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 compounds³ has led us to explore the utility of temporary phosphorus tethers (*P*-tethers) toward

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the synthesis of biologically relevant targets. We have recently described a highly efficient method employing *P*-tethers in conjunction with ring-closing metathesis⁴ (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

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⁽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.

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⁽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.



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-workers¹³ 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

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(10) DuPont Merck concluded that the optimal stereochemical configuration of endocyclic substituted ureas is (4R,5S,6S,7R), 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.

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 unsymmetric¹⁴ cyclic ureas en route to DMP 323 analogues (Scheme 2). Following the



^{*a*} Reagents and conditions: (a) CDI, CH_2Cl_2 , reflux, 69% **6a**; (b) CDI, tetrachloroethane, reflux, 71% **6b**; (c) BnBr, KO'Bu, THF, 78% **7a**, 81% **7b**; (d) ($Cl_3CO)_2CO$, Et₃N, 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

⁽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.

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⁽¹⁴⁾ Unsymmetric DMP 323 derivatives are of particular interest due to their potential to exhibit different solubility and inhibitory profiles relative to their C₂-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



1,3,2-diazaphosphepine-2-oxides **11** ($\mathbb{R}^3 \neq \mathrm{H}$) 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 ($\mathbb{R}^3\mathrm{PCl}_2$) 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 (SOCl₂) to yield pseudo- C_2 -symmetric 1,2,7-thia-diazepane-1-oxide 12, 4c did not react with sulfuryl dichloride¹⁷ (SO₂Cl₂) or sulfamide^{12a} (H₂NSO₂NH₂) to yield the analogous C_2 -symmetric 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



^{*a*} Reagents and conditions: (a) SOCl₂, Et₃N, CH₂Cl₂, 68%; (b) SO₂Cl₂, Et₃N, CH₂Cl₂, no reaction; (c) H₂NSO₂NH₂, pyridine, reflux, no reaction using **4c**, >95% using **4d**; (d) BnBr, K₂CO₃, CH₃CN, 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



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 SO₂Cl₂ reacts with primary amines to afford sulfamides (see ref 15), SO₂Cl₂ 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 ³¹P NMR correlation experiment: the major diastereomers in both the acyclic and cyclic phosphonamides 15 and 16, respectively, exhibit a downfield chemical shift in the ³¹P 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 ³¹P NMR correlation experiment, as well as X-ray data for *major*-16c.



^{*a*} General reaction conditions: 3 mol % OsO₄ (4 wt % solution in H₂O), 1.2 equiv NMO·H₂O, acetone/H₂O. ^{*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 ¹Pr groups. ^{*d*} 1.2 equiv of citric acid was added to facilitate the reaction.²⁶ ^{*e*} ¹H NMR was employed to determine the diastereoselectivity. ^{*f*} ³¹P NMR was employed to determine the diastereoselectivity. ^{*s*} 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 $[C(O), P(O)Me, \text{ or } SO_2]$.

⁽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.