

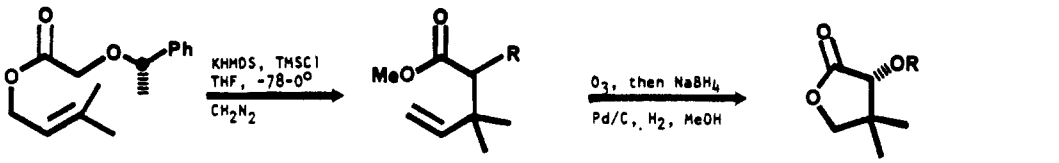
(8) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Heathcock, C. H. *Science (Washington, D.C.)* **1981**, *214*, 395.

Table I. Auxiliary-Directed Rearrangement[a] of Substituted Glycolates 2

entry	glycolate	R	R_L	R_M	yield of 3 + 4, %[b]	ratio 3:4
1	**2a**	Me	Ph	Me	82	3.0:1[c]
2	**2b**	Ph	Ph	Me	77	6.1:1[d]
3	**2c**	Me	*t*-Bu	Me	81	1.6:1[c]
4	**2d**	Me	mesityl	Me	69	2.5:1[d]
5	**2e**	Me	Ph	Et	80	2.3:1[c]
6	**2f**	*i*-Pr	Ph	Me	60	2.4:1[d]
7	**2g**	*cis*-Me	Ph	Me	84	*e,c*
8	**2h**		Ph	Me	52	4.2:1[d]

[a] All reactions carried out by using general procedure of ref 9. [b] Yields are for racemic products purified by flash chromatography. [c] Determined by gas chromatography. [d] Determined by HPLC. [e] Rearrangement gave a 1.1:1 mixture of **5a–6a**; see ref 11.

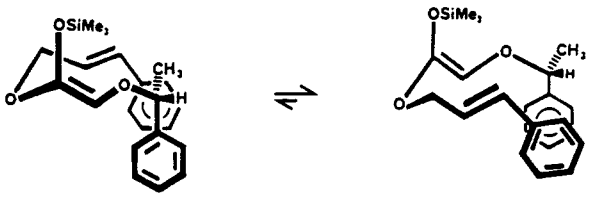
Scheme III



ratio of 3:1.[10,11] Hydrogenation of this mixture afforded *as the only product* ester *rac*-**7**, indicating that the products from Claisen rearrangement of *rac*-**2a** are esters *rac*-**3a** and *rac*-**4a** and that the ratio of these products reflects the degree of asymmetric induction attributable to the external auxiliary (Table I).

To establish the identity of the major diastereomer from these rearrangements, the chiral glycolates (*R*)-**2a** and (*S*)-**2a** were prepared. Enolate Claisen rearrangement of these substrates, followed by HPLC separation, saponification, and hydrogenation of the major diastereomer, gave chiral acids **8**, which were correlated with authentic samples derived from D- and L-alloisoleucine.[12] Thus the major product from rearrangement of (*R*)-**2a** affords (2*S*,3*R*)-**8** ($[\alpha]^{22}_D$ +7.3° (*c* 1.34, H_2O)), while the major product from (*S*)-**2a** gave (2*R*,3*S*)-**8** ($[\alpha]^{22}_D$ −8.4° (*c* 2.35, H_2O)) (Scheme II). The major diastereomer from rearrangement of *rac*-**2a** must therefore be *rac*-**3a**.[13]

Of considerable interest is the fact that the observed auxiliary-directed diastereoselectivity is opposite to that reported by d'Angelo and co-workers for the alkylation of chiral glycolates.[7] In further contrast to these alkylation studies, stereochemical induction in the glycolate Claisen system is relatively insensitive to structure and reaction conditions.[9] We observe two exceptions to this trend: (*Z*)-crotyl glycolate **2g** rearranges with virtually no diastereoselectivity, and cinnamyl glycolates **2b** and **2h** show significantly greater auxiliary-directed selectivity. While the specific role of the homoallylic auxiliary in the events leading to stereochemical induction remains to be defined, two different auxiliary conformations must be responsible for the stereochemical induction reported here for the Claisen rearrangement of allylic glycolates and for the aldol condensation of chiral glycolate enolates.[14] In the case of cinnamyl glycolates **2b** and **2h**, we suggest that the enhanced auxiliary-directed induction results from a favorable π-stacking interaction of the vinylic aryl substituent with the auxiliary (eq 2).[15]



(2)

The auxiliary-directed Claisen rearrangement represents an expedient chiral entry to functionalized acyclic systems, as demonstrated by a short synthesis of (*R*)-(−)-pantolactone, an intermediate in the synthesis of pantothenic acid.[16] Rearrangement of glycolate **9**[9] affords a 2.5:1 mixture of esters **10a** and **10b** (Scheme III); ozonolysis,

(9) In a typical experiment, a solution of glycolate in THF (0.2 M) at −78 °C is treated with potassium hexamethyldisilazane (1.5 equiv) followed immediately by 2.8 equiv of trimethylsilyl chloride. The reaction mixture is allowed to warm to 0 °C and worked up as described previously. While improved chemical yields were obtained at lower temperatures, no enhancement in auxiliary-mediated induction was observed and reaction times are long (>24 h at −78 °C).

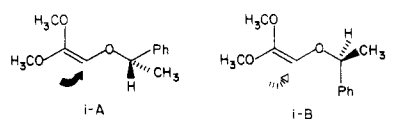
(10) Diastereomer ratios were determined by HPLC (or GC) and ^1H NMR. Individual diastereomers were characterized by 250-MHz ^1H and 90- and 125-MHz ^{13}C NMR, IR and, in cases where correlation with an authentic sample was not possible, elemental analysis.

(11) In addition to the two major products, rearrangement of **2a** affords a third minor (<5%) product, identical in all respects with the major product obtained from rearrangement of the corresponding (*Z*)-crotyl glycolate **2g** (Table I, Entry 7), to which we have assigned structure *rac*-**5a**.

(12) Winitz, M.; Bloch-Frankenthal, L. Izumiya, N.; Birnbaum, S. M.; Baker, C. G.; Greenstein, J. P. *J. Am. Chem. Soc.* **1956**, *78*, 2423. Degradation of D- and L-alloisoleucine (Sigma) using this procedure gave chiral acids **8**: (2*S*,3*R*)-**8** $[\alpha]^{22}_D$ +5.71° (*c* 0.21, H_2O); (2*R*,3*S*)-**8**, $[\alpha]^{22}_D$ −7.17° (*c* 1.13, H_2O).

(13) Similarly, degradation ($LiAlH_4$; H_2, Pd–C; $NaIO_4$; $LiAlH_4$) of the product mixture obtained from rearrangment of (*R*)-**2b** afforded (*S*)-(+)-2-phenyl-1-butanol, $[\alpha]^{19}_D$ +13.2° (*c* 0.20, ether) (lit. $[\alpha]^{25}_D$ +30.0° (*c* 3.54, ether): Levene, P. A.; Mikeska, L. A.; Passoth, K. *J. Biol. Chem.* **1930**, *88*, 27).

(14) Molecular mechanics calculations on ketene acetal i indicate two lowest energy conformations i-A (21.45 kcal) and i-B (20.41 kcal); the auxiliary group in each case is above the plane of the olefin (34° for i-A, 38° for i-B). Calculated dihedral angles COCX: i-A, Me (−81°), H (38°), Ph (157°); i-B, Me (151°), H (−99°), Ph (17°).



(15) A similar model has been proposed for the enantioselective Diels–Alder reaction of mandelate-substituted dienes. See: Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595.

(16) Cf.: Stiller, E. T.; Harris, S. A.; Finkelstein, J.; Keresztesy, J. C.; Folkers, K. *J. Am. Chem. Soc.* **1940**, *62*, 1785.

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.

(17) For an alternative entry to these systems via rearrangement of chiral α-silyl allylic alcohols see: Ireland, R. E.; Varney, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 3668.

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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

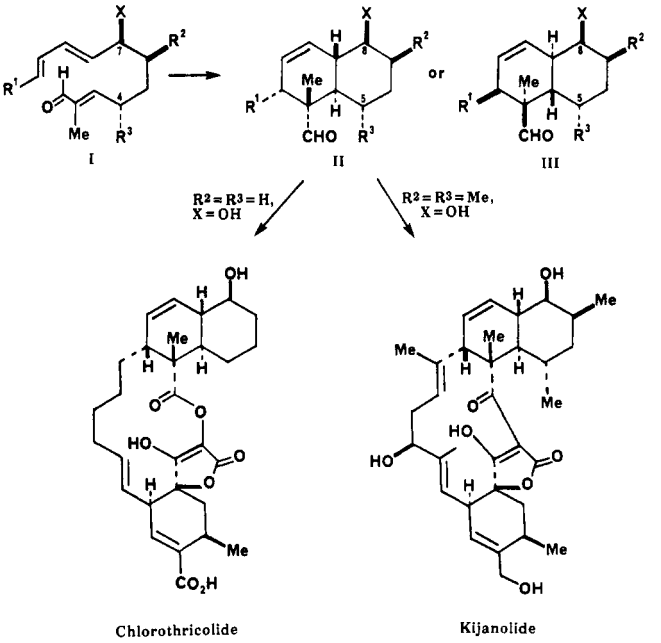
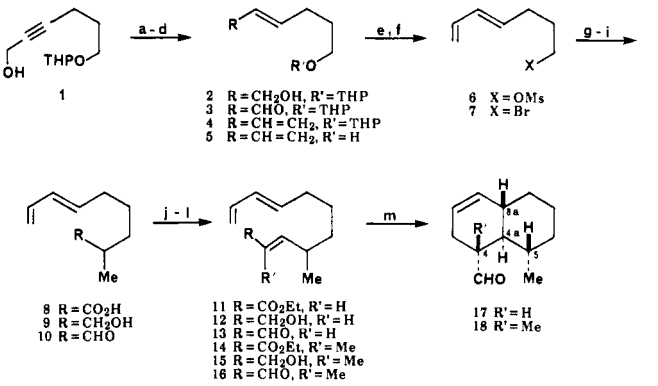


Figure 1. Diastereoselectivity in the intramolecular Diels–Alder approach to the hydronaphthalene segment of macrocyclic antitumor antibiotics.

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.

(1) Kloetzel, M. C. *Org. React.* (*N. Y.*) **1948**, *4*, 1. Holmes, H. L. *Org. React.* (*N. Y.*) **1948**, *4*, 60.

(2) For recent reviews, see: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (b) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (c) Ciganek, E. *Org. React.* (*N. Y.*) **1984**, *32*, 1. (d) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (e) Taber, D. F. "Intramolecular Diels–Alder and Alder Ene Reactions"; Springer-Verlag: Berlin, 1984; pp 1–59.

(3) Reference 2c, pp 44–53; ref 2e, pp 40–45.

(4) Reference 2c, pp 41–44; ref 2e, pp 51–56. For relevant examples involving formation of hydronaphthalenes, see: (a) Vig, O. P.; Trehan, I. R.; Kumar, R. *Indian J. Chem., Sect. B* **1977**, *15B*, 319. (b) Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 6289. (c) Näf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1979**, *62*, 114. (d) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200. (e) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611. (f) Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251. (g) Taber, D. F.; Saleh, S. A. *Tetrahedron Lett.* **1982**, *23*, 2361. (h) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180. (i) Burke, S. D.; Powner, T. H.; Kageyama, M. *Tetrahedron Lett.* **1983**, *24*, 4529. (j) Boeckman, R. K., Jr.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3421. (k) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1985**, *26*, 4327.

(5) Keller-Schierlein, P. W.; Muntwyler, R.; Pache, W.; Zähner, H. *Helv. Chim. Acta* **1969**, *52*, 127. Muntwyler, R.; Widmer, J.; Keller-Schierlein, W. *Helv. Chim. Acta* **1970**, *53*, 1544. Muntwyler, R.; Keller-Schierlein, W. **1972**, *55*, 2017. Brufani, M.; Cerrini, S.; Fedeli, W.; Mazza, F.; Muntwyler, R. *Helv. Chim. Acta* **1972**, *55*, 2094.

(6) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; McFarlane, R. D.; Stephens, R. L. *J. Chem. Soc., Perkin* Trans. *1* **1983**, 1497. Mallams, A. K.; Puar, M. S.; Rossman, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3938.

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