Communications

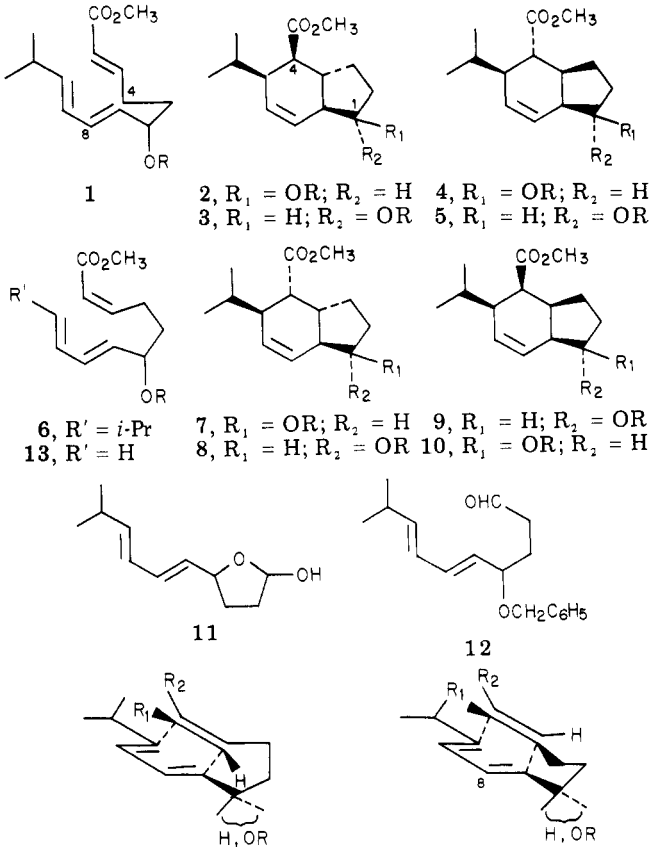
Stereochemical Aspects of the Intramolecular Diels–Alder Reactions of Methyl (*E,E,E*)- and (*Z,E,E*)-6-Alkoxy-11-methyldodeca-2,7,9-trienoate†

Summary: The intramolecular Diels–Alder reactions of isomeric trienes **1** and **6** afford cycloadducts possessing *trans*-perhydroindan nuclei as the major reaction products.

Sir: An increasing number of applications of the intramolecular Diels–Alder reaction in natural product synthesis have been reported in recent years.[1,2] The growing interest in this reaction stems from its potential for regio- and stereospecific construction of complex ring systems. Some detailed studies of the stereochemical aspects of the reaction have been reported.[3] During the course of studies directed toward the total synthesis of (±)-dendrobine[2a] we examined the Diels–Alder reactions of isomeric trienes **1** and **6**. Herein we describe the results of these studies which show that the major products from each series possess *trans*-perhydroindan nuclei. We suggest that conformational and steric effects may be as important as secondary orbital interactions in determining the stereochemical outcome of these reactions.

All-trans trienes **1a**[2a] and **1b**[7a,b] were prepared by treating hemiacetal **11**[2a] or aldehyde **12**,[6,7a,b] respectively, with $(C_6H_5)_3PCHCO_2CH_3$ in CH_2Cl_2 (isolated yields: **1a** (82%); **1b** (74%)). Under these conditions 5% yields of trans,trans,cis trienes **6a**[2a] and **6b**[7a,c] were also isolated. Greater yields of the latter isomers were obtained when the Wittig reaction was performed in MeOH:[4] **6a** (22%) and **1a** (43%) from **11**; **6b** (22%) and **1b** (51%) from **12**. The stereochemistry about the dienophilic double bonds in **1** ($J_{2,3}$ = 16 Hz; C(4)–H, δ 2.28, m) and **6** (C(4)–H, δ 2.76, m) were assigned by ^1H NMR.[5] The trimethylsilyl, acetoxyl, and tetrahydropyranyl derivatives **1c,d** and **6c,d,e** were prepared from **1a** and **6a**, respectively, by standard procedures.[8]

The Diels–Alder adducts derived from these trienes were separated by careful chromatography[9,10] and were fully characterized by spectroscopic and chemical methods (see



1

2, R_1 = OR; R_2 = H **3**, R_1 = H; R_2 = OR **4**, R_1 = OR; R_2 = H **5**, R_1 = H; R_2 = OR

6, R′ = *i*-Pr **13**, R′ = H

7, R_1 = OR; R_2 = H **8**, R_1 = H; R_2 = OR **9**, R_1 = H; R_2 = OR **10**, R_1 = OR; R_2 = H

11 **12**

endo-**1**, $R_1 = CO_2CH_3$; R_2 = H *exo*-**1**, R_1 = H; $R_2 = CO_2CH_3$
exo-**6**, R_1 = H; $R_2 = CO_2CH_3$ *endo*-**6**, $R_1 = CO_2CH_3$; R_2 = H

a, R = H
b, R = $CH_2C_6H_5$ **d**, R = $COCH_3$
c, R = Me_3Si **e**, R = THP

† This paper is dedicated to the memory of Professor R. B. Woodward.

(1) Reviews: (a) Oppolzer, W. *Synthesis* **1978**, 793–802. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1976**, *16*, 10–23. (c) Mehta, G. *J. Chem. Educ.* **1976**, *53*, 551–553. (d) Carlson, R. G. *Annu. Rep. Med. Chem.* **1974**, *9*, 270–279.

(2) (a) Roush, W. R. *J. Am. Chem. Soc.* **1978**, *100*, 3599–3601. (b) Yamamoto, H.; Sham, H. L. *Ibid.* **1979**, *101*, 1609–1611. (c) Näf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1979**, *62*, 114–118. (d) Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 6289–6291. (e) Glass, R. S.; Herzog, J. D.; Sobezak, R. L. *J. Org. Chem.* **1978**, *43*, 3209–3214. (f) Büchi, G.; Henson, A.; Limacher, J. *Ibid.* **1977**, *42*, 3323–3324. (g) Näf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1977**, *60*, 1196–1202. (h) Oppolzer, W.; Fehr, C.; Warneke, J. *Ibid.* **1977**, *60*, 48–58. See also Oppolzer, W.; Flaskamp, E. *Ibid.* **1977**, *60*, 204–207. (i) Breitholle, E. G.; Fallis, A. G. *Can. J. Chem.* **1976**, *54*, 1991–1993; *J. Org. Chem.* **1978**, *43*, 1964–1968.

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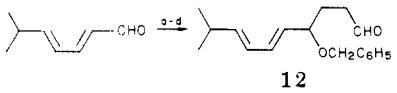
(4) House, H. O.; Jones, V. K.; Frank, G. A. *J. Org. Chem.* **1964**, *29*, 3327–3333.

(5) Jackman, L. M.; Wiley, R. H. *J. Chem. Soc.* **1960**, 2886–2890.

(6) Roush, W. R.; Ph.D. Thesis, Harvard University, Cambridge, Mass. (1977). Aldehyde **12** was prepared as follows:



12

(a) $LiCH_2CH_2CH_2OCH(CH_3)OC_2H_5$, Et_2O, 54%; (b) $C_6H_5CH_2Br$, NaH, DME, 84%; (c) H_3O^+, 92%; (d) CrO_3, pyridine, CH_2Cl_2, 95%. Each intermediate was isolated and fully characterized.[7a,b]

(7) (a) This compound was fully characterized by NMR, IR, mass, and (where appropriate) UV spectroscopy, confirmatory of the structure presented. (b) The combustion analysis for this compound was within 0.4% of theory. (c) The elemental composition of this compound was verified by a precise mass measurement.

(8) (a) Trimethylsilyl ethers **1c** and **6c** were prepared in situ by treating **1a** and **6a** with a slight excess of bis(trimethylsilyl)acetamide in toluene, 23 °C, sealed tube, >5 h. (b) Acetates **1d** (66%) and **6d** (89%) were prepared from **1a** and **6a** by overnight treatment with excess Ac_2O in CH_2Cl_2 containing catalytic amounts of pyridine. (c) THP ether **6e** was prepared from **6a** by treatment with 3 equiv of dihydropyran and a catalytic amount of *p*-TsOH in CH_2Cl_2, 10 min. The crude THP ether, obtained in near quantitative yield, was used without purification.

(9) The products obtained from **1c**, **1d**, **6c**, **6d**, and **6e** were isolated after deprotection.[10]

(10) (a) The crude, cyclized Me_3Si and THP ethers were deprotected by treatment with 1 N HCl in MeOH, 23 °C, ≥15 min. (b) The crude cyclized acetates were deprotected by treatment with 1.0 equiv of methanolic KOH, 23 °C, ≥3 h.

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Table I. The Intramolecular Diels-Alder Reactions of 1 and 6

entry	substrate	reaction conditions, °C, h	% yield[b]	product ratios[a] 2	3	4	5	endo/exo[a]
1	1a[c]	150, 18	71	37[d]	37	(4)	26	70:30[d]
2	1b[e]	270[f]		26	49	5[g]	20	75:25
3		115, 110	64	30	53	4[g]	13	83:17
4	1c[c,h]	150, 15	83	52[d]	31	(4)	17	79:21[d]
5		115, 100	82	53[d]	32	(2)	15	83:17[d]
6	1d[c,h]	150, 18	71	30[d]	45		25	75:25
				7	8	9		
7	6a[i]	150, 6	60	45	32	23		23:77
8	6b[j]	280[f]		36	33	31		31:69
9		115, 44	92	37	29	34		33:67
10	6c[h,i]	180, 2	77	49	28	23		23:77
11		115, 44	71	50	25	25		25:75
12	6d[h,i]	150, 6	58	26	44	30		30:70
13	6e[h,i]	150, 15	65	37	35	28		28:72

[a] Determined by analytical GC and are the normalized average of two to four integrations. The values in parentheses were determined by product isolation. [b] The total yield of chromatographed products. [c] The GC analysis was performed on the Me_3Si ethers using a 7-ft, 4% Zonyl E-7 on Chromosorb G column at 145 °C. [d] Me_3Si ethers 2c and 4c do not resolve by analytical GC. The ratio listed for 2 from 1a, 1c, and 1d represents the total amount of 2 and 4. The endo/exo ratio listed in these cases is corrected for the amount of 4a isolated. [e] The GC analysis was performed at 195 °C on the column described in *c*. [f] This reaction occurred upon injection of triene into the GC port at the indicated temperature. [g] Tentative assignment based upon the detection of four products by GC; this isomer could not be separated from 2b by silica gel chromatography. [h] Products were isolated at R = H after deprotection (see ref 10). [i] The GC analysis was performed at 165 °C on the column described in *c*. [j] The GC analysis was performed using a 7-ft, 4% SE-30 on Chromosorb G column at 240 °C.

paragraph at the end of paper about supplementary material). Examination of the data in Table I indicates that in all cases products possessing trans ring fusions were formed in preference to their cis-fused isomers.[11,12] The product distributions from **1a–d** are moderately temperature sensitive, with lower reaction temperatures increasingly favoring trans-fused products **2** and **3** (entries 2–5). In contrast, the distribution of products from **6a–e** are much less temperature dependent (entries 8–11). Application of the Alder endo rule to the cyclizations of **1** leads to the prediction that **2** and **3** should be the major products formed.[3g] It is interesting to note that the ratio **2/3** is influenced by the alkoxy substituent at C(1) (maximal difference in transition state energy ~0.5 kcal mol^{-1}) and that one epimer is not the major isomer observed in all cases. This effect does not appear to correlate with the steric size of OR. A larger interaction (~1 kcal mol^{-1}) which develops between C(8)–H and OR in the boat transition state leading to **4** markedly destabilizes this state relative to that leading to **5**. A similar interaction in the endo transition states of **6** accounts for the absence of **10** from the observed reaction products.[13] This factor contributes greatly to the endo/exo ratio for **6**, but does not explain the fact that the endo transition state leading to **9** is always higher in energy than one, or both, of the exo transition states leading to **7** and/or **8**; note that in certain instances (entries 7, 10, and 11) the ratio of **9/7** reaches a maximum value of approximately 1:2. All other factors being equal, one would have expected a greater endo/exo ratio from **6** than from **1**.[14]

The results reported for **6** are not primarily a consequence of a destabilizing interaction between the isopropyl and carbomethoxyl groups in the endo transition states, as the product distribution from **13**[7a,c] resembles that from **6**.[15] Rather, analysis of molecular models reveals that bonding geometries similar to those predicted by Kikuchi[16] are more readily attained in the transition states leading to trans-fused products (*endo*-**1** and *exo*-**6**) than in the transition states leading to cis-fused products (*exo*-**1** and *endo*-**6**). This effect, which is a consequence of the conformations adopted by chain linking the diene and dienophile, is apparently large enough to compete with the endo rule in determining the outcome of the cyclizations of **6**. In the case of **1**, the conformational effect and the endo rule are additive.

Studies ongoing in our laboratory are concerned with increasing the stereoselectivity of these cyclizations through control of conformational, steric, and electronic factors. Applications of these methods toward the synthesis of natural products possessing perhydroindan and decalin nuclei are in progress.

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Registry No. **1a**, 71516-83-1; **1b**, 71516-84-2; **1c**, 71516-85-3; **1d**, 71516-86-4; **2a**, 71516-87-5; **2b**, 71516-88-6; **2c**, 71516-89-7; **2d**, 71516-90-0; **3a**, 71516-91-1; **3b**, 71516-92-2; **3c**, 71516-93-3; **3d**,

(11) The assignment of cis fusions to **4**, **5**, and **9** is based largely upon theoretical considerations. We have carefully looked for, and found no evidence of, crossover of products from **1** and **6**. This, together with observations that the 9*Z* isomer of **1** fails to cyclize under conditions employed for **1** and **6**,[2a] suggests that the cis principle holds for the cyclizations discussed herein.

(12) The data in Table I represent kinetically controlled cyclizations. Control experiments established that **2b,c–5b,c** and **7b,c–9b,c** are stable under the most vigorous Diels–Alder conditions utilized.

(13) A fourth band amounting to 3–5% of the total product was observed in the GC traces of the cyclizations of **6b**. Owing to lack of material, this substance, possibly **10b**, has not been isolated or characterized. Only three bands are observed in GC traces of products from **6a**, **6c**, **6d**, and **6e**.

(14) The reaction of (*Z*)-crotonic acid with cyclopentadiene at 110 °C affords an endo/exo ratio of 85:15, whereas the ratio from (*E*)-crotonic acid and cyclopentadiene at 110 °C is 60:40. See: (a) Alder, K.; Gunzl, W. *Chem. Ber.* **1960**, *93*, 809–825. (b) Martin, J. G.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537–562.

(15) The results of these studies will be reported separately.

(16) Kikuchi, O. *Tetrahedron* **1971**, *27*, 2791–2800.

71564-05-1; **4a**, 71516-94-4; **4b**, 71516-95-5; **4c**, 71516-96-6; **5a**, 71549-35-4; **5b**, 71516-97-7; **5c**, 71516-98-8; **5d**, 71516-99-9; **6a**, 71517-00-5; **6b**, 71517-01-6; **6c**, 71517-02-7; **6d**, 71517-03-8; **6e**, 71517-04-9; **7a**, 71517-05-0; **7b**, 71517-06-1; **7c**, 71517-07-2; **7d**, 71517-08-3; **7e**, 71517-20-9; **8a**, 71517-09-4; **8b**, 71517-10-7; **8c**, 71517-11-8; **8d**, 71517-12-9; **8e**, 71517-13-0; **9a**, 71517-14-1; **9b**, 71517-15-2; **9c**, 71517-16-3; **9d**, 71517-17-4; **9e**, 71517-18-5; **11**, 67495-99-2; **12**, 71517-19-6; $(C_6H_5)_3PCHCO_2CH_3$, 2605-67-6.

Supplementary Material Available: Full spectroscopic data for compounds **2a,b**, **3a,b**, **4a**, **5a,b**, **7a,b**, **8a,b**, and **9a,b** and a brief discussion of pertinent structural data (2 pages). Ordering information is given on any current masthead page.

(17) Address correspondance to author at Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Mass. 02139

William R. Roush[17]

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138
and the Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
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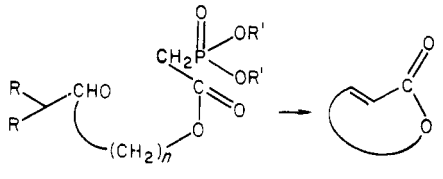
Large-Ring Lactones by Internal Ketophosphonate Cyclizations

Summary: The intramolecular cyclization of phosphonoacetates of hydroxycarbonyl compounds is a useful method for the construction of macrocyclic α,β-unsaturated lactones of 13 and more carbon atoms and of varying degrees of substitution.

Sir: The existence of a variety of macrocylic lactones in natural products had led to a number of methods for their construction. These methods almost always use the lactonization step itself, by suitable activation of the carboxyl group, for the construction of the lactone ring.[1]

We have examined the possibility of forming macrocylic lactones by closing the ring at the carbon α to the ester



linkage by an internal version of the phosphonoacetic ester method.[2] The process would, of course, be especially useful when, as in many of the cytochalasins,[3] the desired system actually is a trans α,β-unsaturated lactone, since this should be the primary result of this type of cyclization.[4] It should be valuable in the construction of lactones involving particularly hindered hydroxyl groups, since the cyclization step is effected at a distance from that function.

The use of ketophosphonates in intramolecular cyclization has been demonstrated previously for the synthesis of five- and six-membered lactams,[5] lactones,[6] and cyclenones.[7] A very recent publication actually describes the use of the reaction in the construction of a 26-membered ring lactone.[8] This particular case, reported after our own work had been completed, involved a precursor in which the substitution pattern imposed considerable rigidity, thereby facilitating ring closure, and the conditions which were effective in that instance were not suitable, in our hands, for the general case. It is important to note that the most difficult cyclizations will, in general, involve the least-substituted precursors (more degrees of freedom). Our aim was, therefore, to find conditions which would give reasonable yields with most precursors.

We now report that the phosphonoacetate cyclization is indeed a viable method for the construction of lactones with rings of 13 or more members. Considerable experimentation was necessary before reasonably satisfactory conditions could be defined; in particular, it was surprising to find that, in a number of instances, appreciable quantities of cyclic dilactones were formed via intermolecular condensation of the aldehydophosphonates. This was true even when high dilution conditions supposedly had been achieved by the very slow introduction (see below) of the aldehydophosphonate to the cyclizing medium.

It was eventually found that lithium bases (either as lithium hexamethyldisilazane or as lithium isopropoxide) in tetrahydrofuran (THF) containing ~1% of hexamethylphosphoramide (HMPA) were able to bring about the desired formation of cyclic lactones.[9,10] Under these conditions, the amount of (dimeric) dilactones formed was usually 1% or less. By this process, the aldehydophosphonoacetate **1** gave the 13-membered ring α,β-unsaturated lactone **2**,[11] while the apposite phosphonates led to **3**[12] and **4** all in 60–70% yields. The 14-membered *tertiary* lactone **5** (a ~7:1 mixture of *E* and *Z* isomers) and the 15-membered lactone **6** were similarly obtained in 40–50% yields.

A detailed experimental procedure is given below for the cyclization of **1** to **2**.

To a stirred solution of HMPA (0.5 mL) in 50 mL of THF kept under argon at room temperature were added simultaneously, by means of motor-driven syringes, a 5-mL solution of the phosphonate **1** (175 mg, 0.5 mM) in 1:1 THF–benzene and a 5-mL THF solution containing 0.55

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(3) For synthesis and references see Stork, G.; Nakahara, Y.; Nakahara, Y.; Greenlee, W. J. *J. Am. Chem. Soc.* **1978**, *100*, 7775–7777.
(4) Another noteworthy approach to α,β-unsaturated macrolides is illustrated by the recent work of Takahashi, T.; Hahiguchi, S.; Kasuga, K.; Tsuji, J. *J. Am. Chem. Soc.* **1978**, *100*, 7424–7425.
(5) Matthews, R. S. Ph.D. Thesis, Columbia University, 1967. Stork, G.; Matthews, R. S. *Chem. Commun.* **1970**, 445–446.
(6) Lehmann, H. G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 300–301.
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(8) Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069–7071. A ketophosphorane has been used to make a 12-membered unsaturated lactone: Wilson, K. E. Ph.D. Thesis, University of Alberta, 1973, as quoted by S. Masamune, ref 1. Some of our results were communicated at the Leermakers Symposium on Synthesis, Wesleyan University, 1977.
(9) The use of a hindered silicon base (Kuwajima, I.; Soto, T.; Arai, M.; Minami, N. *Tetrahedron Lett.* **1976**, 1817–1820) did not give significantly higher yields than simpler bases.
(10) The following general observations were made: the use of sodium or potassium counterions was much less satisfactory than lithium; the (desirable) presence of HMPA made the reaction rather insensitive to the bulk solvent; satisfactory results were obtained with benzene as well as with tetrahydrofuran.
(11) All compounds gave mass spectra and NMR spectra ($CDCl_3$) in accord with indicated structures.
(12) In this case, the lactone was obtained as a 3:2 mixture of *E* and *Z* isomers. The *E* compound had the longer retention time on 1.5% OV-101. Particularly characteristic was the NMR of the vinyl hydrogen β to the carbonyl: δ 6.96 (dt, J = 8, 15.5 Hz) for the *E* and δ 5.98 (dt, J = 8, 11 Hz) for the *Z* isomer. The *E* compound was also made by the method of Yamamoto: Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705–7707.

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