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Synthesis of Carbocyclic Hydantocidins via Regioselective and Diastereoselective Phosphine-Catalyzed [3 + 2]-Cycloadditions to 5-Methylenehydantoins

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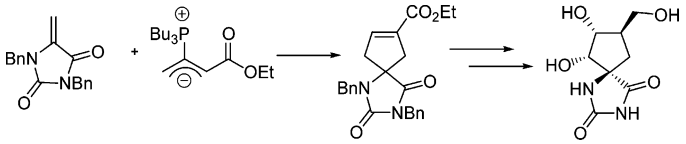
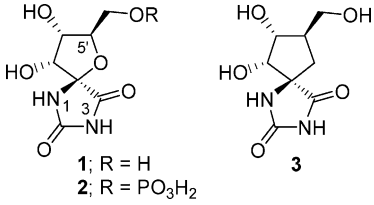


The phosphine-catalyzed [3 + 2]-cycloaddition of 5-methylenehydantoins **4** with the ylides **5**, derived from addition of tributylphosphine to the 2-butynoic acid derivatives, **6a**−**d**, gives spiro-heterocyclic products. The camphor sultam derivative **6b** gives optically active products. Noteable was that the ylides derived from ethyl 2-butynoate and the 3-(2-butynoyl)-1,3-oxazolidin-2-one derivatives **6c** and **6d** gave spiro-heterocyclic products with reverse regioselectivities. The *N*,*N*-dibenzylprotected cycloadduct has been converted to carbocyclic hydantocidin and 6,7-diepi-carbocyclic hydantocidin.

Introduction

Hydantocidin (**1**) is a naturally occurring spironucleoside that was first isolated from the culture broth of *Streptomyces hygroscopicus* SANK 63584[1] and later from other strains of *Streptomyces* including Tu-2474[2] and A1491.[3] Structurally, it features a spirohydantoin attached to D-ribofuranose at the anomeric position. However biologically, it exhibits potent nonselective herbicidal activities against annual weeds and perennial weeds[1] with an efficacy similar to that of glyphosate.[4] In contrast, the phytotoxin showed low toxicity toward micro-organisms, fungi, fish, and mice. In mice it had a LD_{50} > 1000 mg/kg.[1]

Further studies showed that hydantocidin acted as a proherbicide, being phosphorylated at the 5′ position in vivo.[4] In the phosphorylated form (**2**), it strongly binds to its target enzyme, adenylatesuccinate synthetase (Adss).[5−7] This is an enzyme involved in de novo purine synthesis in plants that converts inosine monophosphate (IMP) to adenosine monophosphate (AMP), an enzyme system that no current herbicide targets. It was also shown that hydantocidin was a competitive inhibitor of IMP synthesis with a K_i of 22 nM, which is 1000 times stronger than its competitor.[7] X-ray crystallographic analysis of the Adss-inhibitor complex of phosphorylated hydantocidin **2** established that **2** bound to the same active site and in the same way as AMP.[6,8] Adss is also the site of action for several antibiotics, including hadacidin and alanosine,[9] suggesting that derivatives of hydantocidin that inhibit this enzyme may also have use in therapeutic applications.



1; R = H
2; R = PO_3H_2
3

The fermentation yield of hydantocidin from *Streptomyces* was low,[1] and thus there was a drive for the

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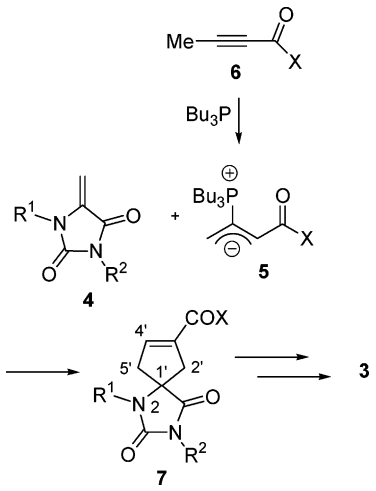
synthesis of optically active hydantocidin and its 15 other possible stereoisomers around its four stereogenic centers.[10−15] However, these studies showed that only the natural configuration of hydantocidin showed any phytotoxic activity. Furthermore, deoxy derivatives of hydantocidin, that is, compounds without the hydroxyl groups, also revealed a dramatic decrease in activity, signifying the importance of the hydrogen bonds to the hydroxyl groups.[5,16,17] *N*-Acetyl derivatives of hydantocidin were found to have no biological activity and therefore further illustrated the importance of hydrogen bonding to the hydantoin ring.[5] Herbicidal activity, however, was maintained when the oxygen in the furan ring was replaced with a carbon to form the carbocyclic analogue (**3**).[18]

Many of the synthetic strategies for the synthesis of hydantocidin and its analogues[10,12,15,19,20] have revolved around the use of sugar derivatives to generate the desired stereochemistry of the hydroxyl groups in the furan ring. By use of this strategy, hexofuranose,[21−24] hexopyranose,[25−27] and tetrofuranose[28] analogues have been generated. One problem associated with this strategy is that anomerization at the spiro carbon (C5) can occur during the synthesis; however, carbocyclic analogues do not suffer from this detriment.[18,29] Other analogues of hydantocidin have involved modification of the hydantoin ring,[30] and it has been shown that thiohydantocidins, where the C2 carbonyl is replaced with a thiocarbonyl, can be produced[14,31] and used without the loss of herbicidal activity.[31]

SCHEME 1



We report here a new strategy for the synthesis of carbocyclic hydantocidin (**3**) and its 3′,4′-diepimer using a phosphine-catalyzed [3 + 2]-cycloaddition of ethyl 2-butynoate **6a** (**6**, X = OEt) with *N*,*N*′-diprotected-5-methylenehydantoins (**4**) to generate the key spiro-heterocyclic system of these target molecules (Scheme 1). The phosphine-catalyzed [3 + 2]-cycloaddition of ethyl buta-2,3-dienoate or ethyl butynoate with electron-deficient alkenes has been established as a useful method for preparing substituted cyclopentenes[32−45] both in racemic and enantio-enriched forms. However, only a few examples of preparing spiro-heterocyclic derivatives using this method have been reported.[36,41−45] Indeed, prior to our initial communication,[42] the phosphine-catalyzed [3 + 2]-cycloaddition reactions of 5-methylenehydantoins had not been described.[42,43]

Results and Discussion

Synthesis of *N*,*N*′-Diprotected-5-methylenehydantoins. Surprisingly, with the exception of *N*,*N*′-dibenzyl-5-methylenehydantoin (**9**),[46,47] the literature is devoid of

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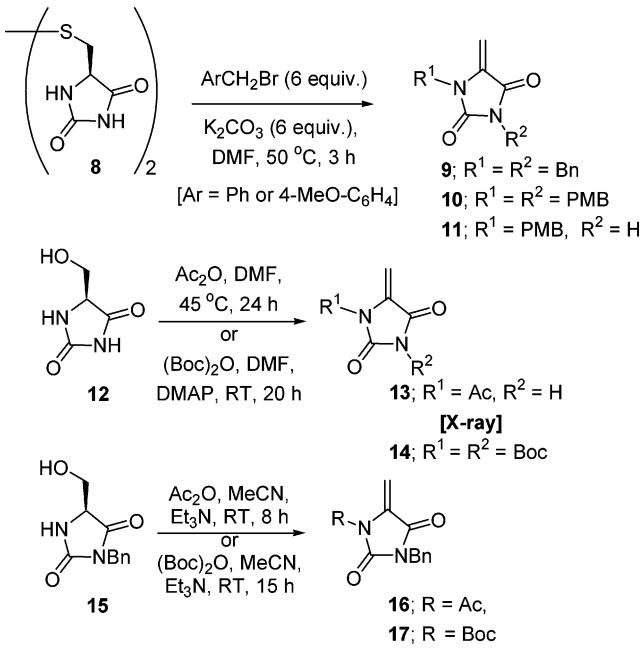
SCHEME 2



methods for the synthesis of usefully diprotected, *N*,*N*′-diprotected-5-methylenehydantoins. Compound **9** and its previously unreported *N*,*N*′-diPMB analogue (**10**) were prepared from the base-catalyzed reactions of cystine hydantoin (**8**)[47] and the appropriate arylmethyl bromide (Scheme 2). The former compound was isolated pure after column chromatography in 83% yield while the latter in only 64% due to concomitant formation of the mono-*N*3-protected-5-methylenehydantoin **11** in 15% yield. Attempts to prepare *N*,*N*′-diacetyl-protected hydantoins from serine hydantoin (**12**)[46,48] or *S*-methylcystein hydantoin (not shown)[46,47] were not successful due to the lability of the *N*3-acetyl group to column chromatography, even though ^{1}H NMR analysis of the crude reaction mixtures showed both nitrogens had been acetylated (Scheme 2). For example, serine hydantoin **12** upon acetylation with an excess amount of acetic anhydride in DMF at 45 °C for 24 h gave, after evaporation of all volatiles, a sample that showed resonances for *N*,*N*′-diacetyl-5-methylenehydantoin; however, after column chromatography only the *N1*-acetyl-5-methylenehydantoin **13** could be isolated in modest yield (34%). The position of the acetyl group in **13** was unequivocally determined by X-ray crystallographic analysis (Supporting Information). This structure was not unexpected considering that the *N*3-nitrogen is flanked by two electron-withdrawing carbonyl groups that makes the *N*3-acetyl group more labile toward acid- or base-catalyzed hydrolysis. The *N*,*N*′-diboc-protected-5-methylenehydantoin **14** was more stable but could only be isolated in 32% yield. High yields (91−92%) of the *N*3-benzyl, *N*1-acetyl, and *N*1-Boc-5-methylenehydantoins **16** and **17** could be obtained directly from *N*3-benzyl serine hydantoin **15**[11] by base-catalyzed N- and O-acylation with concomitant elimination of the *O*-acylated group as shown in Scheme 2.

[3 + 2]-Cycloaddition Reactions of 5-Methylenehydantoins. The results of the phosphine-catalyzed [3 + 2]-cycloaddition reactions of the 5-methylenehydantoins **9**, **10**, **16**, and **17** with the ylide **5** (X = OEt) that was generated in situ from the reaction of ethyl 2-butynoate **6a** and tributylphosphine (TBP) are shown in Table 1. The reaction of 5-methylenehydantoin **9** with ethyl 2-butynoate (2 equiv) and TBP (0.1 equiv) in benzene solution at room temperature (RT) for 15 h gave essentially a single regioisomer (**18**) from ^{1}H NMR analysis of the crude reaction mixture. Column chromatography gave diastereomerically pure and racemic **18** in 81% yield, based on the moles of **9**, along with a small amount (6%) of the tricyclic product **26** (Table 1, entry 1). The structure of **26** was determined from single-crystal X-ray analysis (Supporting Information), which showed that this compound arises from a further cycloaddition reaction on the regioisomer **19** that could not be isolated from the crude reaction mixture. An analogous tricyclic product that could be formed from the reaction of **18** with the ylide **5** (X = OEt) was not detected. The related triphenylphosphonium ylide of **5** (X = OEt) was generated in situ from ethyl buta-2,3-dienoate[49] (2 equiv) and triphenylphosphine (TPP, 0.1 equiv) and reacted with **9** to give an 80:20 mixture of the two regioisomers **18** and **19** that were readily separated by column chromatography (Table 1, entry 2). Pure **18** and **19** (both racemic) were obtained in yields of 65 and 17%, respectively. Soon after our initial communication on this work, Lu's group[43] reported that the TPP-catalyzed [3 + 2]-cycloaddition reaction of ethyl buta-2,3-dienoate and **9** in toluene gave a 65:35 mixture of **18** and **19** in 96% yield, while *tert*-butyl buta-2,3-dienoate gave a 74:26 mixture of the *tert*-butyl ester analogues of **18** and **19**, respectively. They also reported that the combination of *tert*-butyl-2-butynoate/TBP and **9** gave a much enhanced regioselectivity of >97:3. While these two independent studies have been performed using different reaction solvents and concentrations (0.27 M in our case and 0.1 M in Lu's[43]) and ester groups, they both show that the regioselectivity is better using the alkyne/TBP system rather than the allene/TPP system as a precursor to the ylide **5** or its triphenylphosphonium analogue. In our studies, the amount of **19** formed in Table 1, entry 1, is underestimated since at least 6% of this compound is formed but reacts with excess ylide to form the tricyclic compound **26**.

TABLE 1. Tributylphosphine-Catalyzed [3 + 2]-Cycloaddition Reactions of 5-Methylenehydantions with Ethyl 2-Butynonate (6a)

entry	hydantoin	products (yield, %)[b] [ratio **A**:**B**][c]
1	**9**	**18** + **19** (81) [>98:<2] + **26** (6)
2	**9**[a]	**18** + **19** (82) [80:20]
3	**10**	**20** + **21** (86) [83:17]
4	**16**	**22** + **23** (43) [80:20]
5	**17**	**24** + **25** (57) [78:22] + **27** (7)

[a] Ethyl 2,3-butadienoate and Ph_3P were used in this reaction. [b] Total yield of regioisomers **A** and **B** after purification by column chromatography. [c] Ratio determined by ^{1}H NMR on the crude reaction mixture (see discussion for details).

The related PMB analogue (**10**) of **9** gave a 83:17 mixture of regioisomeric cycloaddition products, **20** and **21**, respectively (Table 1, entry 3). Diastereomerically pure **20** could be isolated in 68% yield after column

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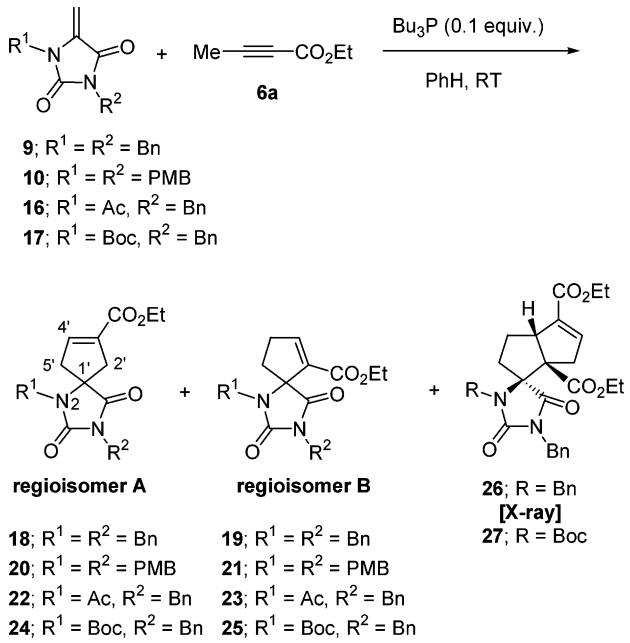
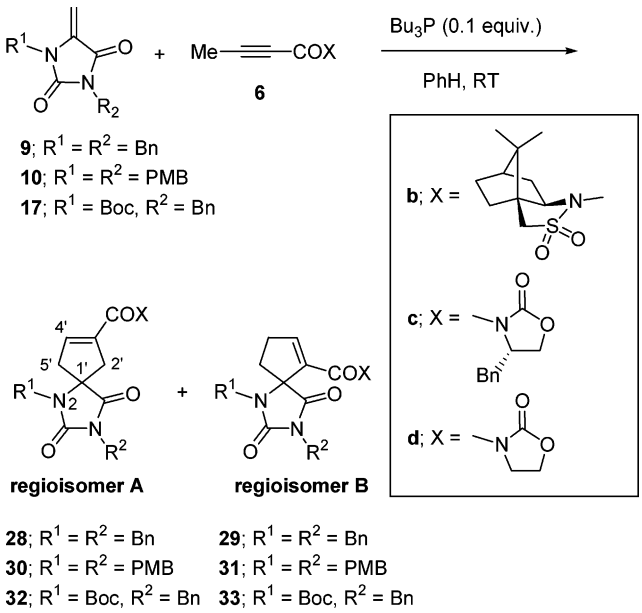
SCHEME 3. Compounds 18−27 are Racemic



SCHEME 4



chromatography. The *N*1-acetyl and *N*1-Boc-*N*3-benzyl-5-methylenehydantoins **16** and **17** also reacted with the ylide derived from **6a** to give **22** and **24** as the major regioisomers, respectively (Table 1, entries 4 and 5). In the latter reaction the tricyclic compound **27** was also isolated in 7% yield and had similar NMR spectral data to those of **26**. Compound **27** was thus assumed to have a similar structure and relative stereochemistry to **26**.

In general, type **A** regioisomers **18**, **20**, **22**, and **24** showed olefinic proton resonances upfield (δ 6.40−6.69) of the corresponding resonances for type **B** regioisomers **19**, **21**, **23**, and **25** (δ 7.02−7.20). Integration of these olefinic resonances, on the crude reaction mixtures, was used to determine the regioselectivities of the reactions reported in Table 1. The structures of **18** and **19** were determined by extensive 2D NMR studies and from single-crystal X-ray analysis of the derivatives, **48** and **50**, of **18**.

To prepare enantiomerically enriched versions of these cycloadducts, the corresponding cycloadditions reactions with the chiral (1*S*)-camphor sultam[50] and the (4*S*)-benzyl-2-oxazolidinone,[50] 2-butynoyl derivatives, **6b** and **6c**, respectively, were examined (Scheme 4 and Table 2). The TBP-catalyzed cycloaddition reaction between **9** and the chiral (1*S*)-camphor sultam 2-butynoyl derivative **6b** gave a single regioisomeric product (**28b**) (Table 2, entry 1) but as a 1:1 mixture of diastereomers. These were readily separated by column chromatography into their pure (1*R*)- ($[\alpha]_D^{22}$ −25 (c 1.7, $CHCl_3$)) and (1*S*)- ($[\alpha]_D^{22}$ −10 (c 1.7, $CHCl_3$)) diastereomers in a combined yield of 74%. The absolute stereochemistry of these diastereomers was determined by single-crystal X-ray analysis of (1*R*)-**28b** (see Supporting Information). In contrast, TBP-catalyzed cycloaddition reaction between **9** and the chiral (4*S*)-benzyl-2-oxazolidinone 2-butynoyl derivative **6c** gave a mixture of regioisomeric products, **28c** and **29c**, in a ratio of 11:89, respectively. Surprisingly, the regioisomer **29c**, a type-**B** regioisomer, was the major product. Diastereomerically pure **29c** could be obtained after purification of the crude reaction mixture by column chromatography, while **28c** was isolated as a 1:1 mixture of diastereomers (Table 2, entry 2). Similar regiochemical results were obtained from the reactions of **6c** with the 5-methylenehydantoins **10** and **17** (Table 2, entries 3 and 4), with **31c** and **33c** being formed as the major regioisomers, respectively, and as single diastereomers. The reaction between **9** and the achiral analogue **6d**[51] of **6c** also favored the formation of regioisomer **B** (**29d**) over regioisomer **A** (**28d**) (**29d**:**28d** = 80:20, Table 2, entry 5). Thus the reactions of 5-methylenehydantoins with the ylides generated from **6a** and **6b** favor regioisomeric products of the type **A**, while ylides derived from the 2-oxazolidinone 2-butynoyl derivatives **6c** and **6d** favor regioisomeric products of the type **B**. In the case of **6c**, these type-**B** products are obtained as single diastereomers**.** The relatively low yields of these cycloadducts were likely due to the instability of the COX group (compare with Scheme 5).

TABLE 2. Tributylphosphine-Catalyzed [3 + 2]-Cycloaddition Reactions of 5-Methylenehydantions with the Chiral 2-Butanoyl Compounds 6b and 6c and Achiral 6d

entry	2-butanoyl derivative 6	hydantoin	yield[a]	products (Ratio **A** [de]:**B** [de])[b]
1	**6b**	**9**	74%	**28b** (100 [0]:0)
2	**6c**	**9**	54%[b]	**28c** + **29c** (11 [0]:89 [98%])
3	**6c**	**10**	32%[c]	**30c** + **31c** (18 [0]:82 [98%])
4	**6c**	**17**	43%	**32c** + **33c** (5 [0]:95 [98%])
5	**6d**	**9**	42%	**28d** + **29d** (20:80)

[a] Total yield of regioisomers **A** and **B** after purification by column chromatography. [b] Ratio determined by ^{1}H NMR on the crude reaction mixture (see discussion for details). [c] 17% of (4*S*)-benzyl-2-oxazolidinone was also isolated. [d] 12% of (4*S*)-benzyl-2-oxazolidinone was also isolated.

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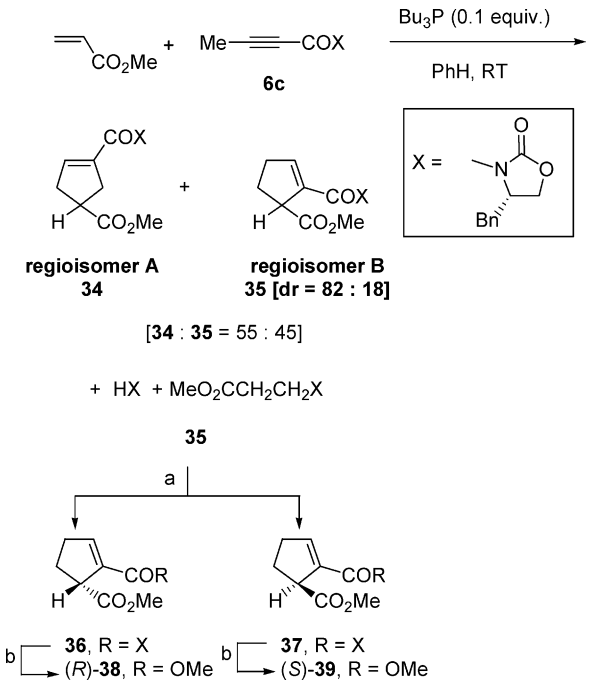
SCHEME 5[a]

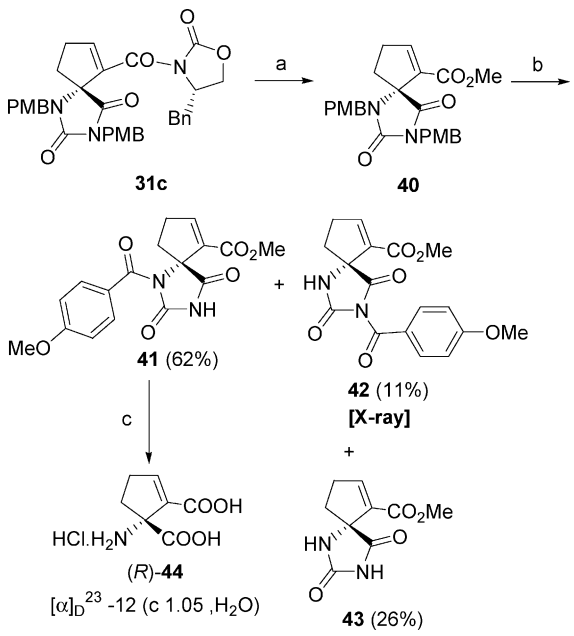


[a] Reagents and conditions: (a) HPLC separation (Supporting Information). (b) $Sm(OTf)_3$, MeOH, reflux, 12 h, 20% (**38**), 37% (**39**).

The reaction of ethyl acrylate with ylide **5** (R = OEt) is known to give an 89:11 mixture of diethyl 3-cyclopropene-1,3-dicarboxylate and diethyl 2-cyclopropene-1,2-dicarboxylate, respectively.[32] Thus the regiochemical sense of this reaction is similar to that of the reactions of **6a** with **9**. Treatment of methyl acrylate with the ylide **6c** gave essentially a 1:1 mixture of the two possible regioisomers **34** and **35** in low yield (39%) (Scheme 5). Products arising from cleavage of the chiral auxiliary (HX and $MeO_2CH_2CH_2X$), presumably by TBP, were also isolated. Diastereomers **36** and **37** (Scheme 5) were formed in a ratio of 82:18 and could be separated by preparative high-performance liquid chromatography (HPLC), while **34** was a 54:46 mixture of diastereomers. Diastereomers **36** and **37** were readily converted to the known dimethyl esters (*R*)-**38** and (*S*)-**39**, respectively.[52] because of the volatility of these diesters, their isolated yields were low (20−37%). Chiral gas chromatography (GC) analysis (Supporting Information) indicated that these diesters were isolated in >98% enantiomeric excess (ee), and the sign of their optical rotations confirmed their absolute stereochemistries.[52]

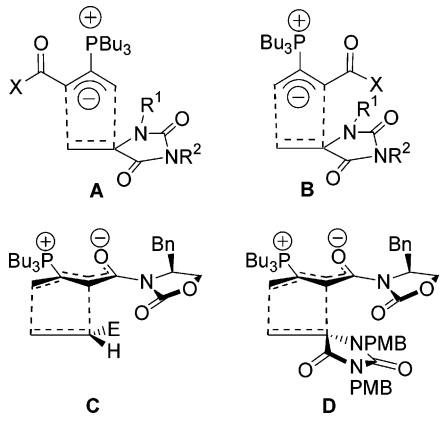
To determine the absolute stereochemistry of **31c**, the chiral auxiliary was removed by treatment with samarium(III) triflate in methanol[53] to give the methyl ester **40** in 70% yield. (Scheme 6). Treatment of **40** with ceric ammonium nitrate in acetonitrile/water gave the desired *N*,*N*-dideprotected derivative **43** [($[\alpha]_D^{24}$ −33 (c 0.45, $CHCl_3$)] in 26% yield plus the monodeprotected/benzylic oxidation products, the amides **41** (62%) and **42** (11%). Compound **42** formed single crystals from which its

SCHEME 6[a]



[a] Reagents and conditions: (a) $Sm(OTf)_3$, MeOH, reflux, 12 h, 70%. (b) CAN, MeCN, RT, 45 min. (c) 10% HCl, 100 °C, 30 min, microwave reactor, 100%.

SCHEME 7



relative structure could be unequivocally determined by X-ray crystallographical structural analysis (Supporting Information), confirming the above regiochemical assignments of our **B**-type regioisomeric cycloaddition products. Microwave-assisted acid hydrolysis of **41** using 1N HCl at 100 °C for 30 min gave the known amino diacid **44**.[41] Its optical rotation ($[\alpha]_D^{23}$ −12 (c 1.05, H_2O)) matched closely in magnitude to that of the *S* enantiomer (ee 88%) of this compound ($[\alpha]_D^{23}$ +11 (c 0.4, H_2O)),[41] and the sign of the rotation indicated that **44** had the *R* stereochemistry.

The difference in regiochemical outcomes between the ylides generated from **6a** and **6c**,**d** with methyl acrylate, **9**, and **10** suggests that electronic effects are responsible for the reversal of regiochemistry rather than steric effects. On the basis of steric considerations only, transition state **A** would be expected to be less sterically crowded and favored over transition state **B** for both ylides (Scheme 7). Preliminary semiemperical calculations (AM1, PC Spartan Pro) on the ylides **5a** (R = OEt)

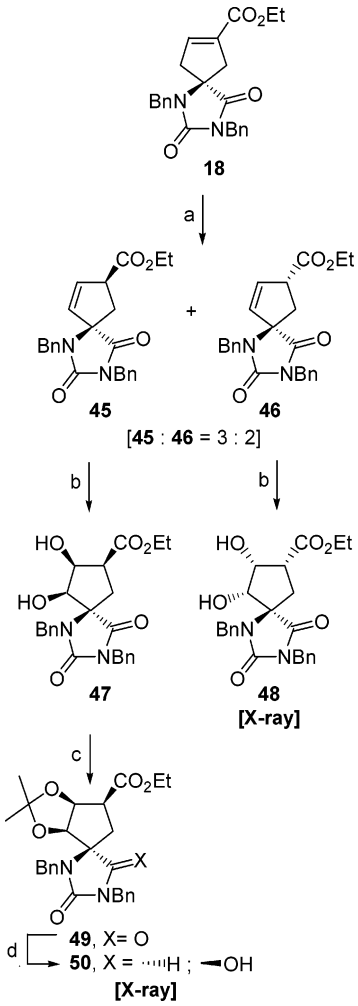
(52) Suemune, H.; Tanaka, M.; Obaishi, H.; Sakai, K. *Chem. Pharm. Bull.* **1988**, *36*, 15−21.
(53) Evans, D. A.; Scheidt, K. A.; Downey, C. W. *Org. Lett.* **2001**, *3*, 3009−3012.

and **5d** (R = *N*-oxazolidinone) suggest that the magnitude of the frontier molecular orbital coefficient of the highest-occupied molecular orbital of **5d** is significantly larger at the γ-position than that in **5a**, consistent with a reversing of the observed regiochemical outcomes.

The absolute stereochemistry of the major **B**-type regioisomeric cycloaddition product **36**, formed in Scheme 5, can be rationalized as arising from the endo transition state **C** (Scheme 7). The ylide **5d** (R = chiral *N*-oxazolidinone) would be expected to have the enolate oxygen and the phosphonium cation in an electrostatically favorable syn-periplanar arrangement, while the endo and exo cyclic carbonyl groups in the ylide would be expected to have an anti-periplanar arrangement to minimize unfavorable dipolar interactions. The stereochemistry observed in cycloadduct **31c**, however, suggests that the related exo-transition state **D** (Scheme 7) may be favored. Indeed, exo-selective Diels–Alder reactions of cyclic exocyclic-methylene dienophiles related to **9**, **10**, and **17** are well documented,[54] and it has been suggested that dipole–dipole interactions between the diene and dienophile are responsible for this selectivity.[54b]

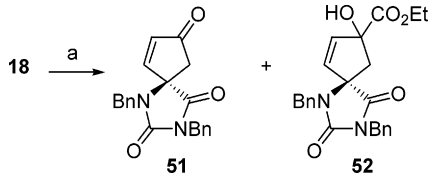
Synthesis of Carbocylic Hydantocidin and its 6,7-Diepimer. Deconjugation of **18** was effected by deprotonation with potassium bistrimethylsilylamide under an argon atmosphere, followed by a low-temperature quench with acetic acid of the resulting enolate (Scheme 8). This gave a 3:2 mixture of the epimeric esters **45** and **46**, respectively, that were readily separated by column chromatography. Intersestingly, deprotonation with potassium bistrimethylsilylamide under a nitrogen atmosphere gave rise to the ketone **51** (42% yield) and the α-hydroxy ester **52** (37% yield) as a single diastereomer (Scheme 9). These compounds presumably arise from the reaction of the enolate anion with traces of molecular oxygen. Cis-dihydroxylation of **45** and **46** using catalytic osmium tetroxide gave the respective diols **47** (74%) and **48** (60%) as single diastereomers; the diol **47** was converted to the acetonide **49** under standard conditions (Scheme 8). The facial selectivity of these dihydroxylation reactions appears to be controlled by the ester group, with both products **47** and **48** arising from dihydroxylation from the most hindered face of the alkene moiety and syn to the ester group. Attempts to convert **49** to the target molecule by selectively reducing the ester group in this compound were thwarted due to competing reduction of the hydantoin carbonyl. For example, attempts to reduce the ester group in **49** with lithium borohydride gave the alcohol **50** in 71% yield and the diol product (structure not shown) from reduction of the hydantoin ring and the ester group. The relative stereochemistry of the compounds shown in Scheme 8 was based on the single-crystal X-ray structures of **48** and **50** (Supporting Information). In contrast, deconjugation of **28b** was highly diastereoselective, and the resulting product **53** was converted to **54**, the chiral methyl ester analogue of **49** (Scheme 10). The overall yield for this process was low, presumably due to the lability of the chiral auxiliary. Compounds **49** (racemic) and **54** had identical NMR spectral characteristics, except for their ester resonances.

SCHEME 8. All Compounds are Racemic[a]



[a] Reagents and conditions: (a) (i) $KN(TMS)_2$, THF, −78 °C, 10 min, (ii) HOAc, −78 °C to RT, 99%. (b) $K_2OsO_4 \cdot 2H_2O$, NMO, acetone/H_2O (4:1), RT, 5 days, 74% (**47**), 60% (**48**). (c) $MeC(OMe)_2Me$, *p*-TsOH, DCM, RT, 8 h, 94%. (d) $LiBH_4$, MeOH, Et_2O, RT, 1 h, 71%.

SCHEME 9. All Compounds are Racemic[a]

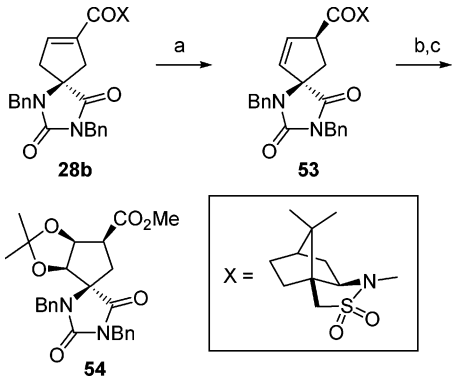


[a] Reagents and conditions: (a) (i) $KN(TMS)_2$, THF, −78 °C, 1 h, (ii) HOAc, −78 °C to RT, 42% (**51**), 37% (**52**).

An alternative and more successful approach to the target compounds is shown in Scheme 11. Acid-catalyzed hydrolysis of the ester group of **45** smoothly gave the carboxylic acid **55** in quantitative yield. Attempts at a base-catalyzed hydrolysis with sodium hydroxide/methanol/water gave **55** as a 5:1 mixture of epimers. Chemoselective reduction of the acid group of **55** to give **56** was achieved in high yield (95%) using a borane-dimethyl sulfide complex. Cis-dihydroxylation of **56** gave a 2:1

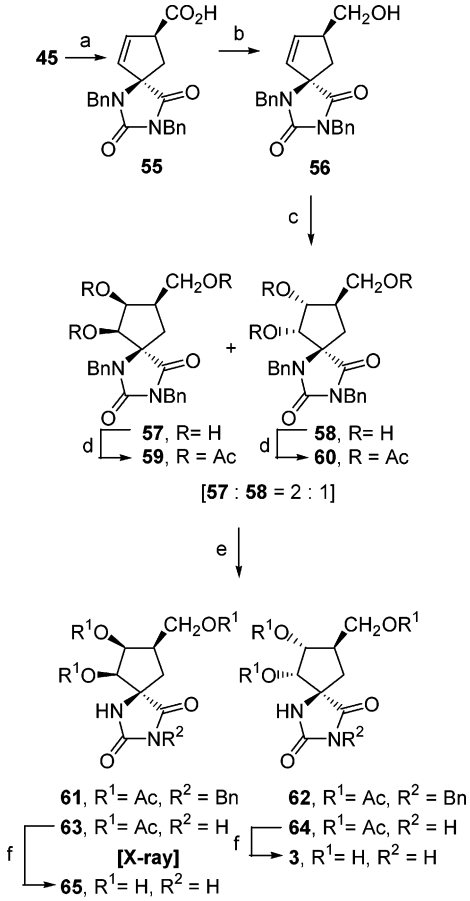
(54) (a) Roush, W. R.; Essenfeld, A. P.; Warmu, J. S.; Brown, B. B. *Tetrahedron Lett*. **1989**, *30*, 7305–7309. (b) Roush, Brown, B. B. *J. Org. Chem*. **1992**, *57*, 3380–3387. (c) Mattay, J.; Mertes, J.; Mass, G. *Chem. Ber*. **1989**, *122*, 327–330. (d) Pyne, S. G.; Dikic, B.; Skelton, B. W.; White, A. H. *Chem. Commun*. **1991**, 1505–1506.

SCHEME 10[a]



[a] Reagents and conditions: (a) (i) $KN(TMS)_2$, THF, −78 °C, 1 h, (ii) HOAc, −78 °C to RT, 90% (a) $K_2OsO_4 \cdot 2H_2O$, NMO, acetone/H_2O (4:1), RT, 5 days, 37% (+46% recovered **53**). (c) $MeC(OMe)_2Me$, *p*-TsOH, DCM, RT, 8 h, 53%.

SCHEME 11. All Compounds are Racemic[a]



[a] Reagents and conditions: (a) 10% HCl, MeCN, 90 °C, 15 h, 99% (b) $BH_3 \cdot DMS$, THF, 0°C, 6 h, 95%. (c) $K_2OsO_4 \cdot 2H_2O$, NMO, acetone/H_2O (4:1), RT, 5 days, 37% (+46% recovered **53**). (d) Ac_2O, pyridine, MeCN, RT, 10 h, 91%. (e) (i) NBS, C_6H_5Cl, 125 °C, 14 h, (ii) H_2O. (f) 10% HCl, THF, reflux, 4 h, 95−99%.

mixture of the diols **57** and **58**, respectively, that could not be readily separated nor could their respective triacetates, **59** and **60**. This reduced diastereoselectivity is consistent with the ester group being responsible for the direction of dihydroxylation in the reactions of compounds **45** and **46**. One explanation for this is the "Cieplak effect" in which the developing vacant C−O σ^* bonds would prefer to overlap with the more electron rich α-C−H σ bond rather than the more electron poor α-C−CO_2Et σ bond.[55] A number of methods were attempted to reductively remove the *N*-benzyl protecting groups in the corresponding acetonide derivatives of **57** and **58** (not shown). Catalytic hydrogenolysis or Birch-type reductions were unsuccessful. The former resulted in recovered starting material, and the latter gave mono-deprotection and/or reduction of the aromtatic rings to dihydrobenzenes and/or reduction of the hydantoin carbonyls. The most successful method proved to be benzylic bromination of a mixture of triacetates **59** and **60** with NBS/AIBN in a solution of chlorobenzene at reflux temperature, followed by hydrolysis on the intermediate benzylbromide with water.[56] Treatment of a 2:1 mixture of **59** and **60**, respectively, with 3 equiv of NBS at 125 °C in a sealed tube for 14 h, followed by the addition of water, gave the fully debenzylated compounds **63** (31% yield) and **64** (15%) along with their mono-debenzylated products **61** (25% yield) and **62** (11% yield). All four compounds were readily separated by flash column chromatography. The structure of **63** was unequivocally established by single-crystal X-ray crystallography (Supporting Information). Acid-catalyzed hydrolysis of the individual triacetates **63** and **64** gave pure samples of 6,7-diepi-carbocyclic hydantocidin **65** and carbocyclic hydantocidin **3**, respectively, in high yields (95−99%). The latter had spectral properties identical to those reported in the literature.[18,29]

In conclusion, we have developed a synthesis of carbocyclic hydantocidins using a phosphine-catalyzed [3 + 2]-cycloaddition reaction of ethyl 2-butynoate with *N*,*N*′-dibenzyl-5-methylenehydantoin to generate the key spiroheterocyclic system of these target molecules. We have also demonstrated the potential of obtaining chiral versions of these molecules using chiral auxiliaries on the 2-butynoate. Clearly other *N*-protecting groups on the hydantoin ring need to be investigated in the future to allow more efficient access to the final structures.

Experimental Section

All ^1H NMR and ^{13}C NMR were determined in $CDCl_3$ solution at 300 and 75 MHz, respectively, unless otherwise noted.

Ethyl 1,3-Dibenzyl-2,4-dioxo-1,3-diazaspiro[4.4]non-7-ene-7-carboxylate (18), Ethyl 1,3-Dibenzyl-2,4-dioxo-1,3-diazaspiro[4.4]non-6-ene-6-carboxylate (19), and Diethyl 1,3-Dibenzyl-2,5-dioxo-2′,3′,3a′,6′-tetrahydro-6a′H-spiro-[imidazolidine-4,1′-pentalene]-4′,6a′-dicarboxylate (26).

Procedure A. To a solution of compound **9** (134 mg, 0.46 mmol) in dry benzene (1 mL) under a N_2 atmosphere was added ethyl 2-butynoate (103 mg, 0.92 mmol) followed by tributylphosphine (9 mg, 0.046 mmol). The reaction mixture was allowed to stir at ambient temperature for 15 h and was then concentrated and then partitioned between diethyl ether and water. The organic extract was dried ($MgSO_4$), concentrated, and purified by column chromatography (30% EtOAc/Pet. Spirits.) to give compound **18** as a colorless oil (150 mg, 81%) and compound **26** as a white solid (14 mg, 6%).

(55) Cieplak, A. S. *J. Am. Chem. Soc*. **1981**, *103*, 4540−4552. Katagiri, N.; Ito, Y.; Kitano, K.; Toyota, A.; Kaneko, C. *Chem. Pharm. Bull*. **1994**, *42*, 2653−2655.

(56) Baker, S. R.; Parsons, A. F.; Wilson, M. *Tetrahedron Lett.* **1998**, *39*, 331−332.

Procedure B. Compound **9** (400 mg, 1.37 mmol) was dissolved in benzene (5 mL), and then ethyl 2,3-butadienoate[49] (307 mg, 2.74 mmol), followed by triphenylphosphine (36 mg, 0.137 mmol), were then added to the solution. The reaction mixture was allowed to stir at ambient temperature for 24 h before it was concentrated and then partitioned between diethyl ether and water. The organic extract was dried ($MgSO_4$), concentrated in vacuo, and then purified by column chromatography (30% EtOAc/Pet. Sp.) to give 2 regioisomers, **18** (361 mg, 65%) and **19** (94 mg, 17%) as oils. Spectral data for **18** and **19** were comparable to those reported in the literature.[43] **26**: white solid (6%), mp 118−120 °C. ^{1}H NMR δ 0.92 (t, 7.2 Hz, 3H), 1.28 (t, 7.2 Hz, 3H), 1.56−1.76 (m, 1H), 1.69−1.76 (m, 1H), 1.93−2.08 (m, 1H), 2.19−2.31 (m, 1H), 2.64 (dd, J = 2.7, 20.7 Hz), 3.78 (q, J = 7.2 Hz, 2H), 3.99 (d, J = 16.8 Hz, 1H), 4.11 (dt, J = 2.4, 20.7 Hz), 4.14−4.22 (m, 2H), 4.25−4.29 (m, 1H), 4.68 (d, J = 14.4 Hz, 1H), 4.86 (d, J = 14.4 Hz, 1H), 5.08 (d, J = 16.8 Hz, 1H), 6.54 (m, 1H), 7.20−7.52 (m, 5H). ^{13}C NMR δ 13.9 (CH_3), 14.3 (CH_3), 29.9 (CH_2), 35.1 (CH_2), 39.8 (CH_2), 43.0 (CH_2), 44.8 (CH_2), 51.7 (CH), 60.4 (CH_2), 61.7 (CH_2), 68.1 (C), 74.0 (C5), 126.0 (CH), 127.3 (CH), 127.7 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 135.9 (C), 137.4 (C), 138.2 (CH), 138.4 (C), 156.2 (C), 163.7 (C), 172.0 (C), 172.9 (C). MS: (CI + ve) m/z 517 (M + 1). HRMS (EI + ve) calcd. for $C_{30}H_{32}N_2O_6$ (M^+): 516.2260. Found: 516.2235.

(5*RS*,7*SR*)-1,3-Dibenzyl-2,4-dioxo-1,3-diazaspiro[4.4]-non-8-ene-7-carboxylic Acid (55). Compound **45** (1.14 g, 2.82 mmol) in CH_3CN (10 mL) was added to 10% HCl (10 mL). The mixture was heated to 90 °C for 15 h before it was cooled to RT and then extracted into ethyl acetate (2 × 50 mL). The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo to give **55** as a white solid (1.05 g, 99%), mp 140−144 °C. ^{1}H NMR δ 2.39 (dd, J = 6.3, 14.4 Hz, 1H), 2.53 (dd, J = 9.0, 14.4 Hz, 1H), 3.86 (ddt, J = 2.4, 6.4, 9.0 Hz, 1H), 4.43 (d, J = 15.9 Hz, 1H), 4.60 (d, J = 15.9 Hz, 1H), 4.71 (s, 2H) 5.32 (dd, J = 2.4, 5.4 Hz, 1H), 6.13 (dd, J = 2.4, 5.4 Hz, 1H), 7.27−7.43 (m, 10H). ^{13}C NMR δ 33.7 (CH_2), 42.8 (CH_2), 43.6 (CH_2), 49.3 (CH), 76.3 (C), 127.7 (CH), 127.9 (CH), 128.2 (CH), 128.5 (CH), 128.5 (CH), 128.7 (CH), 131.0 (CH), 135.9 (C), 136.4 (CH), 137.3 (C), 155.6 (C), 174.3 (C), 177.7 (C). MS: (CI + ve) m/z 377 (M + 1). HRMS (CI + ve) Calcd. for $C_{22}H_{20}N_2O_4$ (M^+): 376.1423. Found: 376.1406.

(5*RS*,8*SR*)-1,3-Dibenzyl-8-(hydroxymethyl)-1,3-diazaspiro[4.4]non-6-ene-2,4-dione (56). To a solution of **55** (900 mg, 2.39 mmol) in THF (20 mL) at 0 °C was added dropwise a 2 M solution of borane.methyl sulfide in THF (1.32 mL, 2.64 mmol). Stirring was continued for 6 h before water (10 mL) was added. After 10 min, the THF was removed in vacuo and the remaining residue was extracted into ethyl acetate (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give an oily residue. Purification by column chromatography (50% EtOAc/Pet. Sp. to 60% EtOAc/Pet. Sp.) gave the title compound **56** as a colorless oil (822 mg, 95%). ^{1}H NMR (CD_3CN) δ 1.76 (dd, J = 6.3, 14.1 Hz, 1H), 2.30 (dd, J = 8.4, 14.1 Hz, 1H), 2.98 (m, 1H), 3.44 (dd, J = 2.1, 5.4 Hz), 4.43 (d, J = 16.2 Hz), 4.52 (d, J = 16.2 Hz), 4.64 (s, 2H), 5.36 (dd, J = 2.4, 5.4 Hz, 1H), 6.08 (dd, J = 2.4, 5.4 Hz, 1H), 7.21−7.39 (m, 10H). ^{13}C NMR δ 34.0 (CH_2), 42.4 (CH_2), 43.2 (CH_2), 47.4 (CH), 64.8 (CH_2), 76.7 (C), 127.4 (CH) 127.7 (CH), 127.8 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 129.2 (CH), 136.0 (C), 137.5 (C), 140.8 (CH), 155.7 (C), 174.9 (C). MS: (CI + ve) m/z 363 (M + 1). HRMS (CI + ve) m/z Calc. for $C_{22}H_{23}N_2O_3$: 363.1708. Found: 363.1705.

(5*RS*,6*SR*,7*RS*,8*RS*)-1,3-Dibenzyl-6,7-dihydroxy-8-(hydroxymethyl)-1,3-diazaspiro[4.4]nonane-2,4-dione (57) and Its Diepimer (5*RS*,6*RS*,7*SR*,8*RS*)-1,3-Dibenzyl-6,7-dihydroxy-8-(hydroxymethyl)-1,3-diazaspiro[4.4]nonane-2,4-dione (58). Compound **56** (670 mg, 1.85 mmol) was dihydroxylated in the same manner as **45** in the synthesis of **47** (Supporting Information). After it was stirred for 3 days at RT, the reaction produced a mixture of cis diols, **57** and **58**, as foams, which could not be separated by column chromatography (460 mg, 63%) and therefore could not be analyzed by NMR. MS: (CI + ve) m/z 397 (M + 1). HRMS (CI + ve) Calcd. for $C_{22}H_{25}N_2O_5$ (MH^+): 397.1763. Found: 397.1765.

(5*RS*,6*RS*,7*SR*,8*RS*)-6-(Acetyloxy)-8-[(acetyloxy)methyl]-1,3-dibenzyl-2,4-dioxo-1,3-diazaspiro[4.4]non-7-yl acetate (59) and (5*RS*,6*SR*,7*RS*,8*RS*)-6-(Acetyloxy)-8-[(acetyloxy)-methyl]-1,3-dibenzyl-2,4-dioxo-1,3-diazaspiro[4.4]non-7-yl Acetate (60). A solution of a mixture of triols **57** and **58** (300 mg, 0.757 mmol) in CH_3CN (5 mL), pyridine (3 mL), and acetic anhydride (5 mL) was stirred at RT for 10 h. After this time, all volatiles were removed in vacuo. The resulting residue was purified by column chromatography (30% EtOAc/Pet. Sp.) to give compound **59** and its diepimer **60** as clear oils in a ratio of 2:1, respectively (determined by ^{1}H NMR integration of their respective acetate resonances) (359 mg, total yield 91%). **59**: ^{1}H NMR δ 1.54 (dd, J = 12.0, 13.8 Hz, 1H), 1.85 (dd, J = 7.8, 13.8 Hz, 1H), 1.94 (s, 3H,), 1.99 (s, 3H), 2.25 (s, 3H,), 2.63 (m, 1H), 3.86 (dd, J = 6.0, 11.1 Hz, 1H), 4.08 (dd, J = 8.7, 11.1 Hz, 1H), 4.31 (d, J = 16.2 Hz, 1H), 4.69 (ABq, J = 7.5 Hz, 2H), 4.99 (d, J = 16.2 Hz, 1H), 5.26 (d, J = 4.2 Hz, 1H), 5.64 (t, J = 4.2 Hz, 1H), 7.23−7.41 (m, 10H). ^{13}C NMR δ 20.0 (CH_3), 20.6 (CH_3), 21.0 (CH_3), 33.8 (CH_2), 37.6 (CH), 42.8 (CH_2), 44.6 (CH_2), 61.3 (CH_2), 68.6 (C), 72.4 (CH), 76.8 (CH), 126.9 (CH), 127.3 (CH), 128.3 (CH), 128.6 (CH), 128.8 (CH), 128.8 (CH), 135.7 (C), 137.8 (C), 156.5 (C), 169.1 (C), 169.2 (C), 170.5(C), 175.9 (C). MS: (CI + ve) m/z 523 (M + 1). HRMS (CI + ve) Calcd. for $C_{28}H_{31}N_2O_8$ (MH^+): 523.2080. Found: 523.2076. **60**: ^{1}H NMR δ 1.68 (s, 3H), 1.96 (m, 2H), 2.00 (s, 3H), 2.03 (s, 3H), 3.07 (m, 1H), 4.03 (apparent d, J = 4.8 Hz, 2H), 4.35 (d, J = 16.2 Hz, 1H), 4.71 (ABq, J = 9.3 Hz, 2H), 4.87 (d, J = 16.2 Hz, 1H), 5.01 (dd, J = 7.2, 8.1 Hz), 5.28 (d, J = 7.2 Hz, 1H), 7.23−7.41 (m, 10H). ^{13}C NMR δ 20.0 (CH_3), 20.4 (CH_3), 20.6 (CH_3), 30.1 (CH_2), 40.8 (CH), 42.4 (CH_2), 43.0 (CH_2), 63.3 (CH_2), 70.0 (CH), 71.2 (C_{spiro}), 71.3 (CH), 127.0 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH), 128.4 (CH), 136.0 (C), 136.8 (CH), 155.9 (C), 169.1 (C), 170.2 (C), 170.5 (C), 171.6 (C). MS: (CI + ve) m/z 523 (M + 1). HRMS: (CI + ve) Calcd. for $C_{28}H_{31}N_2O_8$ (MH^+) 523.2080, Found 523.2076.

(5*RS*,6*RS*,7*SR*,8*RS*)-6,7-Di(acetyloxy)-8-[(acetyloxy)-methyl]-3-benzyl-1,3-diazaspiro[4.4]nonane-2,4-dione (61), (5*RS*,6*SR*,7*RS*,8*RS*)-6,7-Di(acetyloxy)-8-[(acetyloxy)methyl]-3-benzyl-1,3-diazaspiro[4.4]nonane-2,4-dione (62), (5*RS*,6*RS*,7*SR*,8*RS*)-6,7-Di(acetyloxy)-8-[(acetyloxy)methyl]-1,3-diazaspiro[4.4]nonane-2,4-dione (63), and (5*RS*,6*SR*,7*RS*,8*RS*)-6,7-Di(acetyloxy)-8-[(acetyloxy)-methyl]-1,3-diazaspiro[4.4]nonane-2,4-dione (64). To a sealed tube, under a N_2 atmosphere, was added a mixture of compounds **59** and **60** (500 mg, 0.96 mmol), freshly redistilled chlorobenzene (20 mL), recrystallized *N*-bromosuccinamide (511 mg, 2.87 mmol), and azobisisobutyronitrile (47 mg, 0.287 mmol). The reaction tube was sealed and heated to 125 °C with stirring for 14 h where it was then cooled on ice before it was filtered. The filtrate was concentrated in vacuo to give a brown residue, which was redissolved in ethyl acetate (20 mL) and then washed with water (2 × 20 mL). The organic extract was dried and solvent removed in vacuo to give an oily residue that was purified by column chromatography (50% EtOAc/Pet. Sp to 90% EtOAc/Pet. Sp.) to give **61** (103 mg, 25%), and its 6,7-diepimer **62** (45 mg, 11% as oils and compound **63** (101 mg, 31%) and its 6,7-diepimer **64** (50 mg, 15%) were isolated as white solids. **61**: ^{1}H NMR δ 1.84 (dd, J = 9.9, 13.5 Hz, 1H), 1.91 (s, 3H), 2.03 (s, 3H), 2.14 (s, 3H), 2.55 (dd, J = 9.0 Hz, 13.5 Hz, 1H), 2.63 (m, 1H), 4.01 (dd, J = 6.3, 11.1 Hz, 1H), 4.15 (dd, J = 8.1, 11.1 Hz, 1H), 4.63 (s, 2H), 5.15 (d, J = 3.6 Hz, 1H), 5.62 (t, J = 3.6 Hz, 1H), 6.20 (br s, 1H), 7.23−7.38 (m, 5H). ^{13}C NMR δ 20.0 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 36.9 (CH_2), 37.1 (CH), 42.4 (CH_2), 61.8 (CH_2), 65.8 (C), 73.6 (CH), 75.6 (CH), 127.9 (CH), 128.3 (CH), 128.6 (CH), 135.7 (C), 156.6 (C), 169.3 (C), 169.4 (C), 170.7 (C), 174.9 (C). MS: (CI + ve) m/z 433 (M + 1). HRMS (CI + ve) Calcd. for $C_{21}H_{25}N_2O_8$ (MH^+): 433.1603. Found: 433.1603. **62**: ^{1}H NMR δ 1.70 (dd, J = 9.0, 14.1 Hz), 1.91 (s, 3H), 2.06 (s, 3H), 2.07 (s, 3H), 2.53

(dd, J = 9.3 Hz, 14.1 Hz), 2.96 (m, 1H), 4.14 (dd, J = 5.1, 11.4 Hz, 1H,), 4.18 (dd, J = 4.8, 11.4 Hz, 1H), 4.63 (ABq, J = 14.7 Hz, 2H), 5.16 (dd, J = 6.0, 8.1 Hz, 1H), 5.28 (d, J = 6.0 Hz, 1H), 6.78 (br s, 1H), 7.26−7.38 (m, 5H). ^{13}C NMR δ 20.2 (CH_3), 20.6 (CH_3), 20.8 (CH_3), 33.8 (CH_2), 40.5 (CH), 42.3 (CH_2), 63.8 (CH_2), 66.9 (C), 71.9 (CH), 76.8 (CH), 127.9 (CH), 128.4 (CH), 128.6 (CH), 135.8 (C), 156.4 (C), 169.8 (C), 170.4 (C), 170.9 (C), 172.0 (C). MS: (CI + ve) *m/z* 433 (M + 1). HRMS (CI + ve) Calcd. for $C_{21}H_{25}N_2O_8$ (MH^+): 433.1603. Found: 433.1603. **63**: White solid mp 163−165 °C. ^{1}H NMR δ 1.89 (dd, J = 13.8, 17.7 Hz, 1H), 2.04 (s, 3H), 2.06 (s, 3H), 2.16 (s, 3H), 2.60 (dd, J = 9.0 Hz, 17.7 Hz), 2.62 (m, 1H), 4.03 (dd, J = 5.7, 11.1 Hz, 1H), 4.17 (dd, J = 8.1, 11.1 Hz, 1H), 5.14 (d, J = 3.6 Hz, 1H), 5.64 (t, J = 3.6 Hz, 1H), 5.87 (br s, 1H), 7.89 (br s, 1H). ^{13}C NMR δ 20.2 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 37.0 (CH) 37.4 (CH_2), 61.8 (CH_2), 66.9 (C), 73.5 (C(H), 75.7 (CH), 156.7 (C), 169.6 (C), 169.7 (C), 170.8 (C), 176.4 (C). MS: (CI + ve) *m/z* 343 (M + 1). HRMS (CI + ve) Calcd. for $C_{14}H_{19}N_2O_8$ (MH^+): 343.1141. Found: 343.1131. **64**: ^{1}H NMR δ 1.76 (dd, J = 8.4, 14.4 Hz, 1H), 2.08 (s, 3H), 2.09 (s, 3H), 2.10 (s, 3H), 2.63 (dd, J = 10.2, 14.4 Hz, 1H), 2.90 (m, 1H), 4.14 (dd, J = 5.7, 11.4 Hz, 1H), 4.22 (dd, J = 5.4, 11.4 Hz, 1H), 5.22 (dd, J = 5.4, 8.4 Hz, 1H), 5.32 (d, J = 5.4 Hz), 7.24 (br s, 1H), 8.73 (br s, 1H). ^{13}C NMR δ 20.58 (CH_3), 20.6 (CH_3), 20.8 (CH_3), 33.9 (CH_2), 40.0 (CH), 64.1 (CH_2), 67.6 (C), 72.5 (CH), 77.3 (CH), 156.4 (C), 170.2 (C), 170.5 (C), 171.2 (C), 173.1 (C). MS: (CI + ve) *m/z* 343 (M + 1). HRMS (CI + ve) Calcd. for $C_{14}H_{19}N_2O_8$ (MH^+): 343.1141. Found: 343.1133.

(5*RS*,6*SR*,7*SR*,8*RS*)-6,7-Dihydroxy-8-(hydroxymethyl)-1,3-diazaspiro[4.4]nonane-2,4-dione (65). To a solution of compound **63** (35 mg, 0.102 mmol) in THF (1 mL) was added 10% HCl (1 mL). The reaction mixture was heated at reflux for 4 h before all volatiles were removed under reduced pressure to yield the title compound **65** as a white solid (22 mg, 99%), mp 203−204 °C. ^{1}H NMR (CD_3OD) δ 1.74 (dd, J = 9.6, 13.8 Hz), 2.14 (m, 1H), 2.32 (dd, J = 9.6, 13.8 Hz, 1H), 3.58 (dd, J = 6.0, 10.8 Hz, 1H), 3.76 (dd, J = 7.8, 10.8 Hz, 1H), 4.04 (d, J = 3.3 Hz, 1H), 4.14 (t, J = 3.3 Hz, 1H). ^{13}C NMR (CD_3OD) δ 37.0 (CH_2), 42.3 (CH), 62.3 (CH_2), 70.8 (C), 75.1 (CH), 79.2 (CH), 159.4 (C), 180.9 (C). MS: (CI + ve) *m/z* 217 (M + 1). HRMS (CI + ve) Calcd. for $C_8H_{12}N_2O_5$ (MH^+): 217.0824. Found: 217.0823.

(5*RS*,6*SR*,7*RS*,8*RS*)-6,7-Dihydroxy-8-(hydroxymethyl)-1,3-diazaspiro[4.4]nonane-2,4-dione (3). Compound **64** (20 mg, 0.058 mmol) was treated in the same manner as compound **63** for the synthesis of **65**. The reaction gave the title compound **3** as a yellow solid (12 mg, 95%) (mp 150 °C, literature value[18,29] 158−160 °C) with spectral data identical to those reported in the literature.[18,29]

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Supporting Information Available: Full experimental details and characterization data and spectral assignments for all compounds, including chiral GC traces and conditions. Copies of the ^{1}H and ^{13}C NMR spectra of compounds **3**, **9**−**11**, **13**−**20**, **22**, **24**, **26**, **27**, **(1*R*)-28b**, **(1*S*)-28b**, **29c**,**d**, **31c**, **33c**, **36**−**38**, **40**−**43**, **45**−**49**, **50**−**52**, **54**−**56**, and **61**−**65** and crystal/refinement data and the molecular projections of compounds **13**, **26**, **(1*R*)-28b**, **42**, **48**, **50**, and **63**. CCDC depositions: 181271 (**42**), 269432 (**13**), 269433 (**26**), 269434 (**63**), 269435 (**28b**), 269436 (**48**), 269437 (**50**), and 269438 (**50**, ethyl acetate solvate). This material is available free of charge via the Internet at http://pubs.acs.org.

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