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CRYSTAL STRUCTURE OF (1RS, 14SR, 17RS, 18RS)-2,20-DIOXA-17-METHYLTRICYCLO[16,3,0^{1,14},0^{1,18}] HENEICOSA-15-ENE-3,19,21-TRIONE; A MACROCYCLIC LACTONE

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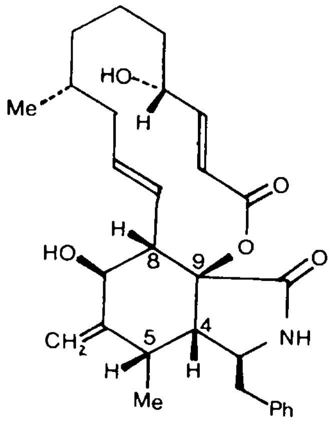
Abstract An X-ray study of the major product of the intramolecular Diels-Alder reaction of the diene-anhydride (**2**) has confirmed it as being the desired cytochalasan analogue (**3**). In particular the cyclisation has been regioselective, and has taken place via the *endo* transition state to generate the adduct with the correct relative configurations at the four chiral centres. Details of the conformational geometry of (**3**) are discussed.

Intramolecular Diels-Alder reactions have not been widely used to prepare macrocyclic rings because of problems with regioselectivity and *exo–endo* stereoselectivity.[2] However, we were interested in the possibility that an intramolecular Diels–Alder reaction could be used to generate the macrocyclic system of the cytochalasans, an important group of fungal metabolites, e.g. cytochalasin B (**1**).[3] In order to test the feasability of this idea, the intramolecular Diels–Alder reactivity of the long-chain diene-anhydride (**2**) was examined. It was hoped that cyclisation would occur with the usual *endo* stereoselectivity to form lactone (**3**) which has both the 14-membered macrocycle of cytochalasin B, and the correct relative stereochemistry at C-4, C-5, C-8 and C-9 (cytochalasan numbering).

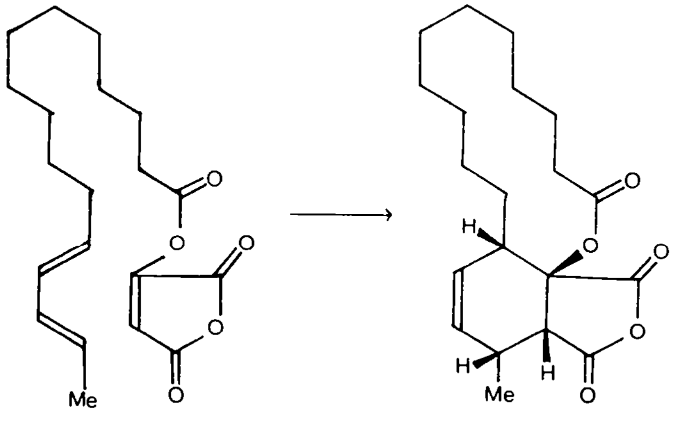
It was found that heating a solution of dieneanhydride (**2**) in toluene under reflux, led to the formation of two products in a 5:1 ratio.[4] The spectroscopic data of the major product, isolated in 27% yield, was consistent with it being the desired cyclised lactone (**3**), but did not unambiguously establish the relative configurations of the four chiral centres. Therefore it was decided to determine the structure of this major product by X-ray crystallography.

RESULTS AND DISCUSSION

The final fractional atomic co-ordinates and isotropic thermal parameters for the non-hydrogen atoms together with their estimated standard deviations are listed in Table 1. Those for the hydrogen atoms are given in Table 2. Figure 1 shows a perspective view of the molecule (ORTEP[5]) and gives the numbering scheme used. Tables 3 and 4 give the bond lengths and valence angles together with their



(**1**)



(**2**) (**3**)

Table 1. Fractional coordinates ($\times 10^4$) and isotropic thermal parameters ($\times 10^3$ A^2) for the non-hydrogen atoms, with estimated standard deviations in parentheses

Atom	x	y	z	U
C(1)	1381(4)	1190(4)	5000	67(3)
C(2)	1727(3)	1098(3)	6650(22)	42(2)
C(3)	1441(3)	504(3)	7463(23)	49(2)
C(4)	929(4)	330(4)	8773(25)	69(3)
C(5)	1395(4)	171(4)	5390(23)	55(2)
C(6)	1809(3)	309(3)	4085(24)	51(2)
C(7)	2326(3)	809(3)	4605(23)	44(2)
C(8)	2220(3)	1265(3)	5245(22)	40(2)
C(9)	2127(3)	1499(3)	3032(22)	45(2)
C(10)	2753(3)	958(3)	2709(24)	50(2)
C(11)	3004(4)	616(4)	2784(23)	58(3)
C(12)	3413(4)	750(4)	780(25)	75(3)
C(13)	3830(4)	1341(4)	632(24)	71(3)
C(14)	4188(4)	1542(5)	2717(27)	87(4)
C(15)	4545(5)	2146(5)	2816(27)	92(4)
C(16)	4282(4)	2472(4)	2966(24)	69(3)
C(17)	3950(5)	2373(4)	5245(25)	75(3)
C(18)	3687(4)	2697(4)	5364(26)	79(3)
C(19)	3302(3)	2531(4)	7407(23)	60(3)
C(20)	2758(3)	2133(3)	6612(23)	46(2)
O(1)	939(3)	1113(3)	5321(24)	102(3)
O(2)	1625(2)	1392(2)	2917(19)	61(2)
O(3)	2440(2)	1752(3)	1565(22)	61(2)
O(4)	2702(2)	1652(2)	6350(20)	41(1)
O(5)	2414(2)	2230(2)	6174(21)	58(2)

Table 2. Fractional coordinates and isotropic thermal parameters ($\times 10^3$) for the hydrogen atoms

Atom	x	y	z	U(Å^2)
H(2)	181	132	826	48
H(3)	168	45	876	53
H(41)	100	59	1022	75
H(42)	78	-7	940	75
H(43)	64	34	763	75
H(5)	102	-17	498	65
H(6)	178	6	264	56
H(7)	250	73	610	50
H(101)	306	136	296	55
H(102)	257	92	104	55
H(111)	320	67	442	64
H(112)	270	21	262	64
H(121)	320	63	-84	81
H(122)	361	53	105	81
H(131)	363	156	48	77
H(132)	407	140	-89	77
H(141)	395	141	426	95
H(142)	444	137	268	95
H(151)	479	227	129	96
H(152)	479	223	433	96
H(161)	458	288	290	74
H(162)	402	238	150	74
Atom	x	y	z	U(Å^2)
H(171)	421	247	671	82
H(172)	365	196	532	82
H(181)	399	311	558	86
H(182)	348	265	377	86
H(191)	330	287	808	66
H(192)	343	236	874	66

estimated standard deviations. Figure 2 shows the torsion angles for the three rings in the structure. Table 5 gives the equations of selected least squares planes and the deviations of particular atoms from them. Figure 3 shows a perspective view of the molecule approximately parallel to the principal plane of the structure. Table 6 lists the intermolecular contacts $\leqslant$ 3.5 Å and Fig. 4 shows a stereo view of the packing of the molecules in the structure.

This study confirms that the major product of the intramolecular Diels–Alder reaction of diene-anhydride (**2**), is the desired cytochalasan analogue (**3**). In particular the cyclisation has been regioselective, and has taken place via the *endo* transition state to generate the adduct with the correct relative configurations at the four chiral centres. This is clearly shown in Fig. 1.

Figures 1–3 also show conformational aspects of this tricyclic system. The cyclohexene ring adopts a slightly perturbed boat conformation with C-3 and C-7 out of the plane defined by C-2, C-5, C-6 and C-8. With respect to the cyclohexene ring, the exocyclic methyl group and the *trans*-fused macrocycle, are equatorial, and the anhydride ring is axial, perpendicular to the C-2, C-5, C-6 and C-8 plane.

The X-ray crystal data of several cytochalasans and their derivatives have been determined, and it has been observed, despite variations in the size and complexity of the macrocyclic ring, that the 6-membered methylenecyclohexane ring usually adopts a skew boat conformation perpendicular to the plane of the lactam ring. The conformation of the cyclohexene-anhydride (**3**) is remarkably similar to this.

The 14-membered macrocycle of our compound is more flexible than that of the cytochalasans and adopts a rather different conformation. The conformations of simple 14-membered cyclic compounds have been of some interest because the 14-membered

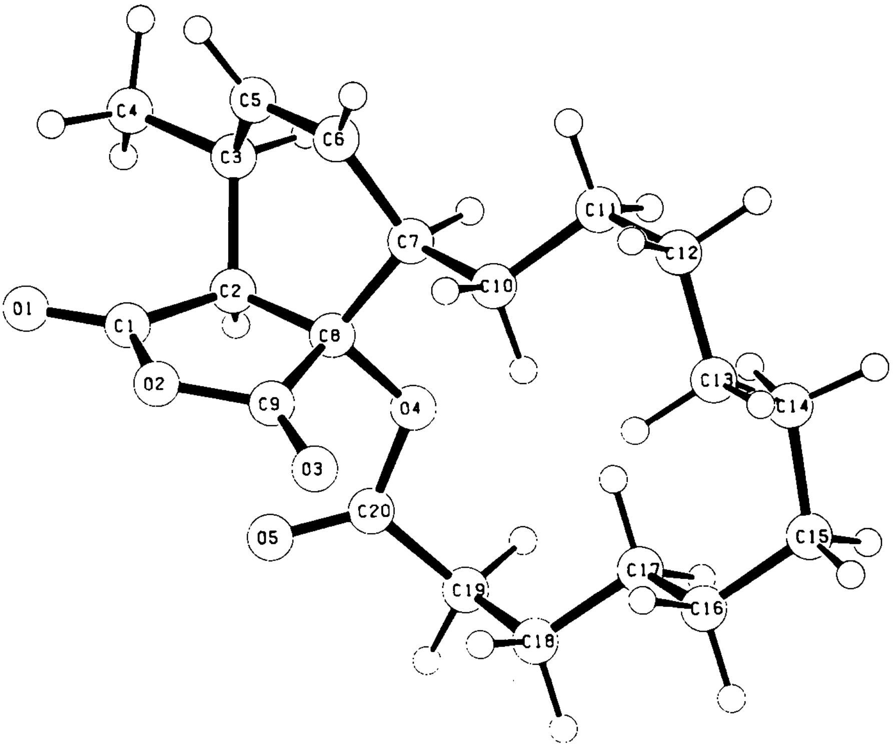

C4
C5
C6
C3
C11
C7
C12
C10
O1
C2
C1
C8
C13
O2
C14
C9
O4
O3
C20
O5
C15
C17
C19
C16
C18

Fig. 1.

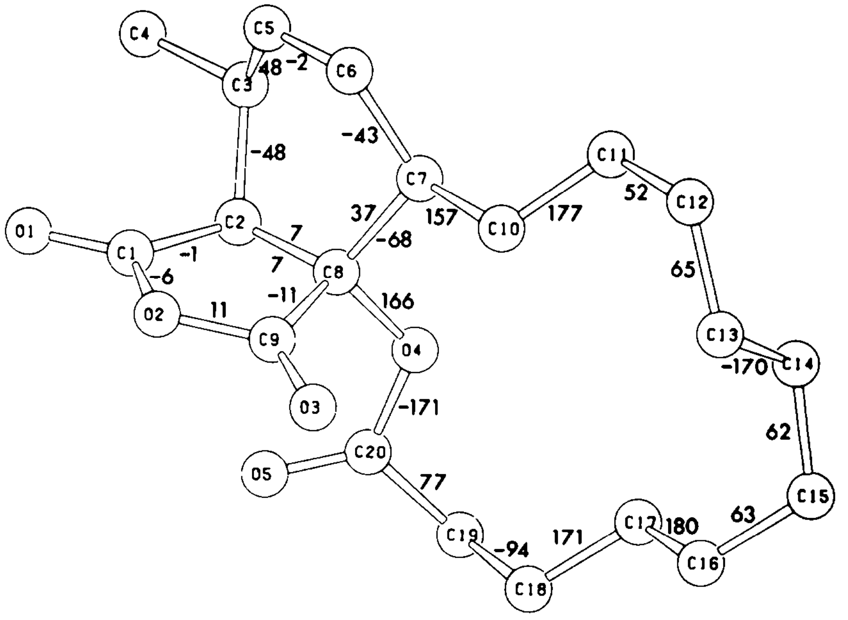

C4
C5
C6
C3
48
-2
-48
-43
C11
C7
52
C12
37
157
C10
177
O1
C2
7
-68
C1
-1
7
-6
C8
65
-11
166
O2
11
C9
O4
C13
-170
C14
O3
-171
62
C20
O5
77
C15
C17
180
63
C19
171
-94
C16
C18

Fig. 2.

Table 3. Bond lengths (Å) with estimated standard deviations in parentheses

C(1)	-	C(2)	1.51(2)	C(1)	-	O(1)	1.21(2)
C(1)	-	O(2)	1.37(1)	C(2)	-	C(3)	1.58(1)
C(2)	-	C(8)	1.51(1)	C(3)	-	C(4)	1.52(2)
C(3)	-	C(5)	1.51(2)	C(5)	-	C(6)	1.31(2)
C(6)	-	C(7)	1.52(1)	C(7)	-	C(8)	1.56(1)
C(7)	-	C(10)	1.55(2)	C(8)	-	C(9)	1.54(2)
C(8)	-	O(4)	1.44(1)	C(9)	-	O(2)	1.34(1)
C(9)	-	O(3)	1.20(1)	C(10)	-	C(11)	1.51(2)
C(11)	-	C(12)	1.57(2)	C(12)	-	C(13)	1.54(1)
C(13)	-	C(14)	1.51(2)	C(14)	-	C(15)	1.54(2)
C(15)	-	C(16)	1.50(2)	C(16)	-	C(17)	1.58(2)
C(17)	-	C(18)	1.49(2)	C(18)	-	C(19)	1.53(2)
C(19)	-	C(20)	1.50(1)	C(20)	-	O(4)	1.34(1)
C(20)	-	O(5)	1.20(1)				

Table 4. Valence angles (Å) with estimated standard deviations in parentheses

O(1)	C(1)	O(2)	119.4(10)	O(1)	C(1)	C(2)	128.3(8)
O(2)	C(1)	C(2)	112.3(9)	C(1)	C(2)	C(3)	110.5(7)
C(1)	C(2)	C(8)	102.8(9)	C(3)	C(2)	C(8)	114.3(9)
C(2)	C(3)	C(4)	114.1(9)	C(2)	C(3)	C(5)	107.6(10)
C(4)	C(3)	C(5)	115.1(7)	C(3)	C(5)	C(6)	119.3(8)
C(5)	C(6)	C(7)	120.4(11)	C(6)	C(7)	C(8)	110.1(8)
C(6)	C(7)	C(10)	113.9(10)	C(8)	C(7)	C(10)	113.8(7)
C(7)	C(8)	C(9)	109.9(10)	C(7)	C(8)	C(2)	114.7(7)
C(7)	C(8)	O(4)	104.0(7)	C(2)	C(8)	C(9)	103.8(8)
C(2)	C(8)	O(4)	114.7(10)	C(9)	C(8)	O(4)	109.8(7)
C(8)	C(9)	O(2)	110.7(9)	C(8)	C(9)	O(3)	127.9(9)
O(2)	C(9)	O(3)	121.4(11)	C(1)	O(2)	C(9)	109.3(10)
C(7)	C(10)	C(11)	112.6(9)	C(10)	C(11)	C(12)	112.1(10)
C(11)	C(12)	C(13)	113.5(11)	C(12)	C(13)	C(14)	113.5(11)
C(13)	C(14)	C(15)	114.7(12)	C(14)	C(15)	C(16)	117.6(11)
C(15)	C(16)	C(17)	113.4(11)	C(16)	C(17)	C(18)	112.9(11)
C(17)	C(18)	C(19)	111.4(11)	C(18)	C(19)	C(20)	109.7(10)
C(19)	C(20)	O(4)	112.0(9)	C(19)	C(20)	O(5)	124.8(9)
O(4)	C(20)	O(5)	123.1(7)	C(8)	O(4)	C(20)	115.6(8)

Table 5. Equations of selected least-squares planes† (in direct space) and the deviations (Å × 10^2) of particular atoms from them

A $-12.784\,\underline{x} + 14.415\,\underline{y} - 4.868\,\underline{z} = -3.846$

[C(8)*, 28; O(4)* -32; C(20)* 18; O(5), 97; C(19)* - 33; C(18),* 41; C(17)*, -34; C(16)*, 49; C(15)*, - 24; C(14)*, -61; C(13)*, 58; C(12),* 18; C(11),* -46; C(10)*, 39; C(7)*, -20]

B $-3.621\,\underline{x} + 24.937\,\underline{y} + 2.264\,\underline{z} = 3.591$

[C(1),* 1; C(2),* 3; C(8)*, -5; C(9)*, 6; O(2),* -5; O(1), 5; O(3), 25]

Dihedral angle between planes A and B = 89.3°

† Defining atoms indicated by an *

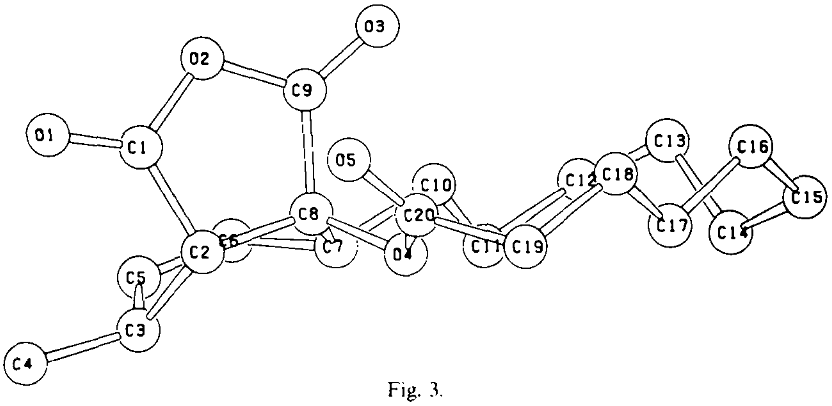


Fig. 3.

Table 6 Intermolecular* contacts ≤3.5 Å

C(2) . . .	O(3^{I})	3.48	C(19) . . .	O(3^{I})	3.41
C(20) . . .	O(3^{I})	3.04	O(4) . . .	O(3^{I})	3.16
O(5) . . .	O(3^{I})	3.43	O(1) . . .	C(5^{II})	3.43
C(19) . . .	O(5^{III})	3.36	C(18) . . .	O(5^{III})	3.32
C(16) . . .	O(5^{IV})	3.49			

* Roman numeral superscripts denote the following equivalent positions relative to the reference molecule at $\underline{x},\underline{y},\underline{z}$:

I $\underline{x}, \underline{y}, 1+\underline{z}$ II $-\underline{y}, \underline{x}-\underline{y}, \underline{z}$

III $2/3-\underline{y}, 1/3+\underline{x}-\underline{y}, 1/3+\underline{z}$ IV $2/3-\underline{y}, 1/3+\underline{x}-\underline{y}, -2/3+\underline{z}$

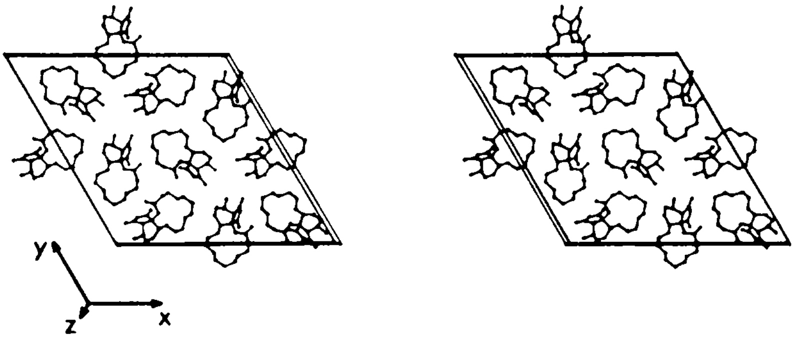


Fig. 4.

ring can adopt a strain-free diamond lattice formation. Indeed molecular models, calculations, and other data for cyclotetradecane have all been interpreted in terms of the [3434] rectangular diamond lattice conformation (**4**),[7] and this conformation was also found, by an X-ray analysis, for cyclotetradecanone.[8] Similarly, cyclotetradeca-1,8-dione[9] and derivatives[10] are also believed to adopt the [3434] diamond lattice conformation. One limitation of this conformation is that geminal substituents can only be accommodated at the corner positions, i.e. at positions 1, 4, 8 and 11 in formula (**4**), without introducing excessive strain.

The 14-membered macrolide ring in the Diels–Alder adduct (**3**) could be considered to have adopted a rather perturbed [3434] conformation. This is shown in Fig. 2, where the torsional angles from C-8 to C-18 via C-12 and C-15, are found to be similar to those required for the [3434] conformation. The corners of this diamond lattice conformation are at C-8, C-12, C-15 and C-19, i.e. the disubstituted carbon, C-8, is at a corner position as expected. However, the ester functionality extensively modifies the conformation in the region of C-18 to C-8 as is shown by the torsional angles in Fig. 2.

EXPERIMENTAL

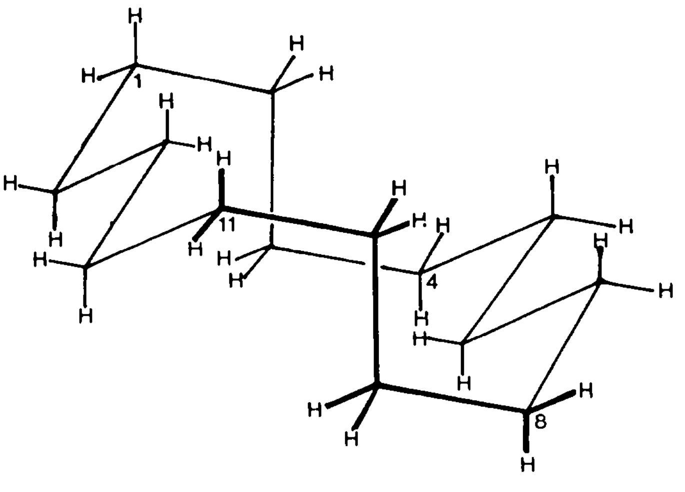
Full details of the preparation and spectroscopic characterisation of the macrolide-anhydride (**3**) will be reported elsewhere.[4] Crystals suitable for single crystal X-ray diffraction were obtained by slow evaporation of a MeOH solution.

Crystals of (**3**) are colourless, hexagonal needles. Accurate lattice parameters were obtained by least-squares refinement of 16 reflections measured on a diffractometer using Mo K_α radiation.

Crystal data. $C_{20}H_{28}O_5$, $M = 348.4$. Trigonal, $a = b = 29.29(1)$, $c = 5.78(1)$, Å. $U = 4294$ Å^3, $D_m = 1.22\,\mathrm{g\,cm^{-3}}$ (by flotation) $D_c = 1.22\,\mathrm{g\,cm^{-3}}$, $Z = 9$, $F(000) = 1692$. Space group $R3$ (No. 146) from systematic absences and cell contents. Mo K_α radiation, $\lambda = 0.7107$ Å, μ (Mo K_α) = 0.5 cm^{-1}.

The space-group and preliminary cell parameters were determined photographically (Co K_α radiation). A total of 1984 reflections were measured (to $2\theta = 46°$) on a card-controlled Picker four-circle diffractometer using Nb filtered Mo K_α radiation. Of that 1501 were independent and 1188 had $F_0 \geqslant 6\sigma(F_0)$. The data were corrected for Lorentz and polarisation factors, but no absorption corrections were applied.

Solution and refinement of the structure. The structure was solved by multi-solution tangent refinement. An initial trial



(**4**)

structure was obtained from an E-map computed using the phases calculated for 130 E's $\geqslant 1.4$. The 17 highest peaks were then used as a basis for further tangent refinement of an extended set of 272 E's $\geqslant 1.1$. The resulting E-map revealed the positions of all 25-non-hydrogen atoms and showed two of the original 17 peaks to be false.

The 25 non-hydrogen atoms were refined isotropically to give $R = 0.087$. Subsequent isotropic refinement including the hydrogen atoms in fixed calculated positions reduced R to 0.067 for the 1188 F's $\geqslant 6\sigma(F)$. In view of the purely stereochemical nature of the analysis, refinement was terminated at this stage. Tables of observed and calculated structure factors may be obtained from the authors.

Computations were carried out using the SHELX-76 program system.

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REFERENCES

[1] Present address: Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY.

[2] E. J. Corey and M. Petrzilka, *Tetrahedron Letters* 2537 (1975).

[3] M. Binder and C. Tamm, *Angew. Chem. Internat. Edn.* **12,** 370 (1973).

[4] Preliminary communcation: S. J. Bailey, E. J. Thomas, W. B. Turner and J. A. J. Jarvis, *J.C.S. Chem. Commun.* 474 (1978).

[5] C. K. Johnson, ORTEP Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee (1965).

[6] M. A. Beno, R. H. Cox, J. M. Wells, R. J. Cole, J. W. Kirksey and G. G. Christoph, *J. Amer. Chem. Soc.* **99,** 4123 (1977); G. M. McLaughlin, G. A. Sim, J. R. Kiechel and C. Tamm, *J.C.S. Chem. Commun.* 1398 (1970); Y. Tsukuda and H. Koyama, *J.C.S., Perkin Trans. II* 739 (1972); A. F. Cameron, A. A. Freer, B. Hesp and C. J. Strawson, *Ibid.* 1741 (1974); G. Büchi, Y. Kitaura, S. S. Yuan, H. E. Wright, J. Clardy, A. L. Demain, T. Glinsukan, N. Hunt and G. N. Wogan, *J. Amer. Chem. Soc.* **95,** 5423 (1973).

[7] J. Dale, *J. Chem. Soc.* 93 (1963); J. Dale, *Acta Chem. Scand.* **27,** 1115 (1973); G. Borgen and J. Dale, *J.C.S. Chem. Commun.* 1340 (1970); J. Dale, *Angew. Chem. Internat. Edn.* **5,** 1001 (1966); F. A. L. Anet, A. K. Cheng and J. J. Wagner, *J. Amer. Chem. Soc.* **94,** 9250 (1972).

[8] P. Groth, *Acta Chem. Scand.* **29A,** 374 (1975); F. A. L. Anet, A. K. Cheng and J. Krane, *J. Amer. Chem. Soc.* **95,** 7877 (1973).

[9] T. Alvik, G. Borgen and J. Dale, *Acta Chem. Scand.* **26,** 1805 (1972).

[10] G. Borgen and J. Dale, *Ibid.* **26,** 1799 (1972); C. J. Brown, *J. Chem. Soc.* (C), 1108 (1966).