Formal Synthesis of (+)- and (−)-Perhydrohistrionicotoxin: A "Double Henry"/Enzymatic Desymmetrization Route to the Kishi Lactam[1]

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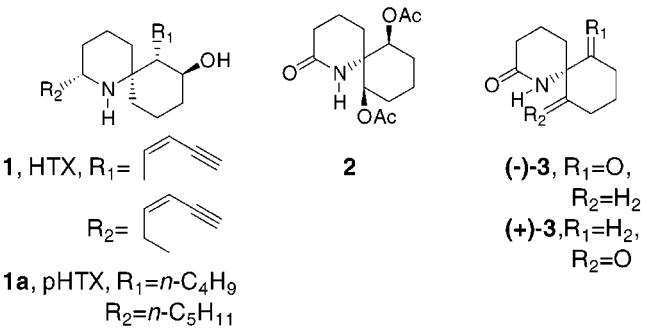
Both antipodes of the Kishi lactam **(3)**, the versatile intermediate for the synthesis of the perhydrohistrionicotoxin (pHTX) alkaloids, have been prepared. The synthetic route involved a "double Henry" condensation between glutaraldehyde and nitroacetal **5** giving meso dioxanyldiol **4** which was acetylated and reduced to afford meso dioxane amide **8**. Ultrasound-promoted deacetalization of **8** followed by Wittig olefination and reduction provided meso amide ester **10**. Hydrolysis of **10** with aqueous acid followed by dehydrative cyclization with dicyclohexylcarbodiimide gave lactamdiol **11**. Acetylation of **11** gave meso diacetate **2** which was an excellent substrate for esterase-mediated hydrolysis to hydroxyacetate **12**. Deoxygenation of **12** using a Barton protocol, followed by Zemplén deacylation and Swern oxidation, gave the (−)-antipode of the Kishi lactam **(3)**. Moffatt oxidation of hydroxyacetate **12** followed by ketal protection and Zemplén deacylation gave ketalalcohol **19**. Barton deoxygenation of **19** followed by ketal hydrolysis gave (+)-**3**.

Over 120 species of brightly colored "poison-dart" frogs live in the tropical rain forests of South America. The glands found in the skin of these frogs produce toxins which are harmful to predators. Some of the skin secretions having higher toxicity are used by South American Indians to poison blowgun darts for hunting.[2] The neurotoxic alkaloids isolated from the skin of the South American frog *Dendrobates histrionicus* are termed the histrionicotoxins **(1)** and have been used extensively as neurological probes for the acetylcholine receptor channel.[3] The spirocyclic core of the histrionicotoxins together with the high unsaturation of the side chains have made these compounds and their perhydro analogues **(1a)** an attractive area where new strategies or methodology may be tested.[4a−c] Our enantioselective route to the perhydro



1, HTX, R_1= R_2=

2

(-)-3, R_1=O, R_2=H_2

(+)-3, R_1=H_2, R_2=O

1a, pHTX, R_1=*n*-C_4H_9 R_2=*n*-C_5H_{11}

analogues **(1a)** centered on the preparation of the meso azaspirocyclic core intermediate **2**, a subject of earlier reports from our laboratory,[5] en route to the Kishi lactam **3**.[6] Thus desymmetrization of meso **2** will allow access to either antipode of **3**; from (+) or (−)-**3**, the desired antipode of **1a** may be obtained by established routes involving installation of the requisite side chains.[6] We chose meso nitrodiol **4**, available from the tandem Henry condensation[7] (eq 1) of glutaraldehyde and nitrodioxane **5**, to serve as the progenitor of meso lactamdiacetate **2** through reduction, two-carbon homologation and spirocyclization.

The Kornblum reaction[8] of commercially available 2-(2-bromoethyl)-1,3-dioxane[9] with sodium nitrite in either

(1) Presented at the 6th Meeting of the European Society of Sonochemistry, Rostock-Warnemünde Germany, May 13, 1998; 216th National Meeting American Chemical Society, Boston, MA, August 23 and 24, 1998; ORGN 143.

(2) Daly, J. W.; Karle, I.; Myers, C. W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870−1875.

(3) (a) Ogama, T.; Warashina, A. *Comp. Biochem. Physiol. C.* **1987**, *88*, 249−254. (b) Rapier, C.; Wonnacott, S.; Lunt, G. G.; Alberquerque, E. X. *FEBS Lett.* **1987**, *212*, 292−296. (c) Oliveira, L.; Madson, B. W.; Kapai, H.; Sherby, S. M.; Swanson, K. L.; Edelfraui, M. E.; Alberquerque, E. X. *Eur. J. Pharmacol.* **1987**, *140*, 331−332. (d) Sobel, A.; Heidmann, T.; Hofler, J.; Changeaux, J. P. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 510−514.

(4) (a) For an early review in the histrionicotoxin area, see: Kotera, M. *Bull. Soc. Chim. Fr.* **1989**, 370−397. (b) HTX syntheses: Carey, S. C.; Aratani, M.; Kishi, Y. *Tetrahedron Lett.* **1985**, *26*, 5887−5890. Stork, G.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 5875−5876. (c) pHTX syntheses and approaches: Tanner, D.; Hagberg, L.; Poulsen, A. *Tetrahedron* **1999**, *55*, 1427−1440. Comins, D. L.; Zhang, Y.; Zheng, X. *J. Chem. Soc. Chem. Commun.* **1998**, 2509−2510. Compain, P.; Gore, J.; Vatele, J.-M. *Tetrahedron Lett.* **1995**, *36*, 4063−4064. Thompson, C. M. *Heterocycles* **1992**, *34*, 979−990. Zhu, J.; Royer, J.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1991**, *32*, 2485−2488. Magnus, P.; DiPierro, M.; Venit, J. J. *J. Org. Chem.* **1989**, *54*, 4298−4301. Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 4852−4856. Tanis, S. P.; Dixon, L. A. *Tetrahedron Lett.* **1987**, *28*, 2495−2498. Tanner, D.; Somfai, P. *Tetrahedron* **1986**, *42*, 5657−5664. Holmes, A. B.; Russell, K.; Stern, S.; Stubbs, M. E.; Wellard, N. K. *Tetrahedron Lett.* **1984**, *25*, 4163−4166. Godleski, S. J.; Heacock, D. J.; Meinhart, S. V.; Wallandael, J. *J. Org. Chem.* **1983**, *48*, 2101−2103. Pearson, A. J.; Ham, P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1421−1425. Keck, G. E.; Yates, J. B. *J. Org. Chem.* **1982**, *47*, 3509−3591. Evans, D. A.; Thomas, E. W. *Tetrahedron Lett.* **1979**, *20*, 411−414. Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, *48*, 4841−4844. Corey, E. J.; Petrzilka, M.; Ueda, Y. *Helv. Chim. Acta* **1977**, *60*, 2294−2302.

(5) Fitch, R. W.; Luzzio, F. A. *Ultrasonics Sonochem.* **1997**, *4*, 99−107.

(6) Aratani, M.; Dunkerton, L. U.; Fukuyama, T.; Kishi, Y.; Kakoi, H.; Suguira, S.; Inoue, S. *J. Org. Chem.* **1975**, *40*, 2009−2001.

(7) Wade, P. A.; Giuliano, R. M. In *Nitro Compounds: Recent Advances in Synthesis and Chemistry*; Feuer, H., Nalson, A. T., Eds.; VCH: New York, 1990; pp 137−265. Lichtenthaler, F. W. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 211−224. Lichtenthaler, F. W. *Chem. Ber.* **1963**, *96*, 845−853. Baer, H. H.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1959**, *81*, 5184−5189. Baer, H. H.; Fischer, H. O. L. *Proc. Natl. Acad. Sci. U.S.A.* **1958**, *44*, 991−993.

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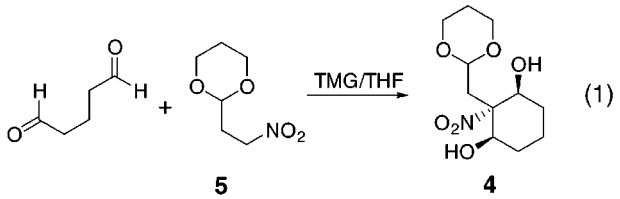
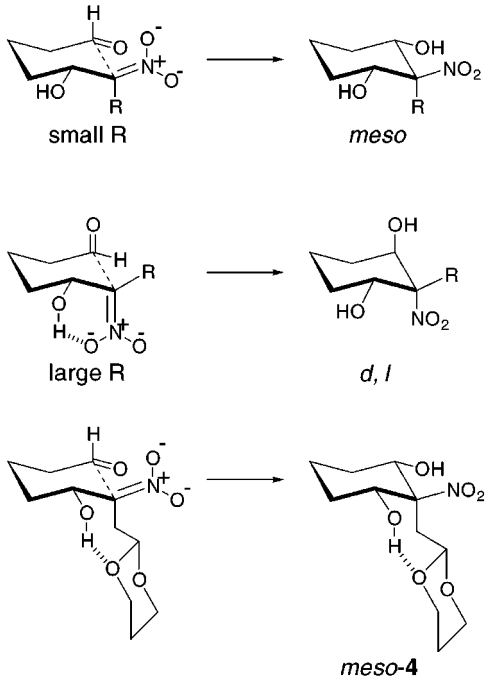


(1)

5 **4**

DMSO or DMF provided nitroacetal **5** in 55% yield as described previously.[5] Considering ready availability, expense, and amenability to scale-up, we examined a direct preparation of **5** from acrolein and nitrous acid followed by acetalization[10] and found this protocol more suitable for our requirements thereby providing **5** in consistent yields of 70−75% on a 30-g scale. Henry condensation of **5** with 50% aqueous glutaraldehyde (1 equiv) in THF with a catalytic amount of 1,1,3,3-tetramethylguanidine (TMG)[11] afforded variable yields of crystalline nitrodiol **4** (55−80%) after silica gel column chromatography. While optimizing the yields of **4** we found that its high degree of crystallinity and near insolubility in a range of solvents facilitated its isolation by direct crystallization from the reaction mixture. The optimal conditions entailed the condensation of **5** with freshly distilled glutaraldehyde in dry THF while employing TMG as the base. This expedient allowed the direct iterative crystallization of **4** from the reaction mixture and resulted in consistent yields of 80−87% on a 5−8-g scale. In contrast to our previous results with similar double Henry condensations using extended nitroacetals,[5] only minimal amounts (5−10%) of the epimeric nitrodiol and tetrahydropyranyl alcohol[12a] could be observed in the crude reaction mixtures containing **4**. Although ^{1}H and ^{13}C NMR analysis suggested the meso configuration of **4**, the formation of the cis,cis diastereomer was not ruled out. Conclusive proof of the trans,trans stereochemistry of **4** was made later in our synthesis (vide infra) by duplication of results reported by the Kishi group with regard to the sodium borohydride reduction of the Kishi lactam (−)-**3** to the trans lactam alcohol (+)-**16**. Given the possible stereochemical pathways and the equilibrium nature of the double Henry reaction, thermodynamic control operates to give the most stable products based on steric or stereoelectronic factors. The transition-state conformations which may be envisioned to account for the diastereoselection in the 6-exo-trig closure of the nitronate on the aldehyde require the orientation of the side chain R in either the pseudoaxial or pseudoequatorial position (Scheme 1).[12b] With small R (H or methyl) occupying the pseudoaxial position, the aldehyde carbonyl will be oriented in the pseudoequatorial position, as the hydroxyl group from the first condensation, thereby resulting in the overall meso configuration. With the increasing size and steric bulk

Scheme 1



of R, as in the cases of extended nitroacetals, the equatorial position is demanded thus requiring a pseudoaxial orientation in the aldehyde carbonyl. Steric repulsion with the side chain is thus minimized and the cis,trans (d, l) diastereomers of **4** are the result. Using the same chairlike transition state, the dioxanyl-substituted side chain R of **4** would also be expected to assume a pseudoequatorial orientation. However, hydrogen bonding is possible between the initially formed alcohol and an oxygen of the dioxanyl side chain thereby restricting its orientation to the axial position. The β-oxygen effect may be further exemplified by the decreased formation of the meso isomers when employing nitropentanal acetals. Presumably the steric effects of the larger side chain and the diminished stability of the hydrogen-bonded species due to greater ring size combine to increase the thermodynamic favorability of the cis,trans (d, l) product. The lesser stability of meso **4** was demonstrated by its epimerization on standing in methanol-d_4 (see Supporting Information) or DMSO-d_6 during the course of several hours to several days while monitoring by ^{1}H NMR. The epimerization of **4** in methanol, a highly polar solvent with hydrogen-bonding capability, is in contrast to its indefinite stability in anhydrous THF, showing little or no epimerization on standing for several days or on heating to reflux during crystallization. While **4** is nearly insoluble in THF, except at reflux, the addition of a small amount of water renders it almost infinitely soluble. Although DMSO does not have the hydrogen donor/acceptor properties of methanol, small amounts of water present in the deuterated solvent are presumably responsible for the behavior. These results leads us to conclude that the disruption or integrity of intramolecular hydrogen bonding is a determining factor in the formation and stability of highly crystalline meso **4**.

The preparation of amidodiacetate **8** was accomplished through amidodiol **6** or nitrodiacetate **7** by a reduction/acetylation sequence (Scheme 2). Our earlier-described protocol for the ultrasound-promoted aluminum amalgam

(8) Kornblum, N.; Powers, J. W. *J. Org. Chem.* **1957**, *22*, 455−456. Kornblum, N.; Larson, H. L.; Blackwood, R. K.; Mooberry, D. D.; Olivetto, E. P.; Graham, G. E. *J. Am. Chem. Soc.* **1956**, *78*, 1492−1501.

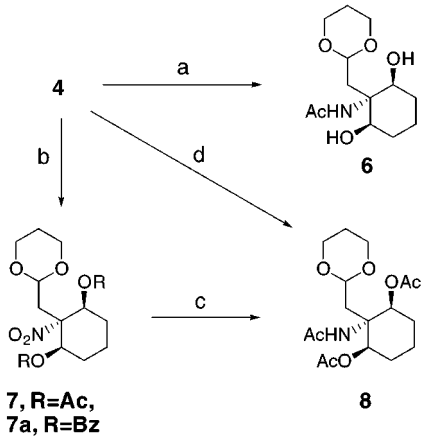
(9) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122−1123.

(10) (a) Miyakoshi, T.; Saito, S.; Kumanotani. *Chem. Lett.* **1981**, 1677. (b) Ohrlein, R.; Schwab, W.; Ehrler, R.; Jager, V. *Synthesis* **1986**, 535−538. (c) Fuji, M.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1992**, *40*, 2344−2352.

(11) (a) Fitch, R. W.; Luzzio, F. A. *Tetrahedron Lett.* **1994**, *35*, 6013−6016. (b) Simoni, D.; Invidiata, F. P.; Manfredini, S.; Ferroni, R.; Lampronti, I.; Pollini, G. P. *Tetrahedron Lett.* **1997**, *38*, 2749−2752.

(12) (a) Lichtenthaler, F. W.; Fleischer, D. *J. Org. Chem.* **1972**, *37*, 1670−1672. (b) McNulty, J.; Mo, R. *J. Chem. Soc. Chem. Commun.* **1998**, 933−934.

Scheme 2[a]

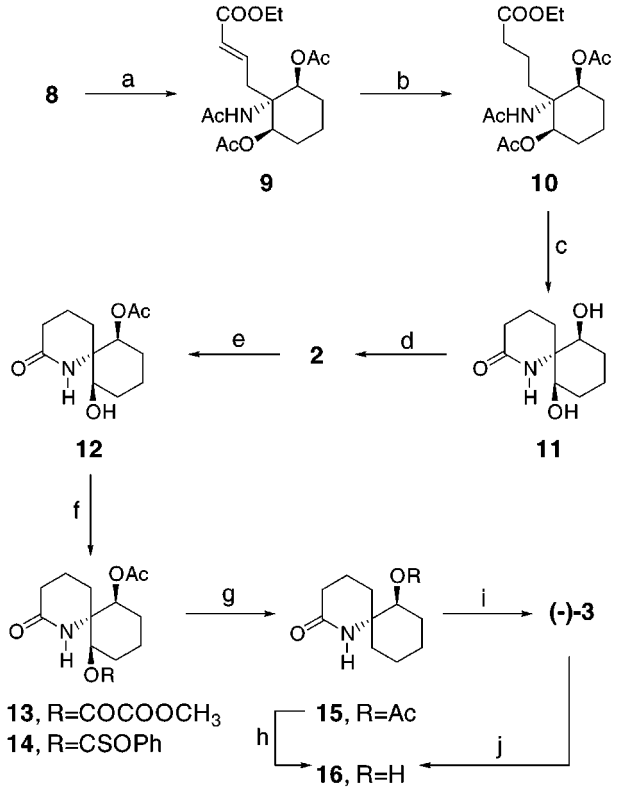


[a] Key: (a) Al(Hg), THF, H_2O, ultrasound then Ac_2O (55%). (b) AcCl or BzCl, DMAP, CH_2Cl_2 (Ac, 81%; Bz, 99%). (c) Ra−Ni, H_2, THF then Ac_2O, pyridine, reflux (91%). (d) Al(Hg), THF, H_2O, triethylamine, ultrasound then Ac_2O, pyridine, reflux (51%) or Al(Hg), THF, H_2O, Ra−Ni, H_2 followed by triethylamine, ultrasound, Ac_2O, pyridine (67%).

reduction/acylation of nitroalkanols[11a] facilitated the conversion of nitrodiol **4** to amidodiol **6**. The employment of power ultrasound and in situ acylation with 1−10 equiv of acetic anhydride was effective in the production of **6** (55%) on a 50-mg scale. The amidodiacetate **8** was obtained in similar fashion (51%) but required acetic anhydride in refluxing pyridine to complete the acetylation. Larger-scale reductions of **4** were not amenable to ultrasound promotion. The desired intermediate aminodiol was accompanied by appreciable amounts of a byproduct spectroscopically consistent with the corresponding hydroxylamine and necessitated the use of Raney nickel to force the reduction to completion. Optimal yields of **8** (67%) were obtained by addition of Raney nickel directly to the reaction mixture following consumption of the nitrodiol by the amalgam while maintaining a hydrogen atmosphere at 65 °C. Difficulties associated with the isolation of products from the tandem treatment with Al(Hg)/Ra−Ni prompted the employment of Raney nickel alone for the reduction of **4**. However, the basicity of the reagent was responsible for providing product containing 25% of the undesired epimer. The epimerization could not be suppressed despite exhaustive washing of the catalyst with water, methanol, and THF. Interestingly, while ultrasound enhanced the rate of reduction of **4** with Raney nickel alone, it did not suppress the epimerization during the reductive process. Rosenthal reported a similar epimerization during the reduction of nitro alcohols in the carbohydrate series[13] and solved the problem by acylating the alcohol function prior to the reduction. Accordingly, treatment of nitrodiol **4** with acetyl chloride or benzoyl chloride in the presence of DMAP provided the crystalline meso nitrodiesters **7** (81%) and **7a** (99%). Reduction of **7** with Raney nickel and hydrogen at 1 atm in THF followed by direct *N*-acetylation with acetic anhydride in refluxing pyridine afforded the crystalline amidodiacetate **8** in 91% yield (Scheme 2). The deprotection/two-carbon homologation of meso **8** to provide unsaturated ester **9** was accomplished in tandem sequence (Scheme 3). Initially, deprotection of amidodiol **6** with aqueous acetic acid

(13) Rosenthal, A.; Cliff, B. L. *Carbohydr. Res.* **1980**, *79*, 63−77.

Scheme 3[a]



[a] Key: (a) AcOH, H_2O, ultrasound, then $EtOCOCH_2PPh_3^+Br^-$, Et_3N (70%). (b) H_2, Pd-C, MeOH (96%). (c) 1.2 N HCl, reflux, then DCC, DMAP, py (91%). (d) AcCl, DMAP, CH_2Cl_2 (77%). (e) pig liver esterase, pH = 7, 14 d (87%). (f) MeOCOCOCl, DMAP, CH_2Cl_2 (87%, **13**) or PhOCSCl, DMAP, CH_2Cl_2 (73%, **14**). (g) Bu_3SnH, AIBN, $PhCH_3$, 95 °C (93%). (h) NaOMe, MeOH (98%). (i) ClCOCOCl, DMSO, CH_2Cl_2 (77%). (j) $NaBH_4$, MeOH (86%).

(80%/80 °C) led to a complex mixture of elimination products and was unsuitable for the subsequent olefination step. Submission of amidoacetate **8** to the same reaction conditions as **6** gave variable crude yields (12−54%) of the sensitive intermediate aldehyde which also was accompanied by unidentified byproducts. Sonochemical-promoted cleavage[14] of the dioxane function of **8** with aqueous acetic acid at 60 °C gave the best yield of the intermediate aldehyde. The crude aldehyde was directly olefinated with ethoxycarbonylmethyltriphenylphosphonium bromide and triethylamine and provided the meso unsaturated ester **9** (70% from **8**) after silica gel column chromatography. Catalytic reduction of ester **9** with 10% palladium on activated charcoal under 1 atm of hydrogen provided the saturated ester **10** as crystalline plates in 96% yield. Ester **10** was converted to spirolactam diacetate **2** by a three-step sequence. Submission of **10** to acid hydrolysis with refluxing 1.2 N HCl followed by concentration of the reaction mixture and direct treatment of the crude dihydroxyamino acid with dicyclohexylcarbodiimide[15] and DMAP in pyridine effected spirolactam formation (91% from **10**). The intermediate spirolactamdiol **11** was acetylated using acetyl chloride and DMAP in CH_2Cl_2 to provide spirolactam diacetate **2** (77% from **11**) as a white solid after silica gel flash column chromatography (Scheme 3).

(14) Petrier, C.; Luche, J.-L. In *Synthetic Organic Sonochemistry*; Luche, J.-L., Ed.; Plenum: New York, 1998; Chapter 2.
(15) Klausner, Y. S.; Bodansky, M. *Synthesis* **1972**, 453−463.

Table 1. Lipase Desymmetrization of Meso Substrates

substrate	lipase[a]	product	yield[b] (ee)
2	PLE	**12**	87% (93)
2	CRL	**12**	36% (50)
7	PLE	NR	
8	PLE	NR	
11[c]	PLE	NR	
11[c]	CRL	NR	

[a] PLE = pig liver esterase; CRL = *Candida rugosa* lipase. [b] Yields are for isolated purified products. [c] Transesterification with vinyl acetate.

Several avenues were explored for the preparation of optically pure monoacetate **12** (Scheme 3). In principle, enzyme-catalyzed transacylation of meso amidodiol **11** with an appropriate enol ester or enzymatic hydrolysis of meso diacetate **2** will generate an excess of antipodal **12**. Both pathways take advantage of desymmetrization where an achiral meso substrate is regioselectively acylated or deacylated to afford a single enantiomeric product.[16] Treatment of lactamdiol **11** with vinyl acetate in the presence of porcine liver esterase (PLE) failed to provide acylated products of any type. However, treatment of lactamdiacetate **2** with PLE using a modification of a method by Seebach and Eberle[17] while maintaining the pH at 7.5 furnished the crystalline (−)-monoacetate **12** in 87% chemical yield and 93% ee as determined by ^{19}F NMR analysis of the Mosher ester derivative.[18,19] In comparison, similar experiments utilizing lipase from *Candida rugosa* provided **12** of only 50% ee as determined by comparison of rotations with recrystallized **12** derived from PLE hydrolysis. In contrast to Seebach's results, the enzymatic hydrolysis of our substrate proceeded at a much slower rate thereby requiring reaction times of 14−21 days at room temperature for reasonable conversion. Furthermore, the earlier meso intermediates in our synthetic scheme such as nitrodiacetate **7** and acetamidodiacetate **8** completely resisted enzymatic hydrolysis (Table 1). The lengthy reaction times exhibited by substrate **2** were in accord with those results reported by Whitesell in connection with the enzymatic hydrolyses of *trans*-2-phenylcyclohexyl acetate and *trans*-2-(1-methyl-1-phenylethyl)cyclohexyl acetate.[20] Presumably the retarded response of our substrate to hydrolysis may be attributed to the greater steric bulk at the spiro carbon which is the center of a neopentyl ester system. The methyloxalate **13**[21] and the phenylthionocarbonate **14**[22] were evaluated for their response to free radical deoxygenation. Treatment of (−)-**12** with methyloxalyl chloride or phenylthionochloroformate and DMAP in CH_2Cl_2 followed by flash column chromatography on silica gel provided **13** (87%) and **14** (73%). Treatment of methyloxalate **13** with tri-*n*-butyltin hydride and AIBN in toluene resulted only in recovery of (−)-**12**, while treatment of thionocarbonate **14** under similar conditions afforded the desired crystalline spirolactam acetate **15** (93%) after purification by silica gel flash column chromatography. The spirolactam acetate **15** was deprotected with sodium methoxide in methanol at room temperature to provide the crystalline spirolactam alcohol **16** in 98% yield (Scheme 3). Corey-Suggs,[23] Moffatt,[24] and Swern[25] conditions were evaluated for the oxidation of spirolactam alcohol **16** to the Kishi ketolactam **3**. Treatment of **16** with pyridinium chlorochromate/silica gel in CH_2Cl_2 gave crystalline (−)-**3** in 28% yield while Moffatt conditions employing DMSO and DCC provided pure (−)-**3** in 73% yield ($[\alpha]_D^{25}$ −59.3). The Swern oxidation proved to be optimal for the spirocyclic lactam alcohol where treatment of **16** with DMSO and oxalyl chloride in CH_2Cl_2 provided (−)-**3** in 77% yield after silica gel flash column chromatography. The unavailability of published high-resolution NMR spectra for comparison prompted us to investigate the relative stereochemistry of our (−)-**3** by chemical methods. As Kishi and co-workers described the preparation of (±)-**16** by reduction of (±)-**3**, we reproduced the result with enantioenriched **3**. Sodium borohydride reduction of (−)-**3** in methanol afforded the resulting alcohol (86%) which was identical in all respects (NMR, IR, melting point, mixed melting point) with the product of the deacetylation of **15** thereby inferring the trans stereochemistry in both compounds.

The conversion of hydroxyacetate (−)-**12** to (+)-**3** was mostly a matter of protecting group manipulation (Scheme 4). Oxidation of (−)-**12** under either Swern conditions (57%) or Moffatt conditions (73%) gave ketoacetate **17** after purification by silica gel column chromatography. Protection of ketoacetate **17** by treatment with ethylene glycol[26] and *p*-toluenesulfonic acid in refluxing toluene gave ketalacetate **18**. The ketalacetate was directly deacetylated with sodium methoxide in methanol to afford the oily hydroxyketal **19** (84% from **17**). The alcohol function of **19** was derivatized with phenylthionochloroformate as previously done with alcohol **12** to provide thionocarbonate **20** (49%, 87% corrected for recovered **12**). Not surprisingly the acylation of **19** was characterized by extended reaction times with relatively sluggish conversion to **20** thus necessitating recovery and recycling of **19**. Phenylthionocarbonate **20** was deoxygenated as before with tri-*n*-butyltin hydride and AIBN at 90 °C to give ketallactam **21** in 90% yield. Deprotection of **21** was effected by employing a mixture of aqueous acetic/trifluoroacetic acid at room temperature and provided (+)-**3** (88%) after silica gel flash column chromatography. Crystalline (+)-**3** was spectrally identical to (−)-**3** ($[\alpha]_D^{25}$ +60.3).

The absolute stereochemical assignment of the ketolactams *R*-(−)-**3** and *S*-(+)-**3** follows from previous inves-

(16) Ohno, M.; Otsuka, M. In *Organic Reactions*; Kende, A. S., Ed.; John Wiley: New York, 1989; Vol. 37, Chapter 1, pp 1−55. Adachi, K.; Kobayashi, S.; Ohno, M. *Chimia* **1986**, *40*, 311−314.

(17) Eberle, M.; Egli, M.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1−21. Eberle, M.; Missbach, M.; Seebach, D. In *Organic Syntheses*; Paquette, L., Ed.; John Wiley: New York, 1990; Vol. 69, pp 19−30.

(18) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

(19) For a discussion on lipase selectivity, see: (a) Jones, J. B. *Pure Appl. Chem.* **1990**, *62*, 1445−1448. (b) Cygler, M.; Grochulski, P.; Kaslauskas, R.; Schrag, J. D.; Bouthillier, F.; Rubin, B.; Serraqu, A. N.; Gupta, A. K. *J. Am. Chem. Soc.* **1994**, *116*, 3180−3186.

(20) Whitesell, J. K.; Lawrence, R. M. *Chimia* **1986**, *40*, 318−321.

(21) Dolan, S. C.; MacMillan, J. *J. Chem. Soc. Chem. Commun.* **1985**, 1588−1589. Zhang, C.; Trudell, M. L. *J. Org. Chem.* **1996**, *61*, 7189−7191.

(22) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585. Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1989**, *54*, 5387−5390.

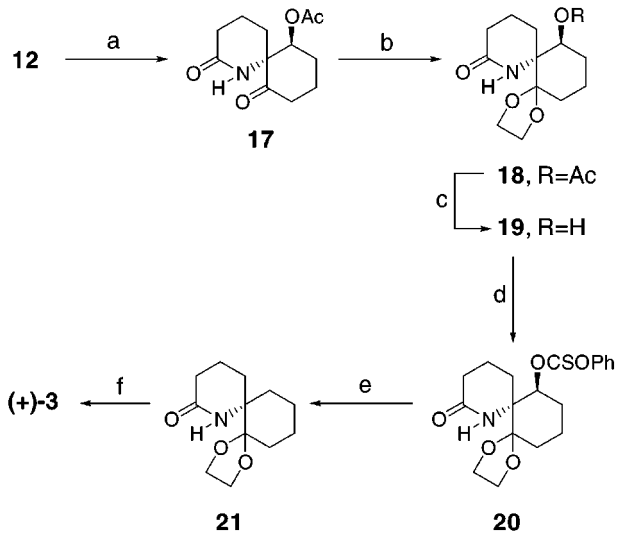
(23) (a) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647−02550. (b) Adams, L. L.; Luzzio, F. A. *J. Org. Chem.* **1989**, *54*, 5387−5390.

(24) Mancusco, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482.

(25) Moffatt, J. J. In *Oxidation*; Augustine, R., Trecker, D. J., Eds.; Marcel Dekker: New York, 1971; Vol. 2, pp 1−64.

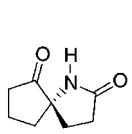
(26) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 2nd ed.; John Wiley: New York, 1991; pp 188−195.

Scheme 4[a]



[a] Key: (a) ClCOCOCl, DMSO, CH_2Cl_2 (57%) or DMSO, DCC, H_3PO_4 (73%). (b) $HOCH_2CH_2OH$, TsOH, $PhCH_3$. (c) NaOMe, MeOH (84% from **17**). (d) PhOCSCl, DMAP, CH_2Cl_2 (87%). (e) Bu_3SnH, AIBN, $PhCH_3$, 95 °C (90%). (f) AcOH, TFA, H_2O (88%).

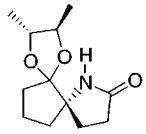
tigations involving lipase selectivity and correlation with the homologous ketolactam **22** and its ketal derivative **23**. Most lipases have been demonstrated to hydrolyze the *pro-R* center with exceptions occurring in cases of long-chain esters and/or small ring substrates. Therefore



S-(+)-**22**

$[\alpha]_D^{25.6}$ +68.2

(C=1, $CHCl_3$)



23

lipase-mediated hydrolysis of the *pro-R* center in meso **2** followed by the deoxygenation sequence at that carbon will give the *R* spiroketolactam (−)-**3**. The preparation of homologous enantiopure ketolactam (*S*)-(+)-**22** and its enantiomer was reported by Nagasaka[27] and their absolute configurations were established by a circular dichroism and X-ray crystallography study of the corresponding (*3R,4R*)-3,4-dimethyldioxolane derivative **23** of ketolactam (*S*)-(+)-**22**. The optical rotations of (*S*)-(+)-**22**, $[\alpha]_D^{25.6}$ + 68.2 (c = 1.0, $CHCl_3$), and its enantiomer, $[\alpha]_D^{24.4}$ −68.0 (c = 1.0, $CHCl_3$) correlated with our (*S*)-(+)-**3** and (*R*)-(−)-**3** with respect to sign of rotation.

In summary, we have developed an efficient synthetic route to both antipodes of the Kishi lactam thereby constituting a formal synthesis of (−)- and (+)-perhydrohistrionicotoxin. Starting from acrolein the synthesis of (−)-**3** required a linear sequence of 13 steps and resulted in a 11% overall yield. Compound (+)-**3** required 15 steps and resulted in a 9% overall yield. The synthesis employed a one-step double Henry nitroaldol condensation which establishes both the tertiary carbon of the azaspirocyclic system and the meso configuration of all subsequent intermediates until stereodiverged by enzymatic desymmetrization. Although there are slight differences in biological activity between the known (+)- and (−)-perhydrohistrionicotoxins, the synthesis provides an avenue for preparing either antipode of the perhydrohistrionicotoxins, with side chains of variable length and complexity, for future biological investigations. With limitations only on the architecture of the side chains to be conjoined to the chiral Kishi lactam, the present methodology will allow for the preparation of a large array of chiral histrionicotoxin analogues.

Experimental Section

General Methods. All reactions were conducted under an atmosphere of dry nitrogen unless otherwise noted. Where required, THF and ether were distilled from Na/benzophenone ketyl, CH_2Cl_2 and pyridine from CaH_2, DMSO from CaH_2 under reduced pressure, and acetone from $CaSO_4$. All other solvents were reagent grade and were used as received. Pig liver esterase (EC 3.1.1.1) was purchased from Sigma-Aldrich as a suspension of 11 mg/mL enzyme in 3.2 M ammonium sulfate (pH 8) at a specific activity of 230 U/mg (ethyl butyrate). Buffer solutions were prepared using reagent grade potassium hydrogen phosphate and potassium hydroxide in analytical grade deionized, distilled water. Gravity column chromatography was carried out using E. Merck silica gel 7734, 70−230 mesh. Flash column[28] chromatography employed E. Merck silica gel 9385, 230−400 mesh. Analytical thin-layer chromatography was performed using glass-backed plates (E. Merck 5715 silica gel 60 F_{254}). Visualization of thin-layer chromatograms utilized 2% anisaldehyde/ethanol stain. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 500.13 and 125.77 MHz, respectively, or 299.95 and 75.42 MHz, respectively. Proton coupling constants (J) are reported in hertz. ^{19}F NMR spectra were recorded at 282.21 MHz. Infrared spectra (FTIR) were taken as a neat film or KBr pellet and are expressed in cm^{-1}. Elemental analyses were carried out at Schwartzkopf Microanalytical Laboratory, Woodside, New York.

***meso*-(1*r*,2*R*,6*S*)-1-Nitrocyclohexane-2,6-diol-1-acetaldehyde, 1,3-Propanediol Acetal (4).** Anhydrous glutaraldehyde was prepared by saturation of a 50% aqueous solution with solid NaCl, extraction with ether, drying over sodium sulfate, concentration, and vacuum distillation with collection of the fraction boiling at 55−56 °C/2.5 mm (lit.[29] 71−72 °C/10 mm). Glutaraldehyde so obtained was anhydrous by ^1H NMR and could be stored for several days at −40 °C. Material stored for 6 weeks had polymerized to a glassy semisolid, but could be depolymerized by heating gently under nitrogen and redistilling. To a solution of nitroacetal (5.84 g, 36.2 mmol) in dry THF (25 mL) was added anhydrous glutaraldehyde (3.50 mL, 36.0 mmol) followed by 1,1,3,3-tetramethylguanidine (0.23 mL, 1.83 mmol). The resulting yellow solution was shaken briefly and allowed to stand over 3 days during which time a first crop (4.52 g) was obtained. The mother liquor was decanted, and the crystals were washed with dry THF (10 mL). The mother liquor was concentrated, and the solids were redissolved by heating and addition of just enough THF to produce a homogeneous yellow-orange solution. Slow evaporation of the solvent afforded a second crop (2.21 g). The process was repeated to obtain four crops totaling 8.21 g (87%) of **4** as colorless prisms: mp 173−175 °C (dec); R_f = 0.22 (19:1 CH_2Cl_2/acetone); IR (pellet) ν 1539, 1343; ^1H NMR (500 MHz, DMSO-d_6) δ 5.10 (br s, 2H [OH]), 4.95 (t, J = 3.8, 1H), 3.67 (m, 4H), 3.67 (t, J = 10.6, 2H), 2.25 (d, J = 3.8, 2H), 1.85 (m, 1H), 1.64 (m, 1H), 1.62 (m, 2H), 1.42 (m, 2H), 1.35 (m, 1H), 1.29 (d, J = 13.2, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 99.8, 98.8,

(27) Nagasaka, T.; Sato, H.; Saeki, S. *Tetrahedron: Asymmetry* **1997**, *8*, 191−194.

(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2924.

(29) Stoll, A.; Lindemann, A.; Jucker, E. *Helv. Chim. Acta* **1953**, *36*, 268−274.

74.0, 66.3, 32.4, 30.4, 25.0, 19.5; MS (ES^+) 284.1 (M + Na); MS (ES^-) 260.3 (M − H). Anal. Calcd for $C_{11}H_{19}NO_6$: C, 50.57, H, 7.33, N, 5.36. Found: C, 50.46, H, 7.29, N, 5.28.

2-(2-Nitroethyl)-1,3-dioxane (5). To a solution of THF (66 mL) and water (33 mL), cooled to 0 °C, was added $NaNO_2$ (20.0 g, 0.29 mol). After dissolution, the resulting biphasic mixture was vigorously stirred and acrolein (11.2 g, 0.20 mol) was added in one portion. Glacial acetic acid (26.2 g, 0.44 mol) was then added from a dropping funnel over 30 min. The solution was stirred at 0 °C (1 h) and adjusted to a pH 1 with concentrated H_3PO_4. The solution was sparged under nitrogen flow until brown nitrogen oxides were no longer observed and saturated with solid NaCl. The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (5 × 50 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried over sodium sulfate, and concentrated to a yellow oil. The crude nitropropanal was dissolved in benzene (100 mL) and then 1,3-propanediol (30 mL, 67.8 mmol) and *p*-toluenesulfonic acid monohydrate (950 mg, 1.5 mmol) were added. The mixture was refluxed with azeotropic removal of water until no further accumulation was noted (5 h). After cooling, the solution was diluted with ether (100 mL) and washed with 10% sodium bicarbonate solution (2 × 40 mL) and brine (2 × 50 mL). The washings were back-extracted with ether (2 × 20 mL), and the combined extracts were dried over Na_2SO_4. Concentration and vacuum distillation afforded 24.15 g (75%) of **5**: bp 73−75 °C/0.002 mm (lit.[10c] 80−83 °C/0.8 mm).

***meso*-(1*r*,2*R*,6*S*)-1-Acetamidocyclohexane-2,6-diol-1-acetaldehyde, 1,3-Propanediol Acetal (6).** Food packaging grade aluminum foil (104 mg, 3.85 mmol) was cut into strips (1.0 × 5.0 cm) and spirally wound about a glass stirring rod. Each coil was individually amalgamated by sequential agitation (using forceps) in ether (20 s), 2% aqueous $HgCl_2$ (20 s), and ether (5 s). As each coil was prepared it was added to a solution of nitrodiol **4** (50.4 mg, 0.19 mmol) dissolved in THF (5 mL) and water (0.2 mL) in a test tube (25 × 100 mm) immersed in a thermostated jacketed reaction vessel at 25 °C. A 1/4 in. microtip ultrasonic probe was immersed below the surface of the liquid (1 cm) and ultrasound (power level 2) was applied. The reaction mixture was sonolyzed (3 h) and acetic anhydride (45 μL, 0.48 mmol) was added. Sonolysis was continued for an additional 60 min. The thick gray slurry was filtered through a fritted glass funnel packed with Celite (1.0 cm), and the filter cake was washed with THF (10 mL). The filtrate was concentrated and flash-chromatographed (EtOAc/MeOH 10:0, 9:1, 25 mL each) to afford 29.2 mg (55%) of **6** as an amorphous white solid: R_f = 0.15 (EtOAc), 0.38 (EtOAc/MeOH 9:1); IR (pellet) ν 3367, 1653; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69 (br s, 1H), 5.51 (br s, 2H), 4.64 (t, J = 4.4, 1H), 4.08, (dd, J = 4.9, 11.8, 2H), 3.73 (td, J = 1.9, 11.8, 2H), 3.42 (br d, J = 10.4, 2H), 2.29 (d, J = 4.4, 2H), 2.06 (m, 1H), 2.02, (s, 3H), 1.74 (m, 2H), 1.65 (m, 1H), 1.34 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 100.7, 75.4, 67.2, 65.3, 29.7, 25.2, 24.1, 20.6; MS (ES^+) 296.5 (M + Na); MS (ES^-) 272.4 (M − H). A less polar byproduct (12.7 mg, 24%) having spectral properties consistent with the corresponding hydroxylamine was isolated as a cloudy yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (t, 1H, J = 5.5), 4.08 (dd, 2H, J = 4.6, 11.5), 2.74 (dt, 2H), 3.69 (m, 2H), 2.03 (m, 1H), 2.0 (d, 2H), 1.75 (m, 3H), 1.45 (m, 2H), 1.27 (m, 2H). Attempts to obtain the compound in sufficient purity for further analyses were unsuccessful.

***meso*-(1*r*,2*R*,6*S*)-2,6-Diacetoxy-1-nitrocyclohexane-1-acetaldehyde, 1,3-Propanediol Acetal (7).** To a suspension of nitrodiol **4** (4.53 g, 17.4 mmol) and DMAP (5.50 g, 45 mmol) in CH_2Cl_2 (80 mL) was added acetyl chloride (3.0 mL, 3.31 g, 42.2 mmol) dropwise by syringe over 20 min. The resulting yellow solution was stirred for 2 h, during which time the diol completely dissolved and a slight precipitate of DMAP·HCl developed. The reaction mixture was diluted with ethyl acetate (50 mL), allowed to stand 10 min, and filtered through a 100 mL fritted glass funnel packed with Celite (1 cm) and silica gel (3 cm). The yellow filtrate was concentrated to half the original volume, diluted with ether (100 mL), and refiltered. The filter cake was washed thoroughly, and the colorless filtrate was diluted with hexanes (100 mL). The solution of diacetate was concentrated and then redissolved with a small amount of ether and allowed to slowly evaporate, affording **7** (4.83 g, 81%) as colorless rhombs: R_f = 0.62 (19:1 CH_2Cl_2/acetone); IR (pellet) ν 1750, 1550; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (dd, J = 4.2, 10.0, 2H), 4.80 (t, J = 4.2, 1H), 4.07, dd, J = 5.1, 10.9, 2H), 3.72 (td, J = 2.3, 12.5, 2H), 2.52 (d, J = 4.2, 2H), 2.05 (qt, J = 5.1, 12.5, 1H), 2.00, (s, 6H), 1.93 (dq, J = 4.4, 13.2, 2H), 1.77 (dp, J = 3.9, 13.4, 1H), 1.64 (m, J = 4.2, 11.2 2H) 1.53 (m, J = 3.9, 11.3, 13.4, 1H), 1.31 (m, J = 1.2, 13.6, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 99.3, 92.6, 74.0, 67.1, 35.1, 27.1, 25.4, 20.9, 18.3; MS (ES^+) 368.0 (M + Na). Anal. Calcd for $C_{15}H_{23}NO_8$: C, 52.17, H, 6.71, N, 4.06. Found: C, 52.06, H, 6.83, N, 3.89.

***meso*-(1*r*,2*R*,6*S*)-2,6-Dibenzoyloxy-1-nitrocyclohexane-1-acetaldehyde, 1,3-Propanediol Acetal (7a).** To a suspension of nitrodiol **4** (96.9 mg, 0.37 mmol) and 4-DMAP (140 mg, 1.14 mmol) in CH_2Cl_2 (2 mL) was added benzoyl chloride (108 μL, 0.93 mmol) dropwise by syringe. The resulting yellow solution was stirred (2 h), concentrated, and flash chromatographed on silica gel (ether/hexanes 1:1) to afford **7a** (177 mg, 99%) as a foam. Crystallization from ether/hexanes yielded colorless prisms: mp 173−174 °Cl R_f = 0.68 (19:1 CH_2Cl_2/acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (dd_{app}, J = 1.2, 8.4, 4H), 7.56 (tt_{app}, J = 1.2, 6.9, 7.5 2H), 7.36 (t_{app}, J = 8.0 4H), 5.92 (t, J = 4.2, 2H), 4.78 (t, J = 4.5, 1H), 3.95 (dd, J = 4.9, 11.1, 2H), 3.64 (dt, J = 2.3, 12.4, 2H), 2.61 (d, J = 4.5, 2H), 1.98 (m, J = 13.4, 4H), 1.93 (m, J = 5.1, 13.1 2H) 1.61 (m, J = 5.0, 1H), 1.22 (m, J = 1.2, 13.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 133.3, 129.8, 129.7, 128.4, 98.3, 91.0, 72.7, 66.8, 37.5, 27.0, 25.2, 16.2; MS (ES^+) 492.5 (M + Na). Anal. Calcd for $C_{25}H_{27}NO_8$: C, 63.96, H, 5.80, N, 2.98. Found: C, 63.74, H, 5.70, N, 2.82.

***meso*-(1*r*,2*R*,6*S*)-1-Acetamido-2,6-diacetoxycyclohexane-1-acetaldehyde, 1,3-Propanediol Acetal (8). A. From 4 by Aluminum Amalgam.** Nitrodiol **4** (62.3 mg, 0.234 mmol) was placed in a test tube (25 × 100 mm) immersed in a thermostated jacketed reaction vessel at 25 °C and dissolved in dry THF (4.5 mL) and water (0.5 mL). Food packaging grade aluminum foil (129 mg, 4.8 mmol) was cut into strips (1.0 × 5.0 cm) and spirally wound about a glass stirring rod. Each coil was individually amalgamated by sequential agitation (using forceps) in ether (20 s), 2% aqueous $HgCl_2$ (20 s), and ether (5 s). As each coil was prepared it was added to the solution at 30-min intervals, during which time ultrasound (power level 2) was applied. After complete addition of the amalgam, the reaction mixture was sonolyzed for an additional 60 min, and triethylamine (0.5 mL) was added. The thick gray slurry was filtered through a fritted glass funnel packed with Celite (1.0 cm), and the filter cake was washed with THF (25 mL). The filtrate containing amine was concentrated and reconstituted in pyridine (1.0 mL) and acetic anhydride (1.0 mL). The solution was refluxed (1 h) and concentrated under vacuum, followed by trituration with CH_2Cl_2. The residue was flash chromatographed (EtOAc/hexanes, 9:1) to afford 47.0 mg (51%) of **8** as colorless needles: mp 154−156 °C; R_f = 0.31 (EtOAc); IR (pellet) ν 3372, 1744; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (br s, 1H), 5.91 (dd, J = 4.6, 11.8, 2H), 5.14 (t, J = 5.6, 1H), 4.14, dd, J = 4.9, 11.6, 2H), 3.79 (t, J = 12.0, 2H), 2.12 (m, 1H), 2.09 (d, J = 5.6, 2H), 2.02, (s, 6H), 1.91 (m, 2H), 1.70 (s, 3H), 1.66 (m, 1H), 1.55 (qt, 1H), 1.40 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 169.2, 100.6, 71.8, 67.0, 32.7, 27.0, 25.6, 24.4, 21.1, 19.4; MS (ES^+) 380.0 (M + Na); MS (ES^-) 356.4 (M − H). Anal. Calcd for $C_{17}H_{27}NO_7$: C, 57.13, H, 7.61, N, 3.92. Found: C, 57.32, H, 7.72, N, 3.93. Alternatively, the yield of **8** was increased to 67% by adding a 50% aqueous slurry of Raney nickel to the suspension on consumption of the aluminum amalgam. Before addition of the Raney nickel to the suspension, it was decanted from the stock aqueous slurry and washed with water, MeOH, and then THF. Following addition of the Raney nickel the flask was fitted with a hydrogen balloon and stirring was continued for 3 h. Workup and chromatography were conducted as described above.

B. From 7 by Raney Nickel. A 50% aqueous slurry of Raney Nickel (2.0 mL) was decanted and washed with water (3 × 5 mL), MeOH (3 × 2 mL), and THF (3 × 4 mL). The solid

was rinsed with THF (5 mL) into a solution of nitrodiacetate **7** (3.45 g 10.0 mmol) in THF (45 mL) in a 100-mL Schlenk tube equipped with a magnetic stir bar and a coldfinger condenser. The solution was purged with hydrogen, heated to just below reflux temperature (60 °C), and vigorously stirred overnight (14 h) under a hydrogen atmosphere (balloon, 1 atm). The mixture was filtered, concentrated, and reconstituted in pyridine (15 mL) and acetic anhydride (15 mL). The solution was refluxed (1 h), and the solvent was removed under vacuum. Crystallization of the residual solid from warm EtOAc/hexanes afforded 3.24 g (91%) of **8** as colorless needles identical in all respects to that obtained by aluminum amalgam. The use of EtOAc as the reduction solvent instead of THF led to similar results.

***meso*-(*E*)-(1*r*,2*R*,6*S*))-1-Acetamido-2,6-diacetoxycyclohexane-2-butenoic Acid, Ethyl Ester (9).** Amide **8** (200 mg, 0.51 mmol) was placed in a test tube (25 × 100 mm). Glacial acetic acid (4.0 mL) and water (1.0 mL) were added. The solution was sonolyzed (power level 2) at ambient temperature (1 h). The solution containing the intermediate aldehyde was concentrated under vacuum and redissolved in CH_2Cl_2 (4.0 mL). Ethoxycarbonylmethyltriphenylphosphonium bromide (443 mg, 1.03 mmol) was added, followed by triethylamine (0.22 mL, 1.58 mmol). The solution was stirred at room temperature (14 h), concentrated to an oil, and flash chromatographed on silica gel (9:1 EtOAc/hexanes) to afford **9** (144 mg, 70%) as an amorphous solid: R_f = 0.48 (EtOAc); IR (pellet) ν 1742, 1685; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (dt, J = 7.6, 15.5, 1H), 5.88 (d, J = 15.7, 1H), 5.39 (dd, J = 4.2, 10.4, 2H), 5.38 (br s, 1H), 4.17 (q, J = 7.2, 2H), 2.97 (dd, J = 1.0, 15.6, 2H), 2.03 (s, 6H), 1.85 (s, 3H), 1.82 (m, 2H), 1.76 (dp, J = 4.1, 13.2, 1H), 1.57 (ad, J = 4.2, 12.5, 2H), 1.48 (qt, J = 4.2, 12.3, 1H), 1.26 (t, J = 7.2, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 169.9, 166.17, 144.9, 123.47, 73.49, 62.7, 60.3, 29.9, 27.1, 24.6, 21.0, 18.9, 14.2; MS (ES^+) 392.4 (M + Na); MS (ES^-) 368.4 (M − H). Anal. Calcd for $C_{18}H_{27}NO_7$: C, 58.52, H, 7.37, N, 3.79. Found: C, 58.48, H, 7.36, N, 3.67.

***meso*-(1*r*,2*R*,6*S*)-1-Acetamido-2,6-diacetoxycyclohexanebutanoic Acid, Ethyl Ester (10).** To a solution of unsaturated ester **9** (60 mg, 0.15 mmol) in methanol (5.0 mL) was added 10% palladium on activated charcoal (6.0 mg) under hydrogen (1 atm). The resulting black suspension was stirred at room temperature (18 h) and filtered through a fritted glas funnel packed with Celite (1.0 cm). The filtrate was concentrated to afford the saturated ester **10** (57.5 mg, 96%) as an off-white solid. Recrystallization afforded colorless needles: mp 116−118 °C; R_f = 0.43 (EtOAc); IR (pellet) ν 1735, 1684; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (br s, 1H), 5.47 (dd, J = 3.7, 10.0, 2H), 4.13 (q, J = 7.2, 2H), 2.33 (t, J = 6.9, 2H), 2.01 (s, 6H), 1.95 (m, 2H), 1.89 (s, 3H), 1.80 (m, 2H), 1.73 (m, 2H), 1.53 (m, 2H), 1.47 (m, 1H), 1.25 (t, J = 7.2, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 170.1, 73.3, 62.1, 60.4, 34.3, 26.9, 26.8, 24.4, 21.1, 18.9, 18.6, 14.2; MS (ES^+) 394.3 (M + Na); MS (ES-) 370.4 (M − H). Anal. Calcd for $C_{18}H_{29}NO_7$: C, 58.21, H. 7.87, N. 3.77. Found: C, 58.46, H, 7.94, N, 3.72.

***meso*-(6*r*,7*R*,11*S*)-2-Oxo-1-azaspiro[5,5]undecan-7,11-diol (11).** Crude saturated ester **10** (17.9 mg, 0.045 mmol) was suspended in 1.2 N HCl (2.0 mL), refluxed (48 h), and concentrated under vacuum to afford the crude intermediate aminocyclohexylbutanoic acid, which was used directly for the next step but was identified from its NMR spectra: ^{1}H NMR (500 MHz, D_2O) δ 3.47 (dd, J = 4.5, 12, 2H), 2.37 (t, J = 5, 2H), 1.7−1.5 (m, 8H), 1.40 (qd, J = 5, 12, 2H), 1.19 (qt, J = 4, 13, 1H); ^{13}C NMR (125 MHz, D_2O, unreferenced) δ 180.5, 77.6, 66.3, 36.6, 31.4, 26.7, 21.9, 21.3. The crude acid was reconstituted in pyridine (1.0 mL). 4-(Dimethylamino)pyridine (18.7 mg, 0.15 mmol) and dicyclohexylcarbodiimide (30 mg, 0.15 mmol) were added, and the solution was stirred at room temperature (24 h). The solution was concentrated under vacuum and flash chromatographed (2:1 EtOAc/MeOH) to afford **11** (9.5 mg, 95%, 91% from **10**) as a white solid: mp 124−126 °C; R_f = 0.22 (4:1 EtOAc/MeOH); IR (pellet) ν 3337, 1644; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (br s, 1H), 3.73 (br s, 2H), 3.39 (dd, J = 4.0, 11.5, 2H), 2.19 (t, J = 5.9, 2H), 1.85 (m, 2H), 1.80 (m, 2H), 1.72 (m, 2H), 1.66 (m, 2H), 1.42 (qd, J = 3.6, 12.9, 2H), 1.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 75.0, 64.3 (C6), 31.2, 29.0, 19.9, 19.2, 19.1; ^{1}H NMR (500 MHz, CD_3OD) δ 3.35 (dd, J = 4.1, 11.4, 2H), 2.20 (t, J = 6.3, 2H), 1.85 (sxt, J = 5.7, 2H), 1.79 (m 2H), 1.73 (dq, J = 2.7, 13.1, 2H), 1.70 (dp, J = 3.1, 13.2, 2H), 1.42 (qd, J = 3.5, 12.8, 2H), 1.31 (qt, J = 3.0, 13.1, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.9, 76.3, 65.1, 32.1, 31.0, 21.1, 20.3, 20.2; MS (ES^+) 222.1 (M + Na); MS (ES^-) 198.3 (M − H).

***meso*-(6*r*,7*R*,11*S*)-7,11-Diacetoxy-1-azaspiro[5,5]-undecan-2-one (2).** To a solution of spirolactam diol **11** (9.5 mg, 0.041 mmol) in dry CH_2Cl_2 (0.50 mL) was added 4-(dimethylamino)pyridine (15.4 mg, 0.12 mmol) followed by acetyl chloride (8.0 μL, 0.11 mmol) by syringe. The solution was stirred (20 min) and directly flash chromatographed to afford **2** (10.0 mg, 77%) as a white solid: mp 128−130 °C; R_f = 0.60 (4:1 EtOAc/MeOH); IR (pellet) ν 1744, 1671; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (br s, 1H), 4.61 (dd, J = 4.0, 10.6, 2H), 2.25 (t, J = 6.4, 2H), 2.01 (s, 6H), 1.93 (m, 2H), 1.85 (m, 4H), 1.73 (m, 1H), 1.48 (m, 2H), 1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 169.9, 76.4, 60.8, 31.3, 27.0, 21.5, 21.0, 19.3, 18.9; MS (ES^+) 305.9 (M + Na). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35, H, 7.47, N, 4.94. Found: C, 59.32, H, 7.36, N, 5.03.

(−)-(6*S*,7*S*,11*R*)-7-Acetoxy-11-hydroxy-1-azaspiro[5,5]-undecan-2-one (12). To a suspension of spirolactam diacetate **2** (105.5 mg, 0.37 mmol) in 0.27 M phosphate buffer (5 mL, pH = 7) was added pig liver esterase (1.0 mL, 2530 U), resulting in a pH of 7.5. The resulting suspension was stirred at room temperature (14 days) with periodic (24−48 h) readjustment of pH to 7.5 using 1 N KOH. When the reaction was judged complete by TLC analysis (performed by direct spotting of the aqueous suspension, followed by removal of water from the TLC plate under vacuum and development), the mixture was saturated with solid NaCl and adjusted to pH 5 with 1.2 N HCl. The solution was then filtered slowly through glass wool. Ethyl acetate (10 × 5 mL) was used to sequentially wash the filter cake and extract the filtrate. The combined washings/extracts were dried over sodium sulfate and concentrated under vacuum to a white solid. The residue was flash chromatographed on silica gel (10 × 100 mm, packed with EtOAc, and eluted with EtOAc/MeOH [10:0/9:1/4:1, 50 mL each]) to afford 78.1 mg (87%) of **12**: mp 165−166 °C; $[\alpha]_D^{25}$ −15.0 (c = 1.04, $CHCl_3$) after crystallization; 93% ee as determined by integration of the ^{19}F signals of the corresponding (*S*)-(+)-MTPA ester, major 4.92, minor 4.42 (relative to 3% TFA in $CDCl_3$) [equally good results could be obtained by integration of the C**H**O MTPA proton resonance (major 4.83, minor 4.91)]; R_f = 0.07 (EtOAc), 0.37, (EtOAc/MeOH, 4:1); IR (film) ν 3317, 1742; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (br s, 1H), 4.66 (dd, J = 4.4, 11.6, 1H), 3.79 (br s, 1H), 3.45 (dt, J = 3.0, 10.9, 1H), 2.23 (t, J = 6.9, 2H), 2.02 (s, 3H), 1.93 (m, 1H), 1.83 (m, 5H), 1.71 (m, 1H), 1.48 (qd, J = 4.4, 12.9, 1H), 1.42 (pd, J = 2.0, 13.2, 1H), 1.36 (qt, J = 3.7, 13.2, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 170.3, 76.8, 75.3, 62.8, 31.3, 28.8, 27.3, 21.2, 20.2, 19.6, 19.1; MS (ES^+) 264.1 (M + Na); MS (ES^-) 240.3 (M − H). Anal. Calcd for $C_{12}H_{19}NO_4 \cdot 1/4H_2O$: C, 58.64; H, 8.00; N, 5.70. Found: C, 58.96; H, 8.18; N, 5.75.

(−)-(6*R*,7*R*,11*S*)-11-Acetoxy-7-methyloxalyloxy-1-azaspiro[5,5]undecan-2-one (13). To a solution of monoacetate **12** (20 mg, 0.08 mmol) in dry dichloromethane (5 mL) was added 4-(dimethylamino)pyridine (16.1 mg, 0.13 mmol), followed by addition of methyloxalyl chloride (12 μL, 0.13 mmol) by syringe. The resulting pale yellow solution was stirred at room temperature followed by addition of EtOAc (5 mL) and concentration to 0.5 mL. The residual oil was flash chromatographed on silica gel (10 × 100 mm) with EtOAc to afford (24.0 mg, 87%) of **13** as an amorphous white solid: $[\alpha]_D^{25}$ −22.5 (c = 0.32, $CHCl_3$); R_f = 0.52 (EtOAc/MeOH, 4:1); IR (neat) ν 1762, 1743; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (br s, 1H, NH), 4.74 (dd, J = 4.4, 11.3, 1H), 4.68 (dd, J = 4.2, 10.9, 1H), 3.86 (s, 3H), 2.31 (ddd, J = 4.6, 7.2, 17.1, 1H), 2.21 (ddd, J = 6.5, 8.6, 17.1, 1H), 2.02 (s, 3H), 1.96 (m, 3H), 1.80 (m, 3H), 1.59 (qd, J = 4.4, 13.0, 1H), 1.48 (pd, J = 3.7, 12.7, 1H), 1.48 (qt, J = 3.9, 13.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 170.0, 157.5, 156.4, 79.6, 76.0, 60.8, 53.7, 31.2, 26.8, 26.7, 21.7, 21.0, 19.1, 18.6; MS (ES^+) 350.4 (M + Na). Anal. Calcd for

$C_{15}H_{21}NO_7 \cdot 1/4H_2O$: C, 54.29; H, 6.53; N, 4.22. Found: C, 54.41; H, 6.96; N, 3.94.

(+)-(6*R*,7*R*,11*S*)-11-Acetoxy-7-phenoxythionocarbonyloxy-1-azaspiro[5,5]undecan-2-one (14). To a solution of monoacetate **12** (129 mg, 0.54 mmol) in dry dichloromethane (8 mL) was added 4-(dimethylamino)pyridine (101 mg, 0.83 mmol), followed by dropwise addition of phenylthionochloroformate (90 μL, 0.65 mmol) by syringe. The resulting pale yellow solution was stirred (24 h) at room temperature followed by addition of EtOAc (5 mL) and concentration to 0.5 mL. The residual oil was flash chromatographed on silica gel (15 × 100 mm) with EtOAc to afford **14** (146.8 mg, 73%) as a white solid: mp 65−80 °C (dec); $[\alpha]_D^{25}$ +57.48 (c = 1, $CHCl_3$); R_f = 0.35 (EtOAc), 0.62 (EtOAc/MeOH, 9:1); IR (neat) ν 1743, 1673; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 7.9, 2H), 7.25 (t, J = 7.4, 1H), 7.06 (d, J = 7.9, 2H), 5.39 (br s, 1H), 5.13 (dd, J = 4.6, 11.6, 1H), 4.68 (dd, J = 4.2, 11.1, 1H), 2.29 (ddd, J = 5.8, 6.7, 17.1, 1H), 2.25 (dt, J = 6.5, 17.1, 1H), 2.19 (dq, J = 3.7, 13.0, 1H), 2.04 (s, 3H, Ac), 2.00 (t, J = 6.3, 2H), 1.90 (m, 1H), 1.84 (p, J = 6.5, 2H), 1.81 (m, 1H), 1.64 (qd, J = 4.2, 13.0, 1H), 1.55 (pd, J = 3.9, 13.2, 1H), 1.48 (qt, J = 3.7, 13.2, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.3, 173.5, 170.0, 153.2, 129.6, 126.7, 121.8, 86.5, 76.2, 61.5, 31.3, 27.0, 26.1, 21.9, 21.0, 19.1, 18.8; MS (ES^+) 400.1 (M + Na); MS (ES^-) 376.4 (M − H). Anal. Calcd for $C_{19}H_{23}NO_5S \cdot 1/4H_2O$: C, 59.75; H, 6.20; N, 3.67. Found: C, 59.81; H, 6.31; N, 3.60.

(+)-(6*R*,7*S*)-7-Acetoxy-1-azaspiro[5,5]undecan-2-one (15). To a solution of thionocarbonate **14** (130 mg, 0.35 mmol) and AIBN (17.2 mg, 0.10 mmol) in dry toluene (13 mL) under argon was added tributylstannane (170 μL, 0.63 mmol) by syringe. The solution was heated (95 °C) in an oil bath (1.5 h) and concentrated under vacuum to an oily residue. The residue was flash-chromatographed on silica gel (10 × 100 mm) packed with EtOAc and eluted with EtOAc/MeOH [9:1/4:1, 25 mL each] to afford **15** (72.4 mg, 93%) as a white solid containing a trace of a tin impurity which could be removed by recrystallization from ether/hexanes to afford colorless prisms: mp 123−124 °C (lit.[6] 143−144 °C for the racemate); $[\alpha]_D^{25}$ +43.9 (c = 1.0, $CHCl_3$); R_f = 0.57 (EtOAc/MeOH, 4:1); IR (neat) ν 1739, 1663; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (br s, 1H), 4.66 (dd, J = 3.9, 9.3, 1H), 2.26 (m, 2H), 2.01 (s, 3H), 1.80 (m, 4H), 1.65 (m, 3H), 1.53 (m, 2H), 1.39 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 170.2, 75.9, 57.2, 36.8, 31.3, 27.0, 25.8, 22.4, 21.3, 21.1, 16.9; MS (ES^+) 248.2 (M + Na). Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.63; H, 8.70; N, 6.22.

(+)-(6*R*,7*S*)-2-Oxo-1-azaspiro[5,5]undecan-7-ol (16). A. From Acetate 15. To a flask containing acetate **15** (54.0 mg, 0.35 mmol) was added a solution of NaOMe prepared by dissolving sodium metal (7.0 mg, 0.30 mmol) in dry MeOH (5 mL). The resulting solution was stirred (1.5 h), and the reaction was quenched by filtration through a pipet packed with silica gel/MeOH and washed with additional MeOH (5 mL). The filtrate was concentrated under vacuum to afford **16** (43.1 mg, 98%) as a white solid: mp 137−139 °C (lit.[6] 160−162 °C for the racemate). Repeated recrystallization from EtOAc/ether/hexanes failed to raise the melting point: $[\alpha]_D^{25}$ +57.5 (c = 1.0, $CHCl_3$); R_f = 0.33 (EtOAc/MeOH, 4:1); IR (neat) ν 3310, 1649; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (br s, 1H), 3.88 (br s, 1H), 3.42 (dt, J = 3.9, 10.9, 1H), 2.28 (ddd, J = 1.6, 4.2, 17.6, 1H), 2.19 (ddd, J = 6.0, 10.6, 17.6, 2H), 1.83 (m, 4H), 1.67 (m, 3H), 1.52 (m, 1H), 1.40 (qd, J = 3.7, 12.3, 1H), 1.31 (m, 2H), 1.25 (qd, J = 3.7, 12.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 75.6, 59.7, 36.7, 31.5, 29.6, 23.7, 22.4, 22.0, 17.2; MS (ES^+) 206.0 (M + Na); MS (ES^-) 182.3 (M − H).

B. From Ketolactam (−)-3. To a solution of ketolactam (−)-**3** in dry MeOH (2 mL) under nitrogen at 0 °C was added solid $NaBH_4$. Upon addition and dissolution of the reagent, gas was evolved. After 15 min TLC analysis indicated consumption of starting ketone. The solution was concentrated and triturated with MeOH (3 × 2 mL) to afford **16** (7.4 mg, 86%) as a white powder. Recrystallization from EtOAc/ether/hexanes afforded colorless rhombs: mp 137−139 °C; mixed mp 136−138 °C, identical in all respects with the previous material obtained by deacylation.

(−)-(6*R*)-1-azaspiro[5,5]undecan-2,7-dione[(−)-3]. To dry dichloromethane (0.5 mL) maintained at −78 °C was added oxalyl chloride (11 μL, 0.12 mmol) by syringe. To this solution was added DMSO (13 μL, 0.18 mmol) by syringe in one portion. The solution was stirred (5 min) followed by dropwise addition of a solution of alcohol **16** (11.3 mg, 0.06 mmol) in dry dichloromethane (0.5 mL). The solution was stirred for an additional 5 min followed by dropwise addition of Et_3N (34 μL, 0.24 mmol) over 5 min. The pale yellow solution was stirred at −78 °C (2 h) and at 0 °C for an additional 12 h. The reaction mixture was diluted with EtOAc (1 mL), and the solvents were removed by rotary evaporation. Flash chromatography of the residual solid on silica gel (5 × 100 mm) packed with EtOAc and eluted with EtOAc/MeOH (10:0/9:1/4:1 [10 mL each]) afforded *(−)*-**3** (8.6 mg, 77%) as a white solid: mp 155−157 °C (lit.[6] 150−152 °C, for the racemate)l $[\alpha]_D^{25}$ −59.3 (c = 1.0, $CHCl_3$); R_f = 0.33 (EtOAc/MeOH, 4:1); IR (neat) ν 1712, 1655; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (br s, 1H), 2.50 (ddd, J = 5.8, 12.2, 13.9, 2H), 2.46 (ddd, J = 3.9, 5.8, 13.9, 2H), 2.33 (dt, J = 6.7, 18.0, 2H), 2.28 (ddd, J = 6.7, 7.4, 18.0, 2H), 2.14 (dq, J = 3.2, 6.8, 1H), 2.04 (m, 2H), 1.88 (ddd, J = 3.5, 9.7, 13.4, 1H), 1.82 (m, 3H), 1.63 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 172.0, 65.2, 40.9, 38.5, 30.8, 29.2, 27.3, 21.6, 17.0; MS (ES^+) 204.2 (M + Na). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.33; H, 8.56; N, 7.86.

(+)-(6*S*,11*S*)-11-Acetoxy-1-azaspiro[5,5]undecan-2,7-dione (17). A. By Swern Oxidation. To solution of oxalyl chloride (82 μL, 0.94 mmol) in dry CH_2Cl_2 (7 mL) under argon at −78 °C was added DMSO (70 μL, 0.99 mmol). The solution was stirred (5 min) followed by dropwise addition of alcohol **12** (78.1 mg, 0.32 mmol) in dry dichloromethane (2.0 mL). The solution was stirred (45 min) followed by dropwise addition of Et_3N (180 μL, 1.29 mmol) over 5 min. The solution was stirred at −78 °C (4 h) and at 0 °C (12 h). The reaction mixture was diluted with EtOAc (1 mL), and the solvent was removed under vacuum. Flash chromatography on silica gel (EtOAc/MeOH [10:0 (25 mL)/9:1 (50 mL)/4:1(50 mL)]) afforded 44.5 mg (57%) of **17** as a colorless oil: $[\alpha]_D$25 +88.2 (c = 2.2, $CHCl_3$); IR (neat) ν 1712, 1655; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (br s, 1H), 4.80 (dd, J = 4.4, 10.9, 2H), 2.50 (m, 2H), 2.31 (dt, J = 5.1, 17.6, 1H), 2.22 (ddd, J = 6.5, 10.2, 17.6, 1H), 2.09 (dq, J = 3.9, 13.9, 2H), 2.04 (s, 3H), 1.99 (m, 3H, 1.90 (m, 1H), 1.83 (m, 1H), 1.60 (m, 1H), 1.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 173.0, 69.9, 75.9, 69.4, 37.0, 30.8, 26.7, 24.7, 21.0, 21.0, 19.9, 17.1; MS (ES^+) 262.2 (M + Na); MS (ES^-) 238.4 (M − H).

B. By Moffatt Oxidation. To a solution of alcohol **12** (26.6 mg, 0.14 mmol) in dry DMSO (1 mL) was added dicyclohexylcarbodiimide (92.4 mg, 0.44 mmol) and crystalline orthophosphoric acid (3.0 mg, 0.03 mmol). The mixture was stirred overnight during which time a precipitate of dicyclohexylurea formed. The mixture was directly flash chromatographed on silica gel with EtOAc (3×) to afford 19.1 mg (73%) of **17**, identical in all respects with the previous material provided by the Swern method.

(+)-(6*S*,12*S*)-12-Acetoxy-7-aza-1,4-dioxadispiro[4,0,5,4]-pentadecan-8-one (18). To a solution of ketolactam **17** (36.7 mg, 0.15 mmol) and ethylene glycol (60 μL, 1.08 mmol) in dry toluene (5 mL) was added TsOH (3.2 mg, 0.02 mmol). The mixture was stirred at reflux (3 h). After the mixture cooled to room temperature it was filtered through silica gel using EtOAc as eluent to afford 46.2 mg (>99%) of crude **18** as an oil containing 15% ethylene glycol. The crude material was used directly for the next step; however, an analytical sample was prepared by acetylation (AcCl/DMAP/CH_2Cl_2) of the mixture followed by separation of **18** from the ethylene glycol diacetate by silica gel column chromatography (EtOAc/MeOH, 9:1): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.65 (br s, 1H), 4.83 (dd, J = 4.9, 11.3, 1H), 4.07 (m, 1H), 3.93 (m, 1H), 3.86 (m, 2H), 2.24 (t, J = 6.5), 2.02 (m, 1H), 2.00 (s, 3H), 1.83 (m, 4H), 1.58 (m, 3H), 1.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.1, 170.1, 111.5, 76.2, 65.6, 65.5, 63.0, 31.3, 30.9, 26.8, 23.3, 21.1, 19.0, 18.7; MS (ES^+) 306.2 (M + Na).

(+)-(6*S*,12*S*)-12-Hydroxy-7-aza-1,4-dioxadispiro[4,0,5,4]-pentadecan-8-one (19). To a solution of ketal **18** (46.2 mg)

in MeOH (1 mL) was added a solution of NaOMe (3 mL). The resulting colorless solution was stirred at room temperature (30 min) and then neutralized by filtration through silica gel. The resulting solution was concentrated and flash chromatographed on silica gel (EtOAc/MeOH [10:0 (10 mL)/9:1 (25 mL)/4:1 (25 mL)]) to afford 31.0 mg (84% from ketolactam **17**) of **19** as white solid: $[\alpha]_D^{25}$ +17.2 (c = 0.64, $CHCl_3$); IR (neat) ν 3343, 1645; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (br s, 1H), 4.03 (m, 1H), 3.86 (m, 3H), 3.66 (br s, 1H), 3.62 (m, 1H), 2.21 (m, 2H) 2.00 (m, 1H), 1.90 (m, 1H), 1.78 (m, 3H), 1.56 (m, 2H), 1.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 111.8, 74.5, 65.3, 65.2, 64.6, 31.2, 30.9, 28.6, 22.0, 19.0, 18.9; MS (ES^+) 264.2 (M + Na). Anal. Calcd for $C_{12}H_{19}NO_4 \cdot H_2O$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.63; H, 8.45; N, 5.38.

(−)-(6*S*,12*S*)-12-Phenoxythionocarbonyloxy-7-aza-1,4-dioxadispiro-[4,0,5,4]pentadecan-8-one (20). To a solution of lactam alcohol **19** 31 mg (0.13 mmol) in dry CH_2Cl_2 (2.0 mL) was added DMAP (24.2 mg, 0.20 mmol) followed by phenythionochloroformate (20.0 μL, 0.14 mmol) by syringe while stirring under nitrogen. The resulting yellow solution was stirred for 24 h, during which time the yellow color discharged. The solution was directly flash-chromatographed on silica gel to afford 23.6 mg (49%, 87% corrected for recovered **19**) of thionocarbonate **20**; and 13.6 mg (44%) of unchanged starting material: $[\alpha]_D^{25}$ −60.4 (c = 1.18, $CHCl_3$); IR (neat) ν 3389, 1665; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 7.6, 2H), 7.25 (td, J = 7.6, 8.5, 1H), 7.06 (dd, J = 7.6, 8.5, 2H), 5.75 (br s, 1H), 5.33 (dd, J = 4.6, 11.1, 1H), 4.11 (m, 1H), 3.95 (m, 1H), 3.90 (m, 2H), 2.26 (m, 2H), 2.19 (m, 1H), 2.06 (m, 1H), 1.93 (m, 1H), 1.89 (m, 1H), 1.80 (m, 1H), 1.64 (m, 2H), 1.60 (m, 2H), 1.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 174.0, 153.3, 129.6, 126.6, 121.9, 111.4, 86.6, 65.6, 63.6, 31.3, 30.8, 25.8, 23.6, 18.7, 18.5; MS (ES) 377 (M + H).

(−)-6*S*)-7-Aza-1,4-dioxadispiro[4,0,5,4]pentadecan-8-one (21). To a solution of thionocarbonate **20** (23.6 mg, 0.06 mmol) in toluene (2 mL) were added AIBN (3.5 mg, 0.02 mmol) and tributylstannane (34 μL, 34.7 mg, 0.12 mmol). The solution was heated to 95 °C (oil bath), and stirring was continued under argon for 2.5 h. The reaction mixture was directly flash chromatographed with EtOAc/MeOH [10:0 (10 mL)/9:1 (25 mL)/4:1 (25 mL)] to afford 13.4 mg (95%) of **21** as a white solid contaminated with ∼5% tin products: R_f = 0.54 (EtOAc/MeOH, 4:1); $[\alpha]_D^{25}$ −33.7 (c = 0.67, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.8 (br s, 1H), 4.03 (m, 1H), 3.93 (m, 1H), 3.87 (m, 2H), 2.29 (dddd, J = 1.4, 3.7, 5.3, 17.5, 1H), 2.20 (ddd, J = 5.6, 10.4, 17.5, 2H), 1.83 (m, 3H), 1.76 (m, 1H), 1.64 (m, 2H), 1.54 (m, 4H), 1.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 110.6, 65.5, 65.2, 59.7, 36.3, 31.5, 25.7, 22.6, 21.5, 17.5; MS (ES) 225 (M + H).

(+)-(6*S*)-1-Azaspiro[5,5]undecan-2,7-dione [(+)-3)]. To a solution of glacial acetic acid (1.6 mL), trifluoroacetic acid (0.7 mL), and water (0.9 mL) was added ketallactam **21** (13.4 mg, 0.06 mmol). The colorless solution was stirred at room temperature (24 h), and the solvent was removed under vacuum to afford a residue which was flash chromatographed (CH_2Cl_2/acetone 9:1) to furnish 9.5 mg (88%) of **(+)-3** as a white solid: $[\alpha]_D^{25}$ +60.3 (c = 0.54, $CHCl_3$). The product was spectrally identical with (−)-**3**, save for direction of optical rotation.

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Supporting Information Available: ^{1}H and ^{13}C spectra of compounds **6**, **11**, **16**−**18**, **20**, **21** and ^{1}H spectra of the epimerization of **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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