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Practical Asymmetric Synthesis of a Non-Peptidic $\alpha_v\beta_3$ Antagonist

Stephen P. Keen,* Cameron J. Cowden,* Brian C. Bishop, Karel M. J. Brands, Antony J. Davies, Ulf H. Dolling, David R. Lieberman, and Gavin W. Stewart

Department of Process Research, Merck Sharp & Dohme Research Laboratories, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, United Kingdom

stephen_keen@merck.com; cameron_cowden@merck.com

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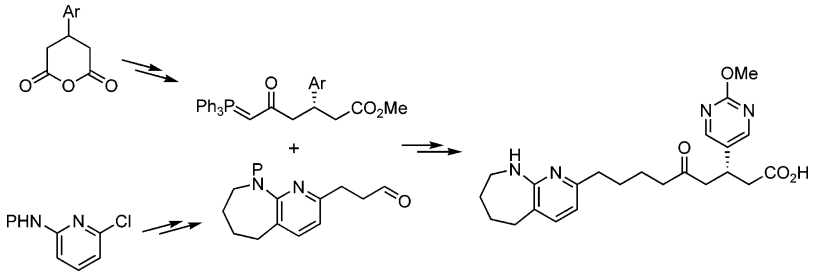

The development of a practical and highly convergent synthesis of an $\alpha_v\beta_3$ antagonist is described. The two key fragments present in this compound, a tetrahydropyrido[2,3-*b*]azepine ring system and a chiral 3-aryl-5-oxopentanoic acid, were constructed independently and then coupled at a late stage using a Wittig reaction. The pyridoazepine moiety was prepared from *N*-Boc 6-chloro-2-aminopyridine via directed *ortho*-metalation/alkylation followed by in situ cyclization. A Suzuki reaction was then used to attach the propionaldehyde side-chain required for Wittig coupling. The coupling partner was prepared from asymmetric methanolysis of a 3-substituted glutaric anhydride followed by elaboration of the acid moiety to the requisite β-keto phosphorane. Using this route, kilogram quantities of the desired drug candidate were prepared.

Introduction

The vitronectin receptor $\alpha_v\beta_3$ is a member of the integrin family, a class of adhesion receptors that mediate cell−cell and cell−matrix interactions.[1] In particular, $\alpha_v\beta_3$ is highly expressed in osteoclasts, multinucleated cells responsible for bone resorption, and is believed to play a critical role in the adhesion and migration of osteoclasts on the bone surface.[2] Furthermore, it has been demonstrated that ligands which bind with high affinity to $\alpha_v\beta_3$, such as RGD-containing peptides or small molecule RGD (Arg-Gly-Asp) mimetics, inhibit bone resorption in vivo.[3] Therefore, $\alpha_v\beta_3$ antagonists are of considerable interest for the treatment of osteoporosis,[4] a disease characterized by a decrease in bone mass resulting from increased bone resorption relative to formation. As part of a program to develop an orally active antagonist of the $\alpha_v\beta_3$ receptor for the treatment of osteoporosis,[5] compound **1** was identified as a candidate for pre-clinical development.

Structurally, **1** consists of a tetrahydropyrido[2,3-*b*]-azepine attached via a 4-carbon tether to a 3-aryl-5-oxopentanoic acid moiety containing the sole chiral center. At the outset, one of the main objectives was to

(1) (a) Hynes, R. O. *Cell* **1992**, *69*, 11−25. (b) Horton, M. A. *Int. J. Biochem. Cell Biol.* **1997**, *29*, 721−725. (c) van der Flier, A.; Sonnenberg, A. *Cell Tissue Res.* **2001**, *305*, 285−298.

(2) (a) Rodan, S. B.; Rodan, G. A. *J. Endocrinol.* **1997**, *154*, S47−S56. (b) Duong, L. T.; Rodan, G. A. *J. Bone Miner. Metab.* **1999**, *17*, 1−6. (c) Teitelbaum, S. L. *Science* **2000**, *289*, 1504−1508.

(3) For example, see: (a) Fisher, J. E.; Caulfield, M. P.; Sato, M.; Quartuccio, H. A.; Gould, R. J.; Garsky, V. M.; Rodan, G. A.; Rosenblatt, M. *Endocrinology* **1993**, *132*, 1411−1413. (b) King, K. L.; D'anza, J. J.; Bodary, S.; Pitti, R.; Siegel, M.; Lazarus, R. A.; Dennis, M. S.; Hammonds, R. G.; Kukreja, S. C. *J. Bone Miner. Res.* **1994**, *9*, 381−387. (c) Engleman, V. W.; Nickols, G. A.; Ross, F. P.; Horton, M. A.; Griggs, D. W.; Settle, S. L.; Ruminski, P. G.; Teitelbaum, S. L. *J. Clin. Invest.* **1997**, *99*, 2284−2292. (d) Yamamoto, M.; Fisher, J. E.; Gentile, M.; Seedor, J. G.; Leu, C.-T.; Rodan, S. B.; Rodan, G. A. *Endocrinology* **1998**, *139*, 1411−1419. (e) Lark, M. W.; Stroup, G. B.; Hwang, S. M.; James, I. E.; Rieman, D. J.; Drake, F. H.; Bradbeer, J. N.; Mathur, A.; Erhard, K. F.; Newlander, K. A.; Ross, S. T.; Salyers, K. L.; Smith, B. R.; Miller, W. H.; Huffman, W. F.; Gowen, M. *J. Pharmacol. Exp. Ther.* **1999**, *291*, 612−617. (f) Miller, W. H.; Alberts, D. P.; Bhatnagar, P. K.; Bondinell, W. E.; Callahan, J. F.; Calvo, R. R.; Cousins, R. D.; Erhard, K. F.; Heerding, D. A.; Keenan, R. M.; Kwon, C.; Manley, P. J.; Newlander, K. A.; Ross, S. T.; Samanen, J. M.; Uzinskas, I. N.; Venslavsky, J. W.; Yuan, C. C.-K.; Haltiwanger, R. C.; Gowen, M.; Hwang, S.-M.; James, I. E.; Lark, M. W.; Rieman, D. J.; Stroup, G. B.; Azzarano, L. M.; Salyers, K. L.; Smith, B. R.; Ward, K. W.; Johanson, K. O.; Huffman, W. F. *J. Med. Chem.* **2000**, *43*, 22−26. (g) Duggan, M. E.; Duong, L. T.; Fisher, J. E.; Hamill, T. G.; Hoffman, W. F.; Huff, J. R.; Ihle, N. C.; Leu, C.-T.; Nagy, R. M.; Perkins, J. J.; Rodan, S. B.; Wesolowski, G.; Whitman, D. B.; Zartman, A. E.; Rodan, G. A.; Hartman, G. D. *J. Med. Chem.* **2000**, *43*, 3736−3745.

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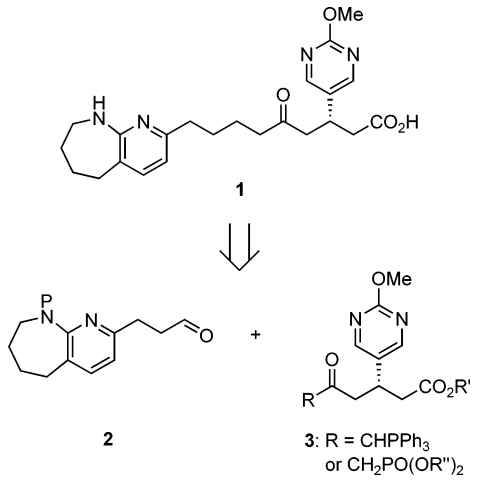
SCHEME 1

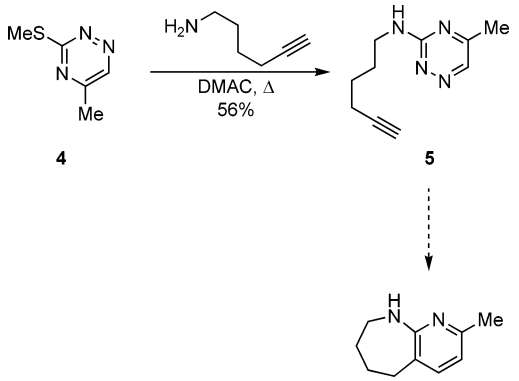


make the synthesis of **1** as convergent as possible. With this in mind, it was envisaged that the carbon−carbon bond α−β to the keto group could be formed late in the synthesis via a Wittig or Horner−Wadsworth−Emmons reaction of aldehyde **2** with the requisite phosphorane/phosphonate **3** (Scheme 1). The success of this proposed route therefore depended upon developing efficient syntheses of these two key fragments. This paper describes the successful accomplishment of these goals.

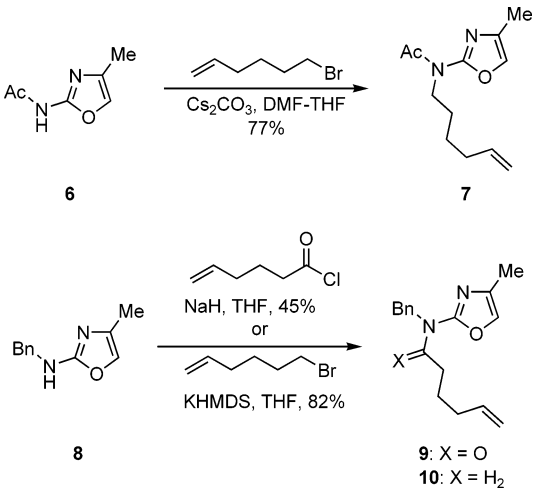
Results and Discussion

Synthesis of Aldehyde 2. It was anticipated that aldehyde **2** would be available from elaboration of a pyridoazepine containing a suitable substituent at C-2. However, reported syntheses of the tetrahydropyrido[2,3-*b*]azepine ring system are limited to several specific examples,[6,7] only a couple of which are compatible with a single C-2 substituent. Of these, we were particularly interested in the intramolecular Diels−Alder reaction of *N*-hex-5-yn-1-yl-5-(trifluoromethyl)-1,2,4-triazin-3-amine, reported by Seitz and co-workers.[7] We quickly discovered, however, that under similar conditions the

SCHEME 2



SCHEME 3



5-methyl analogue (**5**), prepared via reaction of triazine **4**[8] with hex-5-ynylamine,[9,10] does not undergo this cycloaddition (Scheme 2). This is perhaps not surprising given the inverse electron demand nature of these Diels−Alder reactions.[11]

The focus, therefore, switched to alternate intramolecular Diels−Alder substrates. Based on precedent from the Padwa group, for forming the analogous 6,6-fused tetrahydro-1,8-naphthyridine system,[12] the intramolecular Diels−Alder reactivity of oxazole **7**, obtained via alkylation of **6**[13,14] with 6-bromo-1-hexene, was examined (Scheme 3). Disappointingly, under thermal conditions, **7** failed to provide either the desired pyridoazepine or the intermediate Diels−Alder adduct. Attempts to cyclize the analogous oxazoles **9** or **10** proved equally unsuccessful.[15]

(4) For recent reviews on the development of $\alpha_v\beta_3$ antagonists, see: (a) Miller, W. H.; Keenan, R. M.; Willette, R. N.; Lark, M. W. *Drug Discovery Today* **2000**, *5*, 397−408. (b) Duggan, M. E.; Hutchinson, J. H. *Expert Opin. Ther. Pat.* **2000**, *10*, 1367−1383. (c) Hartman, G. D.; Duggan, M. E. *Expert Opin. Invest. Drugs* **2000**, *9*, 1281−1291. (d) Coleman, P. J.; Duong, L. T. *Expert Opin. Ther. Pat.* **2002**, *12*, 1009−1021.

(5) For the most recent publications in a series documenting the discovery of non-peptide $\alpha_v\beta_3$ antagonists, see: (a) Breslin, M. J.; Duggan, M. E.; Halczenko, W.; Hartman, G. D.; Duong, L. T.; Fernandez-Metzler, C.; Gentile, M. A.; Kimmel, D. B.; Leu, C.-T.; Merkle, K.; Prueksaritanont, T.; Rodan, G. A.; Rodan, S. B.; Hutchinson, J. H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4515−4518. (b) Coleman, P. J.; Brashear, K. M.; Askew, B. C.; Hutchinson, J. H.; McVean, C. A.; Duong, L. T.; Feuston, B. P.; Fernandez-Metzler, C.; Gentile, M. A.; Hartman, G. D.; Kimmel, D. B.; Leu, C.-T.; Lipfert, L.; Merkle, K.; Pennypacker, B.; Prueksaritanont, T.; Rodan, G. A.; Wesolowski, G. A.; Rodan, S. B.; Duggan, M. E. *J. Med. Chem.* **2004**, *47*, 4829−4837.

(6) For example, see: (a) Hawes, E. M.; Davis, H. L. *J. Heterocycl. Chem.* **1973**, *10*, 39−42. (b) Jössang-Yanagida, A.; Gansser, C. *J. Heterocycl. Chem.* **1978**, *15*, 249−251. (c) Seitz, G.; Dietrich, S.; Görge, L.; Richter, J. *Tetrahedron Lett.* **1986**, *27*, 2747−2750. (d) Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 2693−2702. (e) Pätzel, M.; Ushmajev, A.; Liebscher, J.; Granik, V.; Grisik, S.; Polievktov, M. *J. Heterocycl. Chem.* **1992**, *29*, 1067−1068.

(7) (a) John, R.; Seitz, G. *Arch. Pharm. (Weinheim, Ger.)* **1989**, *322*, 561−564. (b) John, R.; Seitz, G. *Chem. Ber.* **1990**, *123*, 133−136.

(8) Paudler, W. W.; Chen, T.-K. *J. Heterocycl. Chem.* **1970**, *7*, 767−771.

(9) Müller, T. E.; Pleier, A.-K. *J. Chem. Soc., Dalton Trans.* **1999**, 583−587.

(10) For an example of an analogous reaction between an alkylamine and triazine **4**, see: Jacobsen, N. W.; de Jonge, I. *Aust. J. Chem.* **1987**, *40*, 1979−1988.

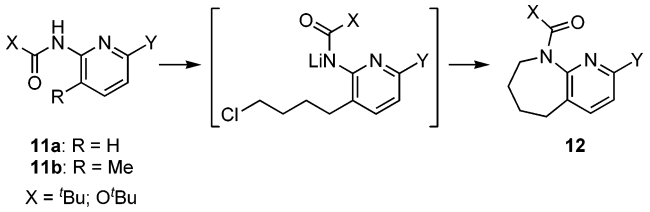
(11) Intramolecular Diels−Alder reactions of 1,2,4-triazines have been used to prepare 2,3-dihydropyrrolo[2,3-*b*]pyridines without electron-withdrawing substituents on the triazine moiety: Taylor, E. C.; Pont, J. L. *Tetrahedron Lett.* **1987**, *28*, 379−382.

(12) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595−3607.

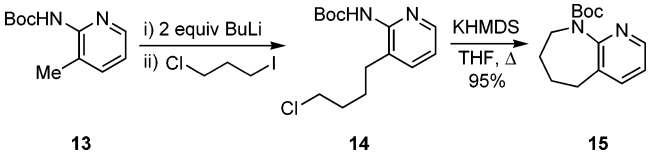
(13) Cockerill, A. F.; Deacon, A.; Harrison, R. G.; Osborne, D. J.; Prime, D. M.; Ross, W. J.; Todd, A.; Verge, J. P. *Synthesis* **1976**, 591−593.

(14) Crank, G.; Foulis, M. J. *J. Med. Chem.* **1971**, *14*, 1075−1077.

SCHEME 4



SCHEME 5

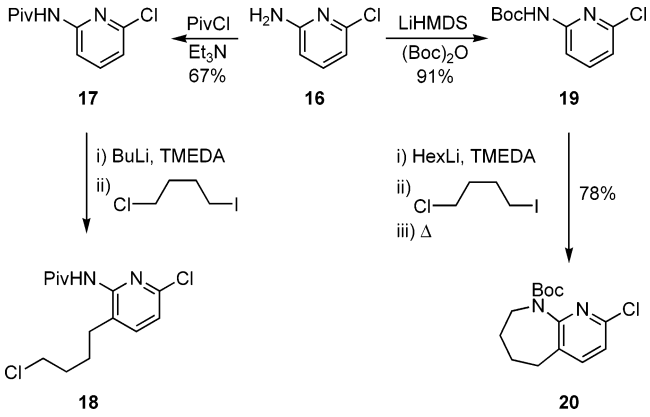


Following the failure of these Diels–Alder approaches, we then considered the possibility of building the tetrahydroazepine ring onto a suitably functionalized pyridine core. We envisaged that directed *ortho*-metalation of an *N*-acyl 2-aminopyridine (**11**) followed by alkylation with a suitable dihaloalkane and in situ cyclization would provide the desired bicycle **12** (Scheme 4).

Several examples of dilithiation and subsequent C-alkylation/acylation of *N*-Boc and *N*-Piv 2-aminopyridines (**11a**)[16,17] and 2-amino-3-picolines (**11b**)[18,19] are documented in the literature. In particular, a previous report from these laboratories had demonstrated that picoline derivative **13** could be converted into the desired cyclization substrate **14**.[19] In that case, however, no attempt at cyclization was made. Using this procedure, chloride **14** was readily obtained in high yield, and we were pleased to find that treating this compound with KHMDS resulted in clean conversion to the desired pyridoazepine **15** (Scheme 5). It was subsequently shown that these two steps could be combined into a single operation to afford pyridoazepine **15** directly from picoline **13**. Thus, after dilithiation of **13** and subsequent alkylation with 1-chloro-3-iodopropane, the resulting reaction mixture, containing lithiated **14**, was simply heated to reflux to afford pyridoazepine **15**.

Although this is a direct and highly efficient route to the tetrahydropyrido[2,3-*b*]azepine ring system, functionalization of **15** at C-2, as required for elaboration to aldehyde **2**, is not trivial. Because 2-amino-3-picolines containing suitable functionality at this position are not readily available, our focus shifted to 2-aminopyridine substrates. Therefore, 2-amino-6-chloropyridine (**16**), prepared from commercially available 2,6-dichloropyridine,[20] was initially converted into the *N*-Piv derivative **17** using a slightly modified literature procedure (Scheme 6).[17] Dilithiation of **17** with BuLi/TMEDA and subsequent reaction with 1-chloro-4-iodobutane afforded a 1:1 mixture of alkylation product **18** and starting pyridine. Surprisingly, cyclization of **18** was not observed upon deprotonation with KHMDS under the previously described conditions. Similarly, Reed and co-workers reported that an analogous *N*-Piv 2-amino-3-(3-chloropropyl)-pyridine failed to cyclize to the desired tetrahydro-1,8-naphthyridine under comparable conditions.[16c]

SCHEME 6



Having already demonstrated that the analogous chloride **14**, containing the *N*-Boc group, could be readily cyclized, we reexamined this chloropyridine route using *N*-Boc derivative **19**. Therefore, *N*-Boc aminopyridine **19** was prepared by deprotonation of aminopyridine **16** with LiHMDS followed by addition of $(Boc)_2O$ (Scheme 6). Dilithiation of **19** with BuLi/TMEDA at −78 °C, followed by addition of 1-chloro-4-iodobutane and warming to ambient temperature, resulted in clean conversion (90–95%) to the chlorobutyl intermediate. Upon heating the resulting reaction mixture to reflux, we were delighted to find that this lithiated intermediate cyclized to afford the desired pyridoazepine **20** in 78% yield. It was subsequently found that this yield can be improved to 86% by transmetalation of dilithiated **19** with CuI prior to addition of the alkylating agent.[21]

With chloropyridoazepine **20** in hand, we envisaged that elaboration into the required aldehyde could be achieved via palladium-catalyzed coupling with a suitable 3-carbon unit. In particular, a Heck reaction of **20** with allyl alcohol would provide aldehyde **24** in a single step. Disappointingly, using either standard Heck conditions[22a] or Jeffery modifications,[22b] none of the desired product was observed. Although iodides are typically used for Heck reactions between aryl/vinyl halides and allylic

(15) *N*-Benzyl oxazole **8** was prepared from benzylcyanamide using the procedure described in ref 13.

(16) (a) Turner, J. A. *J. Org. Chem.* **1983**, *48*, 3401–3408. (b) Venuti, M. C.; Stephenson, R. A.; Alvarez, R.; Bruno, J. J.; Strosberg, A. M. *J. Med. Chem.* **1988**, *31*, 2136–2145. (c) Reed, J. N.; Rotchford, J.; Strickland, D. *Tetrahedron Lett.* **1988**, *29*, 5725–5728. (d) Estel, L.; Linard, F.; Marsais, F.; Godard, A.; Quéguiner, G. *J. Heterocycl. Chem.* **1989**, *26*, 105–112. (e) Turner, J. A. *J. Org. Chem.* **1990**, *55*, 4744–4750. (f) Murray, T. J.; Zimmerman, S. C.; Kolotuchin, S. V. *Tetrahedron* **1995**, *51*, 635–648. (g) Zimmerman, S. C.; Kwan, W.-S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2404–2406. (h) Takayama, K.; Iwata, M.; Hisamichi, H.; Okamoto, Y.; Aoki, M.; Niwa, A. *Chem. Pharm. Bull.* **2002**, *50*, 1050–1059. (i) Eldrup, A. B.; Christensen, C.; Haaima, G.; Nielsen, P. E. *J. Am. Chem. Soc.* **2002**, *124*, 3254–3262.

(17) Thompson, A. M.; Rewcastle, G. W.; Boushelle, S. L.; Hartl, B. G.; Kraker, A. J.; Lu, G. H.; Batley, B. L.; Panek, R. L.; Showalter, H. D. H.; Denny, W. A. *J. Med. Chem.* **2000**, *43*, 3134–3147.

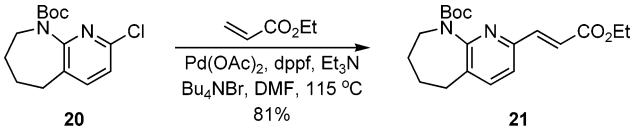
(18) (a) Clark, R. D.; Muchowski, J. M.; Fisher, L. E.; Flippin, L. A.; Repke, D. B.; Souchet, M. *Synthesis* **1991**, 871–878. (b) Curtis, N. R.; Kulagowski, J. J.; Leeson, P. D.; Ridgill, M. P.; Emms, F.; Freedman, S. B.; Patel, S.; Patel, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 585–588.

(19) Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Cottrell, I. F.; Wright, S. H. B. *Synthesis* **1996**, 877–882.

(20) Kaminski, J. J.; Perkins, D. G.; Frantz, J. D.; Solomon, D. M.; Elliott, A. J.; Chiu, P. J. S.; Long, J. F. *J. Med. Chem.* **1987**, *30*, 2047–2051.

(21) For a more detailed discussion on the development and scope of this methodology, see: Davies, A. J.; Brands, K. M. J.; Cowden, C. J.; Dolling, U. H.; Lieberman, D. R. *Tetrahedron Lett.* **2004**, *45*, 1721–1724.

SCHEME 7

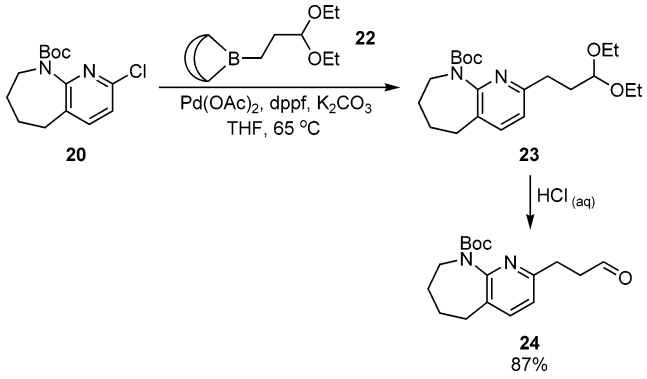


20 **21**

alcohols,[22,23] 2-chloropyridines have been successfully utilized in Heck reactions with other alkenes,[24] as well as in palladium-catalyzed Stille,[25] Suzuki,[26] Negishi,[27] and Sonogashira[28] couplings. We therefore tested the reactivity of chloride **20** in a Heck reaction with ethyl acrylate and were pleased to find that the expected adduct **21** was obtained in high yield (Scheme 7).

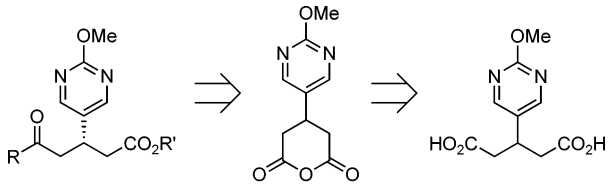
Although ester **21** could theoretically be converted into desired aldehyde **24**, we continued to pursue a more concise method of installing the propionaldehyde chain. Thus, Suzuki coupling of chloride **20** with trialkylborane **22**, prepared from commercially available acrolein diethyl acetal and 9-BBN,[29] was examined (Scheme 8). The only precedent we could find for Suzuki reactions of similar trialkylborane reagents derived from acrolein acetals were a couple of examples which used vinyl triflates as the coupling partners.[30,31] We were, therefore, gratified to find that a $Pd(OAc)_2$/dppf-catalyzed reaction of chloride **20** with borane **22** cleanly afforded the desired acetal **23**

SCHEME 8



20 **23** **24** 87%

SCHEME 9



3: R = $CHPPh_3$ or $CH_2PO(OR'')_2$ **25** **26**

in near quantitative yield (98% after chromatography).[32] Alternatively, the crude Suzuki reaction mixture containing **23** could be treated with hydrochloric acid to afford aldehyde **24** directly.

Synthesis of Phosphorane/Phosphonate 3. With a route to aldehyde **24** in place, we next required a synthesis of its coupling partner, phosphorane/phosphonate **3**. It was hypothesized that this could be obtained via enantioselective desymmetrization of cyclic anhydride **25**, which in turn would be available from dehydration of the corresponding diacid **26** (Scheme 9).

Preparation of diacid **26** started from the known pyrimidine aldehyde **28**,[33] which was obtained from reaction of *O*-methylisourea with vinamidinium salt **27** (Scheme 10).[34] After examining a variety of bases and solvents for this reaction, it was found that biphasic conditions using aqueous $KHCO_3$, with isopropyl acetate as the cosolvent, gave the highest yields of aldehyde **28**. This was then converted into the desired diacid **26** using an adaptation of a procedure reported by Smith and coworkers,[35] which was itself based on original Knoevenagel chemistry. Thus, piperidine-catalyzed condensation of aldehyde **28** with 2 equiv of ethyl acetoacetate, followed

(22) For example, see: (a) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265−272. (b) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287−1289. (c) Jeffery, T. *Tetrahedron Lett.* **1990**, *31*, 6641−6644. (d) Zhao, H.; Cai, M.-Z.; Hu, R.-H.; Song, C.-S. *Synth. Commun.* **2001**, *31*, 3665−3669.

(23) A handful of examples using aryl/vinyl bromides are also known: (a) Groen, M. B.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 301−304. (b) Kao, L.-C.; Stakem, F. G.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1982**, *47*, 1267−1277. (c) Kirby, A. J.; Walwyn, D. R. *Gazz. Chim. Ital.* **1987**, *117*, 667−680. In addition, since completing this work an example utilizing an aryl chloride has been reported: (d) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000.

(24) (a) Li, J.; Chen, S.-H.; Li, X.; Niu, C.; Doyle, T. W. *Tetrahedron* **1998**, *54*, 393−400. (b) Li, J.; Luo, X.; Wang, Q.; Zheng, L.-M.; King, I.; Doyle, T. W.; Chen, S.-H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3159−3164. (c) Niu, C.; Li, J.; Doyle, T. W.; Chen, S.-H. *Tetrahedron* **1998**, *54*, 6311−6318.

(25) For example, see: (a) Pomel, V.; Rovera, J. C.; Godard, A.; Marsais, F.; Quéguiner, G. *J. Heterocycl. Chem.* **1996**, *33*, 1995−2005. (b) Holladay, M. W.; Bai, H.; Li, Y.; Lin, N.-H.; Daanen, J. F.; Ryther, K. B.; Wasicak, J. T.; Kincaid, J. F.; He, Y.; Hettinger, A.-M.; Huang, P.; Anderson, D. J.; Bannon, A. W.; Buckley, M. J.; Campbell, J. E.; Donnelly-Roberts, D. L.; Gunther, K. L.; Kim, D. J. B.; Kuntzweiler, T. A.; Sullivan, J. P.; Decker, M. W.; Arneric, S. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2797−2802. (c) Bates, R. W.; Boonsombat, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 654−656.

(26) For example, see: (a) Ohta, A.; Takahashi, N.; Shirokoma, Y.; Yuasa, K.; Kurihara, T.; Miyamae, H. *Heterocycles* **1990**, *30*, 875−884. (b) Molander, G. A.; Yun, C.-S. *Tetrahedron* **2002**, *58*, 1465−1470. (c) Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416−8423.

(27) For example, see: (a) Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3158−3175. (b) Trécourt, F.; Gervais, B.; Mongin, O.; Le Gal, C.; Mongin, F.; Quéguiner, G. *J. Org. Chem.* **1998**, *63*, 2892−2897. (c) Gauthier, D. R.; Szumigala, R. H.; Dormer, P. G.; Armstrong, J. D.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 375−378.

(28) For example, see: (a) Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. *Synthesis* **1983**, 312−314. (b) Sakamoto, T.; An-naka, M.; Kondo, Y.; Araki, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1890−1894. (c) Kim, T.-S.; White, J. D. *Tetrahedron Lett.* **1993**, *34*, 5535−5536.

(29) Hydroboration of acrolein diethyl acetal with 9-BBN has been reported to give a 98:2 mixture of regioisomers favoring the terminal position: Brown, H. C.; Chen, J. C. *J. Org. Chem.* **1981**, *46*, 3978−3988.

(30) (a) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201−2208. (b) Grigg, R.; Kennewell, P.; Savic, V. *Tetrahedron* **1994**, *50*, 5489−5494. (c) Grigg, R.; Savic, V.; Thornton-Pett, M. *Tetrahedron* **1997**, *53*, 10633−10642.

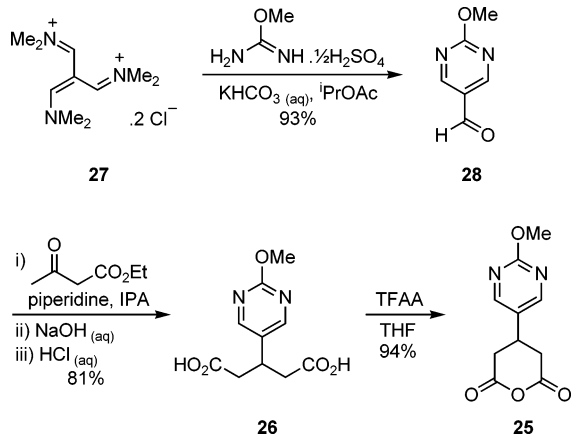
(31) Since completing this work, a couple of examples which use aryl halides as the coupling partners have also been reported: (a) Young, J. R.; Huang, S. X.; Walsh, T. F.; Wyvratt, M. J.; Yang, Y. T.; Yudkovitz, J. B.; Cui, J.; Mount, G. R.; Ren, R. N.; Wu, T.-J.; Shen, X.; Lyons, K. A.; Mao, A.-H.; Carlin, J. R.; Karanam, B. V.; Vincent, S. H.; Cheng, K.; Goulet, M. T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 827−832. (b) Beinhoff, M.; Karakaya, B.; Schlüter, A. D. *Synthesis* **2003**, 79−90.

(32) A more detailed account of this Suzuki coupling has been reported elsewhere: Cowden, C. J.; Hammond, D. C.; Bishop, B. C.; Brands, K. M. J.; Davies, A. J.; Dolling, U. H.; Brewer, S. E. *Tetrahedron Lett.* **2004**, *45*, 6125−6128.

(33) (a) Gupton, J. T.; Gall, J. E.; Reisinger, S. W.; Smith, S. Q.; Bevirt, K. M.; Sikorski, J. A.; Dahl, M. L.; Arnold, Z. *J. Heterocycl. Chem.* **1991**, *28*, 1281−1285. (b) Ragan, J. A.; McDermott, R. E.; Jones, B. P.; am Ende, D. J.; Clifford, P. J.; McHardy, S. J.; Heck, S. D.; Liras, S.; Segelstein, B. E. *Synlett* **2000**, 1172−1174.

(34) McWilliams, J. C.; Buck, E.; Eng, K. K.; Maligres, P. E.; Sager, J. W.; Waters, M. S.; Humphrey, G. R. WO Patent 2002028840.

SCHEME 10

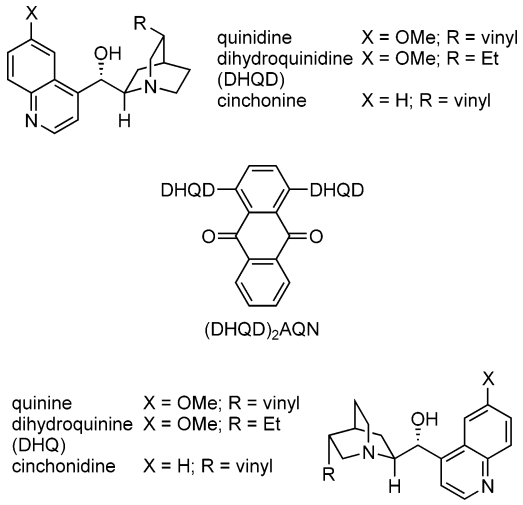


by deacylation/hydrolysis with aqueous NaOH and finally acidification, afforded diacid **26** as a crystalline solid in 81% yield.

Dehydration of diacid **26** using conventional procedures, such as treating with DCC[36] or heating with excess acetic anhydride,[37] resulted in poor yields (50−60%) of anhydride **25**. However, using trifluoroacetic anhydride (TFAA) as the dehydrating agent led to significant improvements.[38] Thus, treating diacid **26** with TFAA resulted in rapid and clean conversion to anhydride **25**, which crystallized directly from the reaction mixture in 94% yield.

Literature precedent indicated that desymmetrization of prochiral anhydride **25**, to set the absolute stereochemistry of our sole stereogenic center, would be best accomplished by enantioselective alcoholysis.[39] The resulting enantiomerically pure half-ester could then be readily converted into the desired phosphorane/phosphonate. There are numerous examples in the literature of asymmetric alcoholysis of cyclic anhydrides;[40] however, we were particularly interested in a publication by Deng and co-workers who reported excellent selectivity using cinchona-based catalysts.[41] Notably, desymmetrization of the more challenging 3-substituted glutaric anhydrides was reported to occur with up to 91% ee.

Therefore, these commercially available catalysts were screened for their ability to catalyze methanolysis of anhydride **25**. Using 10 mol % of catalyst in THF at room temperature, the enantiomeric excesses obtained ranged from very poor to moderate (3−68% ee) with quinine-derived catalysts tending to give products enriched in the (*R*)-enantiomer (*ent*-**29**) and catalysts in the quinidine series favoring the (*S*)-enantiomer (**29**).[42] In the absence of a catalyst, the reaction was very slow and only a trace amount (<5%) of the acid-ester was formed after aging for 48 h. In agreement with Deng's findings, the most promising results were achieved using anthraquinone catalysts $(DHQD)_2AQN$ and $(DHQ)_2AQN$ (68% and 54% ee, respectively),[43] and reaction conditions were further optimized therefore using these catalysts. Changes to concentration, solvent, methanol charge, and catalyst loading were all examined. However, only by lowering the reaction temperature was a significant improvement in enantioselectivity observed [82% ee at −40 °C using $(DHQD)_2AQN$]. Unfortunately, the reaction rate slowed dramatically with decreasing temperature, and, at −40 °C, conversion of anhydride **25** to acid-ester **29** was unacceptably slow (∼50% after 40 h). Moreover, these catalysts are expensive and not readily available in bulk quantities. Desymmetrization of anhydride **25** using naturally occurring cinchona alkaloids was therefore investigated.[44]



Methanolysis of anhydride **25** using either catalytic or stoichiometric amounts of the natural alkaloids, in THF at 20 °C, gave disappointingly low enantioselectivities (3−34% ee). However, by utilizing conditions (toluene, −40 °C) similar to those reported by Bolm and co-workers, for quinine/quinidine-mediated methanolysis of succinic anhydrides,[45] significantly improved enantioselectivities were obtained. Thus, reaction of anhydride **25**

(35) (a) Smith, W. T.; Kort, P. G. *J. Am. Chem. Soc.* **1950**, *72*, 1877−1878. (b) Smith, W. T.; Shelton, R. W. *J. Am. Chem. Soc.* **1954**, *76*, 2731−2732.

(36) de Laszlo, S. E.; Bush, B. L.; Doyle, J. J.; Greenlee, W. J.; Hangauer, D. G.; Halgren, T. A.; Lynch, R. J.; Schorn, T. W.; Siegl, P. K. S. *J. Med. Chem.* **1992**, *35*, 833−846.

(37) For a typical procedure, see: Matsuda, F.; Kawasaki, M.; Ohsaki, M.; Yamada, K.; Terashima, S. *Tetrahedron* **1988**, *44*, 5745−5759.

(38) Using TFAA for dehydration of diacids to five-, six-, and seven-membered cyclic anhydrides has been reported before. For example, see: (a) Boger, D. L.; Hong, J.; Hikota, M.; Ishida, M. *J. Am. Chem. Soc.* **1999**, *121*, 2471−2477. (b) Kim, H. O.; Ji, X.; Melman, N.; Olah, M. E.; Stiles, G. L.; Jacobson, K. A. *J. Med. Chem.* **1994**, *37*, 3373−3382. (c) Boger, D. L.; Baldino, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 11418−11425.

(39) To the best of our knowledge, at the start of this project the only reported asymmetric desymmetrization of cyclic anhydrides using carbon nucleophiles was a single example using chiral Grignard reagents: (a) Real, S. D.; Kronenthal, D. R.; Wu, H. Y. *Tetrahedron Lett.* **1993**, *34*, 8063−8066. More recently, enantioselective desymmetrizations of cyclic anhydrides using either aryl Grignard reagents or diethylzinc in the presence of chiral ligands have been reported: (b) Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1057−1059. (c) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174−175.

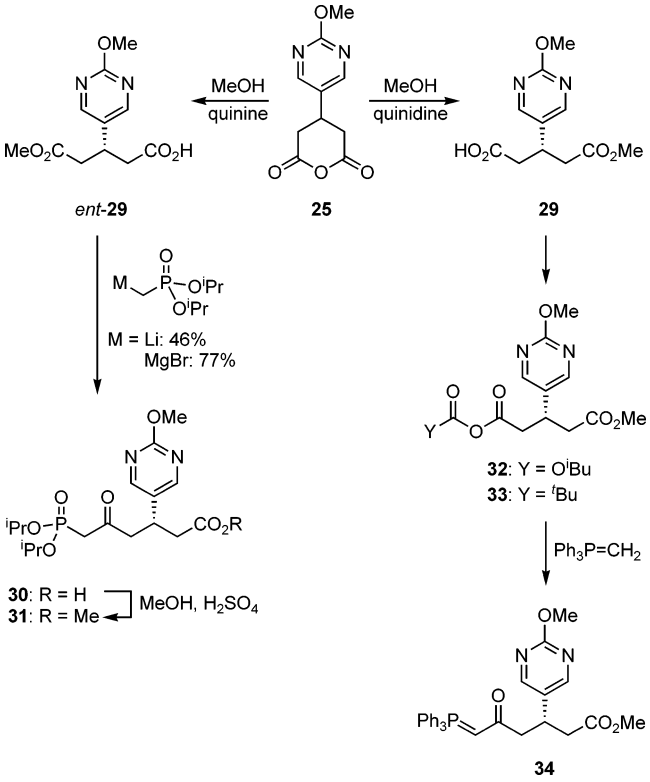
(40) For recent reviews, see: (a) Spivey, A. C.; Andrews, B. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 3131−3134. (b) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965−2984.

(41) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542−9543.

(42) The absolute stereochemistry was assigned by analogy with Deng's results (see ref 41). In addition, completing the synthesis of **1** using the acid-ester obtained from desymmetrization with quinidine-based catalysts provided final material with the correct absolute stereochemistry for the biologically active $\alpha_v\beta_3$ antagonist.

(43) The following catalysts were also screened: $(DHQ)_2PYR$, 3% ee; cinchonidine, 3% ee; hydroquinidine, 5% ee; quinidine, 11% ee; $(DHQ)_2PHAL$, 12% ee; DHQ-CLB, 16% ee; DHQ-MEQ, 16% ee; quinine, 20% ee; DHQ-PHN, 44% ee; DHQD-PHN, 65% ee.

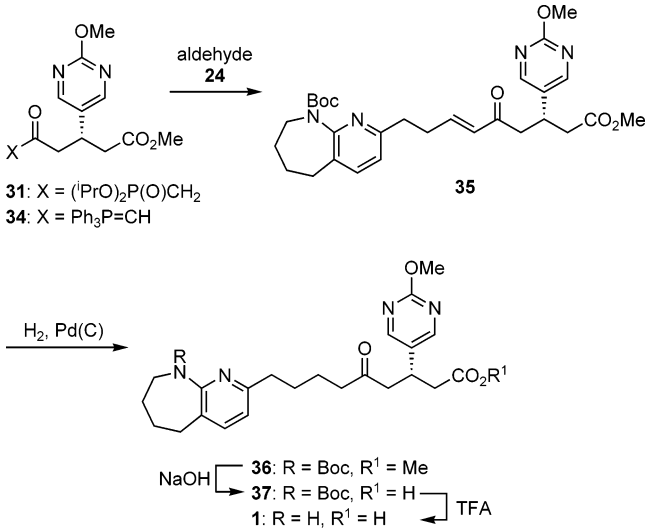
SCHEME 11



with methanol in the presence of 1.0 equiv of quinidine afforded **29** with 62% ee (Scheme 11). Similarly, the analogous reaction with quinine provided *ent*-**29** in 58% ee.[46] Attempts to further improve the enantioselectivity of these reactions by optimization of temperature, solvent, methanol charge, and concentration proved unsuccessful.

We therefore required an upgrade procedure to obtain the desired acid-ester in enantiomerically pure form. It was discovered that for quinine-mediated methanolysis of anhydride **25**, the enantiopurity of the resulting (*R*)-acid-ester could be increased, to 87% ee, by simply filtering off the quinine salt of *ent*-**29** at the end of the reaction (65% yield). Unfortunately, a similar upgrade of (*S*)-acid-ester **29**, via isolation of the quinidine salt from the reaction mixture, was not possible. A breakthrough was achieved, however, when it was discovered that crystallization of acid-ester **29** from aqueous HCl, during a salt-break of the quinidine salt (62% de), was accompanied by an upgrade in enantiopurity to >96% ee.[47] Using this procedure, (*S*)-acid-ester **29** was obtained in typical yields of 60−64%.

SCHEME 12



With a route to both enantiomers of the acid-ester in place, we wished to compare the formation and subsequent coupling performance of β-ketophosphonate **31**[48] and phosphorane **34**. The desired phosphonate was prepared by reaction of acid-ester *ent*-**29** with 4 equiv of lithiated diisopropyl methylphosphonate, followed by esterification of the resulting acid (Scheme 11).[49] The fairly disappointing yield (46%) initially obtained for the first step was significantly improved by transmetalation of the lithiated phosphonate with $MgBr_2$ prior to reaction with *ent*-**29**. Phosphorane **34** was in turn prepared from (*S*)-acid-ester **29** via activation of the acid moiety and subsequent reaction with methylenetriphenylphosphorane. After examining several methods for activating acid-ester **29**,[50] it was found that the best yields of phosphorane **34** were obtained via either isobutoxy anhydride **32** or *tert*-butyl mixed anhydride **33**. Although comparable yields (65−73%) of **34** were obtained using either of these methods, mixed anhydride **33** was found to be more stable and easier to handle.

Completing the Synthesis of 1. With both phosphonate **31** and phosphorane **34** in hand, a comparison of the Wittig and Horner−Wadsworth−Emmons couplings revealed that the reaction of phosphorane **34** with aldehyde **24** occurred in significantly higher yield than the corresponding coupling using phosphonate **31** (Scheme 12). Thus, heating a solution of aldehyde **24** and phosphorane **34** to 80 °C afforded a 90% yield of desired enone

(44) Use of cinchona alkaloids for desymmetrization of meso and prochiral cyclic anhydrides has been documented in the following publications: (a) Hiratake, J.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1717−1719. (b) Hiratake, J.; Inagaki, M.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1053−1058. (c) Aitken, R. A.; Gopal, J.; Hirst, J. A. *J. Chem. Soc., Chem. Commun.* **1988**, 632−634. (d) Aitken, R. A.; Gopal, J. *Tetrahedron: Asymmetry* **1990**, 1, 517−520. (e) Shimizu, M.; Matsukawa, K.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2128−2130. (f) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793−8794. (g) Mittendorf, J.; Benet-Buchholz, J.; Fey, P.; Mohrs, K.-H. *Synthesis* **2003**, 136−140.

(45) (a) Bolm, C.; Gerlach, A.; Dinter, C. L. *Synlett* **1999**, 195−196. (b) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984−6991.

(46) Methanolysis of **25** in the presence of cinchonine or cinchonidine occurred with poor enantioselectivity (<23% ee) under all conditions examined.

(47) A more detailed study of this crystallization, and the different crystal morphologies of acid-ester **29**, revealed that the crystal form of **29** isolated from this ee upgrade was not the most thermodynamically stable form. The observation that extended aging (>6 h) occasionally led to isolation of material with much lower ee (<70%) also supports this conclusion.

(48) The diisopropyl phosphonate was prepared in place of the more commonly used dimethyl analogue due to isolation problems associated with the high water solubility of the intermediate acid in the latter case.

(49) For analogous preparations of β-ketophosphonates from 3-substituted glutaric acid monomethyl esters, see: (a) Karanewsky, D. S.; Malley, M. F.; Gougoutas, J. Z. *J. Org. Chem.* **1991**, *56*, 3744−3747. (b) Konoike, T.; Araki, Y. *J. Org. Chem.* **1994**, *59*, 7849−7854.

(50) Preparation of phosphorane **34** via the acid chloride, imidazolide, or Weinreb amide of **29** resulted in significantly lower yields.

35, whereas deprotonation of phosphonate **31**, using KHMDS, and reaction with aldehyde **24** provided the same product in only 53% yield. A further advantage of the Wittig route is that, unlike phosphonate **31**, which is an oil, phosphorane **34** can be conveniently purified by crystallization. Typically, the Wittig reaction was run in 2-propanol, and the resulting crude reaction mixture, containing enone **35**, was hydrogenated directly to afford keto-ester **36**, in overall assay yields of 81−88%. Crude **36** was then hydrolyzed to keto-acid **37**, which was isolated, in 70% overall yield, via crystallization. Finally, removal of the Boc group provided enantiomerically pure (>99% ee) zwitterionic **1** in typical yields of 74−81%.

Conclusions

In summary, $\alpha_v\beta_3$ antagonist **1** has been synthesized in 17% yield, over the longest linear sequence, via a scalable and highly convergent route. Highlights of this synthesis include a one-pot alkylation/cyclization to construct the seven-membered ring of the pyrido[2,3-*b*]-azepine moiety, highly efficient Suzuki coupling to attach the propionaldehyde side-chain, and enantioselective desymmetrization of a 3-substituted glutaric anhydride to set the sole chiral center.

Experimental Section

***tert*-Butyl *N*-(6-Chloropyridin-2-yl)carbamate (19).** Hexyllithium (34.6 L, 2.5 M in hexanes, 86.5 mol) was slowly added, over 2 h, to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (13.9 kg, 86.1 mol) in THF (50 L) at −5 °C. A solution of 2-amino-6-chloropyridine (**16**) (5.00 kg, 38.9 mol) in THF (10 L), followed by a solution of di-*tert*-butyl dicarbonate (8.63 kg, 39.5 mol) in THF (6.7 L), were then added, ensuring the internal temperature remained below 0 °C. The resulting reaction mixture was aged for 30 min at room temperature and then carefully acidified to pH 3 by addition of 1 M hydrochloric acid (168 L, 168 mol). The two layers were separated, and the aqueous phase was extracted with ^{i}PrOAc (50 L). The combined organic layers were then washed sequentially with 4% aqueous $NaHCO_3$ (50 L) and water (50 L). The resulting organic layer was concentrated to 20 L under reduced pressure and then solvent switched to 2-propanol (20 L). The solvent switch was carried out by adding 65 L of 2-propanol to the batch, concentrating in vacuo to 24 L, adding a second portion of 2-propanol (50 L), and then concentrating to a final volume of 20 L. Product had begun to crystallize from solution by this point, and water (10 L) was then slowly added to the stirred slurry. Once the addition was complete, the slurry was cooled to 5 °C and the solid was isolated by filtration, washing the wet-cake first with cold 2-propanol/water (9.8 L/7.3 L) and then water (10 L). Drying under vacuum at 40 °C furnished *N*-Boc aminopyridine **19** (8.09 kg, 91%) as a white solid: mp 87.5−89 °C (lit.[17] 88−89.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.2 Hz, 1H), 7.61 (dd, J = 8.2, 7.7 Hz, 1H), 7.25 (br s, 1H), 6.98 (d, J = 7.7 Hz, 1H), 1.52 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1, 152.0, 149.2, 140.8, 118.5, 110.4, 81.7, 28.4. Anal. Calcd for $C_{10}H_{13}ClN_2O_2$: C, 52.52; H, 5.73; N, 12.25. Found: C, 52.44; H, 5.70; N, 12.21.

***tert*-Butyl 2-Chloro-5,6,7,8-tetrahydro-9*H*-pyrido[2,3-*b*]azepine-9-carboxylate (20).** Hexyllithium (20.0 L, 2.5 M solution in hexanes, 50.0 mol) was added, over a period of 35 min, to a stirred solution of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (5.85 kg, 50.3 mol) in THF (54.5 L) at −20 °C. The resulting yellow solution was aged for 30 min at this temperature, cooled to −78 °C, and a solution of *N*-Boc aminopyridine **19** (5.23 kg, 22.9 mol) in THF (24 L) was then added over 45 min, maintaining the temperature below −65 °C. The resulting red-brown dianion solution was aged for 1 h at −70 °C, and a solution of 1-chloro-4-iodobutane (7.57 kg, 34.7 mol) in THF (5 L) was then added over 35 min, once again keeping the temperature below −65 °C. Upon completion of the addition, the reaction was left to gradually warm to room temperature overnight and then heated to reflux for 9 h. The resulting solution was cooled to 60 °C and washed with water (54.5 L), while maintaining the internal temperature at >40 °C. The aqueous layer was back-extracted with ^{i}PrOAc (54.5 L), and the combined organic layers were then washed with water (27 L). The resulting organic solution was concentrated in vacuo to a volume of 26 L and then solvent switched to heptane (26 L). Product crystallized from solution during this solvent switch, and the slurry obtained was cooled to 5 °C and aged for 1 h. The solid was then isolated by filtration, washing the wet-cake with cold heptane (10 L). Drying under vacuum at 40 °C afforded pyridoazepine **20** (5.05 kg, 78%) as a white solid: mp 164.5−167.5 °C; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.52 (d, J = 7.9 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 3.9−3.1 (br, 2H), 2.70 (dd, J = 6.4, 5.0 Hz, 2H), 1.84−1.78 (m, 2H), 1.71−1.58 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 155.9, 154.1, 147.5, 141.8, 134.1, 123.0, 80.9, 47.3, 33.3, 29.9, 28.6, 26.2. Anal. Calcd for $C_{14}H_{19}ClN_2O_2$: C, 59.47; H, 6.77; N, 9.91. Found: C, 59.44; H, 6.78; N, 9.86.

***tert*-Butyl 2-(3-Oxopropyl)-5,6,7,8-tetrahydro-9*H*-pyrido[2,3-*b*]azepine-9-carboxylate (24).** A stirred slurry of pyridoazepine **20** (3.32 kg, 11.7 mol), potassium carbonate (3.25 kg, 23.5 mol), palladium(II) acetate (132 g, 0.59 mol), and 1,1′-bis(diphenylphosphino)ferrocene (326 g, 0.59 mol) in THF (16.5 L) was degassed and then put under an atmosphere of nitrogen. A solution of borane **22** in THF [prepared by adding acrolein diethyl acetal (3.51 kg, 27.0 mol) to 9-BBN (57.4 L, 0.41 M in THF, 23.5 mol) at 0 °C and then stirring at room temperature for 5 h] was then added, and the resulting reaction mixture was heated to reflux for 26 h. After cooling to 20 °C, water (66 L) was added and the mixture was stirred for 30 min. The two layers were allowed to settle, and the lower aqueous phase was discarded. ^{i}PrOAc (10 L) was then added, and, after the mixture was stirred for 5 min and allowed to settle, the aqueous phase was again discarded. The resulting organic layer was concentrated, under reduced pressure, to minimum volume and then diluted with ^{i}PrOAc (33 L). Once again, the lower aqueous phase was discarded and the remaining organic layer was concentrated to 10 L and then diluted with ^{i}PrOAc (23 L). The solution obtained was cooled to 0 °C, and pre-cooled (0 °C) 2 M hydrochloric acid (23.3 L, 46.6 mol) was then added. This biphasic mixture was stirred at 0 °C for 4 h, and the two layers were then separated. The aqueous phase was filtered, cooled to 5 °C, and ^{i}PrOAc (16.5 L) was added. The resulting mixture was adjusted to pH 8 by addition of 10% aqueous K_2CO_3 (55 L), and once again the two layers were separated. The aqueous phase was extracted twice with ^{i}PrOAc (2 × 16.5 L), and the combined organic layers were then washed with water (8.3 L). The resulting ^{i}PrOAc solution was solvent switched, under reduced pressure, to 2-propanol (15 L), and this crude solution of aldehyde **24** (3.08 kg, based on HPLC assay) was used in the Wittig reaction directly. HPLC conditions: 250 × 4.6 mm Zorbax RX-C8 column; UV detection at 210 nm; gradient elution with 0.1% phosphoric acid/acetonitrile from 90:10 to 10:90 over 20 min then 10:90 isocratic elution for 5 min; 1.0 mL/min; 35 °C. Retention time for aldehyde **24** = 9.1 min.

Characterization data for an isolated sample of **24**: ^{1}H NMR (250 MHz, CD_2Cl_2) δ 9.82 (t, J = 1.3 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 3.9−3.1 (br, 2H), 3.08−3.00 (m, 2H), 2.92−2.83 (m, 2H), 2.67 (dd, J = 6.3, 5.0 Hz, 2H), 1.86−1.74 (m, 2H), 1.74−1.54 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (63 MHz, CD_2Cl_2) δ 202.1, 157.4, 155.4, 154.1, 139.3, 132.4, 121.7, 80.0, 47.0, 43.1, 33.5, 30.1, 29.9, 28.4, 26.4.

2-Methoxypyrimidine-5-carbaldehyde (28). To a stirred slurry of *O*-methylisourea sulfate (30.4 g, 247 mmol) and vinamidinium salt **27** (90 g, 70 wt % pure, 248 mmol) in ^{i}-

PrOAc (475 mL) was added a solution of $KHCO_3$ (35.0 g, 350 mmol) in water (140 mL) over a 10 min period. Once the addition was complete, the resulting reaction mixture was stirred at room temperature for 40 h and then diluted with water (195 mL). The biphasic mixture was allowed to settle, the two layers were separated, and the aqueous phase was extracted twice with ^{i}PrOAc (2 × 500 mL). The combined ^{i}PrOAc layers were concentrated under reduced pressure (keeping temperature below 40 °C) to a volume of 500 mL and then solvent switched to heptane (500 mL). The resulting slurry was cooled to −8 °C, aged for 1 h, and the solid was then isolated by filtration, washing the wet-cake with pre-cooled heptane (360 mL). Drying under vacuum at 30 °C afforded aldehyde **28** (31.8 g, 93%) as an off-white solid: mp 94−96 °C (lit.[33a] 89−90 °C); ^{1}H NMR (250 MHz, CD_2Cl_2) δ 9.99 (s, 1H), 8.96 (s, 2H), 4.09 (s, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 188.3, 168.2, 161.9, 124.8, 56.2. Anal. Calcd for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.94; H, 4.32; N, 20.10.

3-(2-Methoxypyrimidin-5-yl)pentanedioic Acid (26). To a stirred slurry of aldehyde **28** (9.00 kg, 65.2 mol) in 2-propanol (80 L) was added ethyl acetoacetate (17.8 kg, 136.8 mol). A solution of piperidine (0.56 kg, 6.6 mol) in 2-propanol (10 L) was then added, and the resulting solution was warmed to 50 °C. After being stirred at this temperature for 3.5 h, the reaction mixture was cooled to 0 °C and aqueous NaOH (24.2 kg of 46% w/w aqueous NaOH in 30 L of water, 278.3 mol) was slowly added over a period of 1 h. Once the addition was complete, the reaction mixture was warmed to 23 °C and stirred for 3 h. The resulting biphasic mixture was allowed to settle, the two layers were separated, and the lower aqueous phase was then diluted with saturated aqueous sodium chloride (10.6 kg NaCl in 30 L of water). This aqueous solution was cooled to 0 °C and then acidified, to a pH of 2−3, by careful addition of concentrated hydrochloric acid (19.6 L, 228.3 mol). The resulting slurry was stirred overnight at ambient temperature and then cooled to 5 °C. After aging at this temperature for 1 h, the solid was collected by filtration, washing the wet-cake with water (23 L). Drying under vacuum at 40 °C afforded diacid **26** (12.7 kg, 81%) as a white solid: mp 177−177.5 °C; ^{1}H NMR (250 MHz, CD_3OD) δ 8.52 (s, 2H), 3.98 (s, 3H), 3.54 (tt, J = 9.1, 6.1 Hz, 1H), 2.82 (dd, J = 16.3, 6.1 Hz, 2H), 2.68 (dd, J = 16.2, 9.1 Hz, 2H); ^{13}C NMR (63 MHz, CD_3OD) δ 174.9, 165.9, 160.2, 131.4, 55.6, 40.5, 34.6. Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 49.94; H, 4.95; N, 11.64.

4-(2-Methoxypyrimidin-5-yl)dihydropyran-2,6-dione (25). To a stirred slurry of diacid **26** (11.5 kg, 47.9 mol) in THF (58 L) was slowly added trifluoroacetic anhydride (12.1 kg, 57.6 mol) over a period of 40 min. The resulting reaction mixture was heated to 55 °C, stirred at this temperature for 80 min, and then cooled to 50 °C. Heptane (195 L) was then slowly added over a period of 90 min, during which the temperature of the batch dropped to 30 °C. The resulting stirred slurry was allowed to cool to 23 °C overnight, and the solid was then collected by filtration, washing the wet-cake with 2:1 heptane/THF (51 L). Drying under vacuum at 35 °C afforded anhydride **25** (9.95 kg, 94%) as a beige solid: mp 150.5−152.5 °C; ^{1}H NMR (250 MHz, CD_2Cl_2) δ 8.42 (s, 2H), 3.99 (s, 3H), 3.44 (tt, J = 11.9, 4.4 Hz, 1H), 3.13 (dd, J = 17.3, 4.4 Hz, 2H), 2.87 (dd, J = 17.3, 11.9 Hz, 2H); ^{13}C NMR (63 MHz, CD_2Cl_2) δ 166.0, 165.6, 158.2, 126.3, 55.6, 37.0, 30.0. Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.85; H, 4.55; N, 12.43.

(3*S*)-5-Methoxy-3-(2-methoxypyrimidin-5-yl)-5-oxopentanoic Acid (29). Toluene (180 L) was charged to a vessel containing anhydride **25** (9.0 kg, 40.5 mol) and quinidine (13.15 kg, 40.5 mol) under a nitrogen atmosphere. The resulting slurry was cooled, with stirring, to −40 °C. Methanol (16.4 L, 406 mol), which had been pre-cooled to approximately 5 °C, was then added over 15 min. The internal temperature of the reaction mixture had risen to −35 °C by this point, and the slurry was then stirred at this temperature for 8 h before allowing it to gradually warm to 20 °C overnight. The resulting clear yellow solution was extracted twice with water (2 × 60 L), and the combined aqueous extracts (pH = 5.8) were returned to the empty vessel, rinsing it with water (12 L). To this aqueous solution, concentrated hydrochloric acid (3.39 L, 39.5 mol) was added (pH after addition = 3.8). After the mixture aged for 5 min, (*S*)-acid-ester seed (45 g, 0.18 mol) was added and stirring was continued for a further 10 min. A second portion of concentrated hydrochloric acid (3.39 L, 39.5 mol) was then added, and acid-ester began to crystallize from solution (pH of solution = 1.9). The resulting stirred slurry, which had warmed to 30 °C during acidification, was slowly cooled to 20 °C over 1.5 h and then aged at this temperature for 2.5 h. The solid was collected by filtration, washing the wet-cake with water (24 L). Drying under vacuum at 35 °C afforded the title compound (6.54 kg, 63%) as a white solid. The enantiomeric excess of this product was determined as 97.8% by chiral stationary phase HPLC (250 × 4.6 mm Chirobiotic T column; UV detection at 274 nm; isocratic elution with 80:20 aqueous Et_3N (0.036 M)−AcOH (0.044 M)/methanol for 20 min; 0.5 mL/min; 25 °C. Retention times: (*R*)-acid ester *ent*-**29** = 10.5 min; (*S*)-acid ester **29** = 11.4 min): mp 143.5−145.5 °C; $[\alpha]^{20}_D$ +12.9 (*c* 2.0 in MeOH); ^{1}H NMR (250 MHz, CD_3OD) δ 8.51 (s, 2H), 3.98 (s, 3H), 3.59 (s, 3H), 3.55 (tt, J = 9.0, 6.2 Hz, 1H), 2.86 (dd, J = 16.2, 6.1 Hz, 1H), 2.81 (dd, J = 16.3, 6.2 Hz, 1H), 2.73 (dd, J = 16.2, 9.0 Hz, 1H), 2.67 (dd, J = 16.3, 9.0 Hz, 1H); ^{13}C NMR (63 MHz, CD_3OD) δ 174.8, 173.5, 165.9, 160.2, 131.3, 55.6, 52.3, 40.4, 40.4, 34.6. Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 51.99; H, 5.49; N, 10.81.

Methyl (3*S*)-3-(2-Methoxypyrimidin-5-yl)-5-oxo-6-(triphenylphosphoranylidene)hexanoate (34). A stirred suspension of methyltriphenylphosphonium bromide (18.2 kg, 51.0 mol) in THF (82 L) was cooled to −60 °C. Hexyllithium (20.6 L, 2.4 M in hexanes, 49.4 mol) was then slowly added over a period of 30 min, keeping the internal temperature below −10 °C. Once the addition was complete, the batch was aged at 0 °C for 90 min and then cooled to −80 °C.

In a second vessel, triethylamine (2.37 L, 17.0 mol) was added, over a period of 30 min, to a stirred slurry of acid-ester **29** (4.38 kg, 16.7 mol) and trimethylacetyl chloride (2.06 kg, 17.1 mol) in THF (34 L) at −5 °C. The resulting reaction mixture was aged at −5 to 0 °C for 30 min and then added, over a period of 40 min, to the cooled (−80 °C) ylide mixture prepared above. The resulting batch was aged for 40 min at −70 °C and then quenched into aqueous potassium dihydrogenphosphate (1.20 kg of KH_2PO_4 in 64 L of water, 8.8 mol), keeping the temperature of the quenched mixture between 0 and 10 °C. Once the quench was complete, the batch was extracted twice with ^{i}PrOAc (2 × 85 L) and the combined extracts were washed with half-saturated aqueous NaCl (2 × 38 L). The resulting organic layer was concentrated under reduced pressure to a volume of 25 L, diluted with ^{i}PrOAc (34 L), and then concentrated again to 25 L. Crystallization of the product had occurred during this distillation, and, after cooling to 0 °C, the solid was collected by filtration, washing the wet-cake with *tert*-butyl methyl ether (10.5 L). Drying under vacuum at 30 °C afforded phosphorane **34** (6.28 kg, 71%) as a cream-colored solid: mp 149.0−151.5 °C; $[\alpha]^{20}_D$ −85.9 (*c* 2.0 in MeOH); ^{1}H NMR (250 MHz, CD_2Cl_2) δ 8.42 (s, 2H), 7.61−7.38 (m, 15H), 3.97 (s, 3H), 3.72−3.55 (m, 2H), 3.56 (s, 3H), 2.79 (dd, J = 15.7, 5.9 Hz, 1H), 2.65−2.54 (m, 3H); ^{13}C NMR (63 MHz, CD_2Cl_2) δ 189.3 (d, J = 2 Hz), 172.4, 165.0, 159.1, 133.3 (d, J = 10 Hz), 132.5 (d, J = 3 Hz), 130.6, 129.1 (d, J = 12 Hz), 127.3 (d, J = 91 Hz), 55.0, 53.2 (d, J = 107 Hz), 51.8, 46.8 (d, J = 16 Hz), 40.7, 34.8. Anal. Calcd for $C_{30}H_{29}N_2O_4P$: C, 70.30; H, 5.70; N, 5.47. Found: C, 70.06; H, 5.71; N, 5.23.

***tert*-Butyl 2-[(7*S*)-9-Methoxy-7-(2-methoxypyrimidin-5-yl)-5,9-dioxononyl]-5,6,7,8-tetrahydro-9*H*-pyrido[2,3-*b*]-azepine-9-carboxylate (36).** To the previously prepared solution of aldehyde **24** (3.02 kg, 9.92 mol, based on HPLC assay) in 2-propanol (~15 L) was added phosphorane **34** (4.84

kg, 9.44 mol). The slurry obtained was degassed, put under an atmosphere of nitrogen, and then heated to reflux. After being stirred at reflux for 12 h, the resulting solution of crude enone **35** was allowed to cool to room temperature and then used in the following hydrogenation step directly.

To the crude solution of enone **35** in 2-propanol, prepared above, was added a slurry of wet (58% H_2O) 10% palladium on carbon (1.27 kg) in 2-propanol (25 L). The resulting reaction mixture was degassed, and the vessel was filled with hydrogen to a pressure of 2.8 bar gauge.[51] The reaction mixture was then stirred under this pressure of hydrogen for 2 h. Upon completion of the reaction, the vessel was degassed and put under an atmosphere of nitrogen. The reaction mixture was then filtered, washing the catalyst with 2-propanol (4 × 15 L), and the resulting solution was concentrated under reduced pressure to ~20 L. This crude solution of keto-ester **36** (4.50 kg, based on HPLC assay) was used directly in the subsequent hydrolysis step. HPLC conditions: 250 × 4.6 mm Phenomenex Luna C8(2) 5 μm column; UV detection at 210 nm; gradient elution with aqueous $CH_3(CH_2)_5SO_3Na$ (0.01 M)−KH_2PO_4 (0.025 M)/acetonitrile from 60:40 to 35:65 over 30 min; 1.0 mL/min; 25 °C. Retention time for keto-ester **36** = 19.0 min.

An analytical sample of **36** was obtained, as a colorless oil, by flash column chromatography (EtOAc): ^{1}H NMR (250 MHz, CD_2Cl_2) δ 8.37 (s, 2H), 7.44 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 3.93 (s, 3H), 3.7−3.0 (br, 2H), 3.66−3.52 (m, 1H), 3.57 (s, 3H), 2.91−2.62 (m, 7H), 2.56 (dd, J = 15.9, 8.7 Hz, 1H), 2.48−2.26 (m, 2H), 1.86−1.48 (m, 8H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 208.3, 172.0, 165.4, 159.5, 159.0, 155.6, 154.3, 139.3, 132.2, 130.2, 121.6, 80.1, 55.2, 52.1, 48.1, 47.3, 43.5, 40.2, 37.8, 33.7, 32.2, 30.1, 29.7, 28.6, 26.7, 23.7.

(3*S*)-9-[9-(*tert*-Butoxycarbonyl)-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]azepin-2-yl]-3-(2-methoxypyrimidin-5-yl)-5-oxononanoic Acid (37). The crude solution of keto-ester **36** (4.50 kg, 8.32 mol, based on HPLC assay) in 2-propanol (~20 L), prepared above, was cooled to 0 °C. 2 M aqueous sodium hydroxide (5.6 L, 11.2 mol) was added to the stirred solution over a period of 30 min, and the resulting reaction mixture was then stirred at 0 °C for 2 h. The thin slurry obtained was diluted with water (43 L), warmed to 20 °C, and then washed once with *tert*-butyl methyl ether (43 L) and twice with ^{i}PrOAc (2 × 43 L). To the resulting aqueous layer was added 2 M hydrochloric acid (0.56 L, 1.12 mol) followed by ^{i}PrOAc (43 L). This biphasic mixture was then acidified by careful addition of a second portion of 2 M hydrochloric acid (5.04 L, 10.1 mol). Once addition was complete, the two layers were separated and the aqueous phase (pH = 3.8) was extracted with ^{i}PrOAc (43 L). The two organic layers were combined, washed with water (21 L), and then treated with Ecosorb C-941 activated carbon (0.43 kg). After being stirred for 1 h, at room temperature, the mixture was filtered, washing the carbon with ^{i}PrOAc (2 × 12 L). The filtrate was concentrated, under reduced pressure, to ~20 L and then diluted with ^{i}PrOAc (40 L). Solid began to crystallize from solution at this point, and the slurry was concentrated to 20 L. Heptane (10 L) was then added over a period of 30 min at room temperature, and the slurry was left to stir over the weekend (~65 h). The resulting slurry was cooled to 0 °C and aged for 5 h at this temperature. The solid was then collected by filtration, washing the wet-cake with 2:1 ^{i}PrOAc/heptane (4.5 L). Drying under vacuum at 45 °C afforded keto-acid **37** (3.45 kg, 70% overall yield from phosphorane **34**) as a cream-colored solid. The enantiomeric excess of this product was determined as 96.6% by chiral stationary phase HPLC (150 × 4.0 mm Chromtech Chiral AGP column; UV detection at 210 nm; gradient elution with aqueous KH_2PO_4 (0.025 M)/methanol from 75:25 to 50:50 over 15 min; 0.9 mL/min; 25 °C. Retention times: (3*R*) enantiomer = 8.6 min; (3*S*) enantiomer = 10.0 min): mp 113.5−117.5 °C; $[\alpha]^{20}_D$ −2.7 (*c* 2.0 in MeOH); ^{1}H NMR (250 MHz, CD_2Cl_2) δ 8.42 (s, 2H), 8.2−7.4 (br, 1H), 7.49 (d, J = 7.6 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 4.3−2.5 (br, 2H), 3.94 (s, 3H), 3.66 (app quintet, J = 7.2 Hz, 1H), 2.96 (dd, J = 17.3, 6.8 Hz, 1H), 2.78−2.56 (m, 7H), 2.55−2.33 (m, 2H), 1.85−1.47 (m, 8H), 1.35 (s, 9H); ^{13}C NMR (63 MHz, CD_2Cl_2) δ 208.5, 173.8, 164.9, 159.2, 159.0, 154.9, 154.0, 140.1, 132.7, 130.7, 122.1, 80.4, 55.3, 48.0, 47.2, 43.1, 40.5, 36.9, 33.5, 32.2, 29.9, 29.8, 28.4, 26.4, 23.5. Anal. Calcd for $C_{28}H_{38}N_4O_6$: C, 63.86; H, 7.27; N, 10.64. Found: C, 63.75; H, 7.30; N, 10.46.

(3*S*)-3-(2-Methoxypyrimidin-5-yl)-5-oxo-9-(6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]azepin-2-yl)nonanoic Acid (1). Trifluoroacetic acid (7.36 L, 95.6 mol) was added over a period of 10 min to a solution of keto-acid **37** (3.35 kg, 6.37 mol) in DCM (17 L), maintaining the internal temperature below 30 °C. Once the addition was complete, the resulting reaction mixture was heated to 30 °C. After stirring at this temperature for 2 h, the solution was cooled to 20 °C, and precooled (5 °C) 2 M aqueous NaOH (56.5 L, 113 mol) was carefully added over a period of 20 min. The two layers were then separated, and the aqueous phase was treated with Ecosorb C-941 activated carbon (168 g). After being stirred for 1 h at room temperature, the mixture was filtered, washing the carbon with water (2.4 L). The resulting filtrate was then acidified to pH 6.0 by careful addition of concentrated hydrochloric acid (1.47 L, 17.1 mol), keeping the internal temperature below 20 °C. Once the addition was complete, the mixture was extracted twice with DCM (2 × 33.5 L). The combined organic layers were washed with water (11.3 L) and then solvent switched, using partial vacuum at 40 °C, to 2-propanol (15 L). With the resulting 2-propanol solution still at 40 °C, a small amount of **1** (14.5 g) was added as seed. The batch was then left to stir at this temperature for 12 h. By this point, solid had begun to crystallize from solution and the slurry was allowed to gradually cool to 20 °C overnight. The solid was then collected by filtration, washing the wet-cake with 2-propanol (3 × 3.3 L). Drying under vacuum at 40 °C afforded **1** (2.07 kg, 76%) as a white solid. The enantiomeric excess of this product was determined as 99.4% by chiral stationary phase HPLC (150 × 4.0 mm Chromtech Chiral AGP column; UV detection at 245 nm; gradient elution with 1% triethylamine phosphate$_{(aq)}$/10% IPA in 1% triethylamine phosphate$_{(aq)}$ from 100:0 to 90:10 over 5 min and then to 50:50 over the next 10 min; 0.9 mL/min; 25 °C. Retention times: (3*S*) enantiomer = 6.5 min; (3*R*) enantiomer = 10.0 min): mp 105.5−108.5 °C; $[\alpha]^{20}_D$ −17.1 (*c* 2.0 in MeOH); ^{1}H NMR (250 MHz, CD_2Cl_2) δ 8.41 (s, 2H), 7.25 (d, J = 7.4 Hz, 1H), 6.34 (d, J = 7.3 Hz, 1H), 3.91 (s, 3H), 3.72−3.59 (m, 1H), 3.35−3.27 (m, 2H), 2.97 (dd, J = 16.5, 7.0 Hz, 1H), 2.78−2.41 (m, 9H), 1.91−1.77 (m, 4H), 1.66−1.46 (m, 4H); ^{13}C NMR (63 MHz, CD_2Cl_2) δ 208.4, 177.9, 164.9, 158.5, 158.3, 151.9, 143.0, 132.6, 124.5, 111.5, 55.0, 49.5, 43.5, 42.9, 40.5, 33.1, 32.0, 31.4, 29.0, 28.6, 25.5, 22.3. Anal. Calcd for $C_{23}H_{30}N_4O_4$: C, 64.77; H, 7.09; N, 13.14. Found: C, 64.50; H, 7.07; N, 13.04.

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Supporting Information Available: Experimental procedures and characterization data for compounds **5**, **7**, **9**, **10**, **15**, **17**, **21**, *ent*-**29**, **30**, **31**, and **35**. Alternative procedures for the preparation of **34**. ^{1}H NMR spectra of compounds **5** and **9**. ^{1}H and ^{13}C NMR spectra of compounds **7**, **10**, **24**, **30**, **31**, **35**, and **36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(51) Gauge denotes that the pressure is measured with respect to ambient pressure.