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# Synthesis of 1-aminopyrrolizidine alkaloid (−)-absouline by stereoselective aminoconjugate addition

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ABSTRACT

The diastereoselective aminoconjugate addition of benzylamine and lithiobenzylamine to both *E* and *Z*-configured vinylogous proline derivatives has been investigated. The results from this study have enabled the stereoselective synthesis of the 1-aminopyrrolizidine alkaloid (−)-absouline.



Pyrrolizidine alkaloids are prevalent secondary metabolites that are isolated from plants, insects, bacteria, and fungi.[1] The complete family of [3.3.0]-azabicyclic alkaloids features an impressive variety of biological activities. Derivatives bearing hydroxylmethyl substitution at C1 (or esters thereof) are the most abundant pyrrolizidines. As a simple example, supinidine (**1**) is hepatotoxic and believed to play a role in feeding deterrence.[2] Polyhydroxylated variants have garnered recent interest due to their α-glucosidase inhibitory activity[3] and representative pyrrolizidines **2** and **3** are lead candidates for the treatment of cancer, diabetes, and viral infection.[4]

In contrast to the family in general, 1-aminopyrrolizidines are not widespread and the three known natural products in this subclass are illustrated (**4**–**6**, Fig. 1). Absouline[5] (**4**) and laburnamine[6] (**5**) differ at the C1 amide substituent and exhibit modest anti-proliferative activities. Loline (**6**) is produced by mutualistic fungal endophytes living on turfgrasses.[7] The insecticidal and antifeedant properties of **3** and related derivatives protect the host plant from insect herbivory. In addition to natural aminopyrrolizidine structures, several synthetic derivatives possess bioactivity including oxime **7** and hydrazone **8**, which show cardiotonic activity,[8] and SC52246 (**9**), a selective $5HT_3$ serotonin receptor antagonist.[9]

As part of our program into the synthesis of aminopyrrolizidine alkaloids,[10] we desired a short synthetic route to enantioenriched **10**. Although two racemic[11] and three asymmetric[12] syntheses intercept **10**, the overall length of these sequences led us to pursue a new route centered on incorporation of the 1-amino substituent through heteroconjugate addition to an α,β-unsaturated carbonyl electrophile (e.g., **12a**, Scheme 1). We anticipated that this approach would be direct and has several features that could be exploited in order to control stereoselectivity of the aminoconjugate addition. We selected **4** as our ultimate synthetic target in order to validate the identity of our product by comparison to the spectroscopic data for both natural and synthetic materials.

Reports concerning the conjugate addition of amines[13] or metal amides[13d,14] to α,β-unsaturated esters bearing a γ-stereogenic center were encouraging from a reactivity standpoint; however, 1,2-induction from these examples generally predicted that addition would occur opposite to the desired sense.[15] Nonetheless, we set

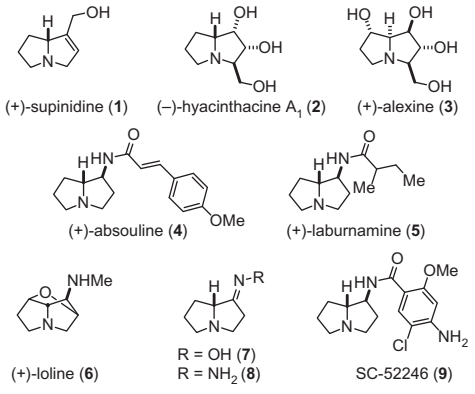


**Figure 1.** Representative pyrrolizidine alkaloids.

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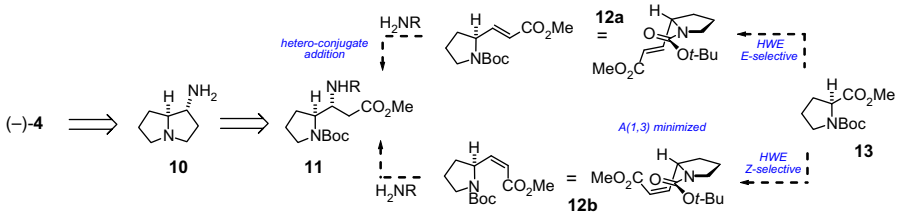



**Scheme 1.** Retrosynthesis of aminopyrrolizidine **10** and (−)-absouline (**4**).

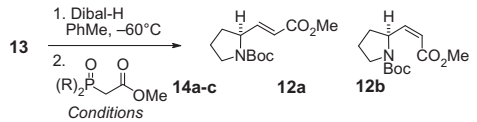
out to evaluate the inherent stereoselectivity of the aminoconjugate addition to both *E*- and *Z*-vinylogous proline derivatives **12a** and **12b**, both of which could be easily prepared from a stereodivergent Horner–Wadsworth–Emmons (HWE) olefination. Additionally, if unsatisfactory results were observed for both geometric isomers, we anticipated that we could enhance the selectivity by resorting to the addition of lithiated homochiral benzyl amine derivatives.[16] Although **12a** and **12b** (and derivatives with different protecting group compositions) have been prepared numerous times[17] and used extensively, the conjugate addition of an amine to these substrates had not been reported. In fact, we were unable to identify any intermolecular heteroconjugate addition to an unsaturated pyrrolidine substrate, although several intramolecular cases have been recently disclosed.[18,10]

In comparing **12a** and **12b**, we anticipated that the *Z*-alkene isomer **12b** would present a greater bias for addition of the amine to the desired alkene α-face due to the conformational restrictions resulting from allylic non-bonding interactions (A1,3-strain). Given our conformational predictions, the size and nature of the proline nitrogen protecting group appeared relevant to alkene facial discrimination; accordingly, we selected the largest carbamate function (Boc). In order to test our hypothesis, we prepared both isomers **12a** and **12b** through HWE olefination on the derived aldehyde of **13**.[19]

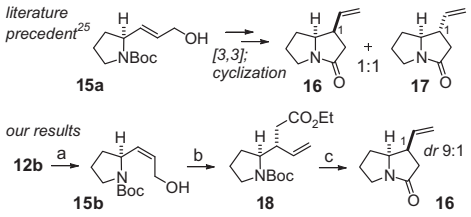
Reduction of proline **13** provided the intermediate carboxaldehyde, which was submitted directly to the HWE reaction.[20] The soft enolization conditions originally discovered by Masamune and Roush were exploited in order to avoid epimerization of the α-stereogenic center of the derived aldehyde.[21] Several phosphonoacetate derivatives and reaction conditions were investigated in order to improve the stereoselectivity for the formation of **12a** and **12b**. The results of this screen are summarized in Table 1.

Reaction with trimethylphosphonoacetate (entry 1, **14a**) afforded a 3:1 mixture of alkene products favoring the *E*-isomer (**12a**). By employing either arylphosphonate **14b** (Ando[22]) or trifluoroethylphosphonate **14c** (Still-Gennari[23]), the selectivity trend could be reversed, slightly favoring the *Z*-isomeric product. Further improvements were achieved by varying the base and additive. Ultimately, a 2:1 ratio of *Z*-**12b**:*E*-**12a** could be obtained using DBU with NaI in THF (entry 4).[24] The *Z*- and *E*-isomeric substrates

**Table 1**
Preparation of vinylogous proline derivatives by HWE reaction




| Entry | | R | Conditions | Ratio **12a**:**12b** | Yield (%) |
|---|---|---|---|---|---|
| 1 | **14a** | MeO | LiCl, *i*-$Pr_2$NEt, MeCN | 3:1 | 72 (**12a**–**b**) |
| 2 | **14b** | PhO | LiCl, *i*-$Pr_2$NEt, MeCN | 4:5 | 36 (**12b**) |
| 3 | **14c** | $CF_3CH_2O$ | LiCl, DBU, MeCN | 2:3 | *nd* |
| 4 | **14b** | PhO | NaI, DBU, THF | 1:2 | 46 (**12b**) |




**Scheme 2.** Claisen rearrangement to probe facial bias of **15a** and **15b**: (a) Dibal-H, $CH_2Cl_2$, −70 °C (80% yield); (b) $MeC(OEt)_3$, 5% $EtCO_2H$, 140 °C; (c) TFA, $CH_2Cl_2$, $Me_2S$; EtOH, $NEt_3$, 80 °C (51% yield, 2 steps).

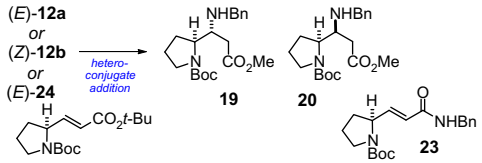
were chromatographically separated to afford 46% isolated yield of **12b** over the two steps.

With both of the isomeric unsaturated esters in hand, we wanted to evaluate our hypothesis regarding a conformational preference for greater facial selection of the *Z*-isomer relative to the *E*-isomer. Because the Johnson orthoester Claisen rearrangement of *E*-allylic alcohol **15a** was known, affording after subsequent cyclization an equal mixture of **16** and **17** (no face selection),[25] we performed the complementary experiment with *Z*-allylic alcohol **15b** (Scheme 2). Claisen rearrangement of **15b** selectively afforded product **18** (dr 9:1). The structure and diastereoselectivity for the reaction was were determined by conversion of **18** into the rigid bicyclic lactam **16**. The favorable selectivity for [3,3]-rearrangement of **15b** validated our conformational predictions and reflects the greater facial bias the *Z*-alkene enforces through A1,3-strain.[26]

With new confidence in our conformational predictions, we sought to evaluate the aminoconjugate addition to isomeric α,β-unsaturated esters **12a** and **12b** and prepare the desired 1-aminopyrrolizidine core. As we began to probe this intermolecular reaction, we initially noted that conjugate addition with each isomer did not replicate the notable selectivity difference that we observed for the model intramolecular Claisen rearrangement. Addition of benzylamine in THF at reflux to *Z*-alkene **12b** or *E*-alkene **12a** produced an identical 3:1 ratio of products **19** and **20** (Table 2; entries 1, 5). The reaction rate was slow, requiring 3 days at elevated temperatures (66 °C) to fully consume the starting material. The resulting addition products **19** and **20** were inseparable by chromatography and the product ratio could not be determined conveniently by NMR due to carbamate rotamers. As such, the product ratio and structure determination was achieved by conversion of the mixture into pyrrolizidines **21** and **22** (see Scheme 3). The exocyclic or endocyclic amine function in **21** and **22** is structurally and spectroscopically distinct which permitted separation of the diastereomers. The structure of **21** was verified by single crystal X-ray analysis on the derived HCl salt.

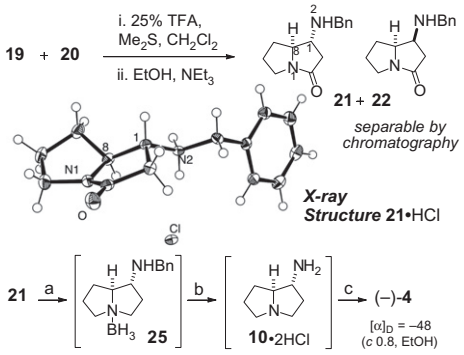
During the course of reactions in THF with *Z*-α,β-unsaturated ester **12b**, isomer **12a** was apparent by TLC. Several trials were not run to full conversion and in these cases **12a** was verified by $^1$H NMR from the unpurified reaction mixture. The presence of **12a**, coupled with the nearly identical results observed for reaction

**Table 2**
Aminoconjugate addition to vinylogous proline derivatives




| Entry | Starting material | Reaction conditions | Product (ratio)[a] | Yield[b] (%) |
|---|---|---|---|---|
| 1 | **12a** | $H_2NBn$, THF, 66 °C (3 d) | **19**:**20** (3:1) | 73 |
| 2 | **12a** | $H_2NBn$, EtOH, 88 °C (2 d) | **19**:**20** (1:1) | 47 |
| 3 | **12a** | $H_2NBn$ *neat*, 25 °C (2 d) | **19**:**20** (2:1) | 62 |
| 4 | **12a** | LiNHBn, THF, −40 °C (2 h) | **23** | 36 |
| 5 | **12b** | $H_2NBn$, THF, 66 °C (3 d) | **19**:**20** (3:1) | 69 |
| 6 | **12b** | $H_2NBn$, EtOH, 80 °C (2 d) | **19**:**20** (7:2) | 92 |
| 7 | **12b** | $H_2NBn$ *neat*, 25 °C (2 d) | **19**:**20** (1:1) | 73 |
| 8 | **12b** | LiNHBn, THF, −40 to 25 °C | *nr* | 0 |
| 9 | **24** | LiNHBn, THF, −40 to 25 °C | *nr* | 0 |

[a] Product ratio determined by conversion of the mixture of **19** and **20** to **21** and **22** (see Scheme 3).
[b] Combined yield of **19** and **20**.




**Scheme 3.** Synthesis of (−)-absouline (**4**): (a) $BH_3$·$Me_2S$, THF, 66 °C; (b) $H_2$, 10% Pd/C, MeOH, HCl; (c) DMAP, $NEt_3$, DCC, 4-methoxycinnamic acid, $CH_2Cl_2$ (58% yield, three steps).

with either **12a** or **12b**, support a reaction mechanism in which isomerization of the *Z*-α,β-unsaturation in **12b** to the *E*-alkene **12a** is competitive with aminoconjugate addition for reactions performed in THF.

In order to improve the heteroconjugate addition selectivity, the reaction solvent and conditions were varied. Reaction with **12b** proceeded to completion in ethanol (2 d, 80 °C) and afforded a 92% combined yield of **19** and **20**. In ethanol, slightly greater selectivity for the addition was observed for **12b** (entry 6) relative to the isomeric *E*-configured material **12a** (entry 2). In the absence of a solvent, heteroconjugate addition could be achieved at ambient temperatures, though with diminished selectivity (Table 2; entries 3, 7). Additionally, the isomerization of *Z*-α,β-unsaturated material **12b**, was not observed for reactions performed in ethanol or without solvent.

Attempted addition of the more reactive lithiated *N*-benzylamine to **12a** or **12b** failed to afford any desired conjugate addition products **19** or **20**; rather, the *Z*-isomeric substrate returned only starting material and the *E*-configured material afforded the benzyl amide **23**.[27] Because unsaturated *t*-butyl esters are known to suppress the rate of 1,2-addition[16]of amide nucleophiles (in favor of 1,4-addition), **24** was prepared via an analogous HWE olefination. Reaction of *E*-α,β-unsaturated *t*-butyl ester **24** with lithiated *N*-benzylamine unfortunately failed to provide any reaction product (entry 9).

To summarize our results, the aminoconjugate addition to vinylogous proline derivatives is a marginal reaction. The approach of the amine (or metal amide) likely encounters significant nonbonding interactions at the γ-position (the pyrrolidine ring). As a result, elevated temperatures are required for the addition of benzylamine and more reactive metal amides preferentially perform as bases, not in the desired sense as nucleophiles. The choice of reaction solvent has a modest effect on product ratios and, the best overall reaction was observed with *Z*-**12b** in ethanol (entry 6, dr 7:2).

Going forward with our best reaction, we prepared the desired aminopyrrolizidine core **10** and completed the synthesis of **4**, a task requiring reduction of both the lactam and *N*-benzyl function in **21**. Reduction of the lactam with borane afforded the stable intermediate pyrrolizidine·$BH_3$ complex **25**. We anticipated that hydrogenolysis (in MeOH) would remove both the borane complex and the benzyl amine.[28] Toward this end, Pearlman's catalyst ($Pd(OH)_2$/C) was investigated with a variety of hydrogen sources (e.g., $H_2$, $HCO_2H$, $NH_4^+HCO_2^-$, $H_2NNH_2$) and, while the borane complex was easily removed, the benzyl group failed to cleave under the conditions explored. Performing the hydrogenolysis in the presence of strong acid proved critical for success of the operation. Reduction with 10% Pd/C under an atmosphere of $H_2$ at reflux in MeOH containing 2.2 equiv of HCl efficiently cleaved the benzyl group and decomposed the borane–amine complex. In this way, aminopyrrolizidine **10** was reliably produced in nearly quantitative yield. In practice, **10** was isolated as the bis-hydrochloride salt in order to circumvent the volatility of the free amine. Largely following precendent[12a] for the final reaction, amide coupling with *trans*-4-methoxycinnamic acid, afforded (−)-absouline (**4**) in 58% yield (three steps) from **21**. The spectroscopic data for our synthetic material agrees with previously published data.[11,12] Furthermore, the magnitude of optical rotation of **4** was consistent with preservation of the stereochemical integrity at C8, the stereogenic center derived from proline.[29]

In summary, we have achieved an efficient synthesis (seven steps, four chromatographic separations) of the 1-aminopyrrolizidine (−)-absouline (**4**) starting from a commercially available proline derivative. In the course of this effort, conditions for a selective HWE reaction were determined in order to prepare the isomeric vinylogous proline derivatives **12a** and **12b**. Additionally, the aminoconjugate addition to both the *E*- and *Z*-unsaturated proline derivatives was explored and optimal results were observed with

(*Z*)-**12b** in ethanol. The selectivity observed for this reaction likely reflects the conformational bias enforced through allylic strain. We believe that the chemistry revealed in this synthetic exercise makes a contribution to the rich field of heteroconjugate addition and will hopefully enable the synthesis of related aminopyrrolizidine alkaloids and β-amino acid derivatives.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.028. These data include MOL files and InChiKeys of the most important compounds described in this article.

## References and notes


1. (a) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773–781; (b) Fu, P. P.; Xia, Q.; Lin, G.; Chou, M. W. *Drug Metab. Rev.* **2004**, *36*, 1–55; (c) Robins, D. J. J. *Nat. Prod. Rep.* **1993**, *10*, 487–497.
2. (a) Mattocks, A. R. *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic: London, 1986; (b) White, L.; Rubiolo, P.; Bicchi, C.; Hartmann, T. *Phytochemistry* **1993**, *32*, 187–196.
3. (a) Wardrop, D. J.; Waidyarachchi, S. L. *Nat. Prod. Rep.* **2010**, *27*, 1431–1468; (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; (c) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875–2886.
4. (a) Vlietinck, A. J.; De Bruyne, T.; Apers, S.; Pieters, L. A. *Planta Med.* **1998**, *64*, 97–109; (b) Taylor, D. L.; Nash, R. J.; Fellows, L. E.; Kang, M. S.; Tyms, A. S. *Antiviral Chem. Chemother.* **1992**, *3*, 273–277; (c) Kato, A.; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Wormald, M. R.; Fleet, G. W. J.; Asano, N. *Carbohydr. Res.* **1999**, *316*, 95–103; (d) Asano, N.; Kuroi, H.; Ikeda, K.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Waston, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1–8.
5. Ikhiri, K.; Ahond, A.; Poupat, C.; Potier, P.; Pusset, J.; Sévenet, T. *J. Nat. Prod.* **1987**, *50*, 626–630.
6. Neuner-Jehle, N.; Nesvadba, H.; Spiteller, G. *Monatsh. Chem.* **1965**, *96*, 321–338.
7. Schardl, C. L.; Grossman, R. B.; Nagabhyru, P.; Faulkner, J. R.; Mallik, U. P. *Phytochemistry* **2007**, *68*, 980–996.
8. Suri, K. A.; Suri, O. P.; Atal, C. K. *J. Indian Chem.* **1983**, *22B*, 822–823.
9. (a) Flynn, D. L.; Zabrowski, D. L.; Becker, D. P.; Nosal, R.; Villamil, C. I.; Gullikson, G. W.; Moummi, C.; Yang, D.-C. *J. Med. Chem.* **1992**, *35*, 1486–1489; (b) Langlois, M.; Fischmeister, R. *J. Med. Chem.* **2003**, *46*, 319–344.
10. Hovey, M. T.; Eklund, E. J.; Pike, R. D.; Mainkar, A. A.; Scheerer, J. R. *Org. Lett.* **2011**, *13*, 1246–1249.
11. (a) Poupat, C.; Christine, C. M.; Ikhiri, K.; Ahond, A.; Mourabit, A. A.; Potier, P. *Tetrahedron: Asymmetry* **2000**, *56*, 1837–1850; (b) Matos, M. N.; Afonso, C. A. M.; Batey, R. A. *Tetrahedron: Asymmetry* **2005**, *61*, 1221–1244.
12. (a) Vargas-Sanchez, M.; Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Org. Lett.* **2005**, *7*, 5861–5864; (b) Tang, T.; Ruan, Y.-P.; Ye, J.-L.; Huang, P.-Q. *Synlett* **2005**, 213–234; (c) Giri, N.; Petrini, M.; Profeta, R. *J. Org. Chem.* **2004**, *69*, 7303–7308.
13. (a) Matsunaga, H.; Sakamaki, T.; Nagaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 3009–3012; (b) Dondoni, A.; Boscarato, A.; Marra, A. *Synlett* **1993**, 256–257; (c) Reetz, M. T.; Röhrig, D.; Harms, K.; Frenking, G. *Tetrahedron Lett.* **1994**, *35*, 8765–8768; (d) Patil, N. T.; Tilekar, J. N.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 1065–1074.
14. (a) Asao, N.; Shimada, T.; Sudo, T.; Tsukada, N.; Yazawa, K.; Gyoung, Y. S.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 6274–6282; (b) Yamamoto, Y.; Asao, N. Tsukada, N. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: London, 1993; pp 1–37.
15. The sense of induction is explained from a modified vinylogous polar-Felkin–Ahn model. For explanation and general review on the topic, see: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223.
16. For reviews on the addition of homochiral amides, see: (a) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833–2891; (b) Krishna, P. R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron: Asymmetry* **2009**, *65*, 9657–9672.
17. Previous preparations of **12a** or **12b** using a Wittig or HWE reaction, though several other methods have been used to prepare vinylogous proline derivatives. None of the following reports utilize Masamune–Roush reaction conditions: (a) Poon, C. Y.; Chiu, P. *Tetrahedron Lett.* **2004**, *45*, 2985–2988; (b) Coz, S. L.; Mann, A.; Thareau, F.; Taddei, M. *Heterocycles* **1993**, *36*, 2073–2080; (c) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533–2534; (d) Arisawa, M.; Takezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett* **1997**, 1179–1180; (e) Chappie, T. A.; Weekly, R. M.; McMills, M. C. *Tetrahedron Lett.* **1996**, *37*, 6523–6526; Priebke, H.; Brueckner, R.; Harms, K. *Chem. Ber.* **1990**, *123*, 555–564; (f) Yang, H.; Jurkauskas, V.; Mackintosh, N.; Mogren, T.; Stephenson, C. R. J.; Foster, K.; Brown, W.; Roberts, E. *Can. J. Chem.* **2000**, *78*, 800–808; (g) Shankaran, K.; Donnelly, K. L.; Shah, S. K.; Guthikonda, R. N.; MacCoss, M.; Humes, J. L.; Pacholok, S. G.; Grant, S. K.; Kelly, T. M.; Wong, K. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4539–4544; (h) Niphakis, M. J.; Turunen, B. J.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6793–6805.
18. Grohs, D. C.; Maison, W. *Tetrahedron Lett.* **2005**, *46*, 4373–4376.
19. *N*-Boc-L-proline methyl ester is commercially available or can be easily prepared from the amino acid by esterification ($SOCl_2$, MeOH) followed by N-protection ($Boc_2O$, $NEt_3$, DMAP). See, for example: Kelleher, F.; Kelly, S.; McKee, V. *Tetrahedron: Asymmetry* **2007**, *63*, 9235–9242.
20. (a) Sato, T.; Tsujimoto, K.; Matsubayashi, K.; Ishibashi, H.; Ikeda, M. *Chem. Pharm. Bull.* **1992**, *40*, 2308–2312; (b) Fulep, G. H.; Hoesl, C. E.; Hofner, G.; Wanner, K. T. *Eur. J. Med. Chem.* **2006**, *41*, 809–824.
21. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.
22. (a) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934–1939; (b) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406–8408.
23. (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408; (b) Hammond, G. B.; Cox, M. B.; Wiemer, D. F. *J. Org. Chem.* **1990**, *55*, 128–132.
24. Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745–4749.
25. Moriwake, T.; Hamano, S.; Saito, S. *Heterocycles* **1988**, *27*, 1135–1139.
26. Related *E*- and *Z*-vinylogous proline derivatives display modest facial selection during dihydroxylation: *E*- gives a 2:1 product ratio; *Z*-, 4:1. See: Izquierdo, I.; Plaza, M. T.; Tamayo, J. A. *Tetrahedron: Asymmetry* **2004**, *15*, 3635–3642.
27. Some reports indicate that the *E* alkene geometry is indispensible for conjugate addition of metal amide salts: Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 3139–3145. Other reports contradict this trend; see Ref. 13d.
28. Blakemore, P. R.; Kim, S. K.; Schulze, V. K.; White, J. D.; Yokochi, A. F. T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1831–1845.
29. The observed optical rotation for our synthetic absouline (**4**): $[\alpha]_D^{25} = -48$ (*c* 0.8, EtOH); −28 (*c* 1.17, $CHCl_3$). This compares favorably with published data: *natural* (+)-**4** (Ref. 5) $[\alpha]_D^{20} = +56$ (*c* 1.0, EtOH); *synthetic* (Ref. 12a) (−)-**4** $[\alpha]_D^{20} = -51$ (*c* 0.4, EtOH); −37 (*c* 1.8, $CHCl_3$); *synthetic* (Ref. 11a) (+)-**4** $[\alpha]_D^{20} = +26$ (*c* 1.05, $CHCl_3$).