Total Synthesis of (±)-15-Deoxyspergualin

Raymond J. Bergeron* and James S. McManis

Department of Medicinal Chemistry, College of Pharmacy, J. Hillis Miller Health Center, University of Florida, Gainesville, Florida 32610

Received October 15, 1986

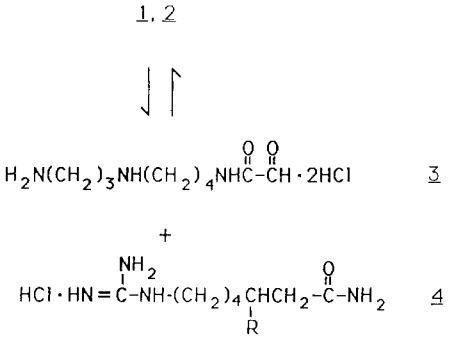
The synthesis of (±)-7-[(aminoiminomethyl)amino]-*N*-[2-[[4-[(3-aminopropyl)amino]butyl]amino]-1-hydroxy-2-oxoethyl]heptanamide trihydrochloride, (±)-15-deoxyspergualin, **2b**, a potent antitumor and antibiotic spermidine alkaloid, is reported. The synthesis is predicated on the development of the protected spermidine N^1,N^4-bis(*tert*-butoxycarbonyl)spermidine (**12**) and guanidine reagent *N,N'*-bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea (**18**). The sensitive alkanolamide moiety of (±)-15-deoxyspergualin (C-11 in **2b**) is formed and then protected as its *tert*-butyldimethylsilyl ether in **21**. The reactive ester group of **21** undergoes aminolysis with **12** to form protected deoxyspergualin **22**. All of the protecting groups in **22** are removed by trifluoroacetic acid to furnish final product **2b**.

(-)-Spergualin (1) (Figure 1) was isolated from the culture filtrates of the bacterium strain *Bacillus laterosporus* BMG 162-aF2[1] and characterized by Umezawa in 1981.[2] The tribasic compound was demonstrated to have both antibiotic and antitumor properties. Specifically, it was active against gram-positive and -negative bacteria and effected life extension in mice with L-1210, EL-4 leukemia, and Ehrlich carcinoma.[1]

(-)-Spergualin (1) has been chemically converted to (-)-15-deoxyspergualin (**2a**) in 2% overall yield.[3] This synthetic analogue is about eight times more active against L-1210 mouse leukemia than **1**.[3] In fact, **2a** "significantly increased the survival time of leukemia L1210-infected mice, even at a concentration of 0.05 mg/kg per day",[4] a dose far below the acute LD_{50} in mice of 35-40 mg/kg.[3] Moreover, ILS values greater than 150% were observed by employing a dose of 25 mg/kg per day.[5] The antitumor activity of deoxyspergualin is thought to arise from oxidation of the primary amine to a cytotoxic aldehyde by monoamine oxidase in vitro. However, the antineoplastic mechanism in vivo is still under investigation.[5]

(-)-Spergualin (racemic at C-11),[6] (±)-15-deoxyspergualin (**2b**),[7] and homologues[8] have been totally synthesized by Umezawa. The key and final step in those syntheses is an acid-promoted addition of the primary amide group of **4** to the highly electrophilic aldehyde of N^8-spermidine glyoxamide **3** in ca. 40% yield, (eq 1).[7] The amino groups in **3** and the guanidine in **4** are deactivated as their hydrochloride salts. This well-known reaction[9] is actually an equilibrium.[8] Therefore the *gem*-carbinol amide functionality at C-11 accounts for the retrograde decomposition of spergualin derivatives at low[5] and high[5] pH's.

This labile two-carbon unit divides the molecule into two segments: spermidine, connected at N-8, and a guanidine-terminated carbon chain. Our retrosynthetic analysis is given in Scheme I. In the last intermediate **5**, the amine



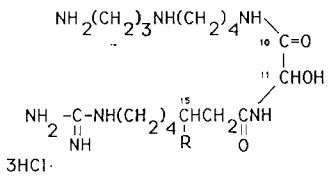
(1)

nitrogens, guanidine, and alcohol are blocked by five protecting groups designated P-P″, which must be removable under conditions mild enough to prevent retroreaction at C-11, ideally at the same time. Formation of the complete deoxyspergualin framework could be effected by acylation of **7** by protected spermidine **6**. Segment **7** could be made by addition of **8** to a glyoxylic acid derivative and then trapping the resulting alcohol with functionality P′. Compound **8**, in which the strongly basic and nucleophilic guanidine group was masked, was required. Since the guanidine was no longer a salt, intermediates would be soluble in organic solvents until the final step.[10] For this purpose, the guanidine synthon of general formula **9** was devised.

For the spermidine portion **6**, we selected *tert*-butoxycarbonyl (BOC) to block the amines. TLC analysis confirmed that authentic (±)-15-deoxyspergualin[11] was stable to cold trifluoroacetic acid, with which BOC groups are removed. A spermidine reagent with three independently removable protecting groups, developed in these laboratories,[12] was readily converted to N^1,N^4-bis(*tert*-butoxycarbonyl)spermidine (Scheme II). N^1-(*tert*-butoxycarbonyl)-N^8-(trifluoroacetyl)spermidine hydrochloride (**10**)[12] was *tert*-butoxycarbonylated as previously described (BOC-ON, triethylamine)[13] to give **11**, which was treated with potassium carbonate in aqueous methanol to free up N^8. Thus N^1,N^4-bis(*tert*-butoxycarbonyl)spermidine (**12**) was obtained in 88% yield from **10**. Umezawa's preparation of intermediate **12** was accomplished starting with 3-hydroxy-1-propanol in 24% overall yield and using *N*-(benzyloxycarbonyl)-1,4-diaminobutane derived from 1,4-diaminobutane.[6] Our more efficient route to spermidine reagent **12** is valuable for the production of spergualins.

(1) Takeuchi, T.; Iinuma, H.; Kunimoto, S.; Masuda, T.; Ishizuka, M.; Takeuchi, M.; Hamata, M.; Naganawa, H.; Kondo, S.; Umezawa, H. *J. Antibiot.* **1981**, *34*, 1619-1621.
(2) Umezawa, H.; Kondo, S.; Iinuma, H.; Kunimoto, S.; Ikeda, Y.; Iwasawa, H.; Ikeda, D.; Takeuchi, T. *J. Antibiot.* **1981**, *34*, 1622-1624.
(3) Iwasawa, H.; Kondo, S.; Ikeda, D.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1982**, *35*, 1665-1669.
(4) Umezawa, H.; Kondo, S.; Takeuchi, T. *Eur. Pat. Appl.* EP 94 632, 1983; *Chem. Abstr.* **1984**, *100*, 120781k.
(5) Brockman, R. W.; Wheeler, G. P. *Proc. Am. Assoc. Cancer Res.* **1985**, *26*, 255.
(6) Kondo, S.; Iwasawa, H.; Ikeda, D.; Umeda, Y.; Ikeda, Y.; Iinuma, H.; Umezawa, H. *J. Antibiot.* **1981**, *34*, 1625-1627.
(7) Umeda, Y.; Moriguchi, M.; Nakamura, T.; Fujii, A.; Takeuchi, T.; Umezawa, H. Ger. Offen. DE 3 506 330, 1985; *Chem. Abstr.* **1986**, *104*, 168275h.
(8) Umeda, Y.; Moriguchi, M.; Kuroda, H.; Nakamura, T.; Iinuma, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1985**, *38*, 886-898.
(9) Zaugg, H. E.; Martin, W. B. *Org. React. (N.Y.)* **1965**, *14*, 52-269.
(10) Zervas, L.; Winitz, M.; Greenstein, J. P. *Arch. Biochem. Biophys.* **1956**, *65*, 573-574.
(11) Kindly provided by Dr. J. P. Davignon, National Cancer Institute.
(12) Bergeron, R. J.; Garlich, J. R.; Stolowich, N. J. *J. Org. Chem.* **1984**, *49*, 2997-3001.
(13) Itoh, M.; Hagiwara, D.; Kamiya, T. *Tetrahedron Lett.* **1975**, 4393-4394.

0022-3263/87/1952-1700$01.50/0 © 1987 American Chemical Society



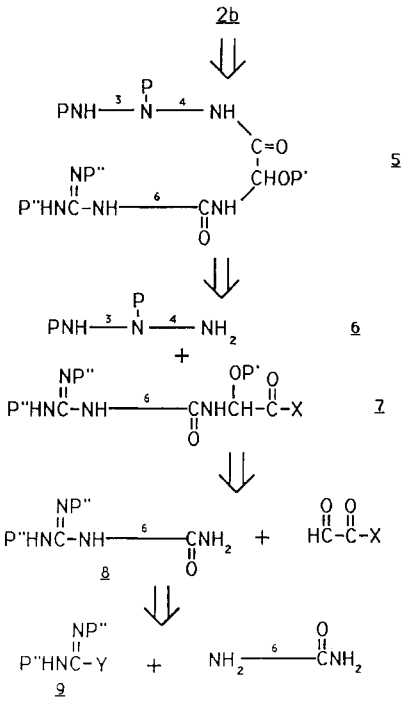
1 R= OH (-)-spergualin

2 R= H deoxyspergualin

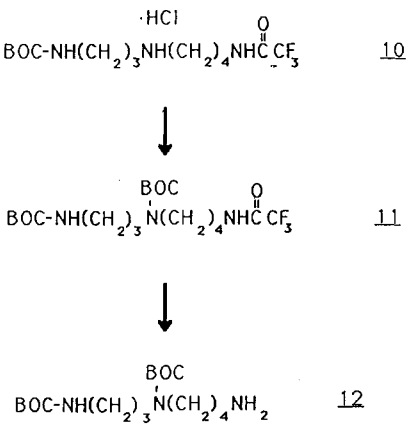
a(-)
b(±)

Figure 1.

Scheme I

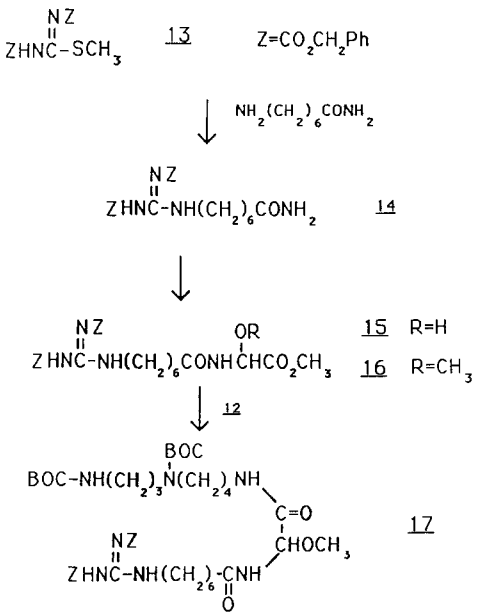


Scheme II



To prepare the guanidine-terminated segment of **2b**, we started with 7-aminoheptanamide.[14] Guanidines are often prepared[15] by the reaction of amines with salts of *S*-methylisothiourea. Modification of the latter reagent was carried out in order to generate protected guanidines,

Scheme III



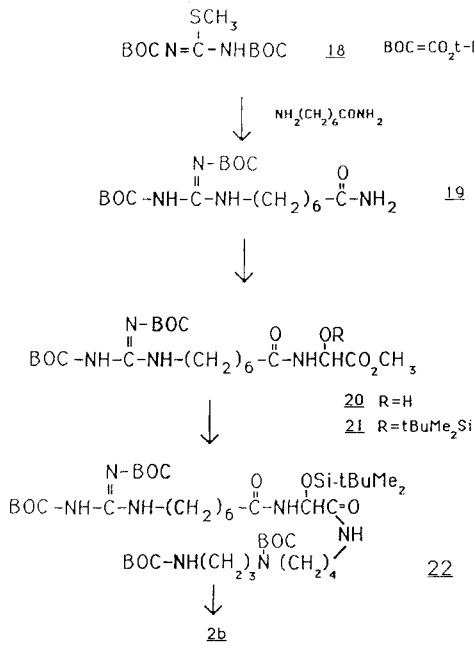
compounds that would be soluble in organic solvents. Specifically, stirring *S*-methylisothiourea hemisulfate with benzyl chloroformate (1.9 equiv, aqueous NaOH, CH_2Cl_2) gave the known *N*,*N*′-bis(benzyloxycarbonyl)-*S*-methylisothiourea (**13**)[16] (Scheme III). Reagent **13** is similar to 2-methylnitroisourea, used for the production of *N*-nitroguanidines.[17] Both *N*-nitro- and bis(benzyloxycarbonyl)guanidines can be deprotected with hydrogen (Pd–C).[18]

Heating isothiourea **13** with 7-aminoheptanamide[14] (1.1 equiv, 1 day, 60 °C) gave masked guanidine–amide **14** (59%) through amine addition to **13** followed by elimination of volatile methyl mercaptan. Protected guanidine–amide **14** was heated in refluxing THF with methyl glyoxalate[19] (1.1 equiv, 11 h) to generate carbinol–amide **15** (36%) still contaminated with primary amide **14** which was removed upon purification of the next intermediate, **16**.

In order to render the amide–aldehyde adduct more stable, Umezawa protected the alcohol in spergualin **1** as its tetrahydropyran derivative during the conversion to **2a**.[3] Acid-promoted exchange of hydroxy by methoxy (0.3 M H_2SO_4 in methanol, room temperature, 4 h) gave α-methoxy ester **16** in 59% yield. Conversion of amide **14** to methyl ester **16** could be accomplished in 68% overall yield without purification of labile intermediate **15**. Although esters usually react sluggishly with amines, α-methoxy-α-acylamino methyl esters are highly electrophilic and form amides in the presence of primary amines at room temperature.[20] Thus N^1,N^4-bis(*tert*-butoxycarbonyl)spermidine (**12**) (1.1 equiv) and methyl ester **16** were allowed to react (40 °C, 1.5 day), providing a 54% yield of amide **17**, which contains the entire deoxyspergualin backbone. Unfortunately, an attempt to change the methyl ether back to the alcohol was not very successful in a model compound. The reaction proceeded very slowly and side products represented a major problem. Moreover,

(14) Berther, C. *Chem. Ber.* **1959**, *92*, 2616–2621.
(15) Robin, Y.; Van Thoai, N. *C.R. Hebd. Seances Acad. Sci.* **1961**, *252*, 1224–1226.
(16) Nowak, K.; Kania, L. *Rocz. Chem.* **1969**, *43*, 1953–1960.
(17) Heyboer, N.; Visser, G. H.; Kerling, K. E. T. *Recl. Trav. Chim. Pays-Bas.* **1962**, *81*, 69–72.
(18) Hofmann, K.; Peckham, W. D.; Rheiner, A. *J. Am. Chem. Soc.* **1956**, *78*, 238–242.
(19) Jung, M. E.; Shishido, K.; Davis, L. H. *J. Org. Chem.* **1982**, *47*, 891–892.
(20) American Cyanamid Company, *MAGME Multifunctional Acrylic Monomer*.

Scheme IV



we anticipated that deprotection of the guanidine by hydrogenolysis could cause reductive cleavage of the C(11)–O bond.[21] Thus this particular approach was abandoned. However, it was clear from the sequence that the backbone could be assembled by employing these two basic segments. What remained was a reconsideration of protecting groups.

The alternative solution was to attach the same protecting group to the guanidine and the polyamine chain, that is, *tert*-butoxycarbonyl. Direct reaction of *N*-α-(benzyloxycarbonyl)arginine with di-*tert*-butyl dicarbonate leads to a mixture of bis(*tert*-butoxycarbonyl)guanidines (N^1,N^3 and N^2,N^3).[22] To avoid the problem of isomers, *S*-methylisothiourea hemisulfate was stirred rapidly with di-*tert*-butyl dicarbonate (1.2 equiv, room temperature) in a biphasic reaction mixture (aqueous $NaHCO_3$, CH_2Cl_2) to give a 90% yield of *N*,*N*′-bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea (**18**), a new and versatile reagent for the production of masked guanidines (Scheme IV). Isothiourea **18** (1.05 equiv) and 7-aminoheptanamide in 2% aqueous THF (50 °C, 3 h) led to bis(*tert*-butoxycarbonyl)guanidine amide **19** (71%). Condensation of the primary amide of **19** with methyl glyoxalate (1.3 equiv, 40 °C, 1 day, THF) generated the secondary alcohol **20** (43%). Even though the reaction was incomplete, excessive heating was avoided to prevent thermal deBOCing of the guanidine. We first carried out ester aminolysis without protecting the alcohol. That is, spermidine compound **12** and the electrophilic ester **20** were stirred in benzene (12 h, room temperature) to give tetrakis(*tert*-butoxycarbonyl)deoxyspergualin, which yielded (±)-15-deoxyspergualin (**2b**) upon exposure to TFA. Unfortunately, the final product was contaminated with 7-guanidinoheptanamide salt due to "retro" reaction during the amide coupling. It was clear that an alcohol protecting group would be necessary. We chose to generate a *tert*-butyldimethylsilyl ether as these are inert to amines but can be unmasked by mild acid.[23] This meant that we would be able to remove all of the protecting groups simultaneously. Alcohol **20** was silylated by the standard procedure (*tert*-butyldimethylsilyl chloride, imidazole, DMF)[23] to **21** (69% yield). α-Silyloxy ester **21** was generated by an improved procedure in 34% yield from primary amide **19** without purification of labile alcohol **20**. Penta-protected deoxyspergualin **22** resulted from heating α-silyloxy methyl ester **21** with primary amine **12** (1.1 equiv, benzene, 38 °C, 46 h) in 47% yield. Although both reactants remained, overheating was avoided to minimize reaction of the bis(*tert*-butoxycarbonyl)guanidine. Finally, upon exposure of **22** to trifluoroacetic acid (room temperature, 40 min), the five protecting groups were simultaneously cleaved to give (±)-15-deoxyspergualin·3TFA. Thus the original plan of removing all of the blocking groups with a single, mild reagent was fulfilled. The tris(trifluoroacetate) salt was exchanged on a CM-Sephadex cation exchange column to the trihydrochloride (water to 1 M aqueous NaCl) and final purification achieved by Sephadex LH-20 (CH_3OH) to provide (±)-15-deoxyspergualin (**2b**) in 71% yield. The final product was identical with a known sample of (±)-15-deoxyspergualin (**2b**)[24] by silica gel TLC and 300-MHz NMR. The overall yield is 7.2%, superior to Umezawa's for **2b** of 3.5%.[7,8]

The synthesis and biological testing of various segments of 15-deoxyspergualin are underway to determine its mechanism of activity. Also further applications of masked guanidine-forming reagents **13** and **18** are being explored.

Experimental Section

All reagents, with the exception of *S*-methylisothiourea hemisulfate (Sigma), were purchased from Aldrich Chemical Company and were used without further purification. Sodium sulfate was employed as a drying agent and solvents were routinely distilled. Melting points are uncorrected. Sephadex LH-20-100 and CM-Sephadex Cation Exchanger were purchased from Sigma Chemical Company. Proton NMR spectra were recorded on a Varian EM-390 or a Nicolet NT-300 instrument, and, unless otherwise noted, were run in $CDCl_3$ with chemical shifts given in parts per million downfield from an internal tetramethylsilane standard (coupling constants are in hertz). IR spectra were recorded on a Beckman Acculab 1 spectrophotometer. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA.

N^1,N^4-Bis(*tert*-butoxycarbonyl)-N^8-(trifluoroacetyl)-spermidine (11). N^1-(*tert*-Butoxycarbonyl)-N^8-(trifluoroacetyl)spermidine hydrochloride (5.68 g, 15.0 mmol), BOC-ON (4.14 g, 16.8 mmol), and triethylamine (3.2 mL, 23.0 mmol) were stirred in THF (175 mL) for at least 1 day. Solvent was removed, the residue was dissolved in CH_3OH, and ammonium hydroxide (2 mL) was added to destroy excess BOC-ON. Solvent was stripped off and the residue dissolved in ether (100 mL), which was washed with cold 5% NaOH (4 × 15 mL) and brine (15 mL). The product was passed through a short silica column (10% EtOH/$CHCl_3$) to give 6.6 g of **11** (quantitative yield): ^{1}H NMR δ 1.3–1.8 (2 s + m, 24 H), 2.95–3.5 (m, 8 H), 5.1 (br s, 1 H), 7.7 (br s, 1 H). Anal. Calcd for $C_{19}H_{34}F_3N_3O_5$: C, 51.69; H, 7.76; N, 9.52. Found: C, 51.58; H, 7.77; N, 9.48.

N^1,N^4-Bis(*tert*-butoxycarbonyl)spermidine (12). Compound **11** (6.6 g, 14.9 mmol) was heated at relux with K_2CO_3 (2.10 g, 15.2 mmol) in water (6 mL) and methanol (100 mL) for 2 h 10 min. The mixture was concentrated, diluted with water, and extracted with $CHCl_3$ (5×). The crude product was chromatographed on silica gel, eluting with 5% NH_4OH/CH_3OH, to give 4.55 g of **12** (88%): ^{1}H NMR δ 1.3–1.9 (2 s + m, 26 H), 2.73 (t, 2 H), 3.0–3.4 (m, 6 H), 5.2 (br s, 1 H); IR (film) 3300–3400, 1700 cm^{-1}. Anal. Calcd for $C_{17}H_{35}N_3O_4$: C, 59.10; H, 10.21; N, 12.16. Found: C, 58.86; H, 10.20; N, 12.04.

7-[N^2,N^3-Bis(benzyloxycarbonyl)guanidino]heptanamide (14). 7-Aminoheptanamide[14] (0.133 g, 0.922 mmol) and *N*,*N*′-bis(benzyloxycarbonyl)-*S*-methylisothiourea (**13**)[16] (0.29 g, 0.81

(21) Auerbach, J.; Zamore, M.; Weinreb, S. M. *J. Org. Chem.* **1976**, *41*, 725–726.
(22) Goenvald, F. C.; Johansen, N. L.; Lundt, B. F. *Pept. Proc. Eur. Pept. Symp., 16th*, **1980**, 111–115.
(23) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.
(24) Kindly provided by Dr. K. Flora, National Cancer Institute.

mmol) were heated at 58 °C in THF (20 mL) and $CHCl_3$ (10 mL) for 22 h (hood). Removal of solvent and then silica gel chromatography ($CHCl_3$ then 10% $CH_3OH/CHCl_3$) gave 0.36 g (98%) of white solid, which was recrystallized from EtOAc, to furnish 0.211 g (59%) **14**: mp 140–141 °C; ^1H NMR δ 1.2–1.8 (m, 8 H), 2.21 (t, 2 H), 3.43 (q, 2 H), 5.13 and 5.19 (2 s, 4 H), 5.5 (br s, 2 H), 7.25–7.5 (m, 10 H), 8.33 (br s, 1 H), 11.77 (br s, 1 H). Anal. Calcd for $C_{24}H_{30}N_4O_5$: C, 63.42; H, 6.65; N, 12.33. Found: C, 63.22; H, 6.72; N, 12.26.

ω-Bis(benzyloxycarbonyl)guanidino α-(Methoxymethyl ester) 16. Methyl glyoxalate[19] (79.2 mg, 0.899 mmol) and **14** (0.288 g, 0.634 mmol) were heated at 40 °C in THF (6 mL) for 38 h. Solvent removal in vacuo afforded crude **15**. Alcohol **15** was stirred (room temperature, Ar) in 0.31 M H_2SO_4 in CH_3OH (10 mL) for 18 h. The solution was poured into cold, dilute $NaHCO_3$ (50 mL) and extracted with ether (4 × 50 mL). After washing with water (3×) and brine, the crude product was chromatographed on a column (silica gel, 3% $EtOH/CHCl_3$) to give 242 mg (68%) of **16**: ^1H NMR δ 1.25–1.8 (m, 8 H), 2.30 (t, 2 H), 3.35–3.55 (q + s, 5 H), 3.82 (s, 3 H), 5.15 and 5.22 (2 s, 4 H), 5.58 (d, J = 9, 1 H, collapses to a singlet with D_2O), 6.5 (br, 1 H), 7.3–7.5 (m, 10 H), 8.3 (br s, 1 H), 11.77 (br s, 1 H). Anal. Calcd for $C_{28}H_{36}N_4O_8$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.23; H, 6.60; N, 9.97.

Pentaprotected Deoxyspergualin 17. Ester **16** (199 mg, 0.358 mmol) and amine **12** (138 mg, 0.399 mmol) were heated in benzene (0.7 mL) at 40 °C for 36 h. Preparative layer chromatography (4% $EtOH/CHCl_3$) gave 167 mg of **17** (54%): ^1H NMR δ 1.2–1.8 (m, 32 H), 2.30 (t, 2 H), 3.0–3.5 (m + s, 13 H), 5.1 (br s, 1 H), 5.13 and 5.19 (2 s, 4 H), 5.50 (d, 1 H, J = 9), 6.9 (br s, 2 H), 7.25–7.5 (m, 10 H), 8.35 (br s, 1 H), 11.8 (br s, 1 H). Anal. Calcd for $C_{44}H_{67}N_7O_{11}\cdot H_2O$: C, 59.51; H, 7.83; N, 11.04. Found: C, 59.21; H, 7.86; N, 10.81.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*S*-methoxyisothiourea (18).** Di-*tert*-butyl dicarbonate (5.81 g, 26.6 mmol) and *S*-methylisothiourea·$^1/_2H_2SO_4$ (2.53 g, 18.2 mmol) were vigorously stirred in a biphasic system, CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ (50 mL), for 1.6 days. Layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2×). After water washing, the crude product contained BOC_2O and was taken up in CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ (50 mL) and stirred with *S*-methylisothiourea·$^1/_2H_2SO_4$ (0.55 g, 3.95 mmol) for 2–3 days and worked up as before. Elution with 15% hexane/$CHCl_3$ and then $CHCl_3$ through a silica gel column afforded 3.46 g (90%) of white solid: mp 122–123 °C; ^1H NMR δ 1.53 (s, 18 H), 2.40 (s, 3 H), 11.63 (br s, 1 H); IR ($CHCl_3$) 3200, 1750 cm^{-1}. Anal. Calcd for $C_{12}H_{22}N_2O_4S$: C, 49.63; H, 7.64; N, 9.65; S, 11.04. Found: C, 49.56; H, 7.68; N, 9.63; S, 11.00.

7-[N^2,N^3-Bis(*tert*-butoxycarbonyl)guanidino]heptanamide (19). Reagent **18** (2.09 g, 7.20 mmol) and 7-aminoheptanamide[14] (0.988 g, 6.85 mmol) were heated at 52 °C for 3 h in THF (52 mL) and water (1 mL) (hood). Solvent was removed, and the residue was treated with 5% $NaHCO_3$, followed by extraction with $CHCl_3$ (2×). After a water wash, the crude product was chromatographed on silica gel (10:45:45 $EtOH/EtOAc/CHCl_3$) to give 1.88 g (71%) of **19**: ^1H NMR δ 1.3–1.8 (m, 26 H), 2.24 (t, 2 H), 3.42 (q, 2 H), 5.5 (br s, 2 H), 8.3 (br s, 1 H), 11.53 (br s, 1 H); IR ($CHCl_3$) 3680, 3540, 3420, 3340, 1725, 1685 cm^{-1}. Anal. Calcd for $C_{18}H_{34}N_4O_5$: C, 55.94; H, 8.87; N, 14.50. Found: C, 55.67; H, 8.86; N, 14.42.

Silylated Bis(*tert*-butoxycarbonyl)guanidine Methyl Ester (21). A solution of amide **19** (0.391 g, 1.01 mmol) and methyl glyoxalate (0.112 g, 1.27 mmol) in THF was heated at 42 °C for 15 h. After solvent removal, imidazole (0.22 g, 3.23 mmol), *tert*-butyldimethylsilyl chloride (0.21 g, 1.39 mmol), and dry DMF (1.0 mL) were added to the intermediate **20**. The solution was stirred for 2 days (room temperature, N_2) and then quenched with water. Ether extraction (5×), followed by water washing (3×), and then brine gave 0.49 g of product. Column chromatography (SiO_2, 5% $EtOAc/CHCl_3$) and then preparative TLC (SiO_2, 4% $EtOAc/CHCl_3$) on a portion of the resulting product furnished 0.201 g of **21** (34% yield): ^1H NMR δ 0.13 and 0.19 (2 s, 6 H), 0.90 (s, 9 H), 1.25–1.8 (m and s, 26 H), 2.24 (t, 2 H), 3.42 (q, 2 H), 3.79 (s, 3 H), 5.84 (d, 1 H, J = 10), 6.54 (br d, 1 H), 8.35 (br s, 1 H), 11.51 (br s, 1 H); IR ($CHCl_3$) 3440, 3340, 1750, 1725, 1690, 1630 cm^{-1}. Anal. Calcd for $C_{27}H_{52}N_4O_8Si$: C, 55.08; H, 8.90; N, 9.52. Found: C, 55.22; H, 8.91; N, 9.47.

Pentakis(*tert*-butoxycarbonyl)-11-silyl-15-deoxyspergualin 22. Ester **21** (158 mg, 0.268 mmol) and N^1,N^4-bis(*tert*-butoxycarbonyl)spermidine (**12**) (102.7 mg, 0.297 mmol) were stirred in benzene (0.5 mL) (Ar) for 46 h at 38 °C. After solvent removal, purification of the crude product by preparative TLC (2:24:74 $EtOH/EtOAc/CHCl_3$) gave 114 mg (47%) of **22**: ^1H NMR δ 0.10 and 0.20 (2 s, 6 H), 0.91 (s, 9 H), 1.2–2.0 (m, 50 H), 2.23 (t, 2 H), 3.0–3.6 (m, 10 H), 5.74 (d, J = 9, 1 H), 6.7 (br s, 2 H), 8.3 (br s, 1 H), 11.53 (br s, 1 H). Anal. Calcd for $C_{43}H_{83}N_7O_{11}Si$: C, 57.24; H, 9.27; N, 10.87. Found: C, 57.08; H, 9.33; N, 10.83.

(±)-15-Deoxyspergualin (2b). To **22** (23 mg, 0.025 mmol) was added trifluoroacetic acid (2 mL). After stirring for 43 min (room temperature, Drierite), excess solvent was removed under a stream of nitrogen, and the residue was dried in vacuo (P_2O_5). Purification was carried out following the literature.[8] First, CM-Sephadex Cation Exchanger (4.06 g), equilibrated in water, was used, eluting with water and 0.2 N, 0.4 N, 0.6 N, 0.8 N (50 mL each), and then 1.0 N aqueous NaCl. Fractions 17–21 (ninhydrin active) were combined and lyophilized, stirred with CH_3OH, and filtered. Next a column of Sephadex LH-20-100 (8.54 g), preswelled in CH_3OH was used (acid-washed glassware). Elution with methanol gave 9 mg of (±)-15-deoxyspergualin (71%): ^1H NMR (300 MHz, D_2O) δ 5.46 (s, 1 H), 3.30 (t, 2 H), 3.05–3.25 (m, 8 H), 2.31 (t, 2 H), 2.10 (quintet, 2 H), 1.55–1.8 (m, 8 H), 1.33–1.45 (m, 4 H), 4.80, HOD. This 300-MHz spectrum was identical with that of a known sample of **2b**.[24] The two samples were identical by cospotting on silica gel TLC (3:2:2:1 1-butanol/pyridine/water/acetic acid).[3]

Acknowledgment. We thank Dr. J. Paul Davignon and Dr. Karl Flora at the National Cancer Institute for providing samples of (±)-15-deoxyspergualin. We would also like to acknowledge Diana L. Tukalo for the preparation of triprotected spermidine reagent.

A Regioselective Synthesis of Cyclopentenones from 4-Thianone

Haruo Matsuyama,* Yasuyuki Miyazawa, Yuji Takei, and Michio Kobayashi

Department of Chemistry, Tokyo Metropolitan University, Setagaya-ku, Tokyo 158, Japan

Received September 17, 1986

Alkyl-substituted 3-cyclopentenones **4** and **5** were prepared in moderate to good yields starting from 4-thianone by the selective alkylation and Ramberg–Bäcklund-type reactions. One route starts with 6-alkyl-1,4-dioxa-8-thiaspiro[4.5]decane 8,8-dioxides (**8**) and another with 7-alkyl-1,4-dioxa-7-(*p*-tolylsulfonyl)-8-thiaspiro[4.5]decane 8,8-dioxides (**15**), followed by acid-catalyzed cleavage of the 1,3-dioxolane ring of 1,4-dioxaspiro[4.4]non-7-enes **9** and **16** to afford **4** and **5**.

Considerable attention has been focused in recent years on cyclic sulfur compounds for the synthesis of interesting compounds.[1] 4-Thianone (**1**) is a heterocyclic compound consisted of five carbon units and a sulfur atom as an

0022-3263/87/1952-1703$01.50/0 © 1987 American Chemical Society