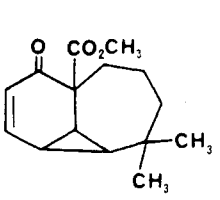
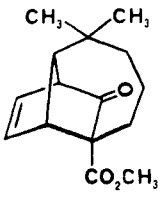
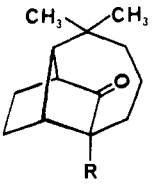


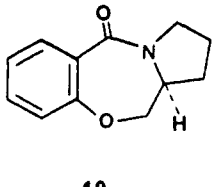
7



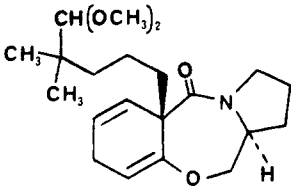
8



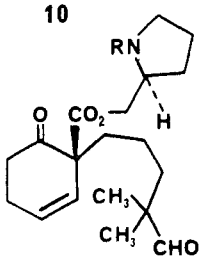
9a R = CO_2CH_3
b R = CO_2H
c R = H
d R = CH_3



10



11



12a R = H
b R = CO_2CH_3

On the other hand, **6** and **7**, in refluxing xylene solution, both rearranged to tricyclic ketone **8** (oil) in ~90% yield.[7] The most efficient protocol for conversion of aldehyde **5b** into tricyclic ketone **8** (~40% overall yield) involves two experimental steps (preparation and thermolysis of **5c**) and is performed without isolation of reaction intermediates.

The efficiency of formation of **6** (43%) may not reflect problems inherent in the cyclization step. A major byproduct in the decomposition of the aziridinyl imine **5c** is the nitrile **5d**, presumably formed by Beckmann-like elimination of *trans*-2,3-diphenylaziridine from **5c**.

Tricycle **8** was converted to **9c**, an intermediate in both the Johnson[1c] and Oppolzer[1d] syntheses of longifolene, by (1) olefin hydrogenation at atmospheric pressure in ethanol with 5% Pd on carbon to give **9a** (92%, mp 101 °C), (2) saponification of **9a** with KOH in methanol–water at 25 °C to give carboxylic acid **9b** (85%, mp 160 °C), and (3) decarboxylation of **9b** in refluxing toluene solution (86%). ^1H NMR, ^{13}C NMR, IR, and mass spectra obtained with our synthetic **9c** compared favorably with spectra kindly provided by Professors Johnson and Oppolzer. Transformation of racemic **9c** to (±)-longicamphenylone (**9d**) and thence to (±)-longifolene (**1**) followed literature procedures.[1]

Benzoxazepenone **10**[8] provided the means for an enantiospecific preparation of (−)-longifolene. Reductive alkylation of **10** gave **11**, isolated as a single diastereoisomer in 96% yield. This substance was converted to enantiomerically pure **3a** by (1) treatment with methanol–hydrochloric acid to give carboxylic ester **12a**, (2) N-acylation of **12a** with methyl chloroformate–sodium bicarbonate to give urethane **12b**, (3) conversion of **12b** to acetal–enol ether **3b** in refluxing methanol–trimethyl orthoformate–hydrogen chloride, and (4) transesterification of **3b** with sodium methoxide in methanol (~75% overall from **11**).

Conversion of optically active **3a** to (−)-longicamphenylone (**9d**) [(+) configuration shown] followed the procedure already described for transformation of racemic **3a** to racemic **9d**. The isolated product was found to have optical rotation equal but opposite to that of (+)-**9d** prepared from (+)-longifolene.[1a,9] Finally, conversion of (−)-**9d** to (−)-longifolene[10] by the literature procedure[1a] confirmed the sense of stereoselection in the Birch reduction–alkylation step.

Acknowledgment. This work was supported by the National Institutes of Health (GM 33061). We thank W. S. Johnson and W. Oppolzer for providing us with spectral data for **9c**. We thank J. P. Dittami for preparation of the dimethyl acetal of 2,2-dimethyl-5-hydroxypentanal.

Supplementary Material Available: Listing of spectral and analytical data for all new compounds prepared in this work (6 pages). Ordering information is given on any current masthead page.

(7) For an earlier report of a vinyl cyclopropane rearrangement in this tricyclic ring system, see: Aumann, R. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 376.

(8) Schultz, A. G.; Sundararaman, P. *Tetrahedron Lett.* **1984**, *25*, 4591.

(9) Naffa, P.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1954**, *21*, 1115.

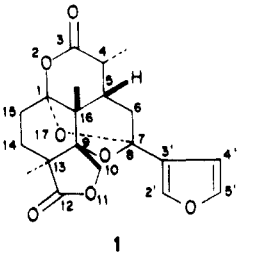
(10) Huneck, S.; Klein, E. *Phytochemistry* **1967**, *6*, 383.

Arthur G. Schultz,* Salvador Puig
Department of Chemistry
Rensselaer Polytechnic Institute
Troy, New York 12181
Received December 20, 1984

Saudin, a Hypoglycemic Diterpenoid with a Novel 6,7-Secolabdane Carbon Skeleton, from *Cluytia richardiana*

Summary: A novel hypoglycemic diterpene named saudin (**1**) was isolated from the petroleum ether extract of *Cluytia richardiana* (Euphorbiaceae) growing in Saudi Arabia and was shown to be a novel 6,7-secolabdane with an unusual arrangement of lactone groups presumably formed via oxidation of the B-ring ketone to an ϵ-lactone followed by hydrolysis, rearrangement, and cyclization to give a highly caged structure.

Sir: We report the isolation and structural elucidation of the hypoglycemic agent saudin (**1**; (−)-(1*R*,4*R*,5*S*,7*R*,9*S*,13*S*,16*R*)-7-(3′-furanyl)-4,13,16-trimethyl-2,8,11,17-tetraoxapentacyclo[7.6.1.$1^{1,7}$.$0^{5,16}$.$0^{9,13}$]-heptadeca-3,12-dione). Saudin (**1**) was isolated from the



1

leaves of the toxic plant *Cluytia richardiana* (L.) family Euphorbiaceae, which grows in the mountainous regions of western and southern Saudi Arabia. Compound **1** apparently derives from the labdane group of prefuranoid diterpenes and is a very novel, highly oxygenated and

0022-3263/85/1950-0916$01.50/0

rearranged example of this group with a unique caged bis ketal backbone.[1,2]

The isolation procedure involved petroleum ether (60–80 °C) extraction to give an orange precipitate which was chromatographed on silica gel with ethyl acetate/hexane (1:1) to give saudin in 0.06% yield. Crystallization of **1** from ethyl acetate–carbon tetrachloride gave crystals melting at 202–203 °C, $[\alpha]_D$ −12° (*c*, 0.094, $CHCl_3$). Absorption at 1760 and 1735 cm^{-1} in the IR and λ_{max}^{EtOH} 207 nm (ϵ 6700) in the UV indicated the presence of two esters, one an apparent γ-lactone, and a furan ring. The molecular formula for saudin was found to be $C_{20}H_{22}O_7$ on the basis of high-resolution MS, *m/z* 374.1376, calcd 374.1365. Other significant peaks in the mass spectrum were observed at *m/z* 176.9 (43.7%) and 94.9 (100%). The latter peak corresponds to a fragment derived from cleavage of the bond β to the furan ring to give a $C_5H_3O_2$ fragment.[3]

Further structural information was obtained by analysis of the 470-MHz proton NMR spectrum of **1** which showed 22 protons,[4] none exchangeable with D_2O. A β-substituted furan ring gave signals at δ 7.55 (dd), 7.40 (t), and 6.43 (dd). Other downfield signals included those for a methylene attached to oxygen (in the γ-lactone) at δ 4.34 (d) and 4.12 (d, J = 9.9) and a quartet of doublets at δ 3.04 for a methine proton coupled to an adjacent methine and methyl ($CH_2CHCHCH_3$). The methyl group in this moiety appeared at δ 1.31, the other methine at δ 2.26, and the methylene protons at δ 2.44 and 1.82. Signals for a $-CH_2CH_2-$ group appeared at δ 2.40, 1.95, 1.85, and 1.75. Two methyl singlets also appeared at δ 1.25 and 1.18. The 50-MHz ^{13}C NMR spectrum showed 20 carbons including signals corresponding to the furan ring (δ 107.90, 125.55, 139.88, and 143.51), two lactone carbonyls (δ 170.95 and 179.29), and three highly oxygenated quaternary centers (δ 82.55, 95.07, and 105.33).

These data indicated saudin to be a very novel, highly oxygenated diterpene but did not allow complete structural assignment. On the basis of this, a single-crystal X-ray study was undertaken. The crystal of saudin belongs to the monoclinic system with diffractometer-measured unit cell parameters of a = 15.891 (3) Å, b = 12.200 (2) Å, c = 9.337 (2) Å, and β = 100.01 (2)°. The calculated density for 4 molecules of $C_{20}H_{22}O_7$ per unit cell was 1.40. The space group was shown to be $P2_1$ from systematic absences. All unique diffraction maxima (2568) with $2\theta \leq 116°$ were measured by using variable speed θ–2θ scans and Cu Kα radiation. Of the 2568 unique reflections, 2393 were judged sufficiently above background ($3\sigma F > F$) after correction for Lorentz/polarization and were used in the structure solution.

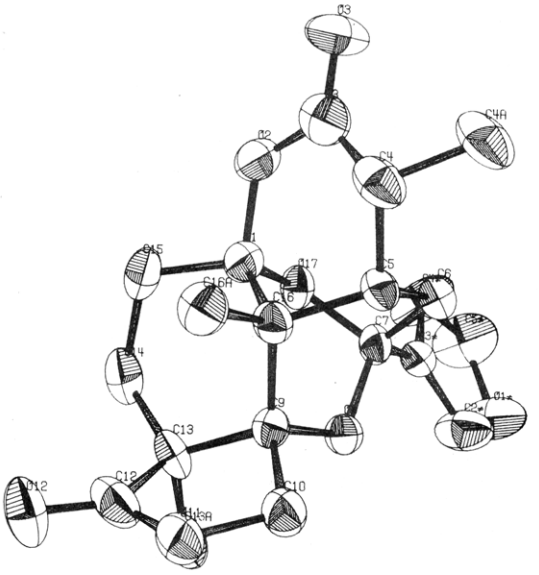
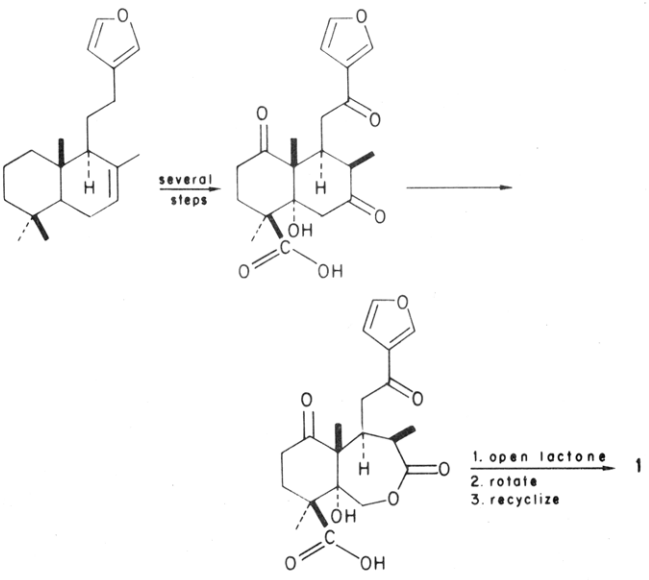


Figure 1.

Scheme I



The structure was solved by using MULTAN82. Refinement of this structure using SHELX proceeded smoothly to a final R factor of 0.060 using anisotropic temperature factors for all non-hydrogen atoms and fixed positions and temperature factors for the hydrogen atoms.[5] A final difference Fourier map revealed no peaks greater than 0.2 e/Å^3.

A computer-generated drawing is shown in Figure 1. The X-ray experiment defined only the relative stereochemistry. This drawing depicts saudin with the same absolute configuration as other labdane-type diterpenes. On completion of the X-ray structure determination, it was possible to assign most of the ^1H and ^{13}C NMR signals unambiguously.

Saudin bears an obvious structural relationship to other labdane-type diterpenes including nepetaefolin.[1-4] However, the structure contains a novel arrangement of lactone groups in a unique polyether lattice and may be formed via oxidation of the B ring ketone to an ϵ-lactone followed by hydrolysis and rearrangement of the B ring to give the

(1) White, J. D.; Marchand, P. S. "Bioorganic Chemistry"; Van Tamelen, E. E., Ed.; Academic Press: New York, 1978; Vol. II, p 337.
(2) VonDreele, R. B.; Pettit, G. R.; Ode, R. H.; Perdue, R. E., Jr.; White, J. D.; Marchand, P. S. *J. Am. Chem. Soc.* **1975**, *97*, 6236.
(3) Burke, B. A.; Chan, W. R.; Prince, E. C.; Manchand, P. S.; Eickman, N.; Clardy, J. *Tetrahedron* **1976**, *32*, 1881.
(4) ^1H NMR (470 MHz, $CDCl_3$) δ 1.18 (3 H, s, methyl), 1.25 (3 H, s, methyl), 1.31 (3 H, d, $J_{4,4a}$ = 6.8 Hz, methyl 4a), 1.75 (1 H, m, H-14 or H-15), 1.82 (1 H, dd, $J_{5,6\alpha}$ = 3, $J_{6\alpha,6\beta}$ = 13.6, H-6α), 1.85 (1 H, m, H-14 or H-15), 1.95 (1 H, m, H-14 or H-15), 2.26 (1 H, ddd, $J_{4,5}$ = 3, $J_{5,6\alpha}$ = 3, $J_{5,6\beta}$ = 10.8, H-5), 2.40 (1 H, dd, H-14 or H-15), 2.44 (1 H, dd, $J_{5,6\beta}$ = 10.8, $J_{6\alpha,6\beta}$ = 13.6, H-6β), 3.04 (1 H, qd, $J_{4,5}$ = 3, $J_{4,4a}$ = 6.8, H-4), 4.12 (1 H, d, $J_{10\alpha,10\beta}$ = 9.9, H-10), 4.34 (1 H, d, $J_{10\alpha,10\beta}$ = 9.9, H-10), 6.43 (1 H, dd, $J_{2',4'}$ = 0.8, $J_{4',5'}$ = 1.6, H-4′), 7.40 (1 H, t, $J_{2',5'}$ = 1.6, $J_{4',5'}$ = 1.6, H-5′), 7.55 (1 H, dd, $J_{2',4'}$ = 0.8, $J_{2',5'}$ = 1.6, H-2′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.33 (q, J = 129 Hz, methyl 4a), 15.22 (q, J = 129 Hz, methyl), 23.59 (q, J = 131 Hz, methyl), 25.68 (t, J = 132 Hz, CH_2), 27.86 (t, J = 130 Hz, CH_2), 32.81 (d, J = 136 Hz, C-5), 35.07 (s, C-16), 36.91 (t, J = 128 Hz, CH_2), 38.07 (d, J = 128 Hz, C-4), 43.24 (s, C-13), 66.96 (d, J = 153 Hz, C-10), 82.55 (s, C-9), 95.07 (s, C-1), 105.33 (s, C-7), 107.90 (d, J = 173 Hz, C-4′), 125.55 (s, C-3′), 139.88 (d, J = 204 Hz, C-2′), 143.51 (d, J = 204 Hz, C-5′), 170.95 (s, C-3), 179.29 (s, C-12).

(5) All crystallographic calculations were performed by using MULTAN82, P. Main, University of York, and SHELX76.

caged diterpene. A proposed biogenesis for **1** is shown in Scheme I.

Compound **1** was administered to alloxanized mice at 40 mg/kg IP with olive oil as a control. Progressive reductions in the blood glucose level from 600 mg % to 300 mg % were observed over a period of 6 h.[6]

A series of terpenoids related to saudin have been isolated from *C. richardiana* and these structures and their biological activity will be reported in a full paper.

Acknowledgment. This investigation was supported by a grant from King Saud University for a joint project between the College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, and the Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907. High-resolution NMR spectra were recorded at the PUBMRL and supported in part by NIH Grant No. RR01077 from the Division of Research Resources. We also are grateful to Prof. J. B. Grutzner for a helpful discussion and the Purdue University Computing Center for a grant of computer time.

(6) The pharmacological evaluation was carried out by Dr. Ageel and Dr. Denshary, Department of Pharmacology, King Saud University, Riyadh, Saudi Arabia.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, and bond angles for **1** and further details on the ^{1}H and ^{13}C NMR spectra (9 pages). Ordering information is given on any current masthead page.

Jaber S. Mossa*
Department of Pharmacognosy and Medicinal Plants
Research Unit, Research Center
College of Pharmacy
King Saud University
Riyadh, Saudi Arabia

John M. Cassady,* Mikhail D. Antoun
Stephen R. Byrn, Ann T. McKenzie
John F. Kozlowski
Department of Medicinal Chemistry
and Pharmacognosy
School of Pharmacy and Pharmacal Sciences
Purdue University
West Lafayette, Indiana 47907

P. Main
Department of Physics
University of York
York, U.K.

Received August 21, 1984