

Semipinacol Rearrangement of *Cis*-Fused β -Lactam Diols into Keto-Bridged Bicyclic Lactams

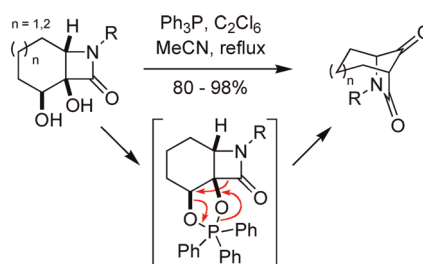
Richard S. Grainger,^{*,†} Marie Betou,[†] Louise Male,[†] Mateusz B. Pitak,[‡] and Simon J. Coles[‡]

School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, U.K., and National Crystallography Service, School of Chemistry, University of Southampton, Southampton SO17 1BJ, U.K.

r.s.grainger@bham.ac.uk

Received March 9, 2012

ABSTRACT



The 6-azabicyclo[3.2.1]octane ring system, prevalent in a range of biologically active molecules, is prepared through a novel semipinacol rearrangement utilizing a cyclic phosphorane or sulfite intermediate. The rearrangement proceeds with exclusive *N*-acyl group migration of a β -lactam ring and results in carbonyl functionality at the 7- and bridging 8-position of the bicycle. Precursor ring-fused β -lactam diols are prepared through a sequence of 4-*exo* *trig* carbamoyl radical cyclization, regioselective dithiocarbamate group elimination, and dihydroxylation.

The 6-azabicyclo[3.2.1]octane ring system is found in a wide variety of biologically active, natural^{1–8} and non-natural products.^{9–11} We have targeted the 7,8-dioxo-6-azabicyclo[3.2.1]octane core structure **1** as a potential useful building block, particularly for the synthesis of C-8 substituted variants.^{3–8} In this letter we report the

synthesis of **1** based on a novel semipinacol rearrangement of a *cis*-fused β -lactam (Scheme 1).^{12,13}

[†] University of Birmingham.

[‡] University of Southampton.

(1) *Securinega* alkaloids: Weinreb, S. *Nat. Prod. Rep.* **2009**, 26, 758–775.

(2) Aphanorphine: Grainger, R. S.; Welsh, E. J. *Angew. Chem., Int. Ed.* **2007**, 46, 5377–5380.

(3) Lyconadin A: (a) Beshore, D. C.; Smith, A. B. *J. Am. Chem. Soc.* **2008**, 130, 13778–13789. (b) West, S. P.; Bisai, A.; Lim, A. D.; Narayan, R. R.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, 131, 11187–11194. (c) Nishimura, T.; Unni, A. K.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2011**, 133, 418–419.

(4) Actinobolamine: Holmes, A. B.; Kee, A.; Ladduwahetty, T.; Smith, D. F. *J. Chem. Soc., Chem. Commun.* **1990**, 1412–1414.

(5) (a) Caldaphnidine M: Zhang, C.-R.; Yang, S.-P.; Yue, J.-M. *J. Nat. Prod.* **2008**, 71, 1663–1668. (b) Calyciphylline F: Saito, S.; Kubota, T.; Kobayashi, J. *Tetrahedron Lett.* **2007**, 48, 3809–3812. (c) Calyciphylline D: Saito, S.; Kubota, T.; Fukushi, E.; Kawabata, J.; Zhang, H.; Kobayashi, J. *Org. Lett.* **2007**, 9, 1207–1209.

(6) Sarain A: Becker, M. H.; Chua, P.; Downham, R.; Douglas, C. J.; Garg, N. K.; Hiebert, S.; Jaroch, S.; Matsuoka, R. T.; Middleton, J. A.; Ng, F. W.; Overman, L. E. *J. Am. Chem. Soc.* **2007**, 129, 11987–12002.

(7) Peduncularine: (a) Hodgson, D. M.; Shelton, R. E.; Moss, T. A.; Dekhane, M. *Org. Lett.* **2010**, 12, 2834–2837. (b) The first total synthesis of peduncularine exploits a keto-bridged bicyclic lactam as a key intermediate: Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, 111, 2588–2595.

(8) Nominine: Peese, K. M.; Gin, D. Y. *Chem.—Eur. J.* **2008**, 14, 1654–1665.

(9) Takeda, M.; Inoue, H.; Noguchi, H. K.; Honma, Y.; Kawamori, M.; Tsukamoto, G.; Yamawaki, Y.; Saito, S.; Aoe, K.; Date, T.; Nurimoto, S.; Hayashi, G. *J. Med. Chem.* **1977**, 20, 221–228.

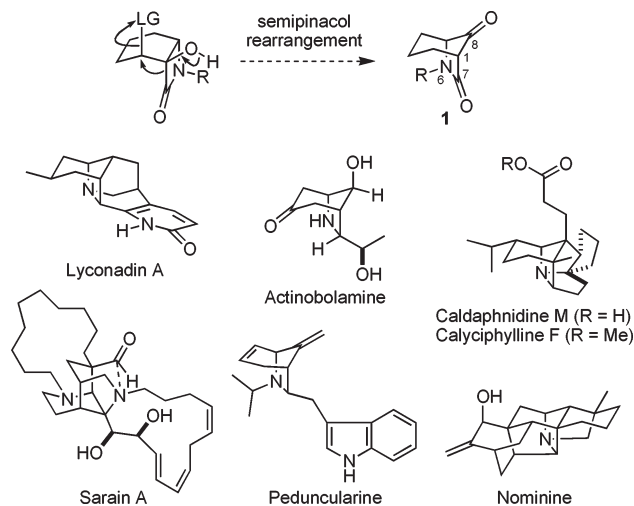
(10) (a) Trigg, D. J.; Kwon, Y. W.; Abraham, P.; Pitner, J. B.; Mascarella, S. W.; Carroll, F. I. *J. Med. Chem.* **1991**, 34, 3164–3171. (b) Carroll, F. I.; Abraham, P.; Mascarella, S. W.; Singh, P.; Moreland, C. G.; Sanker, S. S.; Kwon, Y. W.; Trigg, D. J. *J. Med. Chem.* **1991**, 34, 1436–1440.

(11) Quirante, J.; Vila, X.; Bonjoch, J.; Kozikowski, A. P.; Johnson, K. M. *Bioorg. Med. Chem.* **2004**, 12, 1383–1391.

(12) For a review of the semipinacol rearrangement, see: Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, 111, 7523–7556.

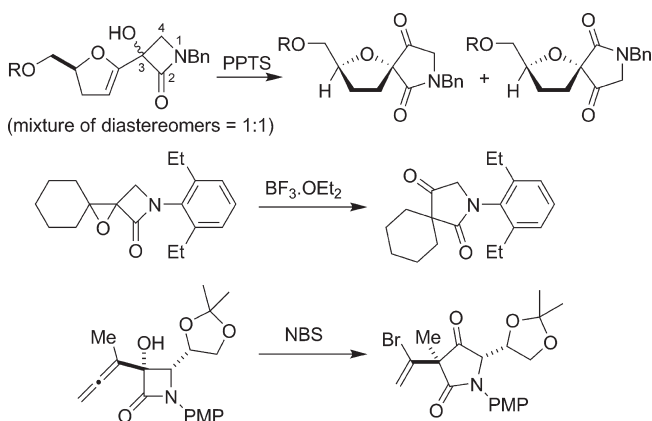
(13) A related rearrangement in the all carbocyclic [4.2.0]-ring system is hampered by the instability of the bridged 1,3-dicarbonyl product: Blanchard, A. N.; Burnell, D. J. *Tetrahedron Lett.* **2001**, 42, 4779–4781.

Scheme 1. Proposed Semipinacol Rearrangement and Representative Natural Products Containing 8-Functionalized 6-Azabicyclo[3.2.1]octane Ring Systems (LG = Leaving Group)



β -Lactams have previously been investigated as precursors to five-membered nitrogen heterocycles,¹⁴ though rarely through rearrangement with C2–C3 bond migration, and only for nonfused ring systems (Scheme 2).^{15–17} Notably in all cases only migration of the *N*-acyl carbon occurs; compounds resulting from migration of the alternative C3–C4 bond of the β -lactam were not observed.

Scheme 2. Previous Examples of Ring Expansion of Mono- and Spirocyclic β -Lactams with *N*-Acyl Group Migration^{15–17}



(14) (a) For a review on the synthetic utility of β -lactams, see: Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437–4492. For more recent examples of ring expansion involving N1–C4 bond migration, see: (b) Dekeukeleire, S.; D'hooghe, M.; De Kimpe, N. *J. Org. Chem.* **2009**, *74*, 1644–1649. (c) Alcaide, B.; Almendros, P.; Cabrero, G.; Callejo, R.; Ruiz, M. P.; Arnó, M.; Domingo, L. R. *Adv. Synth. Catal.* **2010**, *352*, 1688–1700 and references therein.

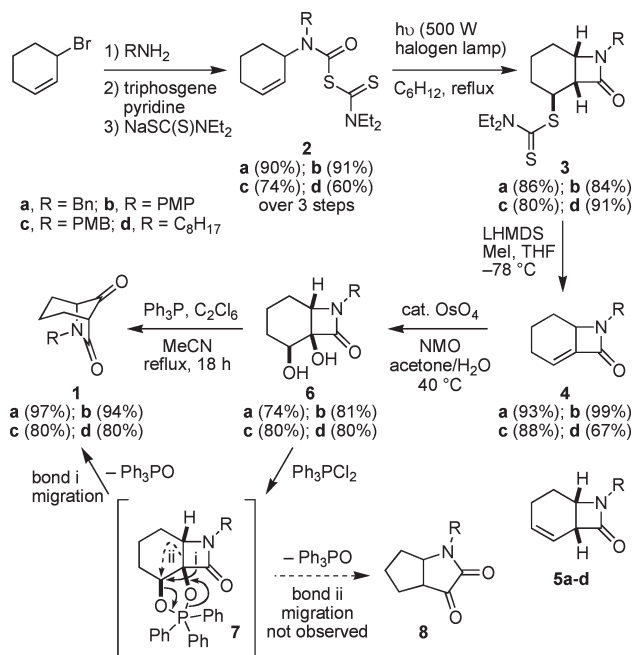
(15) Paquette, L. A.; Brand, S.; Behrens, S. C. *J. Org. Chem.* **1999**, *64*, 2010–2025.

(16) Williams, E. L. *Synth. Commun.* **1992**, *22*, 1017–1021.

(17) (a) Alcaide, B.; Almendros, P.; Luna, A.; Torres, M. R. *Adv. Synth. Catal.* **2010**, *352*, 621–626. (b) Alcaide, B.; Almendros, P.; Luna, A.; Cembellin, S.; Arnó, M.; Domingo, L. R. *Chem.—Eur. J.* **2011**, *17*, 11559–11566.

cis-Fused β -lactams **3** were prepared in four steps (three purifications) from cyclohexenylbromide using our previously reported carbamoyl radical cyclization–dithiocarbamate group transfer methodology (Scheme 3).¹⁸ Initial attempts to prepare a substrate suitable for semipinacol rearrangement (Scheme 1, LG = SC(S)NEt₂) through deprotonation of the β -lactam and oxidation of the resulting anion were unsuccessful, but resulted in the discovery that **3** was prone to dithiocarbamate group elimination using strong bases such as LDA. Optimized conditions for regioselective elimination were therefore determined, with the use of 1.1 equiv of both lithium hexamethyldisilazane and MeI at -78°C providing good to excellent yields of **4**.¹⁹ The MeI is presumed to activate the dithiocarbamate through *S*-alkylation, producing a better leaving group.²⁰ In the absence of MeI, yields were routinely lower (ca. 50%). Use of a large excess base is detrimental to the yield of **4** as the double bond can be moved out of conjugation to give **5**.^{21,22} Dihydroxylation of **4** gave the diol **6** as a single stereoisomer. The stereochemistry of **6** was assigned based on the unlikelihood of forming the alternative highly strained *trans*-fused [4.2.0] bicyclic ring system and confirmed through X-ray analysis of the corresponding cyclic sulfites (*vide infra*).

Scheme 3. Synthesis and Rearrangement of *Cis*-Fused β -Lactam Diols



(18) (a) Grainger, R. S.; Innocenti, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3445–3448. (b) Grainger, R. S.; Innocenti, P. *Heteroatom. Chem.* **2007**, *18*, 568–571.

(19) CCDC 866295 (**1b** hydrate), CCDC 866296 (**4b**), CCDC 866297 (**9b**), CCDC 866298 (**10b**), and CCDC 869870 (**13**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

A screen of standard conditions for the pinacol and semipinacol rearrangement¹² of diols and their derivatives was complicated by unexpected difficulties in selectively activating the secondary over the tertiary alcohol in **6**. Attention therefore turned to the use of cyclic systems for diol activation. The simplest conditions found involve treatment of **6** with a mixture of Ph_3P and C_2Cl_6 in refluxing acetonitrile, which provide the target bridged bicycle **1** in good to excellent yield.^{23b,c} Ph_3PCl_2 , generated in situ, is presumed to react with the diol to form a cyclic phosphorane **7**. There is a strong thermodynamic driving force for rearrangement of **7**, involving strain release through ring expansion of the β -lactam and formation of strong $\text{C}=\text{O}$ and $\text{P}=\text{O}$ bonds. Rearrangements through in situ generated cyclic phosphoranes have rarely been applied in synthesis,²³ and only to carbon–hydrogen bond migrations (Meinwald rearrangement). Hence this is the first example where cyclic phosphoranes have been applied to rearrangement with carbon–carbon bond migration.

Two possible rearrangement pathways are available for **7**, with migration of bond i, in either a concerted or stepwise process, leading to the keto-bridged bicyclic lactam **1**, or migration of bond ii, leading to the fused 2,3-dioxopyrrolidine **8**. We have only observed formation of **1**, irrespective of the *N*-substituent, suggesting that the preference for *N*-acyl group migration, as seen for mono- and spirocyclic β -lactams (Scheme 2), is maintained in fused ring systems. The formation of **1** rather than **8** was initially deduced based on the ^{13}C NMR spectrum of the alcohol obtained upon L-selectride-mediated reduction of the ketone and confirmed by X-ray analysis of the crystallized ketone hydrate of **1b** (see Supporting Information).¹⁹

A second related method, although requiring an additional step, avoids the potential problem of removal of triphenylphosphine oxide from the reaction mixture. Diol **6** was transformed into a 1:1 mixture of diastereomeric cyclic sulfites **9** and **10** (Scheme 4). Thermolysis of the mixture of **9** and **10** in diphenylether at 190 °C cleanly afforded **1** in excellent yield, presumably through loss of SO_2 .²⁴ The process was again compatible with alkyl, benzyl, and aryl *N*-substituents.

Scheme 4. Thermal Rearrangement of Cyclic Sulfites

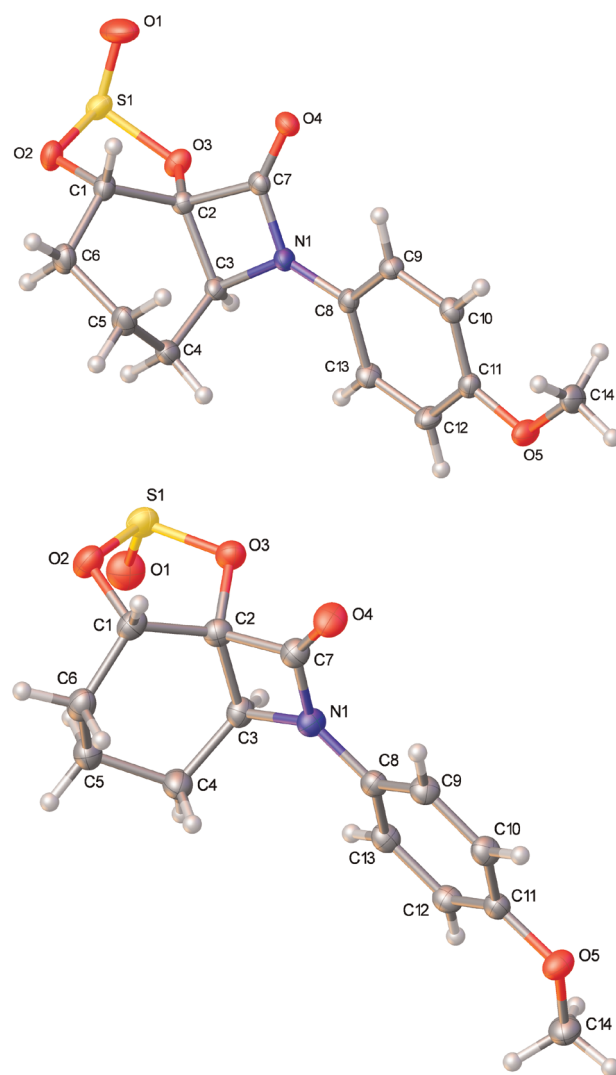
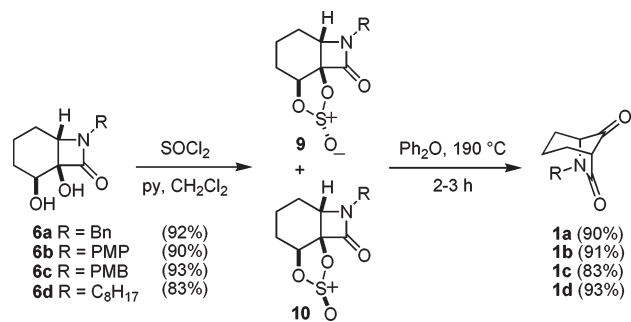


Figure 1. X-ray crystal structures of **9b** (top) and **10b** (bottom). Selected bond lengths and torsion angles: **9b**: C2–C7 1.542(2) Å, C2–C3 1.558(2) Å, O2–C1–C2–C7 140.95(13)°, O2–C1–C2–C3 –117.46(14)°; **10b**: C2–C7 1.5394(17) Å, C2–C3 1.5617(17) Å, O2–C1–C2–C7 147.23(11)°, O2–C1–C2–C3 –108.61(12)°.

(20) Hayashi, T.; Sakurai, A.; Oishi, T. *Chem. Lett.* **1977**, 1483.

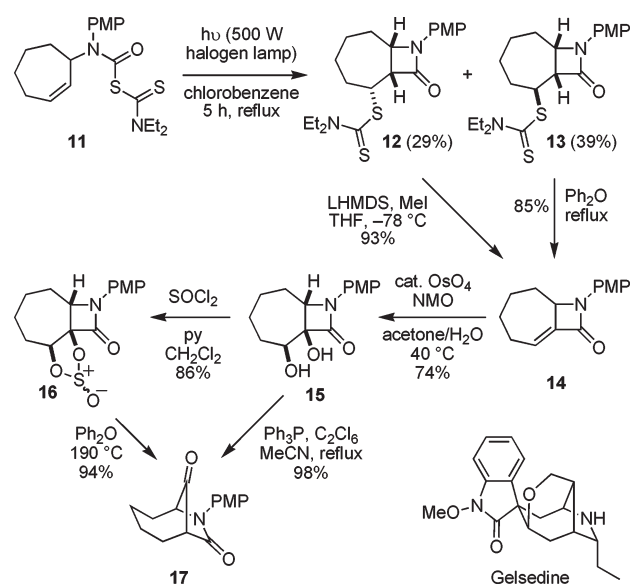
(21) The X-ray crystal structure¹⁹ of **4b** suggests a degree of strain about a nonplanar carbon–carbon double bond. See Supporting Information for details.

(22) We have previously shown that thermal elimination of dithiocarbamate **3a** gives the nonconjugated alkene **5a** in 79% yield: Ahmed, S.; Baker, L. A.; Grainger, R. S.; Innocenti, P.; Quevedo, C. E. *J. Org. Chem.* **2008**, *73*, 8116–8119.

(23) (a) Applequist, D. E.; Gebauer, P. A.; Gwynn, D. E.; O'Connor, L. H. *J. Am. Chem. Soc.* **1972**, *94*, 4272–4278. (b) Decamp, A. E.; Mills, S. G.; Kawaguchi, A. T.; Desmond, R.; Reamer, R. A.; DiMichele, L.; Volante, R. P. *J. Org. Chem.* **1991**, *56*, 3564–3571. (c) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron Lett.* **2000**, *41*, 1959–1962. (d) Defaut, B.; Parsons, T. B.; Spencer, N.; Male, L.; Kariuki, B. M.; Grainger, R. S. *Submitted for publication*.

(24) For semipinacol rearrangements of cyclic sulfites, see: (a) Griffin, G. W.; Manmade, A. *J. Org. Chem.* **1972**, *37*, 2589–2600. (b) Nemoto, H.; Miyata, J.; Hakamata, H.; Nagamochi, M.; Fukumoto, K. *Tetrahedron* **1995**, *51*, 5511–5522.

Scheme 5. Synthesis of the 8,9-Dioxo-7-azabicyclo-[4.2.1]nonane Ring System



Careful chromatography allowed for separation of the two cyclic sulfite diastereoisomers **9b** and **10b**, the structures of which were confirmed by X-ray crystallography (Figure 1).^{19,25} In both cases the C2–C7 bond (the equivalent of bond i in phosphorane **7**, Scheme 3) is shorter than the C2–C3 bond (the equivalent of bond ii in **7**). However, as seen in the O2–C1–C2–C7 and the O2–C1–C2–C3 torsion angles, the migrating C2–C7 bond is better aligned with the breaking C1–O2 bond than the C2–C3 bond.²⁶

(25) The sulfinyl stereocenter in sulfites **9** and **10** was assigned by ¹H NMR and confirmed through X-ray analysis of **9b** and **10b**.¹⁹ The anisotropy of the sulfinyl group results in a downfield shift of the proton adjacent to oxygen (C(10)–H in Figure 1) for **9** (5.25–5.41 ppm) compared with **10** (4.91–5.04 ppm). For examples of the use of sulfinyl group anisotropy for the assignment of stereochemistry, see: (a) Bedford, S. T.; Grainger, R. S.; Steed, J. W.; Tisselli, P. *Org. Biomol. Chem.* **2005**, *3*, 404–406. (b) Tanaka, S.; Sugihara, Y.; Sakamoto, A.; Ishii, A.; Nakayama, J. *J. Am. Chem. Soc.* **2003**, *125*, 9024–9025. (c) Aggarwal, V. K.; Grainger, R. S.; Newton, G. K.; Spargo, P. L.; Hobson, A. D.; Adams, H. *Org. Biomol. Chem.* **2003**, *1*, 1884–1893 and references therein.

(26) Qualitatively, **9b** was found to rearrange faster and in higher yield (45 min, 100% yield) than **10b** (135 min, 87% yield).

(27) For an alternative approach to structures such as **14** based on palladium catalyzed carbonylation of 2-bromoallylamines, see: Mori, M.; Chiba, K.; Okita, M.; Kayo, I.; Ban, Y. *Tetrahedron* **1985**, *41*, 375–385.

(28) van Henegouwen, W. G. B.; Fieseler, R. M.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Org. Chem.* **2000**, *65*, 8317–8325.

The overall strategy is also applicable to the preparation of a larger ring system. Radical cyclization–dithiocarbamate group transfer of amidocycloheptene **11** gave a separable mixture of diastereoisomers **12** and **13** (Scheme 5), with the structure of the latter proven by X-ray crystallography.¹⁹ Elimination of the dithiocarbamate group in **12** proceeded without incident to give the conjugated alkene **14** in excellent yield.²⁷ Surprisingly, **13** proved inert to the combination of LHMDS and MeI but was successfully converted to **14** through thermal elimination.²² Dihydroxylation of **14**, followed by semipinacol rearrangement, via the cyclic sulfite **16** or directly through the phosphorane, gave the keto-bridged bicyclic lactam **17** in excellent yield. The 7-azabicyclo-[4.2.1]nonane ring system is found within members of the *Gelsemium* alkaloids, such as gelsedine and gelselegine.²⁸

In summary, the semipinacol rearrangement of *cis*-fused β -lactam diols can be readily achieved through the intermediacy of a cyclic phosphorane or sulfite. Chemoselective *N*-acyl group migration leads to keto-bridged bicyclic lactams in excellent yield. The presence of both an amide and a ketone in the rearrangement products **1** makes them potentially versatile intermediates for organic synthesis. Future work will concentrate on extension to more highly substituted systems and their application in target synthesis.

Acknowledgment. We thank the EPSRC for funding (studentship to M.B., EP/G031371/1). The NMR spectrometers used in this research were obtained through Birmingham Science City: Innovative Uses for Advanced Materials in the Modern World (West Midlands Centre for Advanced Materials Project 2), with support from Advantage West Midlands (AWM) and part funded by the European Regional Development Fund (ERDF). We thank the EPSRC UK National Crystallographic Service at the University of Southampton for the collection of crystallographic data.

Supporting Information Available. Experimental procedures, analytic data, and copies of ¹H and ¹³C NMR for all new compounds. X-ray crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.