pure **39**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.03–2.20 (m, 13 H), 1.07 (s, 3 H), 1.14 (s, 3 H), 1.76 (br s, 3 H), 3.17 (dd, J = 4.5, 10 Hz, 1 H), 3.38 (s, 3 H), 4.68 (AB q, J = 7 Hz, 2 H), 4.73 (br s, 2 H); mass spectrum m/e (relative intensity) 282 (M^+, 1.9), 267 (23), 205 (24), 192 (45), 179 (78), 162 (38), 149 (28), 135 (31), 121 (42), 107 (45), 101 (35), 95 (43), 81 (29), 71 (26), 45 (100), 43 (61); calcd for $C_{17}H_{30}O_3$ (M^+) m/e 282.2195, found m/e 282.2193.

(1α,4α,4aα,7α,8aβ)-Decahydro-4-(methoxymethoxy)-1,4a-dimethyl-7-(1-methylethyl)-1-naphthalenol (40). A mixture of 1.691 g (6.00 mmol) of isopropenyl alcohol **39** and 0.195 g of 10% platinum on charcoal in 130 mL of ethanol was hydrogenated in a Parr hydrogenator under 50 psi of hydrogen for 70 min. The reaction mixture was filtered through Celite, and the filter cake was washed with 75 mL of EtOAc. The solvents were evaporated under reduced pressure to give 1.688 g (99%) of pure **40**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.89 (d, J = 7 Hz, 6 H), 1.00–2.10 (m, 14 H), 1.03 (s, 3 H), 1.13 (s, 3 H), 3.15 (dd, J = 5.5, 9.5 Hz, 1 H), 3.37 (s, 3 H), 4.67 (AB q, J = 7 Hz, 2 H); mass spectrum, m/e (relative intensity) 284 (M^+, 1.1), 222 (21), 213 (34), 207 (33), 194 (30), 181 (100), 164 (41), 161 (29), 121 (30), 109 (43), 101 (35), 95 (36), 83 (44), 71 (24), 45 (95), 43 (46); calcd for $C_{17}H_{32}O_3$ (M^+) m/e 284.2351, found m/e 284.2361.

(1α,4α,4aα,7α,8aβ)-Decahydro-1,4a-dimethyl-7-(1-methylethyl)-1,4-naphthalenediol (41). A solution of 1.663 g (5.85 mmol) of isopropyl alcohol **40** and two drops of concentrated HCl in 20 mL of methanol was heated at reflux for 75 min, allowed to come to room temperature, and then neutralized with 0.3 N KOH in methanol. The reaction mixture was concentrated under reduced pressure, and the resulting residue was taken up in 100 mL of CH_2Cl_2. The organic layer was washed with 50 mL of brine, dried, and evaporated under reduced pressure. Chromatography of the residue on silica gel (5:1 to 2:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 1.072 g (75%) of pure diol **41**: mp 121 °C (from diisopropyl ether); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.90 (d, J = 7 Hz, 6 H), 0.95 (s, 3 H), 1.03–2.10 (m, 15 H), 1.14 (s, 3 H), 3.24 (dd, J = 4, 10 Hz, 1 H); mass spectrum, m/e (relative intensity) 240 (M^+, 0.5), 222 (32), 207 (22), 183 (40), 181 (87), 164 (64), 161 (50), 137 (21), 121 (69), 109 (52), 101 (58), 95 (61), 83 (39), 72 (100), 43 (63); calcd for $C_{15}H_{28}O_2$ (M^+) m/e 240.2089, found m/e 240.2093.

(1α,4α,4aα,7α,8aβ)-Decahydro-1,4a-dimethyl-7-(1-methylethyl)-1,4-naphthalenediol 4-(4-Methylbenzenesulfonate) (34). The tosylate **34** was prepared from **41** (0.918 g, 3.82 mmol) as described for the synthesis of the tosylate **3**. Workup and chromatography on silica gel (2:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 1.445 g (97%) of pure **34**: mp 104 °C (from petroleum ether (bp 80–100 °C)); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.86 (d, J = 7 Hz, 6 H), 0.90–1.90 (m, 14 H), 1.01 (s, 3 H), 1.10 (s, 3 H), 2.43 (s, 3 H), 4.26 (m, 1 H), 7.32 (d, J = 8 Hz, 2 H), 7.81 (d, J = 8 Hz, 2 H). Anal. Calcd for $C_{22}H_{34}O_4S$: C, 66.97; H, 8.69. Found: C, 67.09; H, 8.77.

(±)-5-*epi*-Nardol (33). The tosylate **34** (0.394 g, 1.00 mmol) was treated with sodium *tert*-amylate (5 equiv) for 17 h as described for the rearrangement of the tosylate **3**. The workup and chromatography on silica gel (30:1 to 25:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.200 g (90%) of (±)-5-*epi*-nardol **33**:[27] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, J = 6.9 Hz, 6 H), 0.96–2.00 (m, 13 H), 1.27 (s, 3 H), 2.53 (m, 1 H), 2.78 (m, 1 H), 4.80 (br s, 1 H), 4.84 (s, 1 H); mass spectrum, m/e (relative intensity) 222 (M^+, 16), 204 (69), 191 (49), 161 (95), 135 (31), 121 (100), 109 (54), 95 (62), 81 (58), 71 (46), 43 (64); calcd for $C_{15}H_{26}O$ (M^+) m/e 222.1984, found m/e 222.1985.

Acknowledgment. We thank Cees J. Teunis and Hugo Jongejan for mass spectral data and elemental analyses and Albertus van Veldhuizen for recording ^{1}H NMR (300 MHz) and ^{13}C NMR spectra.

Registry No. (±)-**3**, 124095-81-4; (±)-**4**, 124149-98-0; (±)-**5**, 87262-05-3; (±)-**6**, 124095-82-5; (±)-**7**, 123994-89-8; (±)-**8**, 123994-90-1; (±)-**9**, 124095-83-6; (±)-**10**, 124095-84-7; (±)-**11**, 123994-91-2; (±)-**12**, 124095-85-8; (±)-**13**, 123994-92-3; (±)-**14**, 123994-93-4; (±)-**15**, 123994-94-5; (±)-**16**, 123994-95-6; (±)-**17**, 123994-96-7; (±)-**18**, 123994-97-8; (±)-**19**, 123994-98-9; (±)-**20**, 123994-99-0; (±)-**21**, 124095-86-9; (±)-**22**, 123995-00-6; (±)-**23**, 124095-87-0; (±)-*cis*-**24**, 123995-01-7; (±)-*trans*-**24**, 123995-15-3; (±)-**25**, 123995-02-8; (±)-**26**, 123995-03-9; (±)-**27**, 123995-04-0; (±)-**28**, 124095-88-1; (±)-**29**, 123995-05-1; (±)-**30**, 123995-06-2; (±)-**31**, 124095-89-2; (±)-**32**, 123995-07-3; (±)-**33**, 124095-90-5; (±)-**34**, 123995-08-4; (±)-**35**, 123995-09-5; (±)-**36**, 123995-10-8; (±)-(*E*)-**37**, 123995-11-9; (±)-(*Z*)-**37**, 123995-16-4; (±)-**38**, 123995-12-0; (±)-**39**, 123995-13-1; (±)-**40**, 123995-14-2; (±)-**41**, 124095-91-6; MED, 126-39-6; $Ph_3P{=}CHCH_3$, 1754-88-7; $Ph_3P{=}CH_2$, 3487-44-3.

(27) According to GC analysis, the purity of **33** was 97%.

Stereoselective Synthesis and Absolute Stereochemistry of Sinefungin

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Sinefungin has been synthesized from D-ribose, L-ornithine, and adenine. L-Ornithine was converted to its δ-nitro analogue **10**, which was coupled to the ribose derived aldehyde **11** by a potassium fluoride catalyzed nitro-aldol reaction. The resulting nitro alcohol **12** was further transformed by dehydration and reduction of the nitrovinyl intermediate to the oxime, which was oxidatively cleaved to ketone **16**. The proper (*S*) stereochemistry at C-6 resulted from a stereoselective hydride reduction of this ketone to the epimeric alcohols in a 92/8 ratio and an S_N2 displacement of the corresponding *O*-tosylate by azide anion. The stereochemistry at C-6 was proved by correlation with the pyrrolidine obtained by cyclization of the tosylate to the α-[(4-methylphenyl)sulfonyl]amino group. The absolute stereochemistry of the pyrrolidine was determined by X-ray crystallographic analysis. Conversion of the azide **23** to sinefungin was accomplished by conversion of the ribose moiety to the corresponding β-acetate, adenosylation, reduction of the azide group to amino, and cleavage of the *tert*-butyl ester and *N*-tosyl protecting groups. The resulting synthetic sinefungin is identical with the natural material, thus providing a stereoselective synthesis and unequivocally establishing the absolute stereochemistry at C-6 as *S*.

The isolation of the antibiotic A-9145, sinefungin, was reported[1] from the fermentation broth of *Streptomyces griseolus*. Sinefungin, later[2] assigned structure **1**, is also produced by *Streptomyces incarnatus*.[3] It is a structural analogue of *S*-adenosylmethionine (**2**, SAM) and of *S*-adenosylhomocysteine (**3**, SAH) and exhibits a variety of biological effects including antiviral,[4] antifungal,[3,5] anti-

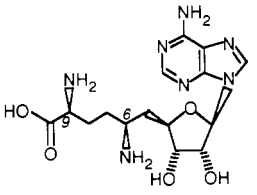
(1) (a) Hamill, R. L.; Hoehn, M. M. *Intersci. Conf. Antimicrob. Agents Chemother., 11th* **1971**, Abstr. 21. (b) Hamill, R. L.; Hoehn, M. M. *J. Antibiot.* **1973**, *26*, 463.

(2) Fuller, R. W.; Nagarajan, R. *Biochem. Pharmacol.* **1978**, *27*, 1981 and references therein.

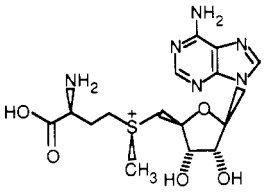
(3) Florent, J.; Lunel, J.; Mancy, D. U.S. Patent 4 189 349, 1980.

0022-3263/90/1955-0948$02.50/0

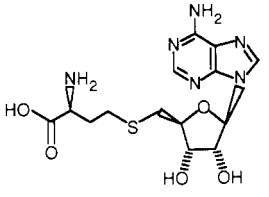
parasitic,[6] and amoebicidal[7] activities stemming primarily from the inhibition of SAM dependent methyl transferase enzymes.[8] The direct or indirect inhibition of these enzymes is currently of considerable interest, particularly in the area of antiviral research.[9] Sinefungin itself, however, is of limited clinical value due to its high in vivo toxicity.[10]



1



2



3

Three total syntheses[11] and several approaches[12] to sinefungin have been reported. Two of the syntheses produce products that are epimeric at C-6; the other gives a stereochemically pure product, but is plagued by a low-yielding separation of C-6 epimeric intermediates. Although the stereochemistry of 1 at C-6 is reported[11a,b] to be *S*, there are no published data to support this assignment. Furthermore, none of the previous syntheses contribute to defining the stereochemistry at C-6. Assignment of *S* stereochemistry at C-9, however, is supported[13] by the biosynthetic incorporation of L-ornithine, enzymatic degradation, and previous syntheses.[11]

We now report a synthesis of sinefungin that selectively sets the stereochemistry at C-6 in the *S* configuration and establish as well the absolute stereochemistry of the natural product by comparison with our synthetic material. The route used to synthesize sinefungin also is amenable to the preparation of analogues varying in substitution at C-1 and C-6.

Results and Discussion

Our synthetic strategy utilized the convergence of three readily available materials: D-ribose (**4**), L-ornithine (**5**), and adenine (**6**). The proper combination of these materials would assemble the entire framework of sinefungin as well as assure the proper stereochemistry at all stereocenters with the exception of C-1 and C-6. The carbon framework of sinefungin was to be built up by coupling a 5-nitro derived, protected L-ornithine to a suitable ribose 5-aldehyde. Following functional group manipulations to introduce the C-6 amino group of sinefungin, the adenine would be incorporated in the late stages of the synthesis to allow for potential flexibility in making analogues of sinefungin with different bases and to avoid carrying a reactive function throughout the sequence. No problems were anticipated in introducing the purine in the desired β-D-ribo configuration based on literature precedent. The most challenging aspect of the synthesis was clearly selective setting, and establishing, of the stereochemistry at C-6 so it could be used for assigning the stereogenicity at C-6 of natural sinefungin. A stereoselective reduction of one of several possible intermediates was expected to induce control at the C-6 center. Formation of an intermediate cyclic structure was perceived as a device for controlling or determining the C-6 stereochemistry and relating it to the other known stereogenic centers in the molecule.

Our synthesis commenced with the known[14] selectively N-protected ornithine derivative **7**, which was esterified by reaction with *O-tert*-butyl-*N,N'*-diisopropylisourea[15] to give **8** (Scheme I). Hydrogenolysis of **8** over Pd/C gave free 5-amine **9**, which was accompanied by a small amount of piperidone **9a** (0–5%). Oxidation of amine **9** with *m*-CPBA[16] gave 5-NO_2 **10** with yields in the 50–60% range. Potassium fluoride[17,12a] catalyzed nitroaldol condensation of **10** with β-D-ribose derived[18] aldehyde **11** in acetonitrile gave nitro alcohol **12** in 86% yield. The diastereomers of **12** could not be separated but were dehydrated as a mixture with DCC/CuCl[19] to give the cis and trans nitroalkenes **13a,b** in 96% yield. Reduction of **13a,b** with zinc and acetic acid[20] produced the oximes **14a,b** in 84% yield.

At this point three options were considered for attempting to stereoselectively set the C-6 center: (1) reduce directly **14a,b** or a closely related alkoximino or acyloximino derivative; (2) reduce a 1,4,5,6-tetrahydropyridazine derivative obtained by linking the α and δ nitrogens of **14a,b**; or (3) effect a stereoselective ketone to alcohol reduction.

All attempts at stereoselectively introducing the C-6 amino group directly via reduction of oxime **14a,b** or a suitable derivative were unsuccessful. Therefore, in order to utilize the existing α-amino stereochemistry in **14a,b** to help induce a stereoselective reduction at C-6, pyridazine **15** was synthesized from **14a,b** by a DCC/CuCl mediated intramolecular nitrogen–nitrogen bond forming reaction.

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(7) Ferrante, A.; Ljungstroem, I.; Huldt, G.; Lederer, E. *Trans. R. Soc. Trop. Med. Hyg.* **1984**, *78*, 837.

(8) Blanchard, P.; Dodic, N.; Fourrey, J. L.; Geze, M.; Lawrence, F.; Malina, H.; Paolantonacci, P.; Vedel, M.; Tempete, C.; Robert-Gero, M.; Lederer, E. In *Biological Methylation and Drug Design*; Borchardt, R. T., Creveling, C. R., Veland, P. M., Eds.; Humana: Clifton, NJ, 1986, pp 435–446.

(9) (a) Broom, A. D. *J. Med. Chem.* **1989**, *32*, 2. (b) McCarthy, J. R.; Jarvi, E. T.; Matthews, D. P.; Edwards, M. L.; Prakash, N. J.; Bowlin, T. L.; Mehdi, S.; Sunkara, P. S.; Bey, P. *J. Am. Chem. Soc.* **1989**, *111*, 1128. (c) Keller, B. T.; Borchardt, R. T. *NATO ASI Ser., Ser. A* **1988**, *143*, 123. (d) Borchardt, R. T. *Neurol. Neurobiol.* **1988**, *40*, 281.

(10) Zweygerth, E.; Schillinger, D.; Kaufmann, W.; Roettcher, D. *Trop. Med. Parasitol.* **1986**, *37*, 255.

(11) (a) Buchanon, J. G.; Flinn, A.; Mundill, P. H.; Wightman, R. H. *Nucleosides Nucleotides* **1986**, *5*, 313. (b) Geze, M.; Blanchard, P.; Fourrey, J. L.; Robert-Gero, M. *J. Am. Chem. Soc.* **1983**, *105*, 7638. (c) Mock, G. A.; Moffat, J. G. *Nucleic Acids Res.* **1982**, *10*, 6223.

(12) (a) Mizuno, Y.; Tsuchida, K.; Tampo, H. *Chem. Pharm. Bull.* **1984**, *32*, 2915. (b) Moorman, A. R.; Martin, T.; Borchardt, R. T. *Carbohydr. Res.* **1983**, *113*, 233. (c) Lyga, J. W.; Secrist, J. A., III *J. Org. Chem.* **1983**, *48*, 1982.

(13) (a) Berry, D. R.; Abbott, B. J. *J. Antibiot.* **1978**, *31*, 185. (b) Hamill, R. L.; Carrell, C. B.; Nash, S. M.; Nagarajan, R. *Abstr. Intersci. Conf. Antimicrob. Agents Chemother., 17th* **1977**, Abstr. 48.

(14) Barass, B. C.; Elmore, D. T. *J. Chem. Soc.* **1957**, 3134.

(15) Reviewed in the following: Mathias, L. J. *Synthesis* **1979**, 561.

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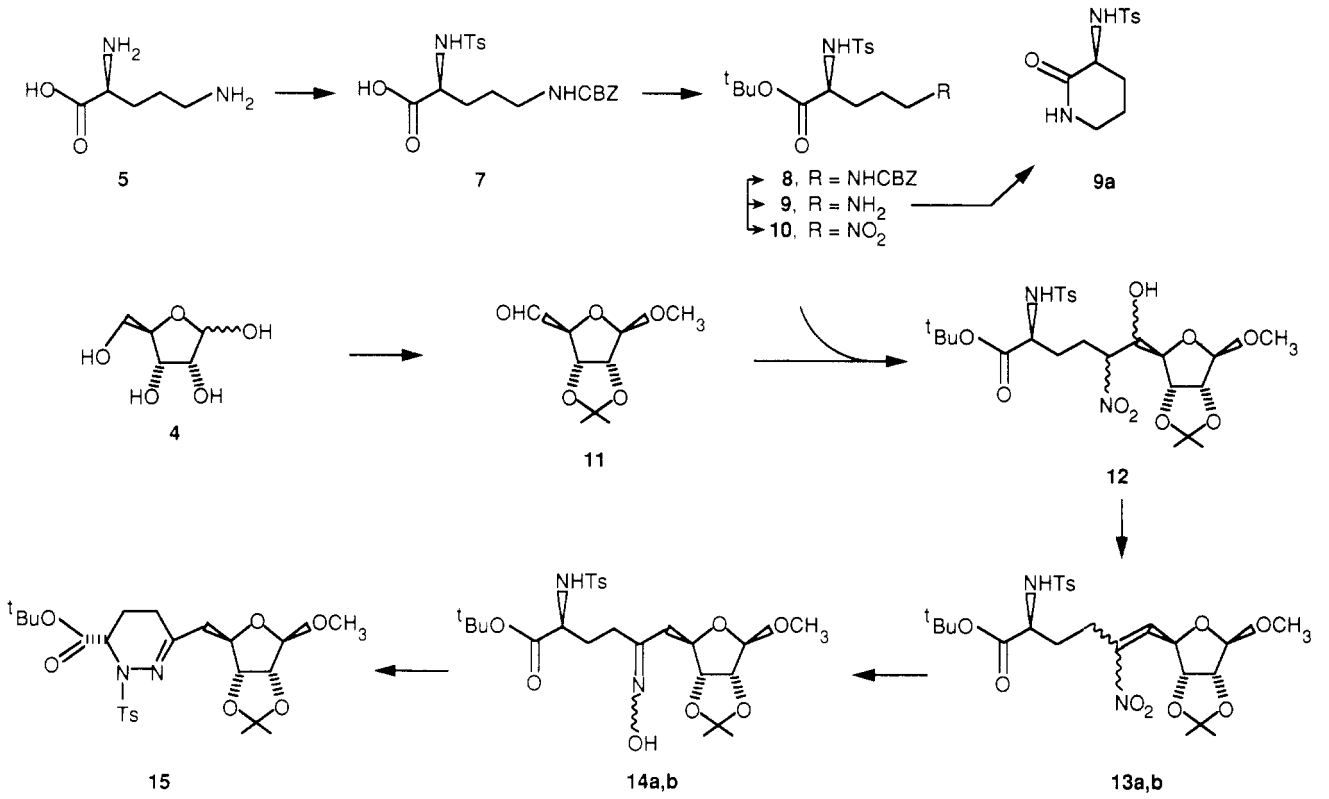
(18) Jones, G. H.; Moffatt, J. G. *Methods Carbohydr. Chem.* **1972**, *6*, 315.

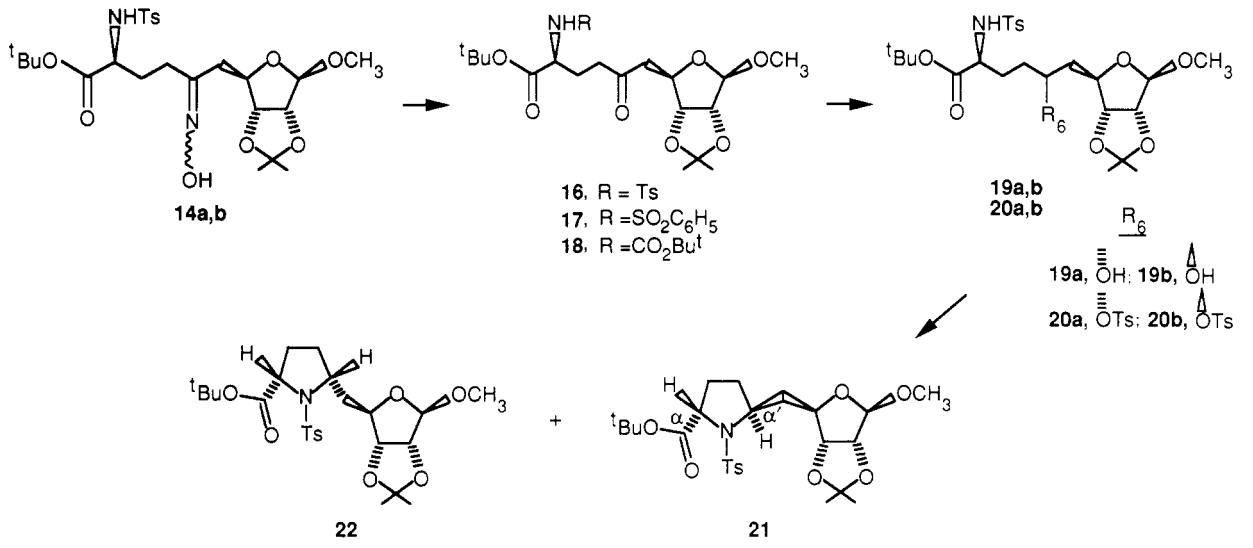
(19) Knochel, P.; Seebach, D. *Synthesis* **1982**, 1017.

(20) Baer, H. H.; Rank, W. *Can. J. Chem.* **1972**, *50*, 1292.

Scheme I



Scheme II



Although the yield of **15** was only 33% (ketone **16** was formed as the principle side product), attempts at reducing the C–N double bond were undertaken. Using a variety of mild selective reducing agents, no reduction of the 2,3 (N=C) bond of **15** was obtained.

A stereoselective reduction of a C-6 ketone to an alcohol could also provide a means of selectively introducing the amino group necessary for sinefungin. This strategy, although less direct than the two previous options, could also provide flexibility for introducing other groups at C-6. Synthesis of the C-6 ketone **16** was conveniently executed in 81% yield by oxidatively hydrolyzing oximes **14a,b** with ceric ammonium nitrate.[21] L-Selectride reduction of **16** gave a high ratio (92/8)[22] of diastereomeric alcohols **19a** and **19b** (Scheme II). The inseparable epimeric alcohols were esterified with *p*-toluenesulfonic acid anhydride[23] in 94% yield, and the tosylates **20a** and **20b**, although difficult to separate by chromatography, gave diastereomerically pure (>99% de) **20a** in 63% yield on a single recrystallization from ether.

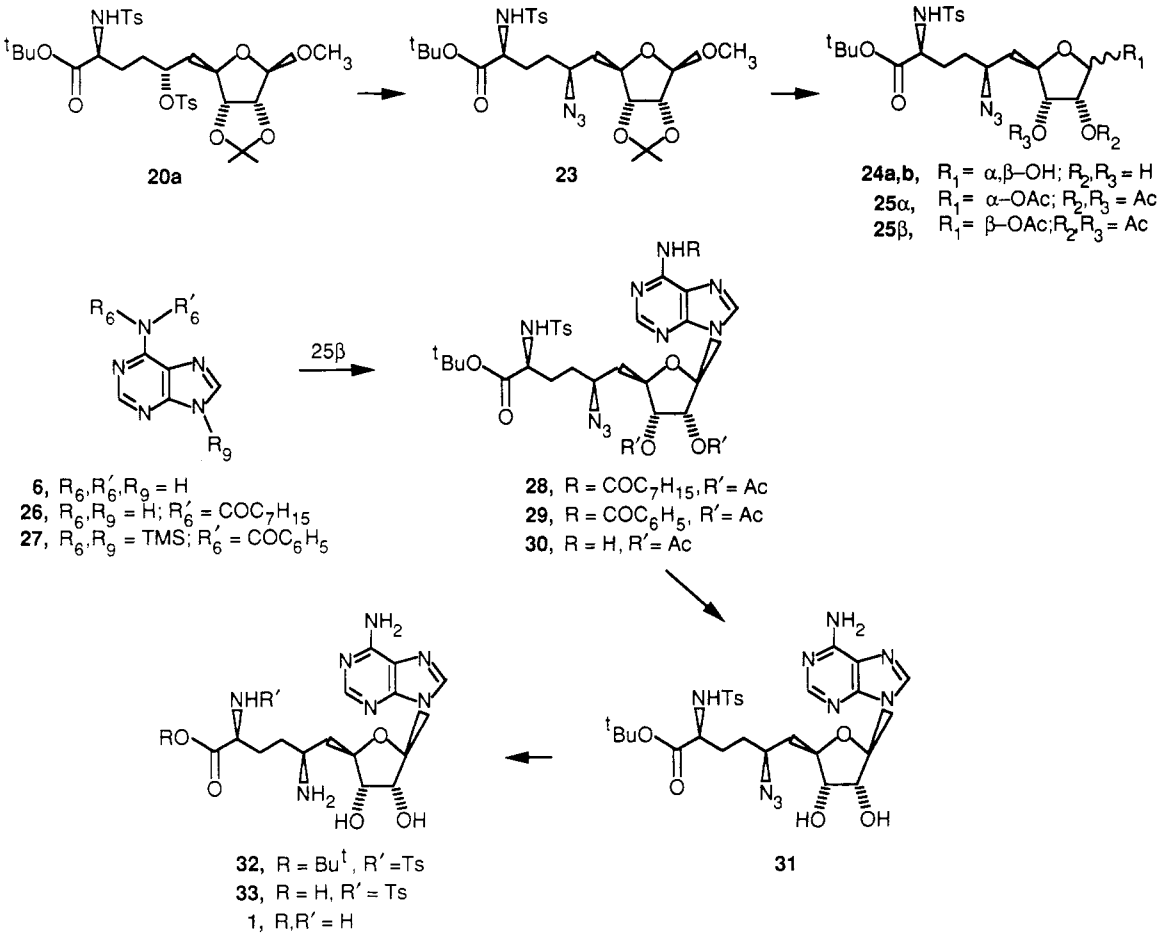
While the precise reason for the high diastereoselectivity in the reduction is not clear, it is clear that the nitrogen protecting group is playing an important role in influencing hydride attack. For example, L-Selectride reduction of **17** and **18** (prepared at an earlier stage of the project) gave diastereomeric ratios of 83/17 and 64/36, respectively. Use

(21) Bird, J. W.; Diaper, D. G. M. *Can. J. Chem.* **1969**, *47*, 145.

(22) Determined by ^{1}H NMR integration of the C1-H.

(23) Use of *p*-toluenesulfonyl chloride resulted in formation of a significant amount of the C-6 chloro compound.

Scheme III



of a variety[24] of other reducing agents generally gave inferior results.

Having found a suitable means of setting the C-6 stereochemistry, it was now necessary to determine whether the major isomer had the *R* or *S* configuration. In order to relate the unknown C-6 stereocenter to the known configuration of C-9, pyrrolidines **21** and **22**, which should be preparable by cyclizing **20a** and **20b**, were considered good candidates for determining the C-6 stereochemistry by using NOE measurements, provided both epimers could be prepared and separated.

The synthesis of pyrrolidine **21** was effected by sodium hydride induced cyclization of diastereomerically pure tosylate **20a** in 93% yield. In order to synthesize diastereomer **22**, larger quantities of **19b**, the minor product in the L-Selectride reduction, were required. Thus a nonselective reducing agent was employed to reduce **16**. Upon treatment of ketone **16** with sodium borohydride, a mixture of **19a** and **19b** was formed in a 55/45 ratio. Tosylation (**20a,b**) followed by cyclization of the mixture gave a 55/45 mixture of epimeric pyrrolidines **21** and **22**. Although these pyrrolidines could not be separated by chromatography, they could be separated by crystallization since **22** is crystalline and **21** is an oil. Three recrystallizations from hexane/benzene yielded pure crystalline **22** (no **21** could be detected by NMR).

The results of the NOE experiments on **21** and **22** proved to be inconclusive. The NOESY cross peaks for α-H, α'-H (of **21** and **22**) were not observable in benzene-d_6 because of unfavorable correlation times for molecules of this size. In cyclohexanol-d_{12}/benzene-d_6, 95/5, more favorable correlation times were obtained; however, the α-H, α'-H cross peaks were not definitive due to T_1 noise. Therefore, suitable crystals of **22** were grown from hexane/ethyl acetate and submitted to X-ray crystallographic analysis. The X-ray structure determination establishes that the protons α and α' to the pyrrolidine nitrogen are cis and that the stereochemistry at α'-C is *R*. Therefore, it follows that the stereochemistry at α'-C of **21** is *S* and it is *R* at C-6 of **20a**.

The absolute stereochemistry of **20a** having been determined, the C-6 *S* amino group was introduced in masked form by treating **20a** with sodium azide, yielding **23** in quantitative yield (Scheme III). In preparation for the stereoselective adenosylation at C-1, the acetonide and methoxy protecting groups on the ribose portion of **23** were selectively removed in high yield (93%) by treatment with HCl in aqueous dioxane to give triols **24a,b**. Acetylation of **24a,b** using acetic anhydride and sodium acetate[25] gave an 84/16 mixture of **25β/25α** in 89% yield,[26] which was easily separated by chromatography.

In the adenosylation reactions, the anomeric β acetate **25β** was superior to **25α**, giving higher yields in shorter reaction times. The best results were obtained with **25β** and excess adenine with $SnCl_4$ in acetonitrile at 22 °C.[27] These conditions gave **30** in a 59% yield. Despite considerable efforts, higher yields could not be obtained. Use of 6-*N*-octanoyladenine[28] (**26**) as substrate gave, in the best

(24) Other reducing agents tried were the following: $Zn(BH_4)_2$, K-Selectride, Red-Al, $LiAl(O\text{-}t\text{-}Bu)_3H$, $NaCNBH_3$, and LS-Selectride.

(25) Use of pyridine as catalyst gave a 2/1 ratio of **25β/25α**.

(26) Recycling of **25α** can be accomplished in high yield (90%) by treatment with K_2CO_3 in methanol followed by reacetylation.

(27) Saneyoshi, M.; Satoh, E. *Chem. Pharm. Bull.* **1979**, *27*, 2518.

case ($SnCl_4$, 1,2-dichloroethane, 83 °C), a 48% yield of **28**. The reaction of **25β** with persilylated 6-*N*-benzoyladenine (**27**)[29] catalyzed by trimethylsilyl triflate or trimethylsilyl perchlorate gave **29** with yields in the 15–35% range. Although the silyl catalysts produced several intermediates which rearranged to **29**, the results were still inferior to those obtained with $SnCl_4$ catalysis for the same reaction (**25β** + **27**) to form **29** with fewer side products but still in only 50% yield. The use of unsubstituted adenine gives somewhat better yields, the reaction and isolation are easier to handle, and the need for a deprotection step is eliminated. One would not expect significant α-substitution to occur,[29,30] and we found none.

Deprotection of nucleoside **30** was accomplished in four maneuvers. The acetyl groups were removed by treatment of **30** with K_2CO_3 in methanol, which gave diol **31** in 88% yield. Hydrogenation of **31** over $Pd(OH)_2/C$ converted azide to amine and yielded **32** in 91%. Crude **32** was immediately treated with aqueous trifluoroacetic acid to cleave the *tert*-butyl ester and give **33**. Brief (1 min) exposure of unpurified **33** to sodium in liquid ammonia at −78 °C removed the *N*-tosyl group and gave sinefungin (**1**) with relatively little side products[31] and with complete consumption of **33**. Longer reaction times and inefficient mixing decreased the yield.

The crude sinefungin was purified by ion-exchange chromatography followed by reverse-phase HPLC. Direct comparison with a sample of the natural material[32] confirmed the identity of **1**. The compounds were identical by reverse-phase HPLC and ^1H NMR. The presence of a clean doublet at δ 5.80 ppm [J = 4.6 Hz; 500 MHz, D_2O, δ relative to dioxane (3.53 ppm) as an internal standard] for the Cl-H in the spectrum of a mixture of natural and synthetic **1** was used as the primary diagnostic tool for assigning the identical stereochemistry at C-6. An epimeric mixture at C-6 is known[11c] to result in overlapping doublets at C1-H.[33]

Conclusion

A synthesis of sinefungin from L-ornithine, D-ribose, and adenine has been completed. One of the highlights of this route is the stereoselective reduction of ketone **16** to **19a**, which subsequently allowed incorporation of the C-6 amino group in the proper *S* configuration. This route provides flexibility in functionalizing the C-6 carbon since other groups could then be introduced selectively via S_N2 displacement of the tosylate in **20a**. Furthermore, analogues at C-1 should be accessible by using bases other than adenine in the Lewis acid mediated coupling with **25β**. Finally, this synthesis of sinefungin provides unambiguous proof that the stereochemistry at C-6 is *S*.

Experimental Section

Tetrahydrofuran was distilled from sodium and benzophenone; acetonitrile was distilled from CaH_2; pyridine was distilled from CaH_2; and dioxane was distilled from sodium. Potassium fluoride was dried by heating its dihydrate to 65 °C over P_2O_5 under high vacuum (0.1 mm) for 48 h. Unless otherwise stated, all other reagents were used as purchased from commercial sources.

^1H and ^{13}C NMR spectra were obtained by using a UCB spectrometer (250-MHz superconducting, FT instrument) or a Bruker AM-500 spectrometer with frequencies reported in parts per million (δ) downfield of internal TMS, and coupling constants in hertz. Melting points were determined on a Büchi melting point apparatus and are uncorrected. After extractive isolation, solutions were dried over Na_2SO_4 and solvents evaporated at water aspirator pressure from a rotary evaporator followed by exposure to a high vacuum (0.1 mm). Silica gel chromatography was conducted with 230–400-mesh silica gel (Merck). Elemental analysis and mass spectra were provided by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley, CA.

1,1-Dimethylethyl (*S*)-2-[[(4-Methylphenyl)sulfonyl]amino]-5-[[(phenylmethoxy)carbonyl]amino]pentanoate (8). To a solution of 132.0 g (314 mmol) of α-*N*-tosyl-δ-*N*-carbobenzoxyornithine (**7**) in 1150 mL of chloroform was added 115 g (575 mmol) of *O*-*tert*-butyldiisopropylisourea dropwise over a 1-h period at 22 °C. After stirring for another 30 min, an additional 55 g (275 mmol) of *O*-*tert*-butyldiisopropylisourea was added rapidly. The mixture was stirred at 22 °C for 22 h, quenched with 70 mL of water, and stirred for 1 h. The biphasic suspension was filtered through Celite, and the organic layer was separated, dried, and evaporated, to give a crude residue (ca. 170 g), which was filtered through silica gel (eluting with 3/2 ethyl acetate/hexane) to remove any remaining diisopropylurea and other polar impurities. Evaporation gave 123.4 g (82%) of **8** as an off-white solid. Recrystallization from methanol/petroleum ether gave an analytically pure sample of **8**: mp 96–97 °C; $[\alpha]^{23}_D$ +30° (*c* 2.0, $CHCl_3$); IR (KBr) 3410, 3270, 1728, 1700, 1172 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.23 (9 H, s), 1.59–1.77 (4 H, br m), 2.38 (3 H, s), 3.20 (2 H, m), 3.73 (1 H, m), 4.86 (1 H, br s), 5.09 (2 H, s), 5.28 (1 H, m), 7.26 (2 H, d, J = 8.2), 7.35 (5 H, m), 7.71 (2 H, d, J = 8.2). Anal. Calcd for $C_{24}H_{32}N_2O_6S$: C, 60.5; H, 6.8; N, 5.9. Found: C, 60.4; H, 6.9; N, 5.8.

1,1-Dimethylethyl (*S*)-5-Amino-2-[[(4-methylphenyl)sulfonyl]amino]pentanoate (9) and (*S*)-3-(Tosylamino)-2-piperidone (9a). To a solution of 105.0 g (221 mmol) of **8** in 900 mL of methanol was added 18.0 g of 10% Pd/C. The mixture was shaken under H_2 (60 psi) for 5 h, at which time another 10.0 g of 10% Pd/C was added and the hydrogenation was continued for 1 day. The reaction mixture was filtered through Celite, and the solvent was evaporated, to give 75.0 g (99%) of **9** as a light brown oil, which later solidified. The product was stored at −20 °C and used as such in the next reaction. Extended storage (several months) of **9** at 22 °C or higher resulted in the formation of a significant amount of **9a**. An analytically pure sample of **9** was prepared by chromatography on silica gel (eluting with 18/2/1 ethyl acetate/methanol/triethylamine) followed by recrystallization from hexane/ethyl acetate: mp 95–96 °C; $[\alpha]^{23}_D$ +25° (*c* 1.6, $CHCl_3$); IR (KBr) 3370, 1735, 1325, 1162, 1096 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (9 H, s), 1.52 (2 H, m), 1.72 (2 H, m), 2.40 (3 H, s), 2.70 (2 H, m), 3.80 (1 H, dd, J = 5.0, 7.0), 7.27 (2 H, d, J = 8.2), 7.72 (2 H, d, J = 8.2). Anal. Calcd for $C_{16}H_{26}N_2O_4S$: C, 56.1; H, 7.7; N, 8.2. Found: C, 56.3; H, 7.7; N, 8.3.

An analytical sample of **9a** was obtained by chromatography on silica gel (applied to the column in dichloromethane and eluted with ethyl acetate) followed by recrystallization (2×) from ethyl acetate: mp 184–184.5 °C; $[\alpha]^{23}_D$ +128° (*c* 1.05, $CHCl_3$); IR (KBr) 3230, 1650, 1420, 1327, 1162, 1095 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.68–2.05 (4 H, m), 2.42 (3 H, s), 3.28 (2 H, m), 3.51 (1 H, m), 5.87 (2 H, br s), 7.31 (2 H, d, J = 8.2), 7.78 (2 H, d, J = 8.2). Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.7; H, 6.0; N, 10.4. Found: C, 53.8; H, 6.0; N, 10.4.

1,1-Dimethylethyl (*S*)-5-Nitro-2-[[(4-methylphenyl)sulfonyl]amino]pentanoate (10). A solution of 8.37 g (24.5 mmol) of **9** in 400 mL of 1,2-dichloroethane at 75 °C was added to a rapidly refluxing solution of *m*-CPBA (33.7 g, 156–166 mmol, 80–85%) in 400 mL of dichloroethane over a period of 1 min. Refluxing was continued for an additional 17 min, and the reaction vessel was then cooled by an external ice bath for 15 min. A precipitate began to form, and the heterogeneous contents were poured into 500 mL of ethyl acetate and 350 mL of saturated

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(29) Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234 and references therein.
(30) Shone, R. L. *Tetrahedron Lett.* **1977**, 993.
(31) Adenosine is known to react with sodium and liquid ammonia [Burk, D. C. *J. Org. Chem.* **1955**, *20*, 643], however, at a slower rate.
(32) Obtained from Sigma and purified by reverse-phase HPLC.
(33) This is consistent with our observation that the ^1H NMR chemical shifts for C1-H and C1-OCH_3 are different for the C-6 epimers of **19**, **20**, and **23**. Also we have seen no evidence (^1H NMR, TLC, and ^{13}C NMR) at any point in the synthesis of any loss of stereochemical integrity at C-9.
(34) Chexray Facility, Department of Chemistry, University of California, Berkeley, California.

Na_2SO_3. The organic layer was separated, washed with saturated $NaHCO_3$ (2 × 400 mL) and brine (400 mL), then dried, and evaporated, to give 11.7 g of a crude light brown oil. The oil was chromatographed on silica gel (eluting with 7/3 hexane/ethyl acetate), and 5.10 g (56%) of **10** was obtained as an off-white solid. An analytical sample was secured by recrystallization from hexane/ethyl acetate: mp 102–103 °C; $[\alpha]^{23}_D$ +36° (*c* 1.0, $CHCl_3$); IR (KBr) 2838, 2498, 1730, 1560 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (9 H, s), 1.60–1.72 (1 H, m), 1.77–1.92 (1 H, m), 2.15 (2 H, m), 2.41 (3 H, s), 3.75 (1 H, m), 4.43 (2 H, t, *J* = 6.6), 5.21 (1 H, d, *J* = 8.6), 7.29 (2 H, d, *J* = 8.3), 7.71 (2 H, d, *J* = 8.3). Anal. Calcd for $C_{16}H_{24}N_2O_6S$: C, 51.6; H, 6.5; N, 7.5. Found: C, 51.7; H, 6.5; N, 7.5.

1,1-Dimethylethyl [Methyl-6-nitro-5,6,7,8,9-pentadeoxy-9(*S*)-[[(4-methylphenyl)sulfonyl]amino]-2,3-O-(1-methylethylidene)-β-D-*ribo*-dec-5-enofuranosid]uronates (13a,b). To a solution of 8.03 g (21.6 mmol) of **10** in 50 mL of acetonitrile were added 9.62 g (47.6 mmol) of aldehyde **11** and 0.63 g (10.9 mmol) of anhydrous potassium fluoride. After stirring at 22 °C under a nitrogen atmosphere for 24 h, the mixture was diluted with 500 mL of ethyl acetate, washed with 10% $NaHSO_3$ (3 × 100 mL) and brine (200 mL), and dried. Evaporation gave 16.1 g of crude solid, which was chromatographed on silica gel (applied to the column in chloroform and eluted with 7/3 hexane/ethyl acetate), to give 10.69 g (86%) of nitro alcohol **12** as a mixture of diastereomers. Separation of the diastereomers was unnecessary, and **12** was used as such in the next reaction. Anal. Calcd for $C_{25}H_{38}N_2O_{11}S$: C, 52.3; H, 6.7; N, 4.9. Found: C, 52.1; H, 6.6; N, 4.9.

To 90 mL of acetonitrile were added 10.1 g (17.5 mmol) of **12**, 7.95 g (38.5 mmol) of dicyclohexylcarbodiimide, and 1.74 g (17.6 mmol) of copper(I) chloride. The mixture was stirred under a nitrogen atmosphere at 35 °C for 16 h, diluted with 500 mL of ethyl acetate, and quenched by the addition of a solution of 9.71 g (77.1 mmol) of oxalic acid dihydrate in 25 mL of methanol. The resulting suspension was filtered through Celite, and the filtrate was washed with saturated $NaHCO_3$ (2 × 200 mL) and brine (200 mL) and dried. Evaporation gave 11.0 g of a crude solid, which was chromatographed on silica gel (eluting with 96/4 chloroform/ethyl acetate), to give 9.39 g (96% from **12**) of the mixture of cis and trans isomers **13a,b**. A pure sample of the less polar (TLC) isomer was obtained by silica gel chromatography (eluting with 2/1 hexane/ethyl acetate): mp 151–152 °C; IR ($CDCl_3$) 3320, 1730, 1525, 1161 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.28 (9 H, s), 1.34 (3 H, s), 1.54 (3 H, s), 1.90 (2 H, m), 2.40 (3 H, s), 2.76 (2 H, t, *J* = 8.2), 3.31 (3 H, s), 3.83 (1 H, m), 4.68 (2 H, s), 4.86 (1 H, d, *J* = 9.3), 5.04 (1 H, s), 5.31 (1 H, d, *J* = 8.4), 7.03 (1 H, d, *J* = 9.3), 7.29 (2 H, d, *J* = 8.3), 7.74 (2 H, d, *J* = 8.2). Anal. Calcd for $C_{25}H_{36}N_2O_{10}S$: C, 54.0; H, 6.5; N, 5.0. Found: C, 53.8; H, 6.5; N, 4.9.

1,1-Dimethylethyl [Methyl-6-hydroximino-5,6,7,8,9-pentadeoxy-9(*S*)-[[(4-methylphenyl)sulfonyl]amino]-2,3-O-(1-methylethylidene)-β-D-*ribo*-decofuranosid]uronates (14a,b). To 5.00 g (8.99 mmol) of **13a,b** in 150 mL of THF was added 4.25 g (64.9 mmol) of zinc dust (freshly activated by stirring in 2 N HCl, then washing twice with water, twice with ethanol, and twice with ether, and drying under high vacuum) followed by 30 mL of 4 N acetic acid. The mixture was stirred at 45 °C for 15 min and then cooled to 0 °C, causing precipitation of zinc salts. The suspension was filtered, and the filtrate was mixed with 250 mL of saturated $NaHCO_3$ and concentrated by evaporation to remove volatile organic solvents. The aqueous mixture was extracted with ethyl acetate (2 × 200 mL), and the combined organics were washed with brine (150 mL) and dried. Evaporation gave 4.9 g of a crude foam, which was chromatographed on silica gel (applied to the column in chloroform and eluted with 7/3 hexane/ethyl acetate), to give 4.10 g (84%) of a mixture of **14a,b** (foam), which was used directly in the next reaction. Careful chromatography allowed for partial separation of **14a** and **14b**. For the higher R_f oxime: IR ($CDCl_3$) 3590, 3350, 1730 cm^{-1}; ^1H NMR δ 1.25 (9 H, s), 1.32 (3 H, s), 1.48 (3 H, s), 1.65–2.10 (4 H, m), 2.39 (3 H, s), 2.50 (1 H, m), 2.82 (1 H, m), 3.37 (3 H, s), 3.77 (1 H, m), 4.48 (1 H, t, *J* = 7.7), 4.65 (2 H, m), 4.96 (1 H, s), 5.84 (1 H, br s), 7.28 (2 H, d, *J* = 8.2), 7.72 (2 H, d, *J* = 8.2). For the lower R_f oxime: IR ($CDCl_3$) 3590, 3320, 1730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.26 (9 H, s), 1.32 (3 H, s), 1.48 (3 H, s), 1.59–2.04 (4 H, m), 2.40 (3 H, s), 2.45 (2 H, m), 3.34 (3 H, s), 3.80 (1 H, m), 4.49 (1 H, m), 4.62 (2 H, m), 4.95 (1 H, s), 5.38 (1 H, d, *J* = 8.9), 7.28 (2 H, d, *J* = 8.3), 7.73 (2 H, d, *J* = 8.3).

Methyl [5-Deoxy-5-[6(*S*)-[(1,1-dimethylethoxy)carbonyl]-1,4,5,6-tetrahydro-1-[(4-methylphenyl)sulfonyl]-3-pyridazinyl]-2,3-O-(1-methylethylidene)-β-D-ribofuranoside (15). To a solution of 200 mg (0.369 mmol) of **14a,b** in 10 mL of dry acetonitrile were added 228 mg (1.11 mmol) of dicyclohexylcarbodiimide and 37 mg (0.369 mmol) of copper(I) chloride. The mixture was stirred at 22 °C for 24 h, diluted with 75 mL of ethyl acetate, and quenched with 280 mg (2.21 mmol) of oxalic acid dihydrate in 3 mL of methanol. The suspension was filtered, and the filtrate was washed with saturated $NaHCO_3$ (2 × 30 mL) and brine (30 mL) and dried. Evaporation gave 300 mg of a crude residue, which was chromatographed on silica gel (eluting with 7/3 hexane/ethyl acetate), to give 64 mg (33%) of **15** as a colorless oil: IR ($CDCl_3$) 2980, 2930, 1735, 1600, 1170, 1150 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.29 (3 H, s), 1.37 (9 H, s), 1.48 (3 H, s), 1.82–2.35 (4 H, m), 2.40 (3 H, s), 2.47 (2 H, d, *J* = 7.7), 3.29 (3 H, s), 4.41 (1 H, t, *J* = 7.7), 4.55 (1 H, d, *J* = 5.9), 4.63 (1 H, d, *J* = 5.9), 4.88 (1 H, m), 4.91 (1 H, s), 7.24 (2 H, d, *J* = 8.1), 7.85 (2 H, d, *J* = 8.1); exact mass calcd for $C_{25}H_{36}N_2SO_8$ (M^+) 524.2183, found 524.2208.

1,1-Dimethylethyl [Methyl-5,7,8,9-tetradeoxy-9(*S*)-[[(4-methylphenyl)sulfonyl]amino]-2,3-O-(1-methylethylidene)-β-D-*ribo*-6-deculofuranosid]uronate (16). A solution of 1.00 g (1.84 mmol) of **14a,b** in 30 mL of ethanol was cooled to −42 °C in a $(CH_2Cl)_2$/acetone/CO_2 cooling bath. A separate solution of 3.54 g (6.46 mmol) of cerium(IV) ammonium nitrate in 20 mL of 0.5 N HNO_3 and 10 mL of ethanol (prepared at 0 °C) was cooled to −23 °C in an externally (CCl_4/CO_2 bath) cooled addition funnel and added rapidly to the solution containing **14a,b**. The heterogeneous mixture was stirred at −42 °C (bath temperature) for 15 min and poured into 100 mL of ice water and 125 mL of ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL) and dried, to give 1.0 g of crude **16**. The product was chromatographed on silica gel (eluting with 7/3 hexane/ethyl acetate), to give 791 mg (81%) of **16**. Two recrystallizations from ethyl acetate/hexane furnished an analytically pure sample: mp 104–106 °C; $[\alpha]^{28}_D$ +4.4° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3340, 1725, 1380, 1350, 1162, 1100 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.21 (9 H, s), 1.32 (3 H, s), 1.50 (3 H, s), 1.68 (1 H, m), 2.12 (1 H, m), 2.39 (3 H, s), 2.55–2.94 (4 H, m), 3.34 (3 H, s), 3.70 (1 H, m), 4.62 (3 H, m), 4.94 (1 H, s), 5.14 (1 H, d, *J* = 9.27), 7.27 (2 H, d, *J* = 8.3), 7.68 (2 H, d, *J* = 8.3). Anal. Calcd for $C_{25}H_{37}NO_9S$: C, 56.9; H, 7.1; N, 2.7. Found: C, 57.0; H, 7.0; N, 2.8.

1,1-Dimethylethyl [Methyl-5,7,8,9-tetradeoxy-9(*S*)-[[(4-methylphenyl)sulfonyl]amino]-2,3-O-(1-methylethylidene)-β-D-*allo*-decofuranosid]uronate (19a) and Its C-6 Epimer 19b. A solution of 1.50 g (2.85 mmol) of ketone **16** in 30 mL of THF was cooled to −78 °C under a nitrogen atmosphere, and 8.6 mL (8.6 mmol) of L-Selectride, 1.0 M in THF, was added dropwise over 15 min. The solution was stirred for 2 h at −78 °C, diluted with 200 mL of ethyl acetate, and quenched with 100 mL of 1 N citric acid. The organic layer was separated, washed with saturated $NaHCO_3$ (75 mL) and brine (75 mL), and dried. Evaporation gave 2.42 g of an oil, which was chromatographed on silica gel (eluting with 3/2 hexane/ethyl acetate), to give 1.21 g (80%) of pure **19a,b** in a ratio of 92/8 (by ^1H NMR integration of C1-H). Recrystallization from ether/petroleum ether increased the diastereomer ratio to 95/5: mp 100–101 °C; IR ($CDCl_3$) 3530, 3340, 1730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.23 (9 H, s), 1.32 (3 H, s), 1.49 (3 H, s), 1.50–1.98 (6 H, m), 2.39 (3 H, s), 3.38 (3 H, s), 3.78 (2 H, m), 4.35 (1 H, m), 4.58 (2 H, m), 4.98 (1 H, s), 5.27 (1 H, d, *J* = 9.3), 7.28 (2 H, d, *J* = 8.3), 7.72 (2 H, d, *J* = 8.3). Anal. Calcd for $C_{25}H_{39}NO_9S$: C, 56.7; H, 7.4; N, 2.6. Found: C, 56.7; H, 7.4; N, 2.7.

1,1-Dimethylethyl [Methyl-5,7,8,9-tetradeoxy-6-O-[(4-methylphenyl)sulfonyl]-9(*S*)-[[(4-methylphenyl)sulfonyl]amino]-2,3-O-(1-methylethylidene)-β-D-*allo*-decofuranosid]uronate (20a). A solution of 1.20 g (2.27 mmol) of **19a,b** (**19a**/**19b**, 92/8) in 30 mL of pyridine was cooled to 0 °C, and 2.37 g (7.26 mmol) of *p*-toluenesulfonic acid anhydride was added in one portion. The solution was stirred at 0 °C for 40 min, diluted with ethyl acetate (200 mL), washed with 1 N citric acid

(4 × 50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL), and dried. Evaporation gave 1.69 g of crude solid, which was chromatographed on silica gel (eluting with 6.5/3.5 hexane/ethyl acetate), to give 1.45 g (94%) of **20a** and its C-6 epimer **20b** in a ratio of 92/8. A single recrystallization from ether gave pure **20a** (63% yield, >99% de): mp 107–108 °C; $[\alpha]^{28}_D$ +11° (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) 3340, 1730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.24 (9 H, s), 1.30 (3 H, s), 1.46 (3 H, s), 1.60–2.10 (6 H, m), 2.40 (3 H, s), 2.44 (3 H, s), 3.35 (3 H, s), 3.64 (1 H, m), 4.13 (1 H, m), 4.47 (1 H, d, *J* = 6.0), 4.57 (1 H, d, *J* = 6.0), 4.75 (1 H, m), 4.91 (1 H, s), 5.08 (1 H, d, *J* = 5.9), 7.28 (2 H, d, *J* = 8.2), 7.33 (2 H, d, *J* = 8.2), 7.69 (2 H, d, *J* = 8.2), 7.78 (2 H, d, *J* = 8.2). Anal. Calcd for $C_{32}H_{45}NO_{11}S_2$: C, 56.2; H, 6.6; N, 2.1. Found: C, 56.2; H, 6.7; N, 2.2.

(2*R*)-*cis*-Methyl [5-Deoxy-5-[5-[(1,1-dimethylethoxy)carbonyl]-1-[(4-methylphenyl)sulfonyl]-2-pyrrolidinyl]-2,3-*O*-(1-methylethylidene)-β-D-ribofuranoside (22) and Its 2*S*-*trans* Epimer 21. A solution of 572 mg (1.09 mmol) of ketone **16** in 15 mL of absolute ethanol was cooled to 0 °C, and 62 mg (1.6 mmol) of sodium borohydride was added. The mixture was stirred at 0 °C for 2 h and then partitioned between ethyl acetate (50 mL) and water (25 mL). The organic layer was washed with 1 N citric acid (25 mL), saturated $NaHCO_3$ (25 mL), and brine (25 mL) and dried. Evaporation gave 574 mg (100%) of a clean mixture of **19a** and **19b** (**19a**/**19b**, 55/45), which was used directly in the next step without further purification.

A solution of 574 mg (1.09 mmol) of **19a,b** (from above) in 15 mL of pyridine was cooled to 0 °C, and 1.13 g (3.46 mmol) of *p*-toluenesulfonic acid anhydride was added. The solution was stirred at 0 °C for 1 h, diluted with ethyl acetate (100 mL), washed with 1 N citric acid (4 × 50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL), and dried. Evaporation gave 871 mg of a crude oil, which was chromatographed on silica gel (eluting with 65/35 hexane/ethyl acetate), to give 660 mg (89%) of **20a,b** (**20a**/**20b**, 55/45), which was used directly in the next step.

To a solution of 655 mg (0.959 mmol) of **20a,b** (from above) in 16 mL of THF cooled to 0 °C was added 51 mg (1.06 mmol) of a 50% mineral oil suspension of sodium hydride. The mixture was stirred for 3 h at 0 °C, diluted with 50 mL of ethyl acetate, washed with 1 N citric acid (25 mL), saturated $NaHCO_3$ (25 mL), and brine (20 mL), and dried. Evaporation gave 700 mg of a crude oil, which was chromatographed on silica gel (eluting with chloroform), to give 456 mg (93%) of a 55/45 mixture of **21**/**22** (ratios determined by ^1H NMR integration of OCH_3). Recrystallization from hexane/benzene gave 260 mg of a 40/60 mixture of **21**/**22**. A second recrystallization from hexane/benzene then gave 134 mg of a 3/97 diastereomeric mixture, while a third recrystallization, also from hexane/benzene, gave 110 mg of pure **22** (no trace of **21** could be detected by ^1H NMR). Recrystallization from hexane/ethyl acetate (by slow cooling to 0 °C over a 5-day period) gave crystals of **22** that were suitable for X-ray analysis: mp 138.5–139.5 °C; $[\alpha]^{23}_D$ −22° (*c* 0.5, $CHCl_3$); IR (KBr) 1740, 1155 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.32 (3 H, s), 1.45 (9 H, s), 1.47 (3 H, s), 1.70–2.00 (5 H, m), 2.37 (1 H, m), 2.42 (3 H, s), 3.47 (3 H, s), 4.10 (1 H, m), 4.17 (2 H, m), 4.55 (1 H, d, *J* = 5.9), 4.64 (1 H, d, *J* = 5.9), 4.97 (1 H, s), 7.29 (2 H, d, *J* = 8.2), 7.73 (2 H, d, *J* = 8.2). Anal. Calcd for $C_{25}H_{37}NO_8S$: C, 58.7; H, 7.3; N, 2.7. Found: C, 58.7; H, 7.3; N, 2.7.

A similar sodium hydride mediated cyclization of diastereomerically pure **20a** gave **21** (93%) as an oil: $[\alpha]^{23}_D$ −88° (*c* 1.1, $CHCl_3$); IR ($CDCl_3$) 1728, 1152 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.33 (3 H, s), 1.46 (12 H, s), 1.92 (2 H, m), 2.21 (4 H, m), 2.41 (3 H, s), 3.21 (3 H, s), 4.01 (2 H, m), 4.24 (1 H, br d, *J* = 7.2), 4.60 (1 H, d, *J* = 6.1), 4.63 (1 H, d, *J* = 6.1), 4.89 (1 H, s), 7.27 (2 H, d, *J* = 8.2), 7.74 (2 H, d, *J* = 8.2). Anal. Calcd for $C_{25}H_{37}NSO_8$: C, 58.7; H, 7.3; N, 2.7. Found: C, 58.8; H, 7.4; N, 2.8.

1,1-Dimethylethyl [Methyl-6(*S*)-azido-5,6,7,8,9-pentadeoxy-9(*S*)-[[(4-methylphenyl)sulfonyl]amino]-2,3-*O*-(1-methylethylidene)-β-D-*ribo*-decofuranosid]uronate (23). To a solution of 881 mg (1.29 mmol) of **20a** in 75 mL of dimethylformamide were added 4.19 g of sodium azide (64.5 mmol) and 3.45 g (64.5 mmol) of ammonium chloride. The mixture was stirred at 22 °C for 16 h, poured into water (300 mL), and extracted with ether (300 mL). The ethereal extract was washed with water (2 × 100 mL) and brine (100 mL) and dried. Evaporation gave 714 mg (100%) of **23** (pure by ^1H NMR). An analytical sample was prepared by two recrystallizations from hexane: mp 90–91 °C; $[\alpha]^{23}_D$ +38° (*c* 1.2, $CHCl_3$); IR (KBr) 3210, 2104, 1736, 1343, 1170, 1097 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (9 H, s), 1.31 (3 H, s), 1.48 (3 H, s), 1.52–1.93 (6 H, m), 2.40 (3 H, s), 3.35 (3 H, s), 3.38 (1 H, m), 3.56 (1 H, m), 4.38 (1 H, m), 4.53 (1 H, d, *J* = 5.9), 4.60 (1 H, d, *J* = 5.9), 4.95 (1 H, s), 5.20 (1 H, d, *J* = 8.8), 7.28 (2 H, d, *J* = 8.3), 7.70 (2 H, d, *J* = 8.3). Anal. Calcd for $C_{25}H_{38}N_4SO_8$: C, 54.1; H, 6.9; N, 10.1. Found: C, 54.5; H, 6.8; N, 10.1.

1,1-Dimethylethyl 6(*S*)-Azido-5,6,7,8,9-pentadeoxy-9(*S*)-[[(4-methylphenyl)sulfonyl]amino]-1,2,3-tri-*O*-acetyl-β-D-*ribo*-decofuranuronate (25β) and Its C-1 Epimer 25α. To a solution of 739 mg (1.33 mmol) of **23** in 135 mL of dioxane was added 45 mL of 4 N HCl. The biphasic mixture was stirred at 22 °C for 96 h and then partitioned between 750 mL of ethyl acetate and 375 mL of 0.5 N Na_2HPO_4, and the aqueous layer was back-extracted with ethyl acetate (2 × 750 mL). The combined organic extracts were washed with brine (250 mL), dried, and evaporated, to give 620 mg (93%) of crude **24a,b** as an off-white solid, which was used directly in the next step.

To a solution of 620 mg (1.24 mmol) of **24a,b** in 80 mL of acetic anhydride was added 1.24 g (15.1 mmol) of sodium acetate. The mixture was stirred at 50 °C for 6.5 h, and the solvent was evaporated. The residue was coevaporated with xylene twice and then partitioned between water (150 mL) and ethyl acetate (200 mL). The organic layer was washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried, and evaporated, to give 859 mg of a foam. This foam was chromatographed on silica gel (eluting with 7/3 hexane/ethyl acetate), to give 554 mg of pure **25β** (eluted first) and 137 mg (89% combined yield from **24a,b**) of an 84/16 mixture of **25α** and **25β** (by ^1H NMR integration of C1-H). For **25β** (foam): $[\alpha]^{23}_D$ +41° (*c* 1.1, $CHCl_3$); IR (KBr) 3290, 2108, 1750, 1375, 1222, 1161 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (9 H, s), 1.52–1.85 (6 H, m), 2.09 (3 H, s), 2.11 (3 H, s), 2.15 (3 H, s), 2.40 (3 H, s), 3.58 (1 H, m), 3.74 (1 H, m), 4.32 (1 H, m), 5.14–5.25 (2 H, m), 5.33 (1 H, d, *J* = 4.8), 6.16 (1 H, s), 7.30 (2 H, d, *J* = 8.2), 7.71 (2 H, d, *J* = 8.2). Anal. Calcd for $C_{27}H_{38}N_4O_{11}S$: C, 51.8; H, 6.1; N, 8.9. Found: C, 51.8; H, 6.3; N, 8.8.

For **25α** (foam): ^1H NMR (250 MHz, $CDCl_3$) δ 1.26 (9 H, s), 1.56–1.95 (6 H, m), 2.08 (3 H, s), 2.12 (3 H, s), 2.14 (3 H, s), 2.40 (3 H, s), 3.54 (1 H, m), 3.75 (1 H, m), 4.36 (1 H, m), 5.00 (1 H, dd, *J* = 4.2, 6.9), 5.23 (1 H, m), 5.27 (1 H, d, *J* = 8.5), 6.39 (1 H, d, *J* = 4.6), 7.29 (2 H, d, *J* = 8.2), 7.72 (2 H, d, *J* = 8.2).

1,1-Dimethylethyl 1-(6-Amino-9*H*-purin-9-yl)-6(*S*)-azido-2,3-di-*O*-acetyl-1,5,6,7,8,9-hexadeoxy-9(*S*)-[[(4-methylphenyl)sulfonyl]amino]-β-D-*ribo*-decofuranuronate (30). To a mixture of 1.08 g (7.99 mmol) of adenine in 50 mL of anhydrous acetonitrile (distilled from P_2O_5 and then from CaH_2) under a nitrogen atmosphere was added 7.64 mL (7.98 mmol) of a 1.05 M solution of $SnCl_4$ in 1,2-dichloroethane. After 15 min of stirring at 22 °C, the adenine dissolved and a solution of 500 mg (0.799 mmol) of **25β** in 15 mL of acetonitrile was added via syringe. An additional 10 mL of acetonitrile was used to complete the transfer. The resulting solution was stirred at 22 °C for 16 h and then partitioned between 500 mL of ethyl acetate and 500 mL of 0.5 N Na_2HPO_4. The aqueous layer was back-extracted with ethyl acetate (250 mL), and the combined organics were washed with brine (250 mL), dried, and evaporated, to give 600 mg of an off-white solid. This solid was chromatographed on silica gel (eluting with ethyl acetate), to give 279 mg (50%; a 59% yield was obtained on an 89-mg scale) of **30** as an amorphous solid: $[\alpha]^{23}_D$ + 37° (*c* 1.2, $CHCl_3$); IR (KBr) 2640–3700, 2109, 1745, 1645, 1245, 1160 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.23 (9 H, s), 1.59–1.95 (6 H, m), 2.07 (3 H, s), 2.15 (3 H, s), 2.36 (3 H, s), 3.50 (1 H, m), 3.80 (1 H, m), 4.37 (1 H, m), 5.54 (1 H, m), 6.09 (2 H, m), 6.41 (2 H, br s), 6.76 (1 H, d, *J* = 9.3), 7.24 (2 H, d, *J* = 8.3), 7.71 (2 H, d, *J* = 8.3), 8.00 (1 H, s), 8.33 (1 H, s).

1,1-Dimethylethyl 1-(6-Amino-9*H*-purin-9-yl)-6(*S*)-azido-1,5,6,7,8,9-hexadeoxy-9*S*-[[(4-methylphenyl)sulfonyl]amino]-β-D-*ribo*-decofuranuronate (31). To a solution of 235 mg (0.335 mmol) of **30** in 20 mL of methanol was added 500 mg (3.62 mmol) of potassium carbonate. The mixture was stirred at 22 °C for 30 min, and then 0.31 mL of acetic acid was added. After an additional 45 min of stirring, the solvent was evaporated and the residue partitioned between water (25 mL) and ethyl acetate (50 mL). The aqueous layer was back-extracted with ethyl

acetate (2 × 20 mL), and the combined organics were washed with brine (25 mL), dried ($MgSO_4$), and evaporated, to give 200 mg of an off-white solid. The solid was chromatographed on silica gel (eluting with 95/5 ethyl acetate/methanol), to give 182 mg (88%) of **31** as a white powder: mp 95–110 °C; $[\alpha]^{23}_D$ +61° (*c* 2.0, $CHCl_3$); IR (KBr) 2480–3700, 2105, 1729, 1642, 1160 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.18 (9 H, s), 1.55–1.98 (6 H, br m), 2.34 (3 H, s), 3.52 (1 H, br s), 3.81 (1 H, br s), 4.14 (1 H, br s), 4.24 (1 H, br s), 4.80 (1 H, br s), 5.20 (1 H, br s), 6.00 (1 H, br s), 6.77 (2 H, br s), 7.22 (2 H, d, *J* = 8.1), 7.70 (2 H, d, *J* = 8.1), 8.03 (1 H, br s), 8.12 (1 H, br s); exact mass calcd for $C_{26}H_{35}N_9O_7S$ (M^+ + H) 618.2462, found 618.2465.

Sinefungin (1). To a solution of 156 mg (0.252 mmol) of **31** in 10 mL of methanol was added 100 mg of palladium hydroxide on carbon (Pearlman's catalyst; weight includes 45% moisture; palladium hydroxide content 20% on a dry weight basis). The mixture was shaken under H_2 at 60 psi for 44 h, diluted with methanol (25 mL) and ammonium hydroxide (10 mL), stirred for 30 min, filtered through Celite, and evaporated, to give 129 mg of amine **32**. The Celite/catalyst mixture was boiled in methanol for 1 h and filtered again. Evaporation gave an additional 7 mg of **32** (total of 136 mg of **32**, 91%). The product was used immediately in the next step without characterization: **31** R_f 0.82 (silica TLC, 5/5/1 chloroform/2-propanol/ammonium hydroxide); **32** R_f 0.42.

A solution of 127 mg (0.215 mmol) of amine **32** in 20 mL of 9/1 trifluoroacetic acid/water was prepared and stirred at 22 °C for 1 h. The solvents were evaporated, to give 180 mg of crude acid **33** as its trifluoroacetate salts. This material was used directly in the next step without purification or characterization: **32** R_f 0.95 (silica TLC, 3/6/1 methanol/chloroform/ammonium hydroxide); **33** R_f 0.32.

To a vigorously stirred (mechanical stirrer with glass paddle) solution of 42 mg of crude **33** in 30 mL of liquid ammonia (freshly distilled from sodium) at −78 °C was added 108 mg of sodium in two portions. After 20–30 s, a blue color persisted. Stirring was continued for an additional 1 min, and then 300 mg of ammonium chloride was added in one portion. The ammonia was evaporated under a stream of nitrogen, and the solid residue was dissolved in water and applied to a column of Dowex 50W-X8 (200–400 mesh, hydrogen form) cation exchange resin which had been washed with methanol and then water. The column was eluted with water and then with 9/1 water/concentrated ammonium hydroxide. The basic fractions, which contained sinefungin, were evaporated, and the residue (22 mg) was subjected to preparative reverse-phase HPLC (Whatman Partisil 10 ODS-3; eluting with 99/1 water/acetonitrile containing 0.03 N ammonium acetate, pH 6.8). The fractions containing sinefungin were repeatedly lyophilized. Sinefungin was thus obtained as a white solid (9 mg; 49% from **33**). The synthetic sinefungin was shown to be identical with natural sinefungin (purchased from Sigma and purified) by HPLC, TLC (3/1/1 methanol/chloroform/ammonium hydroxide), ^1H NMR (D_2O), ^{13}C NMR (D_2O), and UV comparison. The stereochemistry is identical at C-6 (*S*) for the synthetic and the natural material as evidenced by the appearance of C1-H as a clean doublet[11c] (δ 5.80 ppm, *J* = 4.6 Hz) in the ^1H NMR [500 MHz, D_2O, δ relative to dioxane (3.53 ppm) as an internal standard] of a mixture. For synthetic **1**: $[\alpha]^{23}_D$ +10 ± 2° (*c* 0.240, H_2O). For natural **1**: $[\alpha]^{23}_D$ +12 ± 2° (*c* 0.227, H_2O).

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Supplementary Material Available: Crystallographic data for **22** including methods of structure determination, crystal and data parameters, tables of positional parameters and their estimated standard deviations, bond angles, bond distances, anisotropic thermal parameters, torsion angles, root-mean-square amplitudes of anisotropic displacement, least-squares planes, and ORTEP drawings (14 pages). Ordering information is given on any current masthead page.

Studies Dealing with the Alkylation–[1,3]-Rearrangement Reaction of Some Phenylthio-Substituted Allylic Sulfones

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A series of 2-(phenylthio)-3-(phenylsulfonyl)alkenes are easily metalated with *n*-butyllithium, and the resulting carbanion is regioselectively alkylated by alkyl halides in the α-position to give β,γ-unsaturated sulfones in high yield. These substituted phenylthio allyl sulfones undergo a 1,3-sigmatropic phenylsulfonyl shift by thermal, light-induced, and in some cases acid-catalyzed pathways. Rearrangement occurs where the product sulfone is thermodynamically more stable than the starting material. Cross-over experiments and inhibition studies suggest that the thermal/photochemical reaction occurs by a radical chain mechanism involving a phenylsulfonyl radical. Alkylation of the rearranged sulfones could also be performed under mild conditions. A sequential 1,3-rearrangement–cyclization reaction of 3-alkenyl-substituted allylic sulfones was also studied. The cyclization reaction gives either five- or six-membered ring methyl ketones and was accomplished by using sodium phenylsulfinate in 60% aqueous acetic acid. The cyclization step can be considered as being closely analogous to an intramolecular metallo-ene reaction involving a phenylsulfonyl shift.

The stabilization of carbanion centers by adjacent sulfur groups is the basis of many valuable transformations in organic synthesis.[1-9] Monometalated allyl sulfones have played an important role as reactive intermediates in total

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