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Total Synthesis of Carbocyclic Cytochalasans

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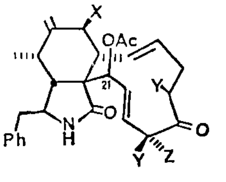
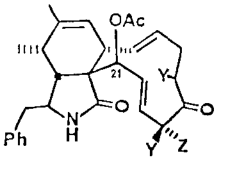
The cytochalasans are molecules of unique biological activity and structural complexity.[1] Here we report the first total synthesis of representative carbocyclic cytochalasans,[2] structures **18** and **19**, which are closely related to cytochalasin D (**1**) and zygosporin G (**2**).[3]



1, X=Z=OH, Y=CH_3; C_{21}-(S)
18, X=Z=Y=H, C_{21}-(R)
21, X=H, Z=OH, Y=CH_3; C_{21}-(S)

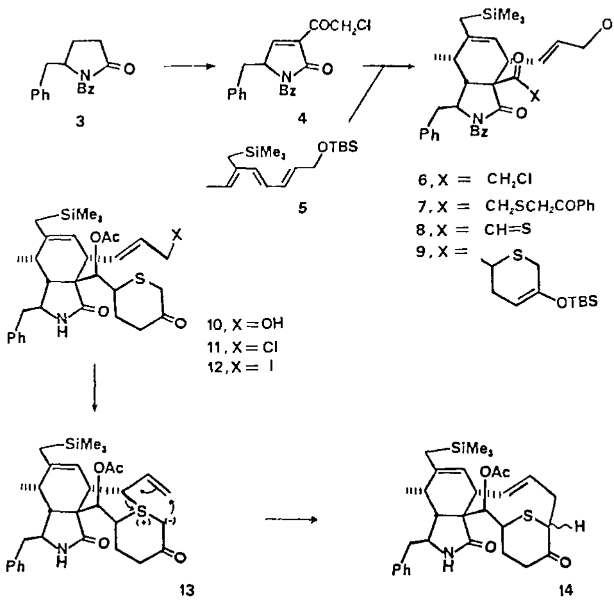


2, Z=OH, Y=CH_3; C_{21}-(S)
19, Z=Y=H; C_{21}-(R)

In 1978, we described the advantages of using *N*-acylpyrrolinones for Diels–Alder reactions in the cytochalasin area and a means to control five of the isoindolone asymmetric centers via the least hindered endo transition state.[4] This same selectivity is maintained with doubly activated dienophiles[5] and is especially high in the optimized system of Scheme I. The unstable dienophile **4**, obtained by a conventional sequence from succinimide (via **3**)[5,6] reacts with triene **5**[5] at room temperature to give a >15:1 mixture of the desired adduct **6** and a minor isomer with the same regiochemistry but unknown stereochemistry. Since **4** is too sensitive for purification, we can only estimate the yield of **4** + **5** → **6** as >90%, but the overall yield of **6** from **3** is 77% on 2-g scale.

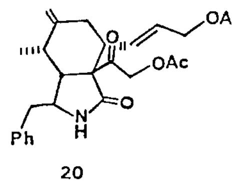
The last four carbons of the 11-membered carbocycle must now be introduced, and they must be incorporated into a sulfur-containing ring in order to use the ring expansion strategy that we had developed earlier.[7] After a long search, this problem has been solved by using thioaldehyde technology.[8] Reaction of **6** with phenacyl thiol/K_2CO_3–THF affords the phenacyl sulfide **7** (88%) and sunlamp irradiation generates the reactive thioaldehyde **8**. When this experiment is performed in the presence of 2-(*tert*-butyldimethylsiloxy)butadiene, a 3:2 diastereomer mixture of thio-Diels–Alder adducts **9** can be isolated. Treatment with DBU/THF (0 °C) improves the isomer ratio to 10:1, and chromatographic separation affords the major isomer in 60% yield based on **8**. After ketone reduction and *N*-benzoyl cleavage with $LiBH_4$/ether followed by silyl ether cleavage (Et_3NH^+ F^-, CH_3OH, 6 h), 50–60% overall to **10**, the stage is set for 11-membered ring construction.

Scheme I

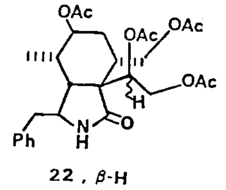


The key reaction involves the 2,3-sigmatropic rearrangement of a bicyclic ylide **13**.[7] This ylide can be generated by heating iodide **12** in acetonitrile/K_2CO_3. In practice the more stable chloride **11** is made from **10** + Bu_3P/CCl_4 (100%) and is stirred with NaI, K_2CO_3, and CH_3CN, 4 h at 70 °C. A 1.3:1 mixture of two diastereomers **14** is formed in 60% yield based on **11**. Both isomers have the crucial *E*-double-bond geometry, and must differ at the new asymmetric (bridgehead) carbon.

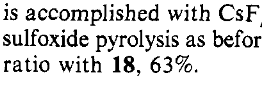
The last stages of synthesis require removal of sulfur and silicon, transformations that (in retrospect) are quite simple. Sulfur methylation of the major ring-expansion product **14** ($^+O(CH_3)_3BF_4^-$, DME) followed by Zn/CH_3CO_2H affords the sulfide **15**, 92%. Pyrolysis of the derived sulfoxide **16** (MCPBA, 90%) in xylene, $CaCO_3$, 140 °C, forms a single olefin **17** (*E*,*E* geometry) in 91% yield. After desilylation with BF_3·AcOH/CH_2Cl_2, O °C, **17** is converted into the cytochalasin D derivative **18** (80%).



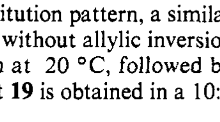
15, X = SCH_3
16, X = $SOCH_3$



17



20



22, β-H
23, α-H

For synthesis of the zygosporin G substitution pattern, a similar sequence can be used. Desilylation of **16** without allylic inversion is accomplished with CsF/Me_2SO, 1.5 h at 20 °C, followed by sulfoxide pyrolysis as before. The product **19** is obtained in a 10:1 ratio with **18**, 63%.

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(1) "Cytochalasins, Biochemical and Cell Biological Aspects"; Tanenbaum, S. W., Ed.; North-Holland Publishing Co.: Amsterdam, 1978.

(2) A total synthesis of a lactone member (phomin = cytochalasin B) of the cytochalasin family has appeared: Stork, G.; Nakahara, Y.; Greenlee, W. G. *J. Am. Chem. Soc.* **1978**, *100*, 7775. Stork, G., Nakamura, E. *Ibid.* **1983**, *105*, 5510. For synthesis of segments related to carbocyclic cytochalasans, see: Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, *104*, 5719. Pyne, S. G.; Spellmeyer, D. C.; Chen, S.; Fuchs, P. L. *Ibid.* **1982**, *104*, 5728. Schmidlin, T.; Gamboni, R.; Strazewski, P.; Tamm, Ch. *Helv. Chim. Acta* **1983**, *66*, 1796 and references therein.

(3) Rothweiler, W.; Tamm, C. *Exerpientia* **1966**, *22*, 750; *Helv. Chim. Acta* **1970**, *54*, 697. Hayakawa, S.; Matsushima, T.; Kimura, T.; Minato, H.; Katagiri, K. *J. Antibiot.* (*Tokyo*) **1968**, *21*, 523. Aldridge, D. C.; Turner, W. B. *J. Chem. Soc. C* **1969**, *923*. Minato, H., Katayama, T. *Ibid.* **1970**, *45*. Aldridge, D. C.; Burrows, B. F.; Turner, W. B. *Chem. Commun.* **1972**, 148.

(4) Vedejs, E.; Gadwood, R. C. *J. Org. Chem.* **1978**, *43*, 376.

(5) Vedejs, E.; Campbell, J. B., Jr.; Gadwood, R. C.; Rodgers, J. D.; Spear, K. L. *J. Org. Chem.* **1982**, *47*, 1534.

(6) Treatment of **3** with 2 equiv of $LiN[SiMe_3]_2$ followed by $ClCH_2COCl$ gives the enol chloroacetate of the α-chloroacetyl product which can be hydrolyzed to the chloroketone by H_2O/silica gel. Selenylation (PhSeCl, NaH) followed by oxidation (MCPBA) affords the dienophile **4**.

(7) Vedejs, E.; Arnost, M. J.; Eustache, J. M.; Krafft, G. A. *J. Org. Chem.* **1982**, *47*, 4384.

(8) Vedejs, E.; Eberlein, T. H.; Varie, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1445. Vedejs, E.; Perry, D. A.; Houk, K. N.; Rondan, G. *Ibid.* **1983**, *105*, 6999.

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To prove the stereochemistry which has been drawn for these products, a chemical correlation with cytochalasin D has been performed. The details are described in the supplementary material, but the key experiments involve ozonolysis, $NaBH_4$ reduction, and acylation of **18**, the diastereomer pair **20** (derived from **6**), and **21** (derived from natural **1**). This degradation sequence converts **20** into two isomeric tetraacetates, **22** and **23**. Similar degradation of **21** affords **23** while synthetic **18** gives **22**. These results prove that isoindolone Diels–Alder stereochemistry is correct and is retained to the end of our synthesis.

In conclusion, we have developed an approach for synthesis of the zygosporin G–cytochalasin D ring systems, 3% overall from succinimide. Subsequent papers will deal with 11-membered ring stereochemistry and functionality.

Acknowledgment. This work was supported by the National Institutes of Health (CA 17918).

Registry No. 1, 22144-77-0; **1**-6-en-12-ol (7-dehydroxy), 83071-41-4; **1**-6-enal (7-dehydroxy), 90741-92-7; **2**, 25374-69-0; (±)-**3**, 90741-72-3; (±)-**4**, 90741-73-4; **5**, 90741-74-5; (±)-**6**, 90741-75-6; (±)-**7**, 90741-76-7; (±)-**8**, 90741-77-8; (±)-**9** (isomer 1), 90741-78-9; (±)-**9** (isomer 2), 90741-79-0; (±)-**10**, 90741-80-3; (±)-**11**, 90741-81-4; (±)-**12**, 90741-82-5; (±)-**14** (isomer 1), 90741-83-6; (±)-**14** (isomer 2), 90821-11-7; (±)-**15**, 90741-84-7; (±)-**16**, 90741-85-8; (±)-**17**, 90741-86-9; (±)-**18**, 90741-87-0; (±)-**19**, 90741-88-1; (±)-**20**, 90741-89-2; **21**, 90865-40-0; (±)-**21**, 90762-73-5; (±)-**22**, 90741-90-5; (±)-**23**, 90741-91-6; PhC(O)-CH_2SH, 2462-02-4; 2-(*tert*-butyldimethylsiloxy)-1,3-butadiene, 80738-05-2; (±)-(3α,3aα,4β,7β,7aα)-2-benzoyl-3-benzyl-4-methyl-5-[(trimethylsilyl)methyl]-7-(3-hydroxyprop-1(*E*)-enyl)-7a-[(chloromethyl)carbonyl]-1,3,3a,4,7,7a-hexahydroisoindol-1-one, 90741-93-8; (±)-(3α,3aα,4β,7β,7aα)-2-benzoyl-3-benzyl-4-methyl-5-[(trimethylsilyl)methyl]-7-(3-acetoxyprop-1(*E*)-enyl)-7a-[(chloromethyl)carbonyl]-1,3,3a,4,7,7a-hexahydroisoindol-1-one, 90762-74-6; (±)-(3α,3aα,4β,7β,7aα)-2-benzoyl-3-benzyl-4-methyl-5-[(trimethylsilyl)methyl]-7-(3-acetoxyprop-1(*E*)-enyl)-7a-[(acetoxymethyl)carbonyl]-1,3,3a,4,7,7a-hexahydroisoindol-1-one, 90741-94-9.

Supplementary Material Available: NMR data for key intermediates and correlation schemes (6 pages). Ordering information is given on any current masthead page.

A Remarkable Alkali-Metal-Centered Zirconium Cluster in Potassium Hexazirconium Tetradecaiodide ($Zr_6I_{14}K$): Synthesis and Characterization

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Synthetic efforts to identify important products in the reactions of zircaloy (~98% Zr) cladding with prominent fission products have led to the discovery of two zirconium iodides containing octahedral metal clusters, purportedly Zr_6I_{12} and $CsZr_6I_{14}$.[2-4] The generally low yield of these products led us to attempt syntheses of the ternary phase utilizing other alkali metals. Reaction of KI, ZrI_4, and Zr metal resulted in a product with powder pattern closely resembling that of $CsZr_6I_{14}$ but, surprisingly, with larger lattice parameters. Subsequent studies indicate this compound is the first example of an unprecedented configuration, an octahedral metal cluster the center of which is occupied by an alkali metal, namely, $Zr_6I_{14}K$. The single-crystal X-ray diffraction results, electron microprobe analysis, magnetic susceptibility data, photoelectron spectroscopic measurements, and extended Hückel calculations on this novel cluster are reported here.

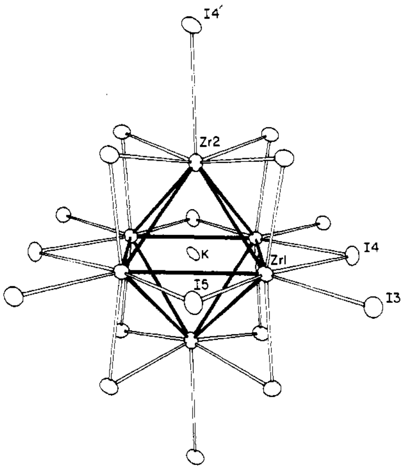

Figure 1. $Zr_6I_{14}K_{1.0}$ cluster with all exo iodines (50% thermal ellipsoids). A C_{2h} symmetry results from a 2-fold axis that passes through I5 and K together with a mirror plane that contains atoms K, I4, and Zr2.

Table I. Comparison of Important Bond Distances (Å) in $CsZr_6I_{14}$, $Zr_6I_{14}K$, and $Zr_6I_{14}K_{0.46}$

		$CsZr_6I_{14}$[a]	$Zr_6I_{14}K$	$Zr_6I_{14}K_{0.46}$
Zr–Zr	interlayer[b]			
	Zr1–Zr1	3.350 (3)	3.494 (3)	3.478 (3)
	Zr1–Zr2 (×2)	3.286 (2)	3.427 (2)	3.408 (3)
	interlayer			
	Zr1–Zr1	3.343 (3)	3.462 (3)	3.447 (3)
	Zr1–Zr2 (×2)	3.298 (2)	3.436 (2)	3.424 (3)
Zr–I^{a-i}[c]	Zr2–I4	3.494 (3)	3.408 (2)	3.377 (2)
Zr–I^{a}	Zr1–13	3.186 (2)	3.124 (2)	3.118 (2)
Zr–K	Zr1–K (×4)		2.460 (1)	2.448 (2)
	Zr2–K (×2)		2.393 (2)	2.382 (3)
Zr–I^{i}(av)		2.884 (2)	2.898 (2)	2.883 (2)

[a] Reference 3. [b] The structure can be described as layered perpendicular to [001], this direction lying approximately from lower left to upper right in Figure 1. [c] Superscripts on I refer to bridging functions (i = inner, edge bridging within cluster; a = outer or exo, bridging between clusters).

Sublimed KI, ZrI_4 (K:I, 1:14), and a large excess of reactor-grade Zr strips were sealed in a tantalum container and heated for 4–6 weeks in a 840–860 °C gradient. The air-sensitive product (10–20% yield) grew as clumps of shiny black gems on the zirconium in the hot end of the container. The clumps were visually separated from the remaining reaction products, α-ZrI_2, β-ZrI_2,[5] ZrI_3, and unreacted KI.

Pertinent X-ray data for two single crystals studied together with those for $CsZr_6I_{14}$ are available as supplementary material. Intensities for two octants were measured by using a four-circle automated diffractometer. The data were corrected for absorption effects by a method previously described.[3] With $Zr_6I_{14}K$, a peak ($Z \sim 18$) was observed in the center of the cluster in an electron density map (R = 14.0%) and a potassium atom was included in the model at that position. The refinement proceeded smoothly (R = 4.5, R_w = 6.3%) with all atoms refined anisotropically and with a potassium occupancy of 1.05 (3). The position of cesium in $CsZr_6I_{14}$ within an iodine polyhedron was empty. Subsequent reactions also formed $Zr_6I_{14}K$-type phases with somewhat smaller cell parameters, and refinement (R = 5.8, R_w = 8.1%) of occupancy and anisotropic thermal parameters (but with K isotropic) led to an X-ray stoichiometry of $Zr_6I_{14}K_{0.46(2)}$.

The $Zr_6I_{14}K_x$ structure is isostructural with Nb_6Cl_{14} and Ta_6I_{14}[6,7] as well as $CsZr_6I_{14}$ (excluding the Cs and K positions). A view of the isolated potassium cluster along with iodine atoms

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[1] Operated for the U. S. Department of Energy by Iowa State University under Contract W-7405-Eng-82. This research was supported by the Office of Basic Energy Sciences, Materials Sciences Division.

[2] Corbett, J. D.; Daake, R. L.; Poeppelmeier, K. R.; Guthrie, D. H. *J. Am. Chem. Soc.* **1978**, *100*, 652.

[3] Guthrie, D. H.; Corbett, J. D. *Inorg. Chem.* **1982**, *21*, 3290.

[4] Occupation of the centers of the octahedral clusters in these compounds by light nonmetals has been suggested previously[3] and is under investigation.

[5] Corbett, J. D.; Guthrie, D. H. *Inorg. Chem.* **1982**, *21*, 1747.

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