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## Total Syntheses of (–)-Pyrimidoblamic Acid and P-3A

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### Abstract

Total syntheses of (–)-pyrimidoblamic acid and P-3A are disclosed. Central to the convergent approach is a powerful inverse electron demand Diels–Alder reaction between substituted electron-deficient 1,2,3-triazines and a highly functionalized and chiral primary amidine, which forms the pyrimidine cores and introduces all necessary stereochemistry in a single step. Intrinsic in the convergent approach is the potential it provides for the late stage divergent synthesis of modified analogs bearing deep-seated changes in either the pyrimidine cores or the highly functionalized C2 side chain common to both natural products. The examination of the key cycloaddition reaction revealed that the inherent 1,2,3-triazine mode of cycloaddition (C4/N1 vs C5/N2) as well as the amidine regioselectivity were unaffected by introduction of two electron-withdrawing groups (–CO<sub>2</sub>R) at C4 and C6 of the 1,2,3-triazine even if C5 is unsubstituted (Me or H), highlighting the synthetic potential of the powerful pyrimidine synthesis.

### Introduction

Bleomycin A<sub>2</sub> (BLM, **1**, Figure 1) is the major component (~70%) of the clinical anticancer drug Bleomoxane, which is currently used for the treatment of Hodgkin’s lymphoma, melanomas, head and neck carcinomas, and testicular cancers.<sup>1–4</sup> BLM exerts its biological effects through a metal ion and oxygen dependent<sup>5–19</sup> DNA cleavage that occurs selectively at 5′-GC or 5′-GT sites.<sup>4, 7, 12, 15, 20–25</sup> Although capable of producing single-strand and double-strand breaks, the latter is believed to be the most biologically relevant event.<sup>26</sup> Despite being an effective therapy for numerous malignancies, BLM treatment is often limited by dose-dependent pneumonitis, lung fibrosis, and skin toxicities, some of which have been attributed to the C-terminal bithiazole appendage.<sup>2–3, 27–28</sup> Thus, there remains an interest in identifying synthetic BLM-based analogs that lack off-target toxicity and maintain efficacy, which can be used as single component oncology drugs.

Each structural unit of BLM contributes an important role in the DNA binding and cleavage cascade. Systematic evaluation of its structure through single site deep-seated modifications prepared by total synthesis has delineated the function of each subunit and the role of their individual substituents.<sup>1, 21, 29–74</sup> These studies, in conjunction with NMR-derived structural models of DNA bound BLM,<sup>75–83</sup> continue to define the remarkable combination of functional, structural, and conformational properties integrated into the natural product. The pyrimidoblamic acid subunit not only participates in the metal chelation and O<sub>2</sub> activation, but it is also responsible for the DNA cleavage selectivity via triplex-like hydrogen bonding to guanine at the 5′-GC and 5′-GT cleavage sites.<sup>76</sup> In such studies, we have additionally

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Supporting Information

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shown that removal of the pyrimidine C5 methyl group, enlisting the functionalized pyrimidine found in P-3A, has no impact in the functional activity of the resulting BLM analog.<sup>56</sup> From these studies, (–)-pyrimidoblamic acid (**2**, Figure 2) and the related peptide-derived natural product, P-3A (**3**, Figure 2), have been identified as key subunits for the continued preparation of improved or simplified bleomycin analogs. Total syntheses of (–)-pyrimidoblamic acid were originally described by Umezawa<sup>32, 42</sup> and Hecht<sup>30, 50</sup> and later by us.<sup>60, 64</sup> While elegant and pioneering in their own regards, these previous efforts have suffered from the inability to fully control the stereochemistry at the benzylic pyrimidine C2 tertiary center (Scheme 1). Similarly, our initial total synthesis of P-3A, whose pyrimidine core differs from that of pyrimidoblamic acid by only the lack of the C5 methyl group, relied on a late stage diastereoselective introduction of the benzylic pyrimidine C2 tertiary center that proceeded with modest diastereoselectivity (87:13).<sup>59, 66</sup>

Recently, we defined the cycloaddition scope and productive reactivity of substituted electron-deficient 1,2,3-triazines with various dienophiles, including the first report of their ability to participate in previously unexplored [4+2] cycloaddition reactions with amidine or imidate heterodienophiles to provide highly substituted pyrimidines.<sup>84–85</sup> These latter studies provided the basis for the potential development of second generation asymmetric total syntheses of (–)-pyrimidoblamic acid and P-3A in which all necessary stereochemistry is installed prior to a late stage [4+2] cycloaddition introduction of the pyrimidine, addressing the common limitation of previously reported routes, permitting the late stage divergent modification of their structures, and further expanding the scope of the 1,2,3-triazine inverse electron demand Diels–Alder reaction to encompass the use of chiral amidines.

We envisioned that the pyrimidine core of (–)-pyrimidoblamic acid would arise from an inverse electron demand Diels–Alder reaction between the highly functionalized amidine **4** and 1,2,3-triazine **5a** (Scheme 2). Additionally, the same amidine **4** and its cycloaddition with 1,2,3-triazine **5b** would produce the pyrimidine core found in P-3A. This late stage convergent assemblage of the pyrimidine cores not only allows the early stage synthesis of the stereochemically rich C2 side chain common to both pyrimidoblamic acid and P-3A, but it also permits the late stage divergent synthesis of the natural products utilizing two different 1,2,3-triazines. Amidine **4** was expected to arise from the reductive alkylation product of N-(triphenylmethyl)-L-asparagine (**6**) with aldehyde **7**. Key to the construction of **4** is the manipulation of intermediates, especially the desired free-based amidine, without sacrificing the stereochemical integrity of the  $\alpha$ -stereocenter, as similar amidines have demonstrated a propensity to epimerize.<sup>86–87</sup> This concern dictated the late stage amidine introduction in order to minimize the potential impact of amidine epimerization. 1,2,3-Triazines **5a** and **5b**, the electron-deficient heterocyclic azadienes for use in the key cycloaddition reaction, were anticipated to arise from an oxidative ring expansion of N-aminopyrazoles **9a** and **9b**.<sup>88–91</sup> A key caveat to the approach is that although the two electron-withdrawing substituents on the 1,2,3-triazines would be expected to enhance their cycloaddition reactivity, it was unknown whether their placement at the C4 and C6 positions would sterically slow the reaction and electronically redirect the mode of cycloaddition (C4/N1 vs C5/N2) with amidines.

## Results and Discussion

### Synthesis of 1,2,3-triazines **5a** and **5b**

The requisite N-aminopyrazole **9a** for oxidative ring expansion to the 1,2,3-triazine **5a** was prepared from **8a** that was accessed by a palladium-mediated tandem cross-coupling/electrocyclization reaction of commercially available ethyl diazoacetate and the vinyl triflate derived from *t*-butyl acetoacetate (Scheme 3).<sup>92</sup> N-Amination of **8a** was accomplished upon

treatment with *O*-4-nitrobenzoylhydroxylamine in the presence of potassium *t*-butoxide (*t*-BuOK) in *N*-methylpyrrolidone (NMP), which yielded *N*-aminopyrazole **9a** in 73% yield in a near 1:1 mixture of inconsequential regioisomers.<sup>93</sup> In an analogous fashion and with similar yield (72%), the requisite *N*-aminopyrazole **9b** used to access 1,2,3-triazine **5b** was prepared from pyrazole **8b**, which was generated from a [3+2] dipolar cycloaddition between ethyl diazoacetate and *t*-butyl propiolate.<sup>94</sup>

Although a range of oxidants have been reported for transforming *N*-aminopyrazoles into 1,2,3-triazines, we have found that the optimal reagent for this oxidative ring expansion reaction is substrate dependent. The ring expansion is often suggested to occur through a nitrene intermediate, which initiates N–N bond migration and inserts the central nitrogen of the 1,2,3-triazine.<sup>90</sup> Adaptation of conditions developed by Ohsawa and colleagues, in which an *N*-aminopyrazole is treated with iodine (I<sub>2</sub>) in the presence of aqueous potassium bicarbonate (KHCO<sub>3</sub>), provided the 1,2,3-triazine **5a** in excellent yield (75%).<sup>91</sup> These conditions also proved effective for the production of **5b**, yielding the 1,2,3-triazine in 68% yield. Notably, 1,2,3-triazines **5a** and **5b** proved stable to extended storage at room temperature and purification by flash chromatography using silica gel. As summarized in Figure 3, the most commonly used oxidants for this transformation (i.e., Pb(OAc)<sub>4</sub>, Ni<sub>2</sub>O<sub>3</sub> and MnO<sub>2</sub>)<sup>88–91</sup> proved unsuccessful in converting **9a** to the desired 1,2,3-triazine **5a**, instead resulting in N–N bond cleavage and reversion to the starting pyrazole **8a**.

Silver(I) nitrate, a commonly utilized nitrene transfer reagent in aziridination,<sup>95–96</sup> alone failed to provide **5a**, but produced **5a** in modest yield (34%) when used in the presence of phenyliodine diacetate (PIDA) as a co-oxidant. Similarly, sodium periodate (NaIO<sub>4</sub>),<sup>84</sup> which promotes the oxidative ring expansion efficiently for 4-substituted *N*-aminopyrazoles, afforded the 1,2,3-triazine **5a** in moderate yield (28%) with a majority (70%) of the material isolated being a mixture of unreacted starting material (**9a**) and free pyrazole (**8a**). Addition of a phase transfer catalyst improved the conversions to as high as 70%, but was less consistent, and the use of tetrabutylammonium periodate failed to generate any desired compound.

### Synthesis of amidine **4**

Amidine **4** was prepared from commercially available *N*-(triphenylmethyl)-*L*-asparagine (**6**) and aldehyde **7** (Scheme 4). Reductive alkylation of **6** with **7** in the presence of excess NaBH(OAc)<sub>3</sub> provided **10** in 84% yield. Treatment of **10** with 1-hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) followed by NH<sub>3</sub>/THF, provided the primary amide **11**. Dehydration of **11** to provide the nitrile **12** was accomplished by treatment with *N*-propanephosphonic acid anhydride (T3P) in the presence of Hunig's base (*i*-Pr<sub>2</sub>NEt). Treatment of **12** with 50% aqueous NH<sub>2</sub>OH cleanly afforded amidoxime **13**. All intermediates up to this stage, including **13**, exhibited a robust stability and no epimerization was observed throughout the reaction sequence. Treatment of **13** with Raney Nickel (Ra-Ni) in the presence of acetic acid (AcOH) in MeOH generated the acetate salt of the desired amidine, which could be filtered through Celite, redissolved in CH<sub>2</sub>Cl<sub>2</sub> and treated with 20% aqueous NaOH to yield the free-based amidine **4**. Chromatographic purification of the amidine **4**, as either the acetate salt or the free base, resulted in partial epimerization. As a result, the crude amidine was used without purification and produced immediately prior to its use. Notably, the free-based amidine epimerized much more readily than the protonated amidine in solution, and if the adjacent secondary amine was protected as the *t*-butylcarbamate (Boc), even more significant slow epimerization of the  $\alpha$ -stereocenter occurred upon amidine formation. Therefore, the free secondary amine is essential to the observed stereochemical stability of the adjacent amidine chiral center.

### [4+2] Cycloaddition reaction of 1,2,3-triazine **5a** with amidine **4**

Effective access to the requisite intermediates **4** and **5a** set the stage for examination of the key inverse electron demand Diels–Alder reaction. Consistent with the electron-deficient character of the 1,2,3-triazine, the cycloaddition reaction was found to proceed at room temperature or lower. Significantly, the intrinsic regioselectivity of the amidine cycloaddition and 1,2,3-triazine cycloaddition mode were unaltered by the C4/C6 substitution with electron-withdrawing groups, and the amidine was found to add exclusively across C4/N1 (C6/N3) with no evidence of a redirected C5/N2 mode of cycloaddition. By design and because of the pseudo C2 symmetric nature of the product pyrimidine, the cycloaddition across C4/N1 versus C6/N3 are indistinguishable, permitting the differential ester protection. Although not all conditions surveyed are included, Figure 4 summarizes representative examples in the optimization of the reaction between **4** and **5a** to provide the desired pyrimidine **14**. In accordance with our previous studies,<sup>84–85</sup> which utilized 2.0 equiv of amidine, the investigation began with this reaction stoichiometry. As summarized in Figure 4, an increase in reaction time and temperature significantly increases the overall yield (entries 1–4). However, increasing the reaction temperature diminished the diastereomeric purity of the product, resulting from competitive amidine epimerization. Notably, we found that the reaction produces a single diastereomer of **14** when conducted at 5 °C in acetonitrile (entry 5). Since the 1,2,3-triazine **5a** is the simpler of the two reaction components, we focused on identifying conditions that employed amidine **4** as the limiting reagent (entries 8 and 9 vs 6 and 7). When the reaction was conducted with 1.0 equiv of amidine **4** and 2.0 equiv of the 1,2,3-triazine **5a**, the yield increased to a respectable 46%. Finally, if the reaction was allowed to stir at 5 °C for 14 h and then warmed to 25 °C for 6 h, **14** was obtained as a single diastereomer in 54% yield.

### Total synthesis of (–)-pyrimidoblamic acid

With an effective route to **14** in hand, the synthesis of (–)-pyrimidoblamic acid was completed (Scheme 5). The secondary amine of **14** was protected as the *t*-butylcarbamate to provide **15** to eliminate oxidation risks later in the synthesis. Chemoselective hydrolysis of **15** with 1 M aqueous NaOH in THF:MeOH (3:1) was followed with a Curtius rearrangement to provide **16** (78% yield over two steps). Removal of the acetonide protecting group with *p*-toluenesulfonic acid monohydrate (*p*-TsOH•H<sub>2</sub>O) in MeOH yielded the Boc-protected amino alcohol **17**, which was subsequently treated with Jones' reagent to give the carboxylic acid **18**. Conversion of **18** to amide **19** was accomplished upon treatment with HOBt and EDCI followed by NH<sub>3</sub>/THF, which provided the fully functionalized and protected (–)-pyrimidoblamic acid **19** in 96% yield. Although attempts to promote a global deprotection with 4 M HCl in EtOAc proved unsuccessful, as the tritylated carboxamide exhibited an unusual stability to these traditional reaction conditions, treatment of **19** with a 3:1 mixture of trifluoroacetic acid (TFA) and CH<sub>2</sub>Cl<sub>2</sub> followed by deliberate counterion exchange with a 1 M aqueous HCl work-up provided (–)-pyrimidoblamic acid (**2**) in quantitative yield and identical in all respects with authentic material.<sup>29, 64</sup>

### Generality of the 1,2,3-triazine/amidine [4+2] cycloaddition

Although the similarity in the pyrimidine cores of (–)-pyrimidoblamic acid and P-3A is striking and may suggest that extrapolation of the approach to P-3A is straightforward, it was not clear what the impact of the C5 substituent might be. With electron-withdrawing groups at the C4- and C6-positions of **5a** and **5b**, it was still unknown whether the C5 methyl group affects the efficiency of the cycloaddition reaction of **5a** and if its absence in **5b** would alter the mode of cycloaddition. Thus, before embarking on the synthesis of P-3A, we first examined the reactions of the two 1,2,3-triazines **5a** and **5b** in parallel. Remarkably, the less substituted 1,2,3-triazine **5b** was even more reactive than **5a**, providing the product

pyrimidine at a faster rate and in a higher yield in its reaction at room temperature with the aliphatic amidine substrate where good conversion to the product was observed even within 5 min (Figure 5). Slower and a more comparable reactivity between **5a** and **5b** were observed with the aryl amidines. Most significant in these studies is the fact that **5b** showed no evidence of a potentially competitive cycloaddition across C5/N2 (vs C4/N1) despite the lack of a C5 substituent. With this knowledge in hand, the total synthesis of P-3A was pursued.

### Total synthesis of P-3A

In accordance with the model substrates, the cycloaddition reaction between **4** and **5b** (25 °C, CH<sub>3</sub>CN, 12 h) yielded the desired pyrimidine **26** in 76% yield as a single diastereomer (Scheme 6). In contrast to the reaction between **4** and **5a**, which requires 5 °C for 12 h prior to warming to 25 °C to prevent competitive epimerization and preserve the amidine stereochemical integrity, the faster reaction between **4** and **5b** can be conducted at 25 °C without compromising the diastereomeric purity of the product and provided the stereochemically pure pyrimidine **26** in even higher yield (76%).

Following a synthetic route modeled on that used to complete the synthesis of (–)-pyrimidoblamic acid, compound **26** was advanced (Scheme 6). Boc-protection of the secondary amine provided compound **27**, which was subjected to saponification of the ethyl ester. However, attempts to selectively hydrolyze the ethyl ester by treatment with 1 M aqueous NaOH in THF/MeOH provided a mixture of compounds, which included those derived from transesterification or hydrolysis of the *t*-butyl ester. By substituting *t*-butanol (*t*-BuOH) for MeOH as the reaction co-solvent the competitive reactions were avoided and the reaction cleanly provided the requisite carboxylic acid, which was subjected to Curtius rearrangement conditions to provide **28** in good yield (82% over two steps). Removal of the acetonide protecting group with *p*-TsOH·H<sub>2</sub>O in MeOH afforded the amino alcohol **29**, which could be transformed to the primary carboxamide **31** in two steps. Global deprotection of **31** was effected by treatment with TFA:CH<sub>2</sub>Cl<sub>2</sub> (3:1) to provide **32**, a key analog of (–)-pyrimidoblamic acid lacking only the C5 methyl group, in quantitative yield. Additionally, treatment of **31** with 1 M aqueous NaOH in THF:MeOH (3:1) results in *t*-butyl ester hydrolysis and provided carboxylic acid (**33**), which was coupled with N<sup>(Im)</sup>-Boc-L-His-L-Ala-O(*t*-Bu) to provide the fully assembled but protected P-3A (**34**). Notably, this coupling reaction enlisted a more highly protected derivative of **32** than our prior efforts,<sup>60, 64</sup> and proceeded more smoothly, providing higher yields of the product **34**. Global deprotection of **34** with TFA:CH<sub>2</sub>Cl<sub>2</sub> (3:1) followed by counterion exchange with a 1 M aqueous HCl work-up provided P-3A (**3**), in quantitative yield and spectroscopically identical in all comparable respects with authentic material.<sup>66, 97</sup>

### Conclusions

Convergent total syntheses of (–)-pyrimidoblamic acid and P-3A were detailed based on the early stage preparation of the chiral highly functionalized C2 side chain and subsequent late stage, divergent construction of the pyrimidine cores through use of a powerful inverse electron demand amidine/1,2,3-triazine [4+2] cycloaddition reaction conducted at 25 °C. In addition to permitting full control of the natural product stereochemistry, the approach provides the opportunity for the late stage divergent synthesis of modified analogs bearing deep-seated changes in either the pyrimidine core (C4 and C5) or the highly functionalized C2 side chain. Such investigations are in progress and will be reported in due course. The examination of the key 1,2,3-triazine cycloaddition reaction with amidines defined non-obvious 1,2,3-triazine substituent effects that maintain or enhance the heterocyclic azadiene reactivity without altering the intrinsic regioselectivity or mode of cycloaddition. These

observations with 1,2,3-triazines extend the utility of the inverse electron demand cycloaddition reactions of electron-deficient heterocyclic azadienes that includes the complementary 1,2,4- and 1,3,5-triazines,<sup>52, 98–105</sup> 1,2,4,5-tetrazines,<sup>106–113</sup> and 1,2-diazines<sup>114–115</sup> in the synthesis of highly substituted and functionalized heterocycles found in complex natural products.<sup>116–117</sup>

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

1. Umezawa H. *Pure Appl Chem.* 1971; 28:665. [PubMed: 4111413]
2. Umezawa, H.; Takita, T.; Saito, S.; Muraoka, Y.; Takahashi, K.; Ekimoto, H.; Minamide, S.; Nishikawa, K.; Fukuoka, T.; Nakatani, T.; Fujii, A.; Matsuda, A. *Bleomycin Chemotherapy.* Academic Press; Orlando, FL: 1985.
3. Mir LM, Tounekti O, Orłowski S. *Gen Pharmac.* 1996; 27:745.
4. Boger DL, Cai H. *Angew Chem Int Ed.* 1999; 38:448.
5. Ishida R, Takahashi T. *Biochem Biophys Res Commun.* 1975; 66:1432. [PubMed: 53051]
6. Sausville EA, Peisach J, Horwitz SB. *Biochem Biophys Res Commun.* 1976; 73:814. [PubMed: 64249]
7. D'Andrea AD, Haseltine WA. *Proc Natl Acad Sci USA.* 1978; 75:3608. [PubMed: 80799]
8. Sausville EA, Peisach J, Horwitz SB. *Biochemistry.* 1978; 17:2740. [PubMed: 80226]
9. Takeshita M, Grollman AP, Ohtsubo E, Ohtsubo H. *Proc Natl Acad Sci USA.* 1978; 1978:5983. [PubMed: 83650]
10. Povirk LC. *Biochem.* 1979; 18:3989. [PubMed: 90519]
11. Burger RM, Peisach J, Horwitz SB. *J Biol Chem.* 1981; 256:11636. [PubMed: 6170635]
12. Sugiura Y, Suzuki T. *J Biol Chem.* 1982; 257:10544. [PubMed: 6179942]
13. Burger RM, Kent TA, Horwitz SB, Munck E, Peisach J. *J Biol Chem.* 1983; 258:1559. [PubMed: 6185486]
14. Ehrenfeld GM, Shipley JB, Heimbrook DC, Sugiyama T, Long EC, van Boom JH, van der Marel GA, Oppenheimer NJ, Hecht SM. *Biochemistry.* 1987; 26:931. [PubMed: 2436656]
15. Kuwahara J, Sugiura Y. *Proc Natl Acad Sci USA.* 1988; 85:2459. [PubMed: 2451823]
16. Long EC, Hecht SM, van der Marel GA, van Boom JH. *J Am Chem Soc.* 1990; 112:5272.
17. Natrajan A, Hecht SM, van der Marel GA, van Boom JH. *J Am Chem Soc.* 1990; 112:3997.
18. Carter BJ, Reddy KS, Hecht SM. *Tetrahedron.* 1991; 47:2463.
19. Burger RM, Tian G, Drlica K. *J Am Chem Soc.* 1995; 117:1167.
20. Murray V, Martin RF. *J Biol Chem.* 1985; 260:10389. [PubMed: 2411722]
21. Carter BJ, Murty VS, Reddy KS, Wang S, Hecht SM. *J Biol Chem.* 1990; 265:4193. [PubMed: 1689722]
22. Dedon PC, Goldberg IH. *Chem Res Toxicol.* 1992; 5:311. [PubMed: 1380322]
23. Kane SA, Natrajan A, Hecht SM. *J Biol Chem.* 1994; 269:10899. [PubMed: 7511612]
24. Zuber G, Quada JC Jr, Hecht SM. *J Am Chem Soc.* 1998; 120:9365.
25. Tse WC, Boger DL. *Chem Biol.* 2004; 11:1607. [PubMed: 15610844]
26. Stubbe J, Kozarich JW, Wu W, Vanderwall DE. *Acc Chem Res.* 1996; 73:133.
27. Hecht SM. *J Nat Prod.* 2000; 63:158. [PubMed: 10650103]
28. Fyfe AJ, McKay P. *J R Coll Physicians Edinb.* 2010; 40:213. [PubMed: 21127762]

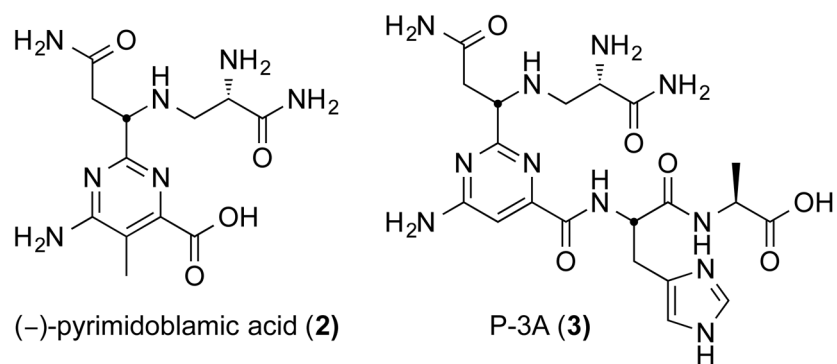
29. Yoshioka T, Muraoka Y, Takita T, Maeda K, Umezawa H. *J Antibiot.* 1972; 25:625. [PubMed: 4119285]
30. Arai H, Hagmann WK, Suguna H, Hecht SM. *J Am Chem Soc.* 1980; 102:6631.
31. Fukuoka T, Muraoka Y, Fujii A, Naganawa H, Takita T, Umezawa H. *J Antibiot.* 1980; 33:114. [PubMed: 6154681]
32. Kobayashi S, Otsuka M, Narita M, Ohno M. *J Am Chem Soc.* 1980; 102:6630.
33. Umezawa Y, Morishima H, Saito S, Takita T, Umezawa H. *J Am Chem Soc.* 1980; 102:6630.
34. Takita T, Umezawa Y, Saito S, Morishima H, Umezawa H. *Tetrahedron Lett.* 1981; 22:671.
35. Aoyagi Y, Katano K, Suguna H, Primeau J, Chang L, Hecht SM. *J Am Chem Soc.* 1982; 104:5537.
36. Aoyagi Y, Suguna H, Murugesan N, Ehrenfeld GM, Chang L, Ohgi T, Shekhani MS, Kirkup MP, Hecht SM. *J Am Chem Soc.* 1982; 104:5237.
37. Henichart J, Houssin R, Bernier J, Cateau J. *J Chem Soc Chem Commun.* 1982:1295.
38. Saito S, Umezawa Y, Morishima H, Takita T, Umezawa H. *Tetrahedron Lett.* 1982; 23:529.
39. Takita T, Umezawa Y, Saito S, Morishima H, Naganawa H, Umezawa H. *Tetrahedron Lett.* 1982; 23:521.
40. Otsuka M, Kittaka A, Takamasa I, Yakashita H, Kobayashi S, Ohno M. *Chem Pharm Bull.* 1985; 33:509. [PubMed: 2410151]
41. Otsuka M, Kobayashi S, Ohno M, Umezawa Y, Morishima H, Umezawa H. *Chem Pharm Bull.* 1985; 33:515. [PubMed: 2410152]
42. Otsuka M, Narita M, Yoshida M, Kobayashi S, Ohno M, Umezawa Y, Morishima H, Saito S, Takita T, Umezawa H. *Chem Pharm Bull.* 1985; 33:520. [PubMed: 2410153]
43. Otsuka M, Kittaka A, Ohno M. *Tetrahedron Lett.* 1986; 27:3639.
44. Kittaka A, Sugano Y, Otsuka M, Ohno M. *Tetrahedron.* 1988; 44:2811.
45. Kittaka A, Sugano Y, Otsuka M, Ohno M. *Tetrahedron.* 1988; 44:2821.
46. Lomis TJ, Siuda JF, Shepherd RE. *J Chem Soc Chem Commun.* 1988:290.
47. Shipley JB, Hecht SM. *Chem Res Toxicol.* 1988; 1:25. [PubMed: 2485129]
48. Brown SJ, Hudson SE, Stephan DW, Mascharak PK. *Inorg Chem.* 1989; 28:468.
49. Suga A, Sugiyama T, Sugano Y, Kittaka A, Otsuka M, Ohno M, Sugiura Y, Maeda K. *Synlett.* 1989:70.
50. Aoyagi Y, Chorghade MS, Padmapriya AA, Suguna H, Hecht SM. *J Org Chem.* 1990; 55:6291.
51. Otsuka M, Masuda T, Haupt A, Ohno M, Shiraki T, Sugiura Y, Maeda K. *J Am Chem Soc.* 1990; 112:838.
52. Boger DL, Dang Q. *J Org Chem.* 1992; 57:1631.
53. Boger DL, Menezes RF. *J Org Chem.* 1992; 57:4331.
54. Boger DL, Menezes RF, Dang Q. *J Org Chem.* 1992; 57:4333.
55. Boger DL, Menezes RF, Dang Q, Yang W. *Bioorg Med Chem Lett.* 1992; 2:261.
56. Boger DL, Yang W. *Bioorg Med Chem Lett.* 1992; 2:1649.
57. Owa T, Haupt A, Otsuka M, Kobayashi S, Tomioka N, Itai A, Ohno M. *Tetrahedron.* 1992; 48:1193.
58. Tan JD, Hudson SE, Brown SJ, Olmstead MM, Mascharak PK. *J Am Chem Soc.* 1992; 114:3841.
59. Boger DL, Honda T. *Tetrahedron Lett.* 1993; 34:1567.
60. Boger DL, Menezes RF, Honda T. *Angew Chem Int Ed.* 1993; 32:273.
61. Guajardo RJ, Hudson SE, Brown SJ, Mascharak PK. *J Am Chem Soc.* 1993; 115:7971.
62. Boger DL, Colletti SL, Honda T, Menezes RF. *J Am Chem Soc.* 1994; 116:5607.
63. Boger DL, Honda T. *J Am Chem Soc.* 1994; 116:5647.
64. Boger DL, Honda T, Dang Q. *J Am Chem Soc.* 1994; 116:5619.
65. Boger DL, Honda T, Menezes RF, Colletti SL. *J Am Chem Soc.* 1994; 116:5631.
66. Boger DL, Honda T, Menezes RF, Colletti SL, Dang Q, Yang W. *J Am Chem Soc.* 1994; 116:82.

67. Boger DL, Colletti SL, Teramoto S, Ramsey TM, Zhou J. *Bioorg Med Chem.* 1995; 3:1281. [PubMed: 8564421]
68. Boger DL, Teramoto S, Honda T, Zhou J. *J Am Chem Soc.* 1995; 117:7338.
69. Boger DL, Ramsey TM, Cai H. *Bioorg Med Chem.* 1996; 4:195. [PubMed: 8814878]
70. Boger DL, Teramoto S, Cai H. *Bioorg Med Chem.* 1996; 4:179. [PubMed: 8814877]
71. Boger DL, Ramsey TM, Cai H, Hoehn ST, Kozarich JW, Stubbe J. *J Am Chem Soc.* 1998; 120:53.
72. Boger DL, Ramsey TM, Cai H, Hoehn ST, Stubbe J. *J Am Chem Soc.* 1998; 120:9149.
73. Boger DL, Ramsey TM, Cai H, Hoehn ST, Stubbe J. *J Am Chem Soc.* 1998; 120:9139.
74. Boger DL, Aquila BM, Tse WC, Searcey M. *Tetrahedron Lett.* 2000; 41:9493.
75. Lehmann TE, Ming L, Rosen ME, Que L Jr. *Biochem.* 1997; 36:2807. [PubMed: 9062108]
76. Wu W, Vanderwall DE, Teramoto S, Lui SM, Hoehn ST, Tang X, Turner CJ, Boger DL, Kozarich JW, Stubbe J. *J Am Chem Soc.* 1998; 120:2239.
77. Manderville RA, Ellena JF, Hecht SM. *J Am Chem Soc.* 1994; 116:10851.
78. Wu W, Vanderwall DE, Stubbe J, Kozarich JW, Turner CJ. *J Am Chem Soc.* 1994; 116:10843.
79. Manderville RA, Ellena JF, Hecht SM. *J Am Chem Soc.* 1995; 117:7891.
80. Wu W, Vanderwall DE, Lui SM, Tang X, Turner CJ, Kozarich JW, Stubbe J. *J Am Chem Soc.* 1996; 118:1268.
81. Wu W, Vanderwall DE, Turner CJ, Kozarich JW, Stubbe J. *J Am Chem Soc.* 1996; 118:1281.
82. Lui SM, Vanderwall DE, Wu W, Tang X, Turner CJ, Kozarich JW, Stubbe J. *J Am Chem Soc.* 1997; 119:9603.
83. Vanderwall DE, Lui SM, Wu W, Turner CJ, Kozarich JW, Stubbe J. *Chem Biol.* 1997; 4:373. [PubMed: 9195876]
84. Anderson ED, Boger DL. *J Am Chem Soc.* 2011; 133:12285. [PubMed: 21736324]
85. Anderson ED, Boger DL. *Org Lett.* 2011; 13:2492. [PubMed: 21488676]
86. Stanfield MK, Woolley DW. *J Org Chem.* 1964; 30:1548. [PubMed: 14290377]
87. Kenda BM, Matagne AC, Talaga PE, Pasau PM, Differding E, Lallemand BI, Frycia AM, Moureau FG, Klitgaard HV, Gillard MR, Fuks B, Michel P. *J Med Chem.* 2004; 47:530. [PubMed: 14736235]
88. Ohsawa A, Arai H, Ohnishi H, Igeta H. *J Chem Soc Chem Commun.* 1980:1182.
89. Ohsawa A, Arai H, Ohnishi H, Itoh T, Kaihoh T, Okada M, Igeta H. *J Org Chem.* 1985; 26:5520.
90. Boulton AJ, Fruttero R, Kalenga Saka JD. *J Chem Soc Perkin Trans I.* 1986:1249.
91. Ohsawa A, Kaihoh T, Itoh T, Okada M, Kawabata C, Yamaguchi K, Igeta H. *Chem Pharm Bull.* 1988; 36:3838.
92. Babinski DJ, Aguilar HR, Still R, Frantz DE. *J Org Chem.* 2011; 76:5915. [PubMed: 21682322]
93. Parlanti L, Discordia RP, Hynes J Jr, Miller MM, O'Grady H, Shi Z. *Org Lett.* 2007; 9:3821. [PubMed: 17718497]
94. Cheung KMJ, Reynisson J, McDonald E. *Tetrahedron Lett.* 2010; 51:5915.
95. Li Z, Capretto DA, He C. *Prog Inorg Chem.* 2009; 56:1.
96. Wentrup C. *Acc Chem Res.* 2011; 44:393. [PubMed: 21452850]
97. Iitaka Y, Nakatani T, Muraoka Y, Fujii A, Takita T, Umezawa H. *J Antibiot.* 1978; 31:1070. [PubMed: 81825]
98. Boger DL, Panek JS. *J Org Chem.* 1981; 46:2179.
99. Boger DL, Panek JS. *J Org Chem.* 1982; 47:3763.
100. Boger DL, Panek JS, Meier MM. *J Org Chem.* 1982; 47:895.
101. Boger DL, Schumacher J, Mullican MD, Patel M, Panek JS. *J Org Chem.* 1982; 47:2673.
102. Boger DL, Panek JS. *Tetrahedron Lett.* 1984; 25:3175.
103. Boger DL, Panek JS, Yasuda M. *Org Synth.* 1987; 66:142.
104. Boger DL, Dang Q. *Tetrahedron.* 1988; 44:3379.
105. Boger DL, Kochanny MJ. *J Org Chem.* 1994; 59:4950.
106. Boger DL, Panek JS. *Tetrahedron Lett.* 1983; 24:4511.

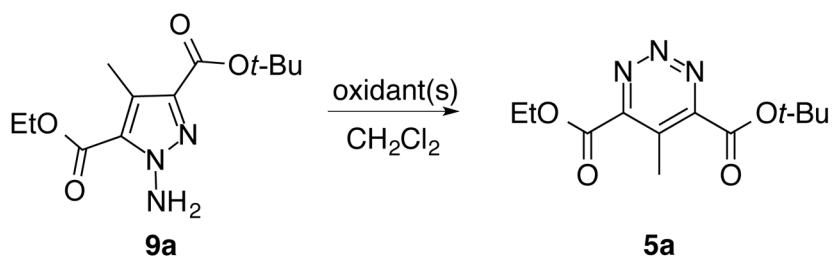


107. Boger DL, Coleman RS, Panek JS. *J Org Chem.* 1985; 50:5377.
108. Boger DL, Sakya SM. *J Org Chem.* 1988; 53:5377.
109. Boger DL, Panek JS, Patel M. *Org Synth.* 1992; 70:79.
110. Sakya SM, Groskopf KK. *Tetrahedron Lett.* 1997; 38:3805.
111. Boger DL, Schaum RP, Garbaccio RM. *J Org Chem.* 1998; 63:6329. [PubMed: 11672266]
112. Soenen DR, Zimpleman JM, Boger DL. *J Org Chem.* 2003; 68:3593. [PubMed: 12713365]
113. Hamasaki A, Ducray R, Boger DL. *J Org Chem.* 2006; 71:185. [PubMed: 16388634]
114. Boger DL, Coleman RS. *J Org Chem.* 1984; 49:2240.
115. Kessler SN, Wegner HA. *Org Lett.* 2010; 12:4062. [PubMed: 20718452]
116. Boger DL. *Tetrahedron.* 1983; 39:2869.
117. Boger DL. *Chem Rev.* 1986; 86:781.





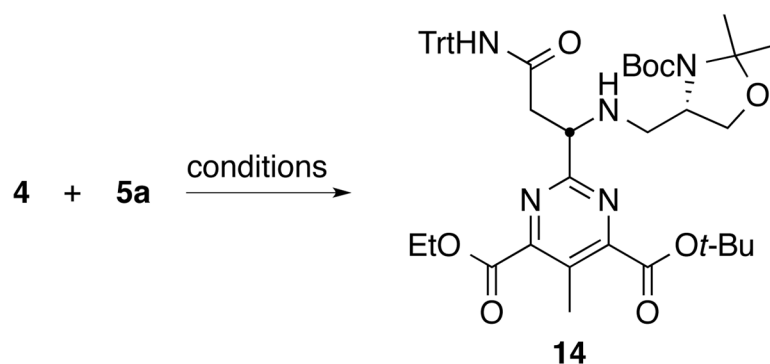
**Figure 2.**  
Structures of (-)-pyrimidoblamic acid and P-3A



oxidant	product(s) (% yield)
$\text{Ni}_2\text{O}_3$	<b>8a<sup>a</sup></b>
$\text{MnO}_2$	<b>8a<sup>a</sup></b>
$\text{Pb}(\text{OAc})_4$	<b>8a<sup>a</sup></b>
$\text{Pb}(\text{OAc})_4 + \text{Ni}_2\text{O}_3$	<b>8a<sup>a</sup></b>
$\text{AgNO}_3$	<b>9a</b> (no reaction)
$\text{AgNO}_3 + \text{PIDA}$	<b>5a</b> (34%), <b>8a</b> (49%)
$\text{NaIO}_4$	<b>5a</b> (28%), <b>8a/9a</b> (70%)
$\text{NaIO}_4, \text{Bu}_4\text{NBr}$	<b>5a</b> (8–70%)
$\text{Bu}_4\text{NIO}_4$	<b>9a</b> (no reaction)
$\text{I}_2, 20\% \text{ aq. KHCO}_3$	<b>5a</b> (75%)

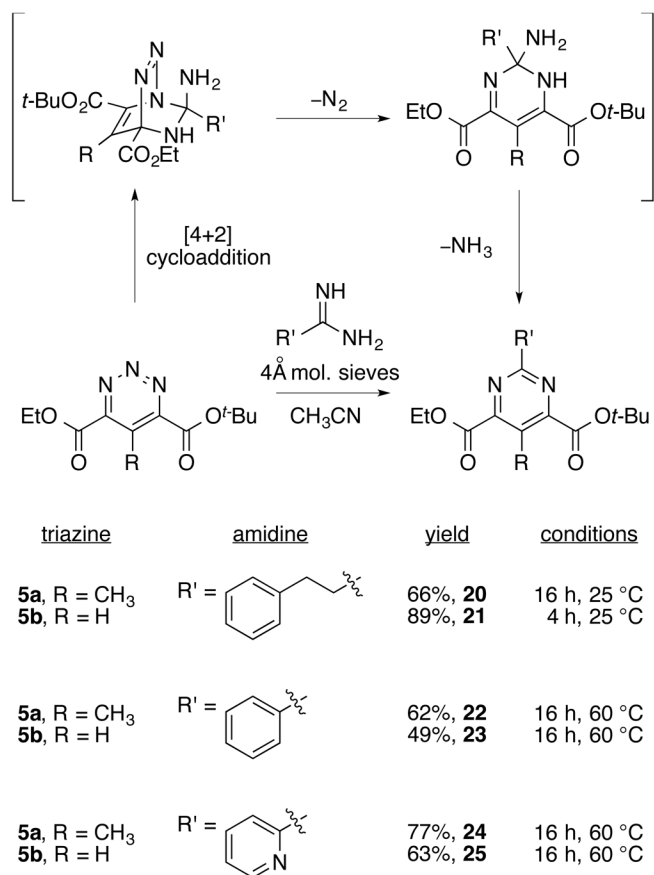
<sup>a</sup> major product, yield not determined

**Figure 3.**  
Oxidative ring expansion survey

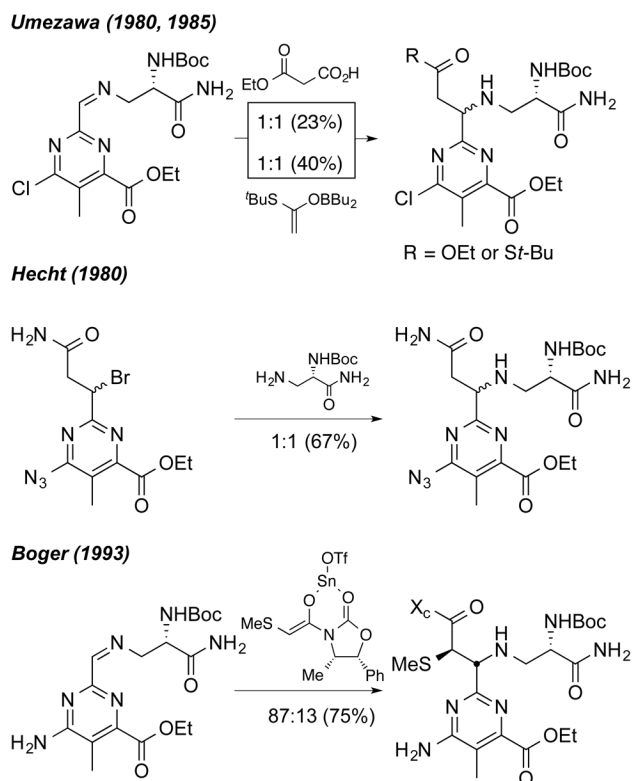


	conditions	yield, <i>dr</i>
2.0 equiv amidine	1. CH <sub>3</sub> CN, 15 h, 25 °C	35%, 7:1
	2. CHCl <sub>3</sub> , 15 h, 25 °C	40%, 4:1
	3. CH <sub>3</sub> CN, 15 h, 85 °C	58%, 3:1
	4. CH <sub>3</sub> CN, 39 h, 25 °C	50%, 7:1
	5. CH <sub>3</sub> CN, 39 h, 5 °C	33%, single diastereomer
	6. CHCl <sub>3</sub> , 39 h, 5 °C	22%, 7:1
	7. CH <sub>3</sub> CN, 24 h, 5 °C then 17 h, 25 °C	43%, single diastereomer
2.0 equiv triazine	8. CH <sub>3</sub> CN, 20 h, 5 °C then 1 h, 25 °C	46%, single diastereomer
	9. CH <sub>3</sub> CN, 14 h, 5 °C then 6 h, 25 °C	54%, single diastereomer

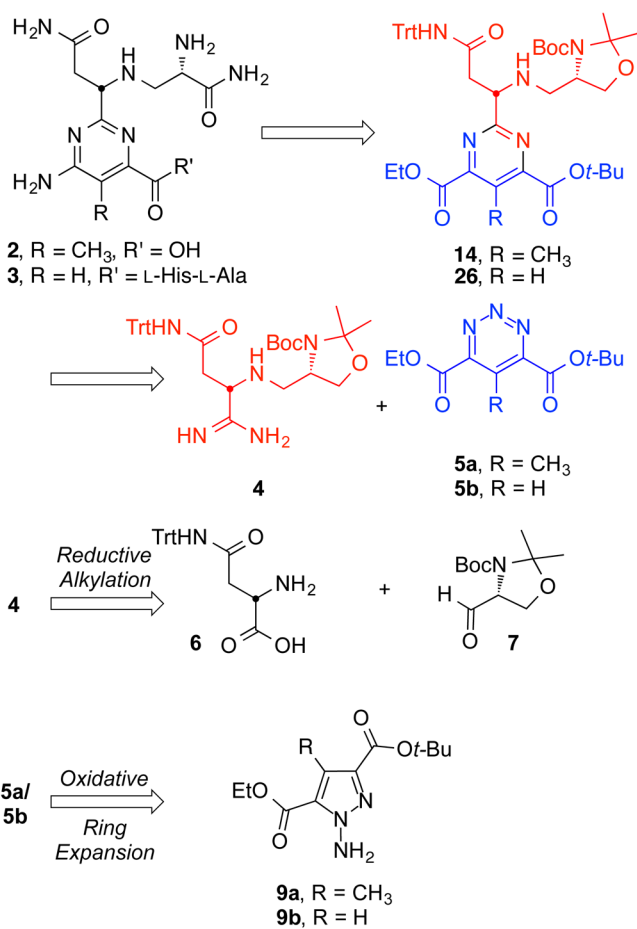
**Figure 4.**  
Optimization of the [4+2] cycloaddition reaction



**Figure 5.** Comparison of the cycloaddition reactions between **5a/5b** and amidines

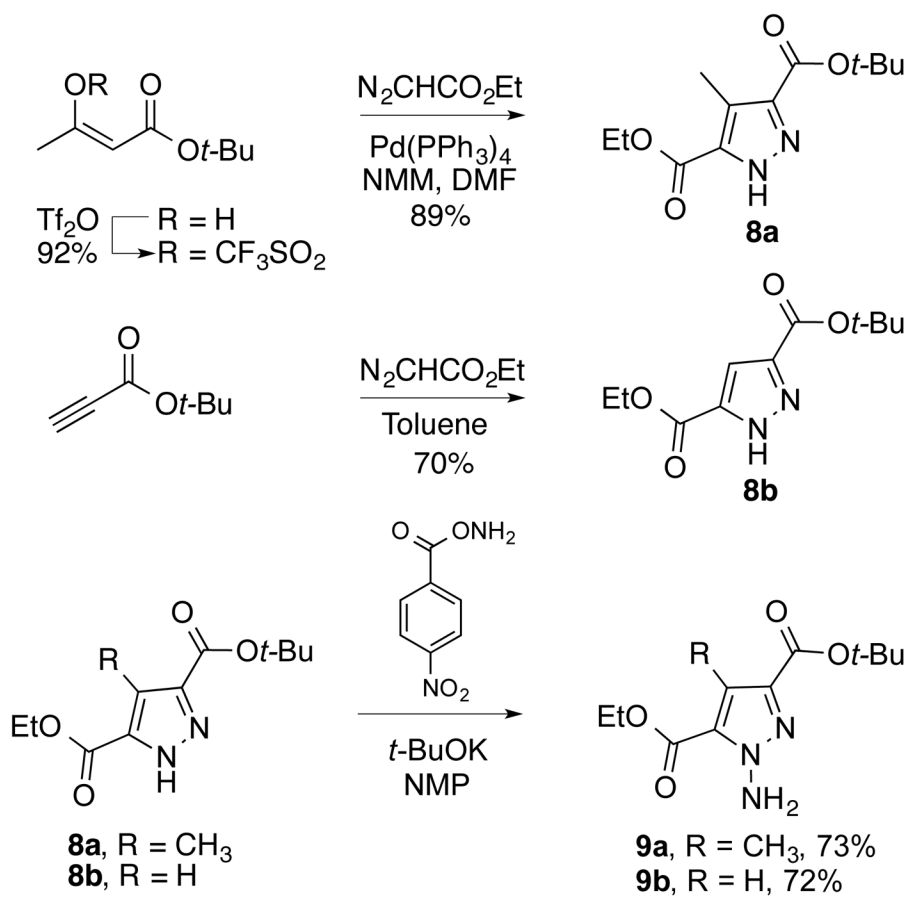


**Scheme 1.**  
Prior late stage installations of the benzylic C<sub>2</sub>-stereocenter of (–)-pyrimidoblastic acid

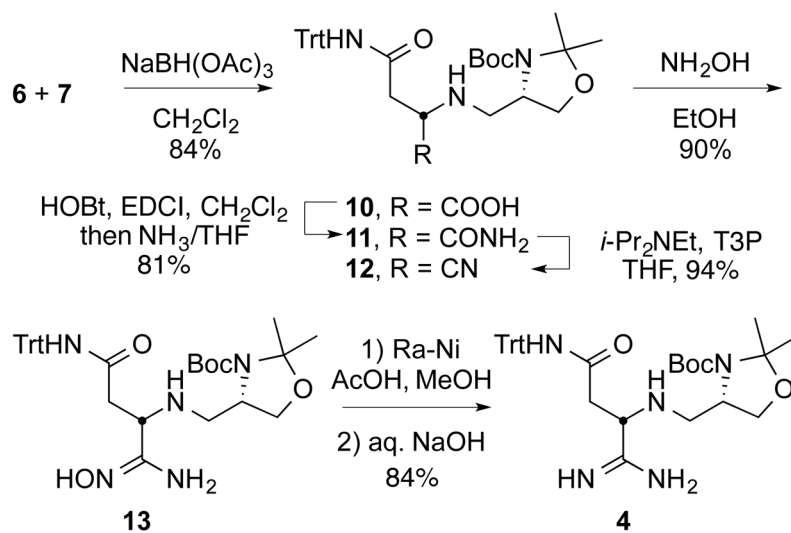


**Scheme 2.**  
Retrosynthetic analysis



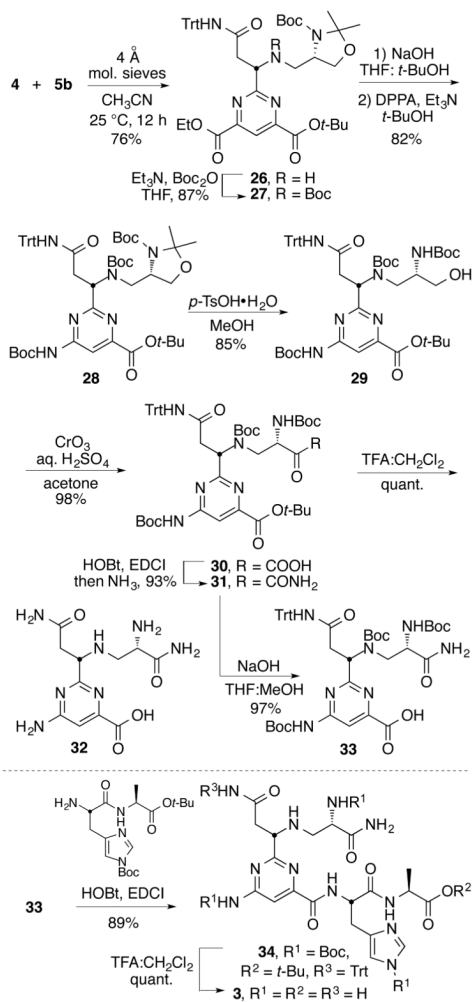


**Scheme 3.**  
 Synthesis of requisite N-aminopyrazoles



**Scheme 4.**  
Synthesis of chiral amidine **4**





**Scheme 6.**  
Total synthesis of P-3A