characteristic of the Me_2Si protons of the resultant ester **7**. This change correlated well with the disappearance of signals in the regions δ 3.7-3.9 and δ 4.1-4.2 associated with the vinylic and allylic ($CHORCH{=}CH_2$) protons of **6**. The silyl esters were cleaved with aqueous HCl in THF. The yields provided in Table I are from the lactones **5** to the homogeneous acids **8**. This initial phase of the investigation did not involve any serious attempts at yield optimization.

Several features of the ten successful cases shown in Table I are deserving of emphasis. The temperatures (105 °C) required for rearrangement to occur in an acceptable time (30 min to 10 h)[22] are considerably lower than those required for the analogous Büchi process.[3] This is in keeping with the trend in acyclic Claisen rearrangements wherein the rate of Ireland's[4] silyl ketene acetal variation is much faster than the classical vinyl ether case,[1] for comparable substitution.

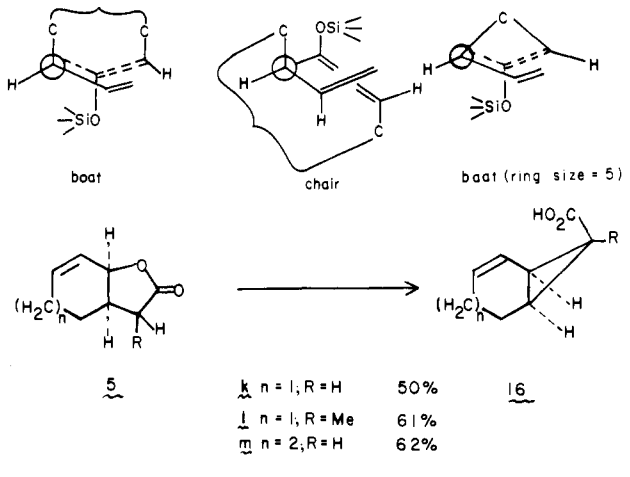
Furthermore, the stereochemical outcome of the **5b** and **5f** entries,[23-25] which were correlated with known compounds, is indicative of a boatlike geometry in the transition state. This topology, which also apparently[26] governs entries **5d**, **e**, **g**, and h was already indicated for the Büchi reaction.[3]

The preference is readily understood in terms of the Newman projection figures shown below. The requirement of cis double bonds in both **6** and **7** is such that the chair form would necessitate joining trans-oriented methylene groups through a zero (for the six-membered ring) or one (for the seven-membered ring) carbon bridge. This is clearly impossible in a concerted setting. The boat variation, while far from strain free, involves no such burden. *It will be noted that even a boat topology, in the case of a five-membered version of system* **6**, *would entail an additional increment of strain.*

Three substrates bearing on this question were investigated. The thermolyses of compounds **5k-m** were conducted from 155-175 °C. *After hydrolysis in the usual way, compounds* **16k-m** *were isolated, apparently arising from [1,3] rearrangement.*

The intercession of a [1,3] mutant of the Claisen rearrangement, where the typical [3,3] process is of unusually high energy, is precedented from the work of Arnold.[27] A palladium-mediated variation of this process was recently described by Trost.[28] What is particularly noteworthy about the cases shown here is the virtually complete specificity in favor of the syn isomer. The origin of this effect is not understood at present. See Scheme III.

Scheme III



The ease of obtaining systems of the type **5**, the relatively mild conditions required for their rearrangement, and the access thereby provided to the thermodynamically less stable cis (**8** from the [3,3] process) or syn (**16** from the [1,3] process) isomers render this retrocyclic Claisen reaction of considerable interest. It is our intention to explore in greater detail the mechanistic and stereochemical details of such rearrangements.

Acknowledgment. This research was begun under P.H.S. Grant C.A. 12107-16,17 and continued on P.H.S. Grant H.L.25217. Additional resources were provided through a grant from Merck, Sharp & Dohme. A National Cancer Institute Postdoctoral Fellowship to R.L.F. and an Andrew Mellon Predoctoral Fellowship to J.F.K., Jr., are gratefully acknowledged. We also acknowledge Professor F. E. Ziegler for his contribution of samples used in the structure determination of compound **8f**.

(22) Half-lives for these cases were generally between 0.5 and 2 h. The ketene acetal of compound **5f** was the fastest reacting substrate with a half-life of 35 min at 95 °C.

(23) The product **8b** was previously known.[24] Compound **8f** was correlated with the previously known[25] methyl ester ethylene thioketal of *cis*-2-phenyl-5-oxocyclohexenecarboxylic acid.

(24) (a) Alder, K.; Vogt, W. *Justus Liebigs Ann. Chem.* **1949**, *564*, 120. (b) Rudenko, A. A.; Metlyaeva, S. Y.; Kucherov, V. F. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1970**, 1224.

(25) Ziegler, F. E.; Condon, M. E. *J. Org. Chem.* **1971**, *36*, 3707.

(26) The stereochemistry of these homogeneous acids was not rigorously determined, but the assignment for the moment rests entirely on analogy with cases **5b** and **5f**.

(27) Arnold, R. T.; Kulenović, S. T. *J. Org. Chem.* **1980**, *45*, 891.

(28) Trost, B. M.; Runge, T. A.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 2840.

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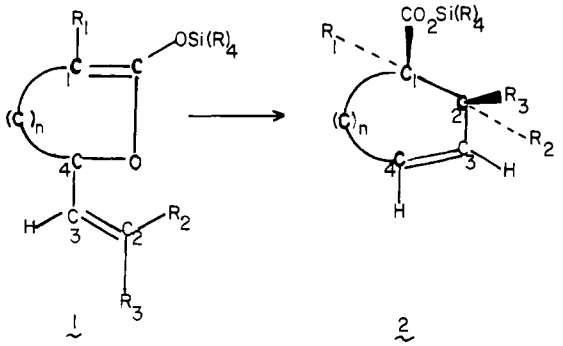
Control of Remote Relative Chiralities: A Stereospecific Total Synthesis of *dl*-Widdrol

Sir:

In the preceding paper,[1] we described the cyclomutative variation of Ireland's allylic ester (silyl) enolate rearrangement.[2] On the basis of the expected[3] boatlike topology of the transition state, the relationship of the geometry of the double bond to the diastereomerism of the sp^3 carbons 1 and 2 is summarized in the expression **1** → **2**.



Below, we consider another stereochemical implication of the process. We sought to demonstrate, by experiment, the relationship of the relative chiralities at C_4 and C_i of the starting lactone derivative, now shown as **3**, with the corresponding chiralities of C_1 and C_i of its rearrangement product, **4**. On reflection, it is recognized that the consequence of this chirality transfer is such that if the vinyl group is, for instance, trans to R in **3** the carbosilyloxy group shall emerge cis to R_1 in **4**. *It should be emphasized that this connectivity involves no suppositions regarding the chair- or boatlike contour of the transition state. It depends only on the assumption of suprafaciality in the chirality transfer.*

(1) Danishefsky, S.; Funk, R.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* preceding paper in this issue.

(2) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(3) Buchi, G.; Powell, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 3126.

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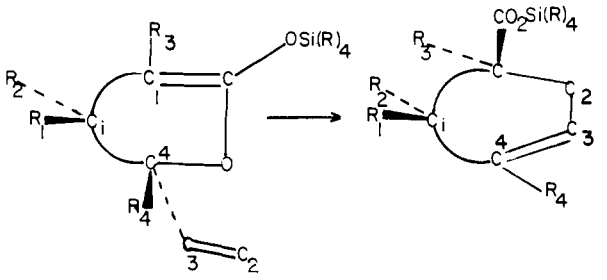
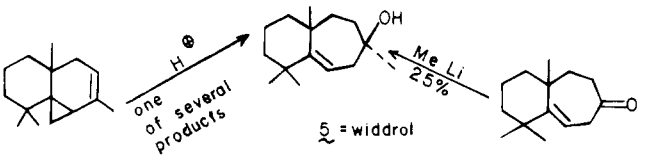


3 4

We demonstrate the inherent potential in this approach to chirality control in the context of a stereospecific total synthesis of the sesquiterpene widdrol (**5**). The relationship of the chemistry of widdrol with that of thujopsene (**6**) was elegantly elucidated by Dauben[4a,b] and by Kitchens.[4c] The total synthesis of thujopsene by Dauben[5] and by Büchi[6] in stereospecific ways constitutes a formal solution to the remote chirality problem posed by widdrol.

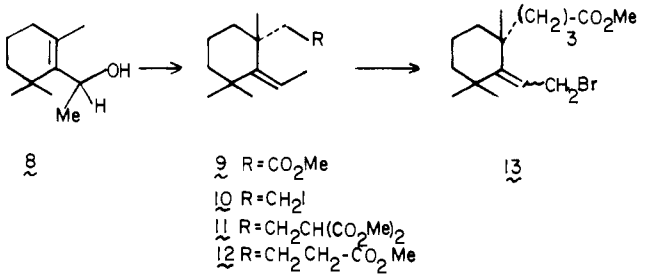
A "direct" total synthesis of widdrol was reported by Enzell.[7] Its key step involved a low-yield addition of methyllithium to the difficulty available ketone **7**.[8] Indeed, the remote center of chirality at the bridgehead in **7** would not be expected to exert a major induction on the stereochemical sense of nucleophilic attack on the ketone. A stereospecific solution to the widdrol problem is provided below.



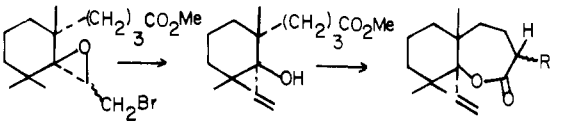
6 = thujopsene 7

Reaction of cyclocitral[9] with methyllithium affords (95%) the allylic alcohol **8**.[10] The latter reacts with triethyl orthoacetate in the presence of propionic acid to give a 64% yield of **9**,[10,11] which is converted in three steps [(i) LAH/Et_2O, reflux; (ii) mesyl chloride/pyridine, 4 °C; (iii) NaI, acetone, reflux] to the iodo compound **10**[10] (58% overall). Through a standard malonic ester alkylation (sodium hydride, dimethyl malonate/DME, reflux), **10** was converted to **11**, which on partial saponification (methanolic aqueous sodium hydroxide, room temperature) and decarboxylation (pyridine, reflux) afforded **12**[10] (75% from **11**). Allylic bromination (*N*-bromosuccinimide, dibenzoyl peroxide/CCl_4, reflux) afforded a crude ca. 1:1 mixture of *E* and *Z* bromides **13**. The next step, which establishes the relative chirality of the type-**3** system (see above), involves epoxidation of **13** under the conditions of Kishi[12] with TBP as the inhibitor. Apparently, both geometric isomers of **13** are epoxidized on the face of the double bond opposite to that bearing the vicinal valeric ester side chain. Thus, reduction of the crude bromomethyl epoxides with zinc in the presence of zinc chloride and methanol gives a 60% yield of the single allylic alcohol **15**.[10]

Saponification of **15** gives the corresponding hydroxy acid which is lactonized through the action of trifluoroacetic anhydride, affording an 85% yield of **16**. Deprotonation of **16** with lithium diisopropylamide in THF at −78 °C followed by quenching with methyl iodide affords **17**[10] as a mixture of epimers[10] in 81% yield.[13] Deprotonation of **17** (LDA/HMPA/THF) followed by quenching with *tert*-butyldimethylchlorosilane afforded the needed substrate **18**.

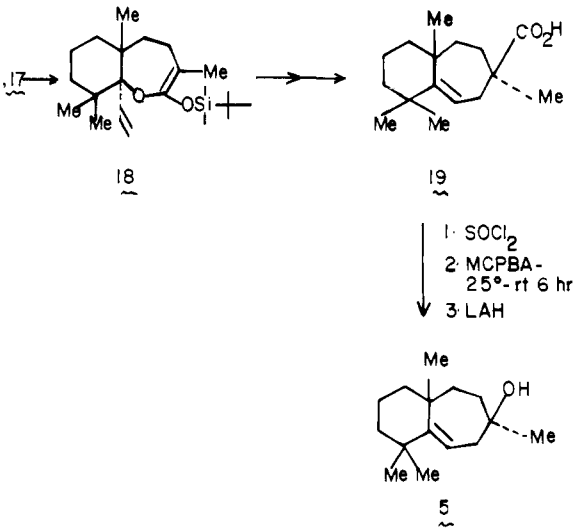


8 9 R = CO_2Me
10 R = CH_2I
11 R = $CH_2CH(CO_2Me)_2$
12 R = CH_2CH_2-CO_2Me
13



14 15 16 R = H
17 R = Me

The crude **18** was heated in toluene at 110 °C for 10 h. Without purification, the product was treated with tetra-*n*-butylammonium fluoride to afford a single acid, **19**, mp 127–128 °C, in 78% yield from **17**. The conversion of **19** to widdrol required the replacement of the quaternary-bound carboxyl group by a hydroxyl function, with retention of configuration. This was accomplished in 56% yield by using, *as a key step, a "carboxy inversion" reaction.*[14a,b,15] Thus, by the sequence shown below, **19** was converted to *dl*-widdrol, mp 83–84 °C, in 56% yield. The solution ($CHCl_3$) infrared, mass spectral, and NMR (600 MHz) spectra as well as TLC characteristics of *dl*-widdrol, thus obtained, are identical with those of an authentic sample furnished by Dr. Alan Hochstetler of the Givuadan Corp.



18 19 5

We believe that this synthesis is suggestive of more general possibilities in translating problems of remote chirality (cf. **6**) to

(4) (a) Dauben, W. G.; Aoyagi, E. I. *J. Org. Chem.* **1972**, *37*, 251. (b) Dauben, W. G.; Friedrich, L. E.; Obershansli, P.; Aoyagi, E. I. *Ibid.* **1972**, *37*, 9. (c) Daeniker, H. U.; Hochstetler, A. R.; Kaiser, K.; Kitchens, G. C. *Ibid.* **1972**, *37*, 1.

(5) Dauben, W. G.; Ashcraft, A. C. *J. Am. Chem. Soc.* **1963**, *85*, 3673.

(6) Büchi, G.; White, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 2884.

(7) Enzell, C. *Tetrahedron Lett.* **1962**, 185.

(8) The reasons for the low yield are not spelled out. In Enzell's paper, there is no mention made of the detection of any *epi*-widdrol.

(9) Gedye, R. N.; Parkash, D. A.; Deck, K. *Can. J. Chem.* **1971**, *49*, 1764.

(10) Satisfactory IR, NMR, and mass spectral data were obtained for this compound.

(11) A related rearrangement was described by Büchi.[6]

(12) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T.; Inoue, S.; Suguira, S.; Kaboi, K. *J. Chem. Soc., Chem. Commun.* **1972**, *64*.

(13) The two epimers were separated by high pressure liquid chromatography. However, they were more conveniently used together.

(14) (a) Denny, D. B.; Sherman, N. *J. Org. Chem.* **1965**, *30*, 376. (b) Kienzle, F.; Holland, G. W.; Jernow, J. L.; Kwoh, S.; Rosen, P. *Ibid.* **1973**, *38*, 3440.

(15) Attempts to carry out a Baeyer–Villager oxidation on the methyl ketone obtained from the reaction of **19** with methyllithium failed to produce any detectable widdrol acetate.

those of more manageable proximate chirality (cf. **13** → **14**). Applications of these findings to the total synthesis of other natural products are currently being pursued.

Acknowledgment. This research was supported by P.H.S. Grant C.A. 12107-16,17 and then by P.H.S. Grant H.L. 25217. Additional resources were provided by a grant from Merck, Sharp & Dohme. The 600-MHz NMR spectra were measured on facilities supported by P.H.S. Grant R.R.00297 for the Mellon, Pitt, Carnegie (M.P.C.) Corporation. We also thank Dr. Alan Hochstetler of the Givuadon Corporation for a sample of widdrol and Professor Paul A. Grieco for β-ionone which was used to prepare cyclocitral.

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Simple, Efficient Total Synthesis of Cantharidin via a High-Pressure Diels–Alder Reaction[1]

Sir:

Cantharidin (**1**) is the active principle of *Cantharis vesicatoria* which, notwithstanding its notoriety as the putative aphrodisiac in "Spanish fly", has found commercial applications in the removal of benign epithelial growths (warts) and as a vesicant.[2] We now report a simple, efficient total synthesis of **1** by a [4 + 2] cycloaddition reaction at high pressure.

Historically, the relative simplicity of the structure and the absence of enantiomeric forms have made cantharidin an enticing but elusive target for total synthesis. The obvious [4 + 2] cycloaddition between dimethylmaleic anhydride and furan was investigated as early as the 1920's, but such a direct synthetic approach failed.[3,4] The synthesis of **1** has been achieved;[5] however, the length and the complexity of these efforts stand in sharp contrast to the uncomplicated structure of **1**.

Earlier studies in these laboratories[6] suggested that the failure of dimethylmaleic anhydride to add to furan was a result of both electronic and steric factors. The electron-donating methyl groups of dimethylmaleic anhydride decrease its dienophilicity, and the extra crowding in the transition state given by these same methyl groups should further reduce its reactivity. Furthermore, furan is a poor Diels–Alder diene due to its aromaticity, and the cycloaddition products derived from it are generally susceptible to thermal cycloreversion,[4] so high reaction temperatures cannot be used.

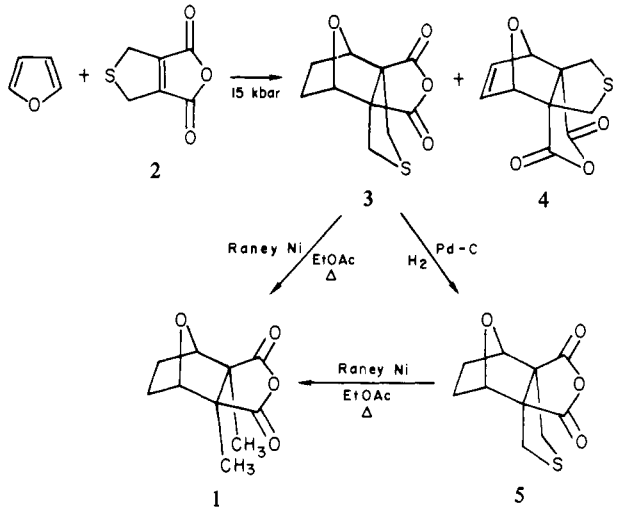
It has previously been reported from these laboratories[6] that pressures in the range of 10–20 kbars (1 kbar = 986.9 atm) greatly facilitate Diels–Alder reactions of furan. Although dimethylmaleic anhydride, itself, will not add to furan even at pressures up to 40 kbars,[7] the earlier studies indicated that a suitable dienophile which overcomes the electronic and/or the steric problems might undergo [4 + 2] cycloaddition with furan. The target dienophile was 2,5-dihydrothiophene-3,4-dicarboxylic anhydride (**2**), a known compound which could be synthesized readily on a large scale.[8] The presence of the sulfur-containing methylene bridge in place of the dimethyl substituents on the maleic anhydride nucleus was anticipated to reduce or eliminate the electron-donating character of these two alkyl substituents, and it was anticipated that this new ring would reduce the steric demands of the disubstituted maleic anhydride.

Table I. Reaction of 2 with 1.2 equiv of Furan at High Pressure

solvent	concn of 2, mol/L	pressure, kbar	time, h	conversion,[a] %	product ratio[a,b] (3:4)
CH_2Cl_2	0.26	15	6	100	85:15
	0.26	8	42	79	85:15
	0.26	4	88	41	80:20
CH_3COCH_3	0.45	15	24	*c*	
	0.45	8	42	81	85:15
	0.45	4	88	49	85:15
CH_3CN	0.45	15	24	*c*	
	0.45	8	42	64[d]	85:15
	0.45	4	88	57	85:15

[a] Determined by NMR spectroscopy. [b] Unless otherwise noted, no other products were observable by NMR spectroscopy. [c] Quantitative analysis of reaction mixture not possible by NMR spectroscopy due to poly-Diels–Alder products; see text. [d] Some diacid formed; see text.

It was found that reaction of **2** with 1.2 equiv of furan in methylene chloride at room temperature for 6 h under 15 kbar pressure effected quantitative conversion to 1:1 cycloadducts as



a 85:15 mixture of isomers. The two adducts could be separated by chromatography on silica gel and were characterized as isomers **3** (mp 112–113 °C, acetone–hexane) and **4** (mp 125–126 °C, chromatograph).[9] The major isomer **3** was hydrogenated over 10 mol % of 10% Pd–C to give **5** (mp 154–155 °C, acetone–hexane) in a quantitative yield. The exo-anhydride stereochemistry was assigned on the basis of the 0.3-ppm downfield shift of one of the two proton doublets for the protons α to the sulfur atom in the NMR spectrum of **5** relative to **3**. Confirmation of this stereochemical assignment was provided by Raney nickel[10] desulfurization of **5** which gave **1**, identical by NMR and IR spectrometry and mixed melting point with a sample of natural cantharidin.[11] More efficiently, the mixture of isomers obtained

(1) This work was supported by the National Science Foundation under Grant 78-04811.

(2) (a) Waddell, T. H.; Jones, H.; Keith, A. L. *J. Chem. Educ.* **1980**, *57*, 341. (b) "Physicians' Desk Reference to Pharmaceutical Specialties and Biologicals", Medical Economics, Inc., 1970 ed., p 1727.

(3) von Bruchhausen, F.; Bersch, H. W. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1928**, *266*, 697.

(4) Diels, O.; Alder, K. *Ber.* **1929**, *62*, 554.

(5) (a) Ziegler, K.; Schenck, G.; Krockow, E. W.; Siebert, A.; Wenz, A.; Weber, H. *Justus Liebigs Ann. Chem.* **1942**, *551*, 1. (b) Paranjape, K. D.; Phalniker, N. L.; Bhide, B. V.; Nargund, K. S. *Proc.-Indian Acad. Sci., Sect. A* **1944**, *19A*, 385. However, this report has been disputed; see ref 5c. (c) Stork, G.; van Tamelen, E. E.; Friedman, L. J.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1953**, *75*, 384.

(6) (a) Dauben, W. G.; Krabbenhoft, H. O. *J. Am. Chem. Soc.* **1976**, *98*, 1992. (b) Rimmelin, J.; Jenner, G.; Rimmelin, P. *Bull. Soc. Chim. Fr.* **1978**, 461.

(7) (a) Gladysz, J. A. *CHEMTECH* **1979**, 372. (b) Dauben, W. G.; Kozikowski, A. P., unpublished results, 1974.

(8) Baker, B. R.; Querry, M. V.; Kadish, A. F. *J. Org. Chem.* **1948**, *13*, 128. In this present study, **2** has been obtained in five steps and 26% overall yield from methyl thioglycolate.

(9) All new compounds reported were characterized by NMR and IR spectroscopy and possessed the proper elemental analysis.

(10) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis", Wiley: New York, 1967; Vol. 1, p 729.

0002-7863/80/1502-6893$01.00/0