gel for analysis and showed the following characteristics: IR (NaCl plate) 2950 (m), 2930 (m), 2850 (m), 1490 (s), 1450 (m), 1250 (s), 1110 (m), 925 (s), 845 (s), 775 (s), 750 (m), 725 (m), 690 cm^{-1} (m); ^1H NMR δ 7.46–7.25 (m, 5 H), 6.95–6.20 (m, 4 H), 2.30 (s, 2 H), 0.99 (s, 9 H), 0.23 (s, 6 H), 0.20 (s, 6 H); mass spectrum, exact mass calcd for $C_{21}H_{32}OSi_2$ m/e 357.2061, obsd 357.2071.

[(*o*-Hydroxyphenyl)methyl]dimethylphenylsilane. To a mixture of the crude benzylsilane from above (3.0 g, 8.42 mmol) and CH_3OH (20 mL) was added $NaOCH_3$ (3 g, 56 mmol). The slurry was stirred vigorously for 3 h, then poured into water (40 mL), and made slightly acidic to litmus with a 6 M solution of HCl. The phenol was extracted with Et_2O (3 × 25 mL), and the combined Et_2O was worked up to give the phenol as an orange oil contaminated with desilylated bibenzyl from the Grignard reaction. Chromatography on silica gel (4 × 10 cm column, 10% Et_2O/PE as eluant) afforded the phenol (1.24 g) as a pale yellow oil (61%): IR (NaCl plate) 3530 (m, br), 1500 (m), 1490 (m), 1455 (s), 1425 (m), 1250 (s), 1220 (m, sh), 1170 (m), 1155 (m), 1110 (s) 850 (s), 830 (s), 750 (s), 730 (s), 695 cm^{-1} (s); ^1H NMR δ 7.53–7.30 (m, 5 H), 6.97–6.63 (m, 4 H), 4.29 (s, 1 H), 2.28 (s, 2 H), 0.28 (s, 6 H); mass spectrum, exact mass calcd for $C_{15}H_{18}OSi$ m/e 242.1127, obsd 242.1121.

2,2-Dimethyl-2-silabenzofuran (29). Dry HBr was bubbled continuously through a stirred solution of the phenol (1.015 g, 4.194 mmol) and $CHCl_3$ (25 mL) for 2 h at 25 °C. Next, a stream of dry nitrogen was passed over the reddish solution which was warmed to 45 °C until the solution volume was ca. 5 mL. Continued concentration in vacuo, followed by molecular distillation (1.5 Torr, bath 78 °C), gave the cyclic silyl ether **29** (490 mg, 71%). The IR spectrum of this oil showed an OH stretch, indicating some decomposition of the silyl ether. An analytical sample was obtained by preparative GLPC (12 × 0.125 in. column, 5% OV-101, Chromosorb W/HP 80/100 mesh, temperature programmed from 140 to 180 °C): IR (NaCl plate) 1600 (m), 1580 (m), 1480 (s), 1460 (s), 1280 (m), 1260 (s), 1230 (s), 1125 (s), 875 (s), 850 (s), 825 (s), 750 cm^{-1} (s); ^1H NMR δ 7.17–6.72 (m, 4 H), 2.07 (s, 2 H), 0.40 (s, 6 H); mass spectrum, exact mass calcd for $C_9H_{12}OSi$ m/e 164.0657, obsd 164.0669.

1,4-Cyclohexanedione *tert*-Butyldimethylsilyl Methyl Ketal (30). To a slurry of 5% Pd/C (0.1 g) in absolute CH_3CH_2OH (20 mL) was added methyl silyl quinone monoketal (2.00 g, 7.87 mmol), and the mixture was hydrogenated in a Parr apparatus at a pressure of 60 psig for 1 h. Workup gave the cyclohexanedione monoketal (2.01 g, 99%), pure by ^1H NMR analysis. An analytical sample was obtained by GLPC (120 × 0.125 in. column, 5% OV-101 on Chromosorb W, 150 °C): IR (NaCl plate) 2960 (m), 2930 (m), 1725 (s), 1255 (m), 1130 (m), 1100 (m), 1055 (m), 835 (m), 775 cm^{-1} (m); ^1H NMR δ 3.32 (s, 3 H), 2.5–2.3 (br, 4 H), 2.2–1.9 (br, 4 H), 0.91 (s, 9 H), 0.15 (s, 6 H); mass spectrum, exact mass calcd for $C_{12}H_{23}O_2Si$ ($M^+ - CH_3O$) m/e 227.1467, obsd 227.1490.

Cyclohexanone *tert*-Butyldimethylsilyl Methyl Ketal (31). To solution of cyclohexanedione monoketal (0.500 g, 1.94 mmol) and CH_3OH (5 mL) was added (*p*-tolylsulfonyl)hydrazine (0.400 g, 2.15 mmol). TLC analysis showed that hydrazone formation was complete after 15 min. The solution was cooled to 0 °C, and $NaBH_4$ (0.4 g, 10 mmol) was added cautiously in portions. When gas evolution subsided, the mixture was heated to reflux for 2 min, cooled, poured into water (30 mL), and extracted with hexane (2 × 15 mL). Workup gave the cyclohexanone methyl silyl ketal (0.400 g, 85%) as a clear oil, containing only minor, volatile impurities by GC analysis (0.125 × 12 in. column, 5% OV-101 on Chromosorb W, 140 °C). Preparative GC (same column/conditions) afforded the analytical sample: IR (NaCl plate) 2940 (s), 2860 (s), 1250 (s), 1105 (s), 1055 (s), 1000 (s), 830 (s), 770 cm^{-1} (s); ^1H NMR δ 3.20 (s, 3 H), 1.7–1.3 (br, 10 H), 0.89 (s, 9 H), 0.11 (s, 6 H); mass spectrum, exact mass calcd for $C_{13}H_{28}O_2Si$ m/e 244.1858, obsd 244.1851.

General Procedure for Kinetics of Cyclohexanone Ketal Hydrolysis. To a 25 °C solution of THF (0.75 mL) and 15% aqueous acetic acid (0.50 mL) in a capped UV cell was injected the ketal, giving a final bisketal concentration of ca. 0.01 M. The mixture was stirred and placed into the spectrophotometer, and the increase in the optical density was monitored at 295 nm. The rate constants were determined as described above. The rate constant measured for the methyl *tert*-butyldimethylsilyl ketal of cyclohexanone under these conditions was 8.23×10^{-2} s^{-1} while that for the dimethyl ketal of cyclohexanone was 7.15×10^{-2} s^{-1}.

Acknowledgment. We acknowledge partial support from the National Science Foundation and the National Institutes of Health and thank Professors Eliel, Tidwell, and Kresge for helpful comments.

Supplementary Material Available: Preparation of 3-bromo-4,5-dimethylbenzoic acid, 3,4,5-trimethylbenzoic acid, *p*-(*tert*-butyldimethylsiloxy)benzaldehyde, *p*-(*tert*-butyldimethylsiloxy)benzoic acid, and *o*-cresol *tert*-butyldimethylsilyl ether and representative kinetic data and plots (6 pages). Ordering information is given on any current masthead page.

Bacterial Sterol Surrogates. Determination of the Absolute Configuration of Bacteriohopanetetrol Side Chain by Hemisynthesis of Its Diastereoisomers

Philippe Bisseret* and Michel Rohmer

Ecole Nationale Supérieure de Chimie de Mulhouse, 3, rue Alfred Werner, F-68093 Mulhouse Cedex, France

Received December 8, 1988

The 32*R*,33*R*,34*S* configuration of the side chain of bacteriohopanetetrol, a representative compound of a wide-spread bacterial triterpenoid series, was established by correlation with the eight synthetic stereoisomers.

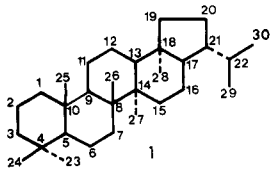
Triterpenoids derived from the pentacyclic hopane skeleton (1) or hopanoids are widely distributed in bacteria[1] and were first known from their ubiquitous molecular fossils in the organic matter of all sedimentary rocks.[2] Numerous experiments performed on biological membrane models as well as on several biological systems have shown that the prokaryotic hopanoids act much more like the sterols from eukaryotes, i.e. as membrane stabilizers.[3]

(1) Rohmer, M.; Bouvier-Navé, P.; Ourisson, G. *J. Gen. Microbiol.* **1984**, *130*, 1137.

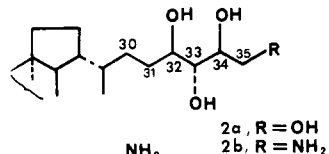
(2) Ourisson, G.; Albrecht, P.; Rohmer, M. *Pure Appl. Chem.* **1979**, *51*, 709.

0022-3263/89/1954-2958$01.50/0

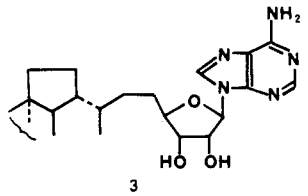
Bacteriohopanetetrol (**2a**) possess the C_5 polyhydroxylated unit encountered in all major prokaryotic triterpenoids.[4] Until recently, the absolute configuration of the three asymmetric centers of this unit remained unknown. The chemical correlation of adenosylhopane (**3**) isolated from the purple bacterium *Rhodopseudomonas acidophila* with bacteriohopanetetrol (**2a**)[4h] supported a configuration in C-32, C-33, and C-34 similar to the one resulting from the attachment of a D-ribose through its terminal C-5 carbon atom to the hopane skeleton, i.e. 32*R*, 33*R*, and 34*S*.



1



2a, R = OH
2b, R = NH_2



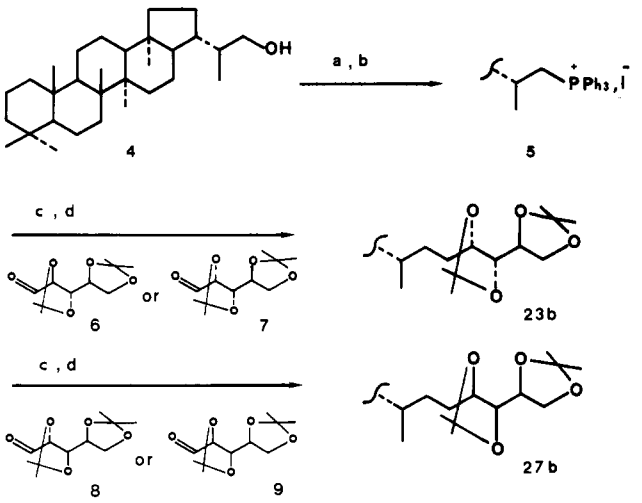
3

To establish the configuration of this important structural feature of many hopanoids, we decided to prepare the eight different bacteriohopanetetrol side chain diastereomers. A direct condensation with a protected *aldehydo*-pentose has been employed in the synthesis of guggultetrols[5] and in the elaboration of the tetrahydroxypentane portion of methanopterin.[6] We have found that such a linkage to the hopane skeleton at C-30 was of limited value and could be advantageously replaced by a step-by-step construction outlined in Scheme II.

Results and Discussion

Direct Condensation on Hopane Skeleton at C-30 (Scheme I). Using Rydon's iodination,[7] the starting hopanol (**4**) was easily converted to an iodide. The obtention of the phosphonium salt (**5**) proved unsuccessful by the classical way of prolonged reflux of a toluene or an acetonitrile solution of the iodo compound with an excess of triphenylphosphine, reflecting the steric hindrance due to the hopane skeleton. On the other hand, heating the iodide with an excess of melted triphenylphosphine under solvent-free conditions quantitatively gave the required phosphonium iodide. This procedure has been used for the preparation of diphosphonium salts from dihalides[8] but is rarely used for the obtention of simple phosphonium salts.[9] Wittig condensation of the ylide derived from **5** with the four diisopropylidene-*aldehydo*-pentoses (**6–9**),[5a] followed by hydrogenation, gave only diacetonide **23b** in 8% yield from either **6** or **7** and only diacetonide **27b** in 8% yield from either **8** or **9**. The Wittig condensations

Scheme I[a]



[a] (a) $(PhO)_3P^+Me$, I^- (THF, DMF, HMPT), 20 °C, 3 h; (b) Ph_3P (4 equiv), 140 °C, 30 min; (c) *n*-BuLi (THF, HMPT), 20 °C, 15 min, then aldehydopentose–diacetonide; (d) H_2, PtO_2 (EtOAc), 20 °C, 18 h.

with **5** were disappointing not only because of their very low yield but also because of an epimerization at carbon 2 of *aldehydo*-ribose **6** and -lyxose **8**, leading to tetrol derivatives **23b** and **27b** of respectively 32*S*,33*R*,34*S* and 32*R*,33*S*,34*S* configuration instead of the expected 32*R*,33*R*,34*S* and 32*S*,33*S*,34*S* isomers.

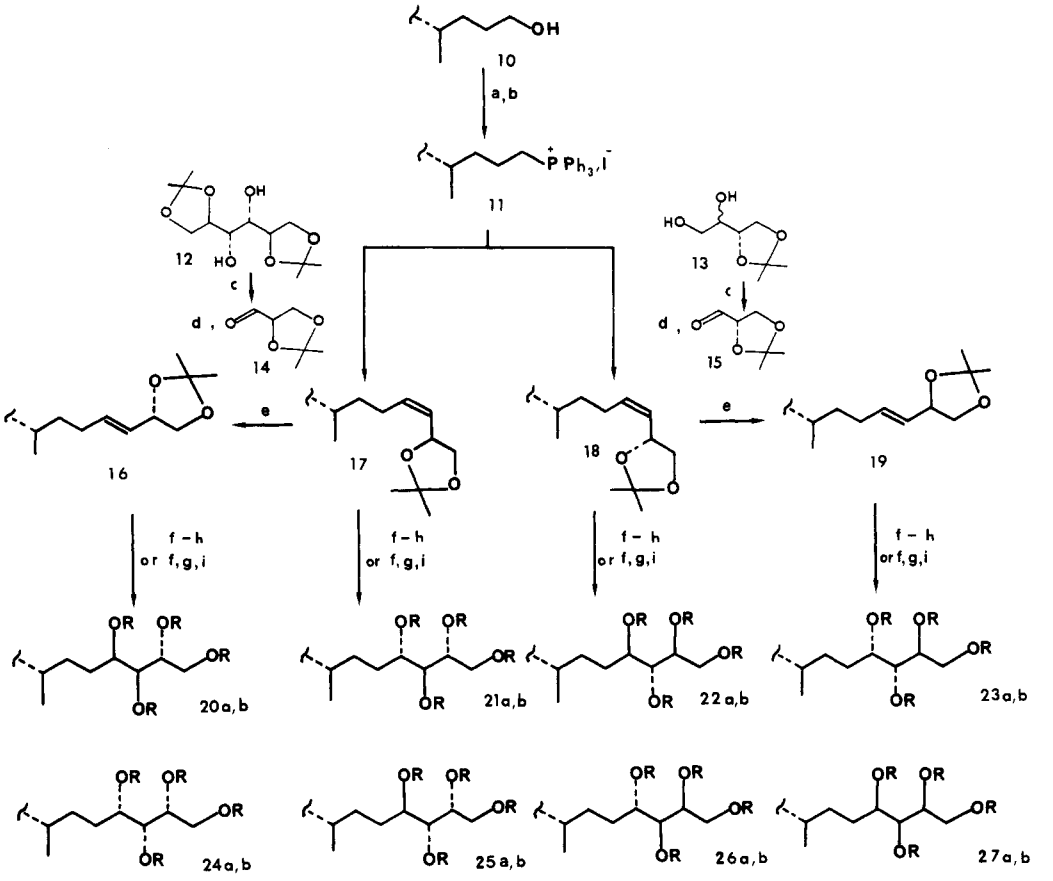
High-field NMR spectra of the diacetonides obtained from *aldehydo*-ribose **6** and -arabinose **7** were superposable to the spectrum of (32*S*,33*R*,34*S*)-diacetonide **23b** obtained stereospecifically (see Scheme II); similarly, the spectra of the diacetonides produced from **8** and **9** were identical with the spectrum of (32*R*,33*S*,34*S*)-diacetonide **27b**. Although not mentioned during the preparation of the guggultetrol diastereoisomers,[5a] such an epimerization has been reported in the literature.[9a,10] It would result from an enolization of the aldehydes under basic conditions, leading on one hand to the most stable aldehyde and offering on the other hand in the case of sterically hindered Wittig reactions, the priority of forming *aldehydo*-pentoses bearing the less hindered configurations. Since the majority of the products isolated under the Wittig conditions turned out to result from the decomposition of the phosphonium salt **5** (i.e. olefins, C_{30} iodide), we decided to switch to a more elegant step-by-step preparation, motivated in other respects by the recent access to several bacteriohopane derivatives, including amino triol **2b**, from large scale fermentations.

Condensations at Carbon C-32. The eight required diastereoisomers were successfully prepared as tetracetates (**20a–27a**) and diacetonides (**20b–27b**) from 2-(30′-hopyl)ethanol (**10**) making use of (*R*)- and (*S*)-isopropylideneglyceraldehydes **14** and **15** as outlined in Scheme II. The key reaction here is Kishi's well-documented stereoselective osmylation.[5a,11]

In the presence of an excess of the Rydon's salt, in a dipolar aprotic medium, precipitation of C_{32} iodide was almost immediate from **10**. The preparation of phosphonium iodide **11** was best accomplished under solvent-free

(3) Rohmer, M. In *Surface structures of microorganisms and their interaction with the mammalian host*; Schrinner, E., Richmond, M. H., Seibert, G., Schwarz, U., Eds.; Verlag Chemie: Weinheim, 1988; pp 227–242.
(4) (a) Förster, H. J.; Biemann, K.; Haigh, W. G.; Tattrie, N. H.; Colvin, J. R. *Biochem. J.* **1975**, *135*, 133. (b) Rohmer, M.; Ourisson, G. *Tetrahedron Lett.* **1976**, 3633. (c) Langworthy, T. A.; Mayberry, W. R.; Smith, P. F. *Biochim. Biophys. Acta* **1976**, *431*, 550. (d) Renoux, J. M.; Rohmer, M. *Eur. J. Biochem.* **1985**, *151*, 405. (e) Neunlist, S.; Rohmer, M. *Biochem. J.* **1985**, *228*, 769. (f) Neunlist, S.; Holst, O.; Rohmer, M. *Eur. J. Biochem.* **1985**, *147*, 561. (g) Rohmer, M.; Ourisson, G. *J. Chem. Res. (S)* **1986**, 356. (h) Neunlist, S.; Bisseret, P.; Rohmer, M. *Eur. J. Biochem.* **1988**, *171*, 245.
(5) (a) Kumar, V.; Dev, S. *Tetrahedron* **1987**, *43*, 5933. (b) Kjaer, A.; Kjaer, D.; Skrydstrup, T. *Tetrahedron* **1986**, *42*, 1439.
(6) White, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 6434.
(7) Landauer, S. R.; Rydon, H. N. *J. Chem. Soc.* **1953**, 2224.
(8) Maercker, A. *Org. React.* **1965**, *14*, 270.
(9) (a) Lichtenthaler, F. W.; Lorenz, K.; Ma, W. Y. *Tetrahedron Lett.* **1987**, *28*, 47. (b) Cunningham, J.; Gigg, R. *J. Chem. Soc.* **1965**, 2968.
(10) Freeman, F.; Robarge, K. D. *Carbohydr. Res.* **1986**, *154*, 270.
(11) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

Scheme II[a]



[a] (a) $(PhO)_3P^+Me$, I^- (THF, DMF, HMPT), 20 °C, 15 min; (b) Ph_3P (3 equiv), 140 °C, 20 min; (c) A-26, IO_4^-; (d) *n*-BuLi (THF, HMPT), 20 °C, 5 min; (e) $(PhS)_2$, $h\nu$ (C_6H_{12}), 30 °C, 20 min; (f) OsO_4, NMO (THF), 20 °C, 18 h; (g) $HClO_4$ aqueous 10% (THF, MeOH), 20 °C, 12 h; (h) Ac_2O, Py (1:1, v/v), 20 °C, 12 h; (i) acetone, $FeCl_3$, 20 °C, 12 h. A letter a following a figure refers to tetracetate derivatives (R = Ac) obtained by steps f–h; a letter b to 32,33-, 34,35-diacetonide derivatives obtained by steps f, g, i.

conditions as described for the obtention of **5**. The next step required a convenient access to small-scale preparations of optically pure glyceraldehyde derivatives **14** and **15** compatible with Wittig reactions involving less than 0.1 mmol of phosphonium salt, owing to the relative scarcity of the starting hopanol **10**. For this purpose, neither the reported final purification of **14** and **15** by distillation[12] nor their TLC purification on Et_3N desactivated silica were appropriate. Indeed, the latter method gave at least 5% epimerization of the aldehydes as shown after analysis of the corresponding alcohols by Mosher's method.[13] We finally adapted two published preparations of **14** and **15**[14,15] by making use of resin-supported reagents (Scheme II).[16]

In the case of the delicate preparation of enantiomer **15**,[12] (*S*)-erythrulose turned out to be the starting molecule of choice. Other small-scale preparations from ascorbic acid[17] or by Swern oxidation[18] of commercial (*R*)-isopropylideneglycerol failed, leading respectively to very low yields and to optically impure aldehyde.[19] The glyceraldehydes prepared as described proved to be of 100% enantiomeric purity (Mosher's method[13]). Owing to their well-known instability,[12] they were used just after isolation. Contrary to the results with phosphonium **5**, Wittig reactions at C-32 with **11** proceeded with satisfactory yields to give olefins **17** and **18** of almost exclusive (>90%) *Z* configuration. Isomerization to *E* compounds **16** and **19** was achieved photochemically in the presence of diphenyl disulfide.[20] At this stage the optical purity of the *Z* olefins **17** and **18** at C-34 was checked by 100-MHz ^{13}C NMR spectroscopy with no detectable cross-contamination (5%).

Cis hydroxylation of the olefins using osmium tetraoxide and *N*-methylmorpholine oxide as a cooxidant took advantage of the empirical rule of Kishi: the regioselectivity observed was that reported for other α,β-unsaturated isopropylidenes.[11]

As tetrol derivatives, diacetonides **20b–27b** and tetracetates **20a–27a** were prepared. For analysis and differentiation of these diastereoisomers, neither mass spectrometry nor IR was informative, showing no significant differences between compounds. Only a poor differentiation between diacetonides with enantiomeric side chains, i.e. **20b** and **23b**, **21b** and **22b**, **24b** and **27b**, and **25b** and **26b**, was found in high-field ^1H NMR spectroscopy.

(12) For a recent review on the chemistry of (*R*)- and (*S*)-2,3-*O*-isopropylideneglyceraldehyde, see: Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.
(13) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(14) Le Cocq, J.; Ballou, C. E. *Biochemistry* **1968**, *33*, 728.
(15) De Wilde, H.; De Clercq, P.; Vandewalle, M.; Roper, H. *Tetrahedron Lett.* **1987**, *28*, 4757.
(16) Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1985**, *26*, 1305.
(17) (a) Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304. (b) Takano, S.; Numata, H.; Ogasawara, K. *Heterocycles* **1982**, *19*, 327.
(18) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.
(19) For an example of epimerization during a Swern oxidation, see ref 4b.
(20) Sonnet, P. E. *Tetrahedron* **1980**, *77*, 557.

Table I. Selected ^1H NMR (400 MHz, $CDCl_3$) Chemical Shifts[a]

compd (config C-32, C-33, C-34)	C-18β[b] C-14α	C-18α	C-22	32-H	33-H	34-H	35-Ha	35-Hb	acetate(s)
tetracetates natural product (*R,R,S*)	0.949 (2 s)	0.688 (s)	0.909 (d, *J* = 6.3)	5.03 (dt, *J* = 4.0, 9.5)	5.23 (dd, *J* = 4.0, 6.0)	5.27 (dt, *J* = 2.5, 6 .0)	4.15 (dd, *J* = 6.5, 12.0)	4.39 (dd, *J* = 2.5, 12.0)	2.057, 2.077 2.084, 2.090
22a (*R,R,S*)	0.949 (2 s)	0.688 (s)	0.909 (d, *J* = 6.3)	5.03 (dt, *J* = 4.0, 9.5)	5.23 (dd, *J* = 4.0, 6.0)	5.27 (dt, *J* = 2.5, 6.0)	4.15 (dd, *J* = 6.5, 12.0)	4.39 (dd, *J* = 2.5, 12.0)	2.057, 2.078 2.085, 2.090
21a (*S,S,R*)	0.947 (s) 0.952 (s)	0.691 (s)	0.926 (d, *J* = 6.4)	5.01 (dt, *J* = 4.0, 9.0)	5.23 (dd, *J* = 4.0, 6.0)	5.29 (ddd, *J* = 2.5, 6.0, 16.5)	4.15 (dd, *J* = 6.4, 12.0)	4.40 (dd, *J* = 2.5, 12.0)	2.058, 2.080 2.084, 2.090
26a (*S,S,S*)	0.944 (s) 0.949 (s)	0.685 (s)	0.902 (d, *J* = 6.4)	5.01 (dt, *J* = 3.3, 7.5)	5.25 (dd, *J* = 3.3, 7.3)	5.36 (ddd, *J* = 5.0, 7.0, 7.3)	3.96 (dd, *J* = 7.0, 11.7)	4.24 (dd, *J* = 5.0, 11.7)	2.041, 2.057 2.088, 2.128
25a (*R,R,R*)	0.947 (2 s)	0.688 (s)	0.896 (d, *J* = 6.4)	5.02 (dt, *J* = 3.0, 11.0)	5.24 (dd, *J* = 3.0, 7.0)	5.34 (m)	3.96 (dd, *J* = 7.0, 11.6)	4.24 (dd, *J* = 5.0, 11.6)	2.040, 2.058 2.088, 2.132
23a (*S,R,S*)	0.942 (s) 0.949 (s)	0.690 (s)	0.906 (d, *J* = 6.4)	5.13 (m)	5.30 (dd, *J* = 2.0, 8.0)	5.13 (m)	4.13 (dd, *J* = 5.0, 12.5)	4.23 (dd, *J* = 2.5, 12.5)	2.064, 2.066 2.073, 2.144
20a (*R,S,R*)	0.947 (2 s)	0.689 (s)	0.902 (d, *J* = 6.3)	5.12 (m)	5.30 (dd, *J* = 3.0, 8.0)	5.12 (m)	4.14 (dd, *J* = 5.0, 12.5)	4.24 (dd, *J* = 3.0, 12.5)	2.062, 2.065 2.074, 2.137
27a (*R,S,S*)	0.951 (2 s)	0.692 (s)	0.899 (d, *J* = 6.4)	5.05 (m)	5.27 (m)	5.27 (m)	3.97 (dd, *J* = 5.0, 12.0)	4.36 (dd, *J* = 3.5, 12.0)	2.062, 2.086 2.090, 2.105
24a (*S,R,R*)	0.944 (s) 0.950 (s)	0.688 (s)	0.909 (d, *J* = 6.3)	5.04 (m)	5.30 (m)	5.30 (m)	3.96 (dd, *J* = 5.0, 12.0)	4.38 (dd, *J* = 3.5, 12.0)	2.064, 2.087 2.094, 2.111

[a] Chemical shifts are given as δ values with three significant figures in the case of sharp peaks only; *J* values in hertz; δ values for the not-listed methyl groups are the same for all compounds, i.e. C-4β, 0.796 (s), C-4α, 0.817 (s), C-10β, 0.851 (s). [b] In case of two singlets, interchangeable assignments.

Table II. ^{13}C NMR (100 MHz, $CDCl_3$) Assignments[a] of Tetracetates

carbon[b]	natural product	**22a**	**21a**	**26a**	**25a**	**23a**	**20a**	**27a**	**24a**
20	27.4	27.4	27.4	27.3	27.4	27.3	27.4	27.4	27.3
21	45.9	45.8	45.7	45.6	45.8	45.8	45.7	45.7	45.6
22	36.0	36.0	36.5	36.3	36.2	36.5	36.3	36.1	36.4
25	15.8	15.7*	15.8	15.7*	15.7*	15.8	15.6*	15.7*	15.8
28	15.8	15.8*	15.8	15.8*	15.8*	15.8	15.8*	15.8*	15.8
29	19.7	19.7	19.9	20.0	19.7	19.8	19.8	19.7	19.8
30	30.8	30.8	31.1	30.6	30.5	30.9	30.7	30.5	30.6
31	26.2	26.1	26.4	26.7	26.7	27.5	27.2	26.9	27.0
32	69.5	69.4	69.4	68.2	68.2	68.4	68.4	69.4	69.5
33	71.6	71.5	71.5	70.8	70.3	70.0	70.4	71.2	70.9
34	71.9	71.9	72.6	71.0	71.1	71.2	70.9	71.6	72.1
35	62.1	62.0	62.0	62.0	62.0	61.9	61.9	61.9	61.9
	169.6	169.6	169.6	169.8	169.8	169.7	169.7	169.8	169.8
acetate	169.8	169.8	169.8	170.0	170.0	169.8	169.8	169.9	169.9
carbonyl	170.2	170.2	170.2	170.1	170.1	170.4	170.5	170.2	170.3
groups	170.5	170.5	170.5	170.4	170.4	170.5	170.5	170.3	170.2
acetate	20.6	20.6	20.6	20.6 (2)	20.6 (2)	20.6	20.5	20.5	20.5
methyl	20.7	20.7	20.7	20.7	20.7	20.8 (3)	20.6	20.6	20.6
groups	20.8 (2)	20.8 (2)	20.8 (2)	20.8	20.8		20.8 (2)	20.7	20.7
								20.8	20.8

[a] Assignments marked with an asterisk can also be reversed; chemical shifts are given as δ values. [b] δ values for the carbons not listed are identical for all the compounds, i.e. C-1 (40.2), C-2 (18.6), C-3 (42.0), C-4 (33.2), C-5 (56.0), C-6 (18.6), C-7 (33.2)$^+$, C-8 (41.6)$^{++}$, C-9 (50.3), C-10 (37.3), C-11 (20.8), C-12 (23.9), C-13 (49.2), C-14 (41.7)$^{++}$, C-15 (33.6), C-16 (22.6), C-17 (54.3), C-18 (44.3), C-19 (41.5), C-23 (33.3)$^+$, C-24 (21.5), C-26 (16.4)$^{+++}$, C-27 (16.5)$^{+++}$; assignments bearing the same superscript may be interchanged.

The 400-MHz ^1H NMR data of the synthetic tetracetates were more informative as shown Table I. Matching spectra correspond to pairs of compounds bearing enantiomeric side chains, i.e. **20a** and **23a**, **21a** and **22a**, **24a** and **27a**, and **25a** and **26a**. The difference between each pair of spectra is best noted by inspection of their acetate methyl shifts. For each pair, the most clear-cut difference appears in the chemical shift of the doublet corresponding to the methyl group at C-22, ranging from 0.017 to 0.004 ppm.

Larger amounts of each one of the eight diastereoisomers were needed in order to measure their ^{13}C NMR data and optical rotations. Kishi's osmylation of allylic acetonides, though of essential diagnostic value, was inadequate to prepare sufficient material of the minor derivatives **24–27**. For that purpose we repeated the osmylation on the diols obtained after acidolysis of the acetonides **16–19**.[21] This should result in little or no regioselectivity.[11] This proved to be the case since after acetylation and careful TLC separation we obtained approximative ratios of **21a**/**25a** = **22a**/**26a** = 1 and **20a**/**24a** = **23a**/**27a** = 2. All ^{13}C NMR data for the eight tetracetates are presented Table II. The chemical shifts of carbon atoms C-32, C-33, C-34, and C-35 from the side chain are especially valuable as they differ one from another by at least one clear-cut value even for compounds with enantiomeric side chains.

(21) These acidolyses were quantitatively effected by treating the acetonides **16–19** in presence of acidic resin Amberlyst A-15 (20 °C, 12 h, THF–MeOH, 1:1, v/v).

These hemisyntheses provided the eight bacteriohopanetetrol diastereoisomers of different side-chain configuration. Each diastereoisomer could be differentiated one from another by comparison of the ^1H and ^{13}C high-field NMR spectra of their tetracetates. This enabled us to confirm that the tetrol samples isolated until now from bacteria were homogeneous and not contaminated by detectable amounts of other stereoisomers and to assign unambiguously the 32*R*, 33*R*, and 34*S* configuration to the natural tetrol after its comparison with the hemisynthetic compounds[4h,22] (melting point, $[\alpha]_D$, TLC, ^1H and ^{13}C NMR of tetracetates and melting point, TLC, ^1H NMR of diacetonides). This configuration is in full accordance with the results obtained from labeling experiments. Indeed, incorporation of ^{13}C-labeled acetate into the bacteriohopane derivatives of several bacteria showed that the polyhydroxylated C_5 unit arises from a D-ribose derivative issued from the nonoxidative pentose phosphate cycle and linked via its C-5 carbon atom to the hopane skeleton.[23]

These synthetic tetrol stereoisomers will serve in the future as reference material for the tetrol derivatives found in microorganisms or those isolated from geological sedimentary rock samples.[24]

Experimental Section

General Methods. Melting points of recrystallized compounds (CH_2Cl_2/MeOH) were measured on a Reichert-Jung micro hot stage apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker W200 or a Bruker W400 spectrometer with $CHCl_3$ (δ = 7.270 ppm) as internal standard for ^1H NMR or $CDCl_3$ (δ = 76.90 ppm) for ^{13}C NMR analysis. Signal assignments were supported by comparison with published hopanoid spectra.[4,25] Mass spectra were recorded in the electron-impact mode on a LKB 9000 S spectrometer after deposition of the sample on a tungsten wire. Optical rotations were determined on a Perkin-Elmer 241 MC spectropolarimeter at 24 °C (1-dm cell, $CHCl_3$ solution). IR spectra were measured on a Perkin-Elmer 781 spectrometer in CCl_4. For analytical TLC, we used Merck glass-backed silica gel plates 60 F-254 with a silica gel thickness of 0.25 mm; after development, the spots were visualized at 366 nm after aspersion with a 0.2% ethanolic solution of berberin chlorhydrate. For preparative purposes, compounds were purified either on the above commercial plates or on homemade glass-backed Merck 60 PF-254 silica gel plates (20 × 20 cm, silica gel thickness of 1 mm) depending on the quantities of compounds. All air- and moisture-sensitive reactions were run under argon in oven-dried or flame-dried glassware. Photoreactions were performed with a low-pressure Hg lamp under argon gas.

Materials. Di-*O*-isopropylidenealdehydopentoses **6–9** were obtained from the corresponding pentoses (FLUKA) as already described.[5b] (22*S*)-Hopan-30-ol (**4**) and 2-(30′-hopyl)ethanol (**10**) were prepared as before.[4h,b] L-(*S*)-Erythrulose (98% pure) was purchased from Aldrich and dried *prior* to use by solvent evaporation of toluene–MeOH solutions. Di-*O*-isopropylidene of D-mannitol was purchased from Fluka. Before use in moisture-sensitive reactions, THF was distilled from lithium aluminum hydride, DMF and HMPT from CaH_2, pure acetone was allowed to stand 12 h in presence of 3-Å molecular sieves.

(22*S*)-30-Hopyl Iodide. To hopan-30-ol (**4**; 60 mg, 0.14 mmol) in solution in THF (3 mL), DMF (1 mL), and HMPT (0.2 mL) was added methyltriphenoxyphosphonium iodide (80 mg, 0.17 mmol). After 3 h in the dark at 20 °C, evaporation of THF, and TLC purification (eluent, Cy–EtOAc–NEt_3, 85:10:5), we obtained the iodo compound as a white solid (55 mg, 73%): mp 221–222 °C dec; ^1H NMR (200 MHz) δ 0.705 (3, s, 18α-CH_3), 0.797 (3, s, 4β-CH_3), 0.819 (3, s, 4α-CH_3), 0.852 (3, s, 10β-CH_3), 0.952 (6, s, 8β- and 14α-CH_3), 1.042 (3, d, J = 6.5 Hz, 22-CH_3), 3.21 (1, dd, J = 5.5 Hz, 10.0 Hz, 30-Ha), 3.33 (1, dd, J = 3.0 Hz, 10.0 Hz, 30-Hb); mass spectrum, m/z (relative intensity) 538 (M^+, 100), 523 (M^+ – Me, 18), 412 (2), 369 (M^+ – side chain, 11), 317 (ring C cleavage,[26] 71), 191 (ring C cleavage, 45).

Hopyltriphenylphosphonium Iodide (5). Hopyl iodide (40 mg, 0.075 mmol) was mixed in a mortar with triphenylphosphine (80 mg, 0.3 mmol). Heating under Ar for 30 min at 140 °C and washing with cold CCl_4 gave a quantitative yield of the desired phosphonium **5**: ^1H NMR (200 MHz) δ 0.284 (3, s, 18α-CH_3), 0.779 (3, s), 0.790 (3, s), 0.830 (6, s), 0.905 (3, s), 1.058 (3, d, J = 6.5 Hz, 22-CH_3), 3.05 (1, t, J = 15 Hz, 30-Ha), 4.25 (1, t, J = 15 Hz, 30-Hb), 7.8 (15, m, aromatic protons).

Wittig Condensation at C-30: General Procedure. To a stirred suspension of phosphonium iodide **5** (20 mg, 0.025 mmol) in THF (1 mL) was added dropwise at 20 °C under Ar a hexane solution of *n*-BuLi (1.6 M) until the medium becomes homogeneous and deep blood-red (ca. 200 μL). Further addition of HMPT (4 drops) resulted in an even darker solution. After 15 min, a THF solution (1 mL) of aldehyde (**6–9**; 25 mg) was introduced dropwise with good stirring at 30 °C; 10 min later, water was added (ca. 0.2 mL). After TLC separation (eluent, hexane–EtOAc, 98:2, v/v), the olefins were hydrogenated (H_2; PtO_2; EtOAc–Cy, 5:1, v/v; 20 °C; 12 h) to give after a final TLC the diacetonide **23b** (1.2 mg, 8%) starting from **6** and **7** or **27b** (1.2 mg, 8%) from **8** and **9**. Melting point and ^1H NMR (200 MHz) data were similar to those of **23b** and **27b** prepared by Wittig condensation at C-32.

2-(30′-Hopyl)ethyl Iodide. To 2-(30′-hopyl)ethanol (**10**; 200 mg, 0.44 mmol) in solution in THF (10 mL), DMF (2 mL), and HMPT (1 mL) was added methyltriphenoxyphosphonium iodide (0.4 g, 0.88 mmol). One minute after the dissolution of the solids, the required iodide begins to precipitate. After 15 min at 20 °C, cold MeOH (ca. 5 mL) was added to complete the precipitation. Final washing with MeOH and drying under vacuum yielded the iodide as a white solid (220 mg, 90%); mp 224.5–226 °C dec; ^1H NMR (200 MHz) δ 0.711 (3, s, 18α-CH_3), 0.796 (3, s, 4β-CH_3), 0.819 (3, s, 4α-CH_3), 0.851 (3, s, 10β-CH_3), 0.937 (3, d, J = 6.5 Hz, 22-CH_3), 0.953 (6, s, 8β- and 14α-CH_3), 3.11 (1, dd, J = 6.5 Hz, 9.0 Hz, 32-Ha), 3.25 (1, dd, J = 6.5 Hz, 9.0 Hz, 32-Hb); mass spectrum, m/z (relative intensity) 566 (M^+, 100), 551 (M^+ – Me, 11), 440 (7), 438 (M^+ – HI, 6), 369 (M^+ – side chain, 17), 345 (ring C cleavage, 70), 219 (16), 217 (7), 191 (ring C cleavage, 53).

[2-(30′-Hopyl)ethyl]triphenylphosphonium Iodide (11). The preceding iodide (200 mg, 0.35 mmol) was mixed in a mortar with triphenylphosphine (0.4 g, 1.5 mmol). Heating under Ar for 20 min at 140 °C and washing with cold CCl_4 gave a quantitative yield of the desired phosphonium **11**: mp 308–311 °C; ^1H NMR (200 MHz) δ 0.637 (3, s, 18α-CH_3), 0.803 (6, s), 0.839 (3, s), 0.912 (6, s), 3.75 (2, m, 32-H), 7.8 (15, m, aromatic protons).

Wittig Condensation at C-32: General Procedure. To a stirred suspension of phosphonium iodide **11** (150 mg, 0.18 mmol) in THF (4 mL) was added dropwise at 20 °C under Ar a hexane solution of *n*-BuLi (1.6 M) until the coloration turns blood-red (ca. 0.4 mL). Further addition of HMPT (5 drops) resulted in a darker solution. After 5 min, a THF (2 mL) solution of freshly prepared aldehyde (**14** or **15**; 70 mg; for obtention, see after) was injected dropwise at 20 °C with good stirring and was followed by a total decoloration of the medium. After addition of water (0.5 mL) and TLC purification (2×: hexane, EtOAc, 98:2, v/v), the required olefins **17** or **18** (50 mg; 50%) and **16** or **19** (3 mg, 6%) were obtained as white solids.

16: mp 159–160 °C; ^1H NMR (400 MHz) δ 0.698 (3, s, 18α-CH_3), 0.795 (3, s, 4β-CH_3), 0.818 (3, s, 4α-CH_3), 0.851 (3, s, 10β-CH_3), 0.927 (3, d, J = 6.3 Hz, 22-CH_3), 0.951 (6, s, 8β- and 14α-CH_3), 1.391 (3, s, Me from acetonide), 1.429 (3, s, Me from acetonide), 1.92 (1, m), 2.11 (1, m), 3.554 (1, t, J = 8.0 Hz, 35-Ha), 4.06 (1, dd, J = 6.0 Hz, 8.0 Hz, 35-Hb), 4.46 (1, dt, J = 6.0 Hz, 8.0 Hz, 34-H), 5.42 (1, dd, J = 8.0 Hz, 15.5 Hz, 33-H), 5.79 (1, dt, J = 6.5 Hz, 15.5 Hz, 32-H); mass spectrum, m/z (relative intensity) of the corresponding 34,35-diol, 512 (M^+, 45), 497 (M^+ – Me, 15), 494 (M^+ – H_2O, 27), 479 (M^+ – Me – H_2O, 16), 369 (M^+ – side chain, 16), 367 (49), 291 (36), 273 (ring C cleavage, 41), 256 (47),

(22) Renoux, J. M. Thèse de Docteur-Ingénieur, Université de Haute Alsace, Mulhouse, France, 1984.
(23) (a) Flesch, G.; Rohmer, M. *Eur. J. Biochem.* **1988**, *175*, 405. (b) Flesch, G.; Rohmer, M. *J. Chem. Soc., Chem. Commun.* **1988**, 868.
(24) Mycke, B.; Narjes, F.; Michaelis, W. *Nature* **1987**, *326*, 179.
(25) Wilkins, A. L.; Bird, P. W.; Jager, P. M. *Magn. Reson. Chem.* **1987**, *25*, 503.
(26) Budzikiewicz, H.; Wilson, J. M.; Djerassi, C. *J. Am. Chem. Soc.* **1963**, *85*, 3688.

242 (15), 236 (13), 231 (16), 228 (16), 213 (13), 191 (ring C cleavage, 100); IR (CCl_4) 2995 (m), 2950 (s), 2935 (s), 2875 (m), 1465 (w), 1455 (w), 1390 (w), 1380 (m), 1370 (m), 1260 (m), 1155 (w), 1060 (m), 1030 (w), 970 (w), 860 (w) cm^{-1}.

17: mp 133–134 °C; ^1H NMR (400 MHz) δ 0.694 (3, s, 18α-CH_3), 0.795 (3, s, 4β-CH_3), 0.818 (3, s, 4α-CH_3), 0.851 (3, s, 10β-CH_3), 0.942 (3, d, J = 6.3 Hz, 22-CH_3), 0.951 (6, s, 8β- and 14α-CH_3), 1.407 (3, s, Me from acetonide), 1.431 (3, s, Me from acetonide), 1.99 (1, m), 2.15 (1, m), 3.51 (1, t, J = 8.0 Hz, 35-Ha), 4.06 (1, dd, J = 6.0 Hz, 8.0 Hz, 35-Hb), 4.84 (1, dt, J = 6.0 Hz, 8.0 Hz, 34-H), 5.39 (1, t, J = 9.5 Hz, 33-H), 5.62 (1, dt, J = 7.0 Hz, 9.5 Hz, 32-H); ^{13}C NMR (100 MHz) see spectrum of **18** except C-22 (35.6); IR and mass spectra, see spectral data for **16**.

18: mp 129–131 °C; ^1H NMR (400 MHz), superposable with the spectrum of **17**; ^{13}C NMR (100 MHz) δ 15.8 (C-25 and C-28), 16.4 (C-26 or C-27), 16.5 (C-26 or C-27), 18.6 (C-2 and C-6), 19.9 (C-29), 20.9 (C-11), 21.5 (C-24), 22.7 (C-16), 23.9 (C-12), 24.5 (C-30)$^+$, 25.9 (Me acetonide)$^+$, 26.7 (Me acetonide)$^+$, 27.5 (C-20), 33.1 (C-4), 33.2 (C-7 or C-23), 33.3 (C-7 or C-23), 33.6 (C-15), 35.8 (C-22), 36.3 (C-31)$^+$, 37.3 (C-10), 40.2 (C-1), 41.5 (C-19), 41.6 (C-8 or C-14), 41.7 (C-8 or C-14), 42.0 (C-3), 44.3 (C-18), 45.9 (C-21), 49.2 (C-13), 50.4 (C-9), 54.4 (C-17), 56.0 (C-5), 69.4 (C-34 or C-35), 71.9 (C-34 or C-35), 108.9 (C(CH_3)$_2$), 126.7 (C-32 or C-33), 135.5 (C-32 or C-33) ($^+$tentative assignment); IR and mass spectra, see spectral data for **16**.

19: mp 174–175.5 °C; ^1H NMR (400 MHz) δ 0.694 (3, s, 18α-CH_3), 0.797 (3, s, 4β-CH_3), 0.819 (3, s, 4α-CH_3), 0.852 (3, s, 10β-CH_3), 0.926 (3, d, J = 6.3 Hz, 22-CH_3), 0.953 (6, s, 8β- and 14α-CH_3), 1.391 (3, s, Me from acetonide), 1.430 (3, s, Me from acetonide), 1.92 (1, m), 2.10 (1, m), 3.556 (1, t, J = 8.0 Hz, 35-Ha), 4.05 (1, dd, J = 6.0 Hz, 8.0 Hz, 35-Hb), 4.46 (1, dt, J = 6.0 Hz, 8.0 Hz, 34-H), 5.41 (1, dd, J = 8.0 Hz, 15.5 Hz, 33-H), 5.78 (1, dt, J = 6.5 Hz, 15.5 Hz, 32-H); IR and mass spectra, see spectral data for **16**.

(*R*)-*O*-Isopropylideneglyceraldehyde (14). 1,2:5,6-Di-*O*-isopropylidene-D-mannitol (**12**, 200 mg) was dissolved in distilled water (5 mL) and stirred for 2 h at 20 °C with freshly prepared Amberlyst A-26 resin IO_4^- (ca. 1 g). After filtration, EtOAc extraction, and careful evaporation of the solvent, aldehyde **14** (60 mg) was isolated as a colorless good-smelling liquid: ^1H NMR (60 MHz) δ 1.4 (3, s, methyl from acetonide), 1.5 (3, s, methyl from acetonide), 4.0 (3, m), 9.6 (1, d, J = 2 Hz, aldehyde); optical purity >99% after Mosher's method on the corresponding alcohol.[13] It was used immediately after preparation.

(*S*)-*O*-Isopropylideneglyceraldehyde (15). To a solution of dry L-(*S*)-erythrulose (300 mg) in acetone (20 mL) was added powdered anhydrous $CuSO_4$ (350 mg). After 12 h of stirring at 28 °C and removal of the solid and TLC (Cy–EtOAc, 8:2, v/v), we obtained a colorless syrup (240 mg), which was quickly dissolved in MeOH (10 mL) and subjected during 2 h at 20 °C to reduction in presence of freshly prepared Amberlyst A-26 resin BH_4^- (ca. 1.2 g).[16] Simple filtration and MeOH evaporation gave the required mixture of diols (**13**, 200 mg). An analytical portion (15 mg) of this mixture was acetylated (Ac_2O–Py) and gave after TLC (3×, Cy–EtOAc, 7:1, v/v) the two acetates of diols **13** (9.5 mg for the major, 2.5 mg for the minor). Major acetate: ^1H NMR (400 MHz) δ 1.356 (3, s, Me from acetonide), 1.437 (3, s, Me from acetonide), 2.067 (3, s, acetate), 2.129 (3, s, acetate), 3.80 (1, dd, J = 6.0 Hz, 8.5 Hz, 4-Ha), 4.05 (1, dd, J = 6.5 Hz, 8.5 Hz, 4-Hb), 4.15 (1, dd, J = 7.0 Hz, 12.0 Hz, 1-Ha), 4.27 (1, ddd, J = 5.0 Hz, 6.0 Hz, 6.5 Hz, 3-H), 4.32 (1, dd, J = 4.0 Hz, 12.0 Hz, 1-Hb), 5.16 (1, ddd, J = 4.0 Hz, 5.0 Hz, 7.0 Hz, 2-H). Minor acetate: ^1H NMR (400 MHz) δ 1.359 (3, s, Me from acetonide), 1.430 (3, s, Me from acetonide), 2.076 (3, s, acetate), 2.095 (3, s, acetate), 3.87 (1, dd, J = 6.0 Hz, 8.5 Hz, 4-Ha), 4.08 (1, dd, J = 7.0 Hz, 8.5 Hz, 4-Hb), 4.12 (1, dd, J = 6.0 Hz, 12.0 Hz, 1-Ha), 4.24 (1, dt, J = 6.0 Hz, 6.5 Hz, 3-H), 4.49 (1, dd, J = 3.0 Hz, 12.0 Hz, 1-Hb), 5.08 (1, dt, J = 3.0 Hz, 6.5 Hz, 2-H).

The rest of **13** in solution in distilled water (10 mL) was treated for 2 h with Amberlyst A-26 resin IO_4^- (ca. 1.5 g, freshly prepared[16]) to give after filtration, EtOAc extraction, and slow evaporation of the solvent the required aldehyde (**15**, 110 mg, global yield from erythrulose: 35%) as a colorless good-smelling liquid: ^1H NMR (60 MHz), see NMR of **14**; optical purity >99%.[13]

Trans Isomerization of 17 and 18 under Irradiation. Olefin **17** or **18** (10 mg) was dissolved in cyclohexane (1 mL) in the presence of diphenyl disulfide (5 mg). After 30 min of irradiation at 30 °C, under Ar, TLC separation led to olefin trans **16** or **19** (6 mg, 60%). Melting point, MS, ^1H NMR data: see above.

Osmylation According to Kishi:[11] Typical Procedure. To the olefin (**16–19**; 5 mg) in solution in THF (1 mL) was successively added an acetone–water (2:1, v/v) solution of *N*-methylmorpholine *N*-oxide (1% weight; 0.2 mL) and a solution of osmium tetraoxide (2.5% weight in ^{t}BuOH; 25 μL). After 12 h in the dark at 20 °C and evaporation of the solvent under N_2, TLC (eluent, Cy–EtOAc–Et_3N, 60:45:5, v/v/v) yielded in each case to separation of the two isomeric diols (major diol, 2.5 mg; minor diol, 0.5 mg).

For analyses, each diol was then easily converted either into tetracetate derivatives (**20a–27a**, steps g and h, Scheme II) or into diacetonide derivatives (**20b–27b**) in presence of acetone (1 mL) and anhydrous ferric chloride (ca. 10 mg).

Analysis of tetracetates 20a–27a: ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz), see Tables I and II; mp (**20a**) 185–187 °C, (**21a**) 182–184 °C, (**22a**) 180–182 °C, (**23a**) 183–184.5 °C, (**24a**) 193–194 °C, (**25a**) 184–186 °C, (**26a**) 178–180 °C, (**27a**) 188–190 °C; $[\alpha]_D$ (**20a**) +48 ± 3°, (**21a**) +44 ± 3°, (**22a**) +37 ± 3°, (**23a**) +31 ± 3°, (**24a**) +42 ± 3°, (**25a**) +58 ± 3°, (**26a**) +24 ± 3°, (**27a**) +32 ± 3°; IR, given from **20a**, identical description for other isomers (CCl_4), 3000 (w), 2955 (s), 2935 (s), 2870 (w), 1755 (s), 1460 (w), 1390 (w), 1370 (m), 1250 (m), 1220 (s), 1045 (m); mass spectrum, m/z (relative intensity) given for **22a** 714 (M^+, 27), 699 (M^+ – Me, 8), 654 (M^+ – AcOH, 5), 639 (M^+ – AcOH – Me, 4), 493 (ring C cleavage, 100), 386 (18), 369 (M^+ – side chain, 18), 191 (ring C cleavage, 37).

Analyses of Diacetonides 20b–27b. 20b: mp 208–209 °C; ^1H NMR (400 MHz) δ 0.715 (3, s, 18α-CH_3), 0.796 (3, s, 4β-CH_3), 0.819 (3, s, 4α-CH_3), 0.851 (3, s, 10β-CH_3), 0.944 (3, d, J = 6.3 Hz, 22-CH_3), 0.954 (6, s, 8β- and 14α-CH_3), 1.355 (6, s, Me from acetonide), 1.392 (3, s, Me from acetonide), 1.415 (3, s, Me from acetonide), 3.58 (1, t, J = 7.5 Hz, 35-Ha), 3.90 (1, dt, J = 4.0 Hz, 7.5 Hz, 32-H), 3.96 (1, dd, J = 5.0 Hz, 7.5 Hz, 35-Hb), 4.03 (1, dt, J = 5.0 Hz, 8.0 Hz, 34-H), 4.12 (1, dd, J = 6.0 Hz, 8.0 Hz, 33-H).

21b: mp 199–200 °C; ^1H NMR (400 MHz) δ 0.717 (3, s, 18α-CH_3), 0.797 (3, s, 4β-CH_3), 0.819 (3, s, 4α-CH_3), 0.852 (3, s, 10β-CH_3), 0.955 (6, s, 8β- and 14α-CH_3), 0.962 (3, d, J = 6.3 Hz, 22-CH_3), 1.328 (3, s, Me from acetonide), 1.344 (3, s, Me from acetonide), 1.398 (6, s, Me from acetonide), 3.92 (2, m), 4.09 (3, m); mass spectrum was similar to that of **22b**.

22b: mp 188.5–189.5 °C; ^1H NMR (400 MHz) δ 0.716 (3, s, 18α-CH_3), 0.794 (3, s, 4β-CH_3), 0.817 (3, s, 4α-CH_3), 0.851 (3, s, 10β-CH_3), 0.952 (6, s, 8β- and 14α-CH_3), 0.955 (3, d, J = 6.3 Hz, 22-CH_3), 1.325 (3, s, Me from acetonide), 1.344 (3, s, Me from acetonide), 1.396 (6, s, Me from acetonide), 3.9 (2, m), 4.1 (3, m); mass spectrum, m/z (relative intensity) 626 (M^+, 94), 611 (M^+ – Me, 40), 568 (M^+ – acetone, 17), 553 (M^+ – Me – acetone, 15), 525 (7), 467 (9), 405 (ring C cleavage, 49), 369 (M^+ – side chain, 25), 347 (M^+ – acetone – side chain, 78), 289 (14), 256 (13), 231 (13), 191 (ring C cleavage, 100).

23b: mp 148.5–149.5 °C; ^1H NMR (400 MHz) δ 0.710 (3, s, 18α-CH_3), 0.795 (3, s, 4β-CH_3), 0.817 (3, s, 4α-CH_3), 0.850 (3, s, 10β-CH_3), 0.944 (3, d, J = 6.3 Hz, 22-CH_3), 0.952 (6, s, 8β- and 14α-CH_3), 1.352 (6, s, Me from acetonide), 1.390 (3, s, Me from acetonide), 1.412 (3, s, Me from acetonide), 3.58 (1, t, J = 7.5 Hz, 35-Ha), 3.86 (1, dt, J = 4.0 Hz, 7.5 Hz, 32-H), 3.96 (1, dd, J = 5.0 Hz, 7.5 Hz, 35-Hb), 4.03 (1, dt, J = 5.0 Hz, 7.5 Hz, 34-H), 4.12 (1, dd, J = 6.0 Hz, 8.0 Hz, 33-H).

24b: mp 178–181 °C; ^1H NMR (400 Hz) δ 0.712 (3, s, 18α-CH_3), 0.796 (3, s, 4β-CH_3), 0.819 (3, s, 4α-CH_3), 0.851 (3, s, 10β-CH_3), 0.941 (3, d, J = 6.3 Hz, 22-CH_3), 0.954 (6, s, 8β- and 14α-CH_3), 1.393, 1.408, 1.416, 1.436 (each: 3, s, Me from acetonide), 3.67 (1, dd, J = 4.5 Hz, 8.0 Hz, 35-Ha), 3.82 (1, t, J = 7.5 Hz, 33-H), 3.86 (1, dt, J = 4.0 Hz, 8.0 Hz, 32-H), 4.03 (1, dd, J = 6.0 Hz, 8.0 Hz, 35-Hb), 4.14 (1, ddd, J = 4.5 Hz, 6.0 Hz, 7.5 Hz, 34-H).

25b: mp 137–139 °C; ^1H NMR (400 MHz) δ 0.708 (3, s, 18α-CH_3), 0.795 (3, s, 4β-CH_3), 0.817 (3, s, 4α-CH_3), 0.850 (3, s, 10β-CH_3), 0.940 (3, d, J = 6.3 Hz, 22-CH_3), 0.952 (6, s, 8β- and 14α-CH_3), 1.372, 1.384, 1.466, 1.508 (each: 3, s, Me from acetonide), 3.64 (1, t, J = 8.0 Hz, 35-Ha), 4.05 (3, m), 4.17 (1, dd, J = 6.5 Hz, 11.0 Hz).

26b: mp 147–148 °C; ^1H NMR (400 MHz) δ 0.708 (3, s, 18α-CH_3), 0.795 (3, s, 4β-CH_3), 0.818 (3, s, 4α-CH_3), 0.850 (3, s, 10β-CH_3), 0.945 (3, d, J = 6.3 Hz, 22-CH_3), 0.953 (6, s, 8β- and 14α-

CH_3), 1.374, 1.389, 1.465, 1.507 (each: 3, s, Me from acetonide), 3.66 (1, t, J = 8.0 Hz, 35-Ha), 4.03 (3, m), 4.16 (1, dd, J = 12 Hz, 6 Hz).

27b: mp 196–197 °C; ^{1}H NMR (400 MHz) δ 0.706 (3, s, 18α-CH_3), 0.794 (3, s, 4β-CH_3), 0.817 (3, s, 4α-CH_3), 0.849 (3, s, 10β-CH_3), 0.939 (3, d, J = 6.3 Hz, 22-CH_3), 0.951 (6, s, 8β- and 14α-CH_3), 1.397, 1.410, 1.418, 1.437 (each: 3, s, Me from acetonide), 3.68 (1, dd, J = 4.5 Hz, 8.0 Hz, 35-Ha), 3.82 (1, t, J = 7.5 Hz, 33-H), 3.89 (1, dt, J = 3.0 Hz, 7.5 Hz, 32-H), 4.03 (1, dd, J = 6.0 Hz, 8.0 Hz, 35-Hb).

Acknowledgment. We thank E. Krempp for all NMR measurements, Dr. G. Teller for the mass spectra, Rhône-Poulenc for the generous gift of aminobacteriohopanetriol, and the Ministère de l'Education Nationale (Réseau Européen de Laboratoires) and the Centre National de la Recherche Scientifique (Unité de Recherche Associée 135) for financial support.

Registry No. **2a**, 51024-98-7; **4**, 38706-33-1; **4** (iodide), 120446-11-9; **5**, 120446-13-1; **6**, 120522-08-9; **7**, 23568-31-2; **8**, 120522-09-0; **9**, 120522-10-3; **10**, 62139-14-4; **10** (iodide), 120446-12-0; **11**, 120446-14-2; **12**, 1707-77-3; (*S,S*)-**13**, 91274-05-4; (*S,R*)-**13**, 114185-09-0; (*S,S*,)-**13** (diacetate), 120446-17-5; (*S,R*)-**13** (diacetate), 120446-16-4; **14**, 15186-48-8; **15**, 22323-80-4; **16**, 120446-15-3; **17**, 120522-11-4; **18**, 120522-12-5; **19**, 120522-13-6; **20a**, 120522-14-7; **20b**, 120522-15-8; **21a**, 120522-16-9; **21b**, 120522-17-0; **22a**, 59893-93-5; **22b**, 112259-34-4; **23a**, 120522-18-1; **23b**, 120522-19-2; 24a, 120522-20-5; **24b**, 120522-21-6; **25a**, 120522-22-7; **25b**, 120522-23-8; **26a**, 120522-24-9; **26b**, 120522-25-0; **27a**, 120522-26-1; **27b**, 120522-27-2; $(PhO)_3P^+MeI^-$, 17579-99-6; L-(*S*)-erythrulose, 533-50-6.

Notes

Expedient Synthesis of Ebselen and Related Compounds

Lars Engman*

Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden

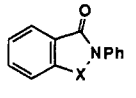
Anders Hallberg

Draco AB, Box 34, S-221 00 Lund, Sweden

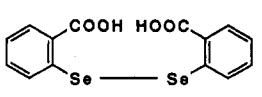
Received November 7, 1988

Introduction

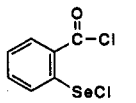
It was recently found that ebselen, 2-phenyl-1,2-benzisoselenazol-3(2*H*)-one (**1b**), is effective for the treatment of diseases caused by cell damage due to increased formation of active oxygen metabolites.[1-3] These pharmacological effects have been attributed to glutathione peroxidase like[4] properties of the simple organoselenium compound. Previous syntheses of ebselen all rely on multistep reactions involving 2,2′-diselenobis(benzoic acid) (**2**) as an intermediate. In the earliest and shortest approach (still useful according to patent literature[5]), this material was converted to a selenenyl chloride benzoyl chloride **3**, which was treated with aniline to give ebselen.[6] Another more recent reaction sequence involves the three-step conversion of diselenide **2** to 2-(methylseleno)benzanilide (**4b**), which was cyclized to give ebselen by treatment with PCl_5 followed by hydrolysis.[7] In the following we describe an operationally simple one-pot preparation of ebselen and related compounds from benzanilide using ortholithiation[8] methodology.



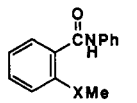
1 a X=S
b X=Se
c X=Te



2



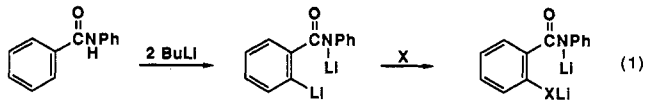
3



4 a X=S
b X=Se
c X=Te

Results

The chalcogens sulfur, selenium, and tellurium are all known to readily insert into the carbon–lithium bond of various organolithium compounds.[9] It was therefore not surprising to find that elemental selenium was rapidly consumed when added to a solution of the readily available[10] benzanilide-derived dianion **5** in THF at 0 °C (eq 1).



(1)

5

6 a X=S
b X=Se
c X=Te

Structure **6b** of the insertion product was confirmed by methylation which occurred exclusively on selenium to give, after aqueous workup, 2-(methylseleno)benzanilide (**4b**) in 76% yield. Similarly, the reaction of dianion **5** with sulfur and tellurium gave, after methylation, compounds **4a** (81%) and **4c** (70%), respectively.

The cyclization of dianion **6b** to ebselen was tried by using a variety of oxidants. Treatment with bromine or iodine in stoichiometric amounts at −78 °C, followed by warming to ambient temperature, produced ebselen in low yields (≤20%). A better result (42%) was obtained by using iron(III) chloride. However, the best yield of ebselen (63%) was obtained by using copper(II) bromide (2 equiv;

(1) Müller, A.; Cadenas, E.; Graf, P.; Sies, H. *Biochem. Pharmacol.* **1984**, *33*, 3235.
(2) Wendel, A.; Fausel, M.; Safayhi, H.; Tiegs, G.; Otter, R. *Biochem. Pharmacol.* **1984**, *33*, 3241.
(3) Parnham, M. J.; Graf, E. *Biochem. Pharmacol.* **1987**, *36*, 3095.
(4) For a recent study concerning the redox chemistry of a selenocysteine model system, see: Reich, H. J.; Jasperse, C. P. *J. Am. Chem. Soc.* **1987**, *109*, 5549.
(5) Eur. Pat. Appl. EP 44453.
(6) Lesser, R.; Weiss, R. *Ber. Dtsch. Chem. Ges.* **1924**, *57*, 1077.
(7) Weber, R.; Renson, M. *Bull. Soc. Chim. Fr.* **1976**, 1124.
(8) Gschwent, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.
(9) See: Engman, L.; Hellberg, J. S. E. *J. Organomet. Chem.* **1985**, *296*, 357 and references cited therein.
(10) Mao, C.-L.; Barnish, I. T.; Hauser, C. R. *J. Heterocycl. Chem.* **1969**, *6*, 475.

0022-3263/89/1954-2964$01.50/0