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A Concise Route to Structurally Diverse DMP 323 Analogues via Highly Functionalized 1,4-Diamines

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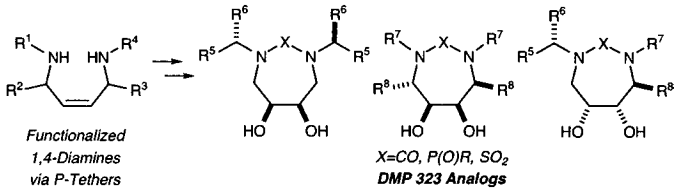
ABSTRACT



The utility of functionalized 1,4-diamines, produced via a temporary phosphorus tether (P-tether)/ring-closing metathesis (RCM)/hydrolysis sequence, is demonstrated in the synthesis of structurally diverse DMP 323 analogues. These 1,4-diamines are transformed into various seven-membered heterocycles via insertion of the appropriate nuclei "X". Subsequent derivatization generates heterocyclic diols that are similar in structure to DMP 323, a notable member of a class of highly potent inhibitors of HIV protease.

Temporary tethers have become powerful tools in organic synthesis to expedite the assembly of complex molecules.[1,2] Our interest in the development of new methods involving organophosphorus compounds[3] has led us to explore the utility of temporary phosphorus tethers (*P*-tethers) toward the synthesis of biologically relevant targets. We have recently described a highly efficient method employing *P*-tethers in conjunction with ring-closing metathesis[4] (RCM) to assemble functionalized 1,4-diamines containing the (*Z*)-1,4-diamino-but-2-ene subunit.[5] Although temporary tethers have been used in a wide variety of synthetic applications,[1,2] to our knowledge this report was the first example of the rapid tethering and subsequent coupling of two amines using a mononuclear tether.[6] In the report described herein, the utility of various 1,4-diamines produced using our temporary *P*-tether protocol is demonstrated in the synthesis of an array of seven-membered heterocycles analogous to DMP 323.

Cyclic ureas DMP 323 and DMP 450 are notable members of a promising class of highly potent HIV protease inhibitors initially developed at DuPont Merck Laboratories (Scheme

(1) For a comprehensive review on disposable tethers, see: (a) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289−2338. For recent examples of temporary tethers used in organic synthesis, see: (b) Crimmins, M. T.; Hauser, E. B. *Org. Lett.* **2000**, *2*, 281−284. (c) Bertozzi, F.; Olsson, R.; Frejd, T. *Org. Lett.* **2000**, *2*, 1283−1286. (d) Sukeda, M.; Shuto, S.; Sugimoto, I.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2000**, *65*, 8988−8996. (e) Chebolu, R.; Zhang, W.; Galoppini, E.; Gilardi, R. *Tetrahedron Lett.* **2000**, *41*, 2831−2834.

(2) For use of tethers in RCM reactions, see: (a) O'Leary, D. J.; Miller, S. J.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 1689−1690. (b) Evans, P. A.; Murthy, V. S. *J. Org. Chem.* **1998**, *63*, 6768−6769. (c) Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429−1432. (d) Gierasch, T. M.; Chytil, M.; Didiuk, M. T.; Park, J. Y.; Urban, J. J.; Nolan, S. P.; Verdine, G. L. *Org. Lett.* **2000**, *2*, 3999−4002. (d) Rodriguez, J. R.; Castedo, L.; Mascarenas, J. L. *Org. Lett.* **2000**, *2*, 3209−3212. (e) Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2000**, *65*, 7913−7918. (f) Sakamoto, Y.; Okazaki, M.; Miyamoto, K.; Nakata, T. *Tetrahedron Lett.* **2001**, *42*, 7633−7636. (g) Micalizio, G. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 152−154.

(3) Moore, J. D.; Sprott, K. T.; Wrobleski, A. D.; Hanson, P. R. *Org. Lett.* **2002**, *4*, 2357−2360. (b) Stoianova, D. S.; Hanson, P. R. *Org. Lett.* **2001**, *3*, 3285−3288. (c) Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. *Synthesis* **2001**, 612−620 and references therein. (d) Stoianova, D. S.; Hanson, P. R. *Org. Lett.* **2000**, *2*, 1769−1772.

(4) For recent reviews, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013−3043. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388.

(5) Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. *Org. Lett.* **2001**, *3*, 3939−3942. All 1,4-diamines described in this manuscript were prepared using this protocol.

(6) We have also reported the synthesis of 1,4-diamines via a phthalamide tether/RCM/hydrolysis sequence; see ref 2e.

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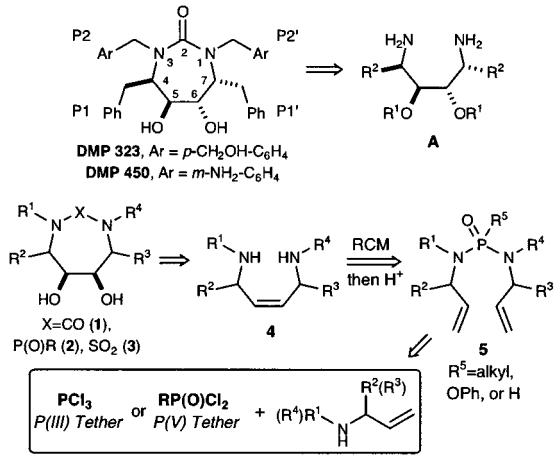
Scheme 1

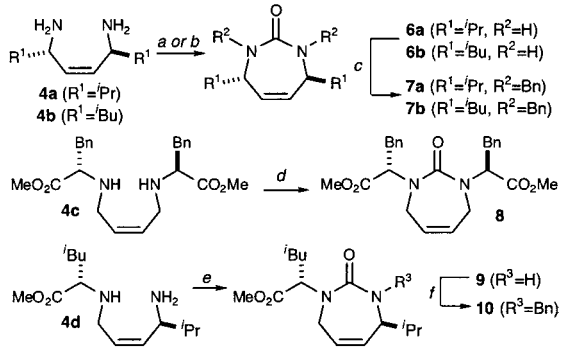


1).[7] The synthesis of these compounds involved the use of a 1,4-diamine synthon of the general structure **A** as the key synthetic intermediate.[8] Carbonylation, followed by *N*-benzylation, provided cyclic ureas with substituents occupying the P1/P1′/P2/P2′ positions. Extensive investigations were carried out to elucidate the effects of varying P1/P1′/P2/P2′ residues,[9] as well as P1/P1′ and hydroxyl group stereochemistry.[10] It was found that each of these factors significantly influence inhibitor potency by accentuating hydrophobic (P1/P1′), hydrogen bonding (P2/P2′), and catalytic aspartate (diol functionality) interactions with the enzyme. Although cyclic ureas have been the most widely examined, independent studies by DuPont Merck,[11] Hallberg and co-workers,[12] and Karlén and co-workers[13] have also shown that sulfamide analogues of DMP 323 display high inhibitory activity.

With each of these points in mind, we reasoned our *P*-tether strategy would allow for the rapid assembly of a diverse set of heterocycles analogous to DMP 323, including cyclic ureas **1**, phosphonamides **2**, and sulfamides **3** (Scheme 1). The seven-membered heterocyclic diols **1**−**3** are derived from 1,4-diamines **4** via insertion of the appropriate nuclei "X," followed by osmium-mediated dihydroxylation. As previously demonstrated, 1,4-diamines **4** are accessed via a RCM/hydrolysis sequence upon *P*-tethered amines **5**, which can be constructed following appropriate choice of both the *P*-tether [P(III) or P(V)] and the allylic amines.[5] For the initial studies contained in this report, the more readily available, L-amino acid derived allylic amines were employed to establish our new method.[10]

To this end, we applied the strategy above to the synthesis of both C_2-symmetric and unsymmetric[14] cyclic ureas en route to DMP 323 analogues (Scheme 2). Following the

Scheme 2[a]



[a] Reagents and conditions: (a) CDI, CH_2Cl_2, reflux, 69% **6a**; (b) CDI, tetrachloroethane, reflux, 71% **6b**; (c) BnBr, KO^{t}Bu, THF, 78% **7a**, 81% **7b**; (d) $(Cl_3CO)_2CO$, Et_3N, CH_2Cl_2, −78 °C, 38%; (e) CDI, CH_2Cl_2, reflux, 46%; (f) BnBr, KHMDS, 18-crown-6, THF, −78 to 0 °C, 71%.

DuPont Merck protocol,[8] C_2-symmetric cyclic ureas **7** with substituents occupying P1/P1′/P2/P2′ positions were generated by carbonylation and subsequent *N*-benzylation of primary 1,4-diamines **4a**,**b**.[15] Optimal conditions for carbonylation of secondary 1,4-diamine **4c** involved the use of triphosgene to furnish C_2-symmetric urea **8** where α-amino substitution occupies the exocyclic P2/P2′ positions.[16] In a

(7) Lam, P. Y. S.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bachelor, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C.-H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Vittanen, S. *Science* **1994**, *263*, 380−384. (b) De Lucca, G. V.; Lam, P. Y. S. *Drugs Future* **1998**, *23*, 987−994 and references therein.

(8) Nugiel, D. A.; Jacobs, K.; Worley, T.; Patel, M.; Kaltenbach, R. F., III; Meyer, D. T.; Jadhav, P. K.; De Lucca, G. V.; Smyser, T. E.; Klabe, R. M.; Bacheler, L. T.; Rayner, M. M.; Seitz, S. P. *J. Med. Chem.* **1996**, *39*, 2156−2169. (b) Pierce, M. E.; Harris, G. D.; Islam, Q.; Radesca, L. A.; Storace, L.; Waltermire, R. E.; Wat, E.; Jadhav, P. K.; Emmett, G. C. *J. Org. Chem.* **1996**, *61*, 444−450. (c) Confalone, P. N.; Waltermire, R. E. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K. G., Ed.; Marcel Dekker: New York, 1999; pp 201−219.

(9) For evalutation of P1/P1′ substituents, see: (a) Nugiel, D. A.; Jacobs, K.; Cornelius, L.; Chang, C.-H.; Jadhav, P. K.; Holler, E. R.; Klabe, R. M.; Bacheler, L. T.; Cordova, B.; Garber, S.; Reid, C.; Logue, K. A.; Gorey-Feret, L. J.; Lam, G. N.; Erickson-Vittanen, S.; Seitz, S. P. *J. Med. Chem.* **1997**, *40*, 1465−1474. (b) Patel, M.; Bacheler, L. T.; Rayner, M. M.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Seitz, S. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 823−828. For evalutation of P2/P2′ substituents, see: (c) Han, Q.; Chang, C.-H.; Li, R.; Ru, Y.; Jadhav, P. K.; Lam, P. Y. S. *J. Med. Chem.* **1998**, *41*, 2019−2028. (d) Rodgers, J. D.; Johnson, B. L.; Wang, H.; Erickson-Viitanen, S.; Klabe, R. M.; Bacheler, L.; Cordova, B. C.; Chang, C.-H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 715−720.

(10) DuPont Merck concluded that the optimal stereochemical configuration of endocyclic substituted ureas is (4*R*,5*S*,6*S*,7*R*), as demonstrated in DMP 323 (Scheme 1). However, a model study (Ar = Ph) revealed that the analogous *cis*-diol (*RSRR*) exhibited comparable HIV protease binding affinity (K_i = 6.0 nM) relative to the *trans*-diol (*RSSR*, K_i = 3.6 nM); see: Kaltenbach, R. F., III; Nugiel, D. A.; Lam, P. Y. S.; Klabe, R. M.; Seitz, S. P. *J. Med. Chem.* **1998**, *41*, 5113−5117.

(11) De Lucca, G. V *J. Org. Chem.* **1998**, *63*, 4755−4766.

(12) Hultén, J.; Bonham, N. M.; Nillroth, U.; Hansson, T.; Zuccarello, G.; Bouzide, A.; Åqvist, J.; Classon, B.; Danielson, U. H.; Karlén, A.; Kvarnström, I.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 885−897. (b) Hultén, J.; Andersson, H. O.; Schaal, W.; Danielson, H. U.; Classon, B.; Kvarnström, I.; Karlén, A.; Unge, T.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1999**, *42*, 4054−4061.

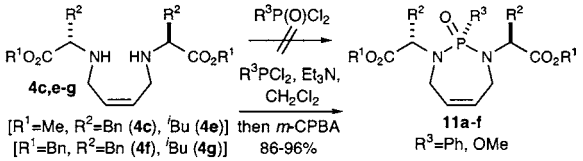
(13) Schaal, W.; Karlsson, A.; Ahlsen, G.; Lindberg, J.; Andersson, H. O.; Danielson, U. H.; Classon, B.; Unge, T.; Samuelsson, B.; Hultén, J.; Hallberg, A.; Karlén, A. *J. Med. Chem.* **2001**, *44*, 155−169.

(14) Unsymmetric DMP 323 derivatives are of particular interest due to their potential to exhibit different solubility and inhibitory profiles relative to their C_2-symmetric counterparts; see: (a) Wilkerson, W. W.; Dax, S.; Cheatham, W. W. *J. Med. Chem.* **1997**, *40*, 4079−4088. (b) De Lucca, G. V.; Kim, U. T.; Liang, J.; Cordova, B.; Klabe, R. M.; Garber, S.; Bacheler, L. T.; Lam, G. N.; Wright, M. R.; Logue, K. A.; Erickson-Viitanen, S.; Ko, S. S.; Trainor, G. L. *J. Med. Chem.* **1998**, *41*, 2411−2423. (c) Patel, M.; Kaltenbach, R. F., III; Nugiel, D. A.; McHugh, R. J., Jr.; Jadhav, P. K.; Bacheler, L. T.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Garber, S.; Reid, C.; Seitz, S. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1077−1082.

manner similar to the synthesis of **6a**, unsymmetric cyclic urea **10** was prepared from unsymmetric 1,4-diamine **4d**. Although a direct RCM approach to seven-membered cyclic ureas **6**−**10** would be ideal, our repeated attempts to affect RCM upon acyclic urea dienes were unsuccessful. A detailed account of these findings is forthcoming.

Our interest in *P*-heterocycles has recently driven our efforts toward phosphorus-containing analogues of DMP 323, where the phosphonyl group serves as a carbonyl surrogate. *P*-Heterocycles **11** were initially targeted, where exocyclic α-amino substitution occupies the P2/P2′ positions (Scheme 3). We previously reported that a direct RCM approach to

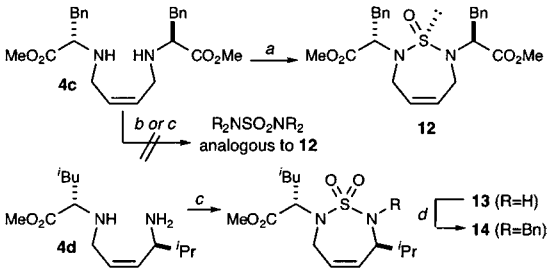
Scheme 3



1,3,2-diazaphosphepine-2-oxides **11** ($R^3 \neq H$) is not feasible because of the inability to generate the corresponding acyclic phosphonamide diene precursors.[2e,3c] Consequently, it is necessary to first synthesize the C_2-symmetric 1,4-diamines **4c,e**−**g**, followed by coupling with a phosphorus dichloride. As a result of the steric demands imposed by α-branched, secondary 1,4-diamines **4c,e**−**g**, coupling with P(V)-dichlorides was unsuccessful to give **11**. To overcome this steric congestion, P(III)-dichlorides (R^3PCl_2) were implemented. Subsequent oxidization at phosphorus yielded **11** containing α-amino substitution at P2/P2′.

In an attempt to utilize 1,4-diamines **4c,e**−**g** in the synthesis of sulfamide analogues of **11**, we observed a reactivity profile comparable to that described in Scheme 3. Whereas 1,4-diamine **4c** coupled successfully with thionyl chloride ($SOCl_2$) to yield pseudo-C_2-symmetric 1,2,7-thiadiazepane-1-oxide **12**, **4c** did not react with sulfuryl dichloride[17] (SO_2Cl_2) or sulfamide[12a] ($H_2NSO_2NH_2$) to yield the analogous C_2-symmetric sulfamide (Scheme 4).[18,19] We surmised that unsymmetric 1,4-diamine **4d**, being less sterically hindered due to the presence of a primary amino group, would exhibit different reactivity relative to that of

Scheme 4[a]

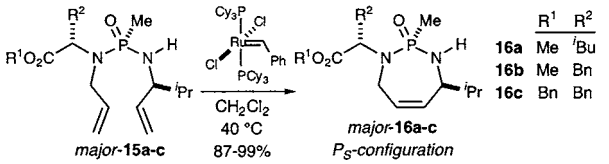


[a] Reagents and conditions: (a) $SOCl_2$, Et_3N, CH_2Cl_2, 68%; (b) SO_2Cl_2, Et_3N, CH_2Cl_2, no reaction; (c) $H_2NSO_2NH_2$, pyridine, reflux, no reaction using **4c**, >95% using **4d**; (d) BnBr, K_2CO_3, CH_3CN, 70 °C, 92%.

4c in the formation of unsymmetric sulfamide **13**. As anticipated, subjection of **4d** to a solution of sulfamide in refluxing pyridine smoothly yields **13**. *N*-Benzylation provides unsymmetric seven-membered sulfamide **14**.

We next focused our attention on metathesis product **16a** in order to produce unsymmetric phosphorus-containing analogues of DMP 323 (Scheme 5). While initially utilizing

Scheme 5



16a as a temporary *P*-tethered substrate en route to **4d**,[5] we found that good levels of diastereoselectivity (ca. 7−13:1) were achieved in the formation of acyclic phosphonamide **15a**; however, the absolute stereochemistry at phosphorus was not immediately determined. We deemed it necessary to first determine the stereochemistry at phosphorus prior to dihydroxylation.[20] As a result, the (*S*)-configuration at phosphorus (P_S) was unambiguously assigned to the major diastereomer using X-ray crystallographic analysis of the crystalline derivative *major*-**16c**.[21]

Conversion of the cyclic olefin to the diol via *cis*-dihydroxylation is the final step toward the title DMP 323 analogues.[10] Thus, osmium-mediated dihydroxylation was carried out on various seven-memberd heterocyclic alkenes,

(15) We have developed a direct RCM route to both sulfamide and phosphonamide analogues of **6**. For sulfamide derivative, see: Dougherty, J. M.; Probst, D. A.; Robinson, R. E.; Moore, J. D.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron* **2000**, *56*, 9781−9790. For phosphonamide derivative, see ref 3c.

(16) Since **4c** was completely consumed during the course of this reaction, the low isolated yield of **8** could be attributed to competing oligomer formation; see: McCusker, J. E.; Grasso, C. A.; Main, A. D.; McElwee-White, L. *Org. Lett.* **1999**, *1*, 961−964.

(17) Although SO_2Cl_2 reacts with primary amines to afford sulfamides (see ref 15), SO_2Cl_2 is a notoriously poor electrophile toward secondary amines; see: Barluenga, J.; Lopez-Ortiz, J. F.; Tomas, M.; Gotor, V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1891−1895.

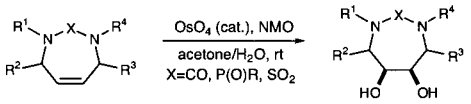
(18) We postulate that the steric congestion of the 1,4-diamines **4c,e**−**g**, as well as subtle steric and electronic differences in the electrophiles, contribute to the failure of this reaction. See refs 2e and 17.

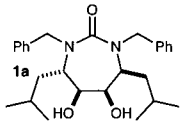
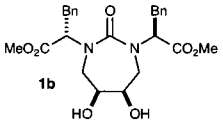
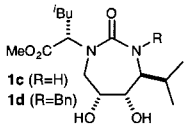
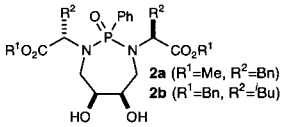
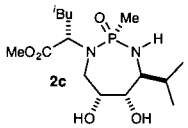
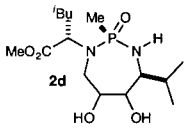
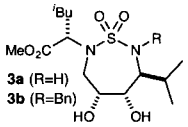
(19) For our direct RCM strategy to generate cyclic sulfamides analogous to **12** and related to **14**, see ref 15.

(20) We initially believed that the phosphonyl moiety could serve as a stereodirecting group to augment the inherent diastereofacial bias for dihydroxylation anti to the isopropyl group.

(21) While *major*-**16c** exists as colorless crystals, **15a**−**c** and *major*-**16a,b** exist as colorless oils. Consequently, the unambiguous assignment of the (*S*)-configuration at phosphorus for *major*-**16a** was accomplished using the following ^{31}P NMR correlation experiment: the major diastereomers in both the acyclic and cyclic phosphonamides **15** and **16**, respectively, exhibit a downfield chemical shift in the ^{31}P NMR relative to the minor diastereomers. This evidence supports the P_S assignment for *major*-**16a**. See Table 2 in the Supporting Information for details of the ^{31}P NMR correlation experiment, as well as X-ray data for *major*-**16c**.

Table 1[a]



entry	cyclic olefin	heterocyclic diol	% yield[b] (ds)
1	**7b**[c,d]	 **1a**	>95
2	**8**	 **1b**	>95
3	**9**	 **1c** (R=H) **1d** (R=Bn)	80 (>20:1)[e]
4	**10**		86 (>20:1)[e]
5	**11a**	 **2a** (R^1=Me, R^2=Bn) **2b** (R^1=Bn, R^2=^{i}Bu)	>95 (5.6:1.0)[f,g]
6	**11f**		>95 (5.8:1.0)[f,g]
7	*major*-**16a**	 **2c**	60 (7.6:1.0)[f]
8	*minor*-**16a**	 **2d**	-- (1.8:1.0)[f,h]
9	**13**	 **3a** (R=H) **3b** (R=Bn)	79 (11.0:1.0)[e]
10	**14**		83 (5.9:1.0)[e]

[a] General reaction conditions: 3 mol % OsO_4 (4 wt % solution in H_2O), 1.2 equiv NMO·H_2O, acetone/H_2O. [b] Isolated yields after flash chromatography. [c] Various attempts using **7a** were unsuccessful, presumably because of steric hindrance about the cyclic olefin caused by the vicinal ^{i}Pr groups. [d] 1.2 equiv of citric acid was added to facilitate the reaction.[26] [e] ^{1}H NMR was employed to determine the diastereoselectivity. [f] ^{31}P NMR was employed to determine the diastereoselectivity. [g] The stereochemistry at phosphorus was not unambiguously determined. [h] Product **2d** was not isolated.

the results of which are summarized in Table 1. Oxidation of unsymmetric seven-membered heterocycles is of particular stereochemical interest because of the potential for diastereoselective osmylation (entries 3, 4, and 7−10).[22] Dihydroxylation of both *N*-H cyclic urea **9** and *N*-benzyl cyclic urea **10** provided diols **1c** and **1d**, respectively, each as a single diastereomer by NMR (entries 3 and 4), with osmylation occurring anti to the isopropyl group as evidenced by crystallographic analysis of **1d**.[23] Conversely, while *N*-H sulfamide **13** gave high selectivity (11.0:1.0, entry 9), diastereoselection diminished for *N*-benzyl sulfamide **14** (5.9:1.0, entry 10).[24] We were surprised to find that *minor*-**16a**, where the phosphonyl oxygen resides anti to the isopropyl group, gave lower selectivity (1.8:1.0, entry 8) relative to that of *major*-**16a** (7.6:1.0, entry 7). Contrary to our hypothesis,[20] it is obvious that a cooperative directing effect of the phosphonyl oxygen and the isopropyl group is not the major factor governing diastereoselectivity.[25]

In conclusion, the synthetic utility of 1,4-diamines produced via temporary *P*-tethers has been demonstrated in the synthesis of a number of structurally diverse seven-membered heterocyclic diols analogous to DMP 323. Future work involves the use of D-amino acid derived allylic amines,[10] as well as utilizing other methods for functionalizing the cyclic olefin moiety. Preliminary biological evaluation of the analogues described has been promising and will be reported in due course.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) These unsymmetric heterocycles differ only in the type of nuclei connecting the two amino functionalities [C(O), P(O)Me, or SO_2].

(23) X-ray data for **1d** can be found in the Supporting Information.

(24) Preliminary molecular modeling experiments (SYBYL v. 6.8 using MMFF94 force field; see Supporting Information) suggest that *N*-substitution effects the orientation of the endocyclic isopropyl group in cyclic sulfamide **14**, leading to diminished diastereoselectivity.

(25) Molecular modeling experiments similar to those described in ref 24 suggest that significant conformational changes in the seven-membered ring may lead to the observed differences in diastereoselectivity between *major*-**16a** and *minor*-**16a**.

(26) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421−433.