Pergamon

Tetrahedron Letters 42 (2001) 3483–3486

TETRAHEDRON LETTERS

Facile transformation of 3,4-disubstituted 2-azetidinones to chiral 5,6-dihydro-2-pyridones

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Received 20 February 2001; revised 15 March 2001; accepted 21 March 2001

Abstract—Chiral 5,6-disubstituted-5,6-dihydro-2(1*H*)-pyridones were prepared efficiently from readily accessible 3,4-disubstituted-2-azetidinones having preadjusted substituents and stereochemistry through the reductive ring opening of 2-azetidinones followed by *Z*-selective installation of acetate moiety and re-cyclization to 2-pyridones.

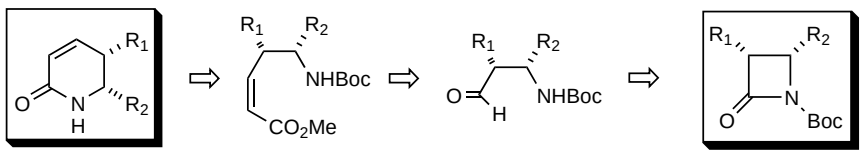
A number of alkaloids containing piperidine, indolizidine ring system and polyhydroxylated piperidines (azasugars) are found frequently in nature and many of these alkaloids display a wide range of interesting biological activity.[1,2] As a result of such interests, these alkaloids have become important synthetic targets.[3]

The 2-azetidinone (β-lactam) skeleton is well known as the key structural element of the most widely employed class of antibacterial agents, the β-lactam antibiotics.[4] As a consequence, diverse methods for practical and stereoselective ring formation of 2-azetidinone have been developed.[5] With a plethora of methods for the synthesis of 2-azetidinone available, applications of 2-azetidinones as efficient chiral synthons for other classes of molecules have been subjected to many investigations.[6] For example, transformations of 2-azetidinones by external reagents to nonproteogenic amino acids and peptides[6d] and ring expansion of 2-azetidinones by internal or external nucleophiles to 2-pyrrolidinones[6c] were reported. However, to our knowledge, there was no report for the preparation of 5,6-dihydro-2-pyridones from 2-azetidinones.

For the preparation of chiral 5,6-dihydro-2-pyridones which can be served as valuable intermediates for azasugars and other piperidine alkaloids, we envisaged that two-carbon addition to 2-azetidinones will provide an easy access to 5,6-dihydro-2-pyridones and 3,4,5,6-tetrahydro-2-pyridones having substitutents and stereochemistry preadjusted at the 2-azetidinone stage. We report herein our preliminary result on the facile synthesis of 5,6-disubstituted-5,6-dihydro-2(1*H*)-pyridones and 3,4,5,6-tetrahydro-2(1*H*)-pyridones from readily available 3,4-disubstituted-2-azetidinones through the reductive ring opening of 2-azetidinones followed by *Z*-selective installation of acetate moiety and re-cyclization to 2-pyridones (Scheme 1).

The requisite optically pure 2-azetidinones were easily prepared from Bose–Manhas β-lactam **1**[7] as described in Scheme 2. *trans*-*N*-PMP-4-Formyl-2-azetidinone **2b** was prepared from the *cis*-*N*-PMP-4-formyl-2-azetidinone **2a**[8] by regiospecific C4-epimerization with dimethylamine as reported.[9]

Transformation of *cis*-*N*-Boc-2-azetidinone **6a** to 5,6-dihydro-2-pyridones **10a** was effected via a two-carbon



Scheme 1.

Keywords: azetidinones; pyridones; piperidines.

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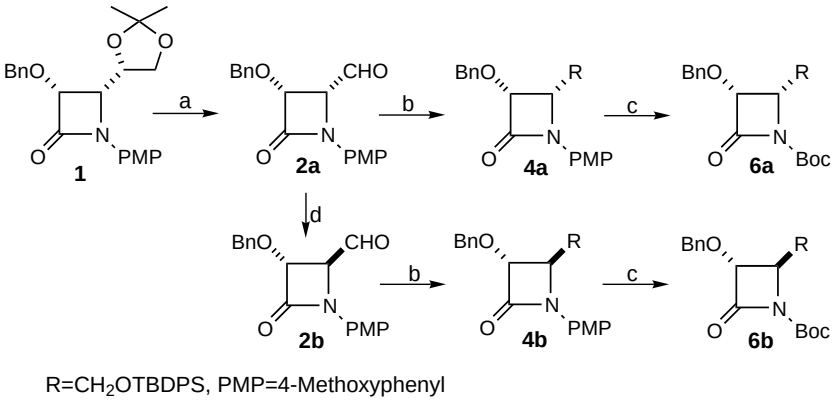
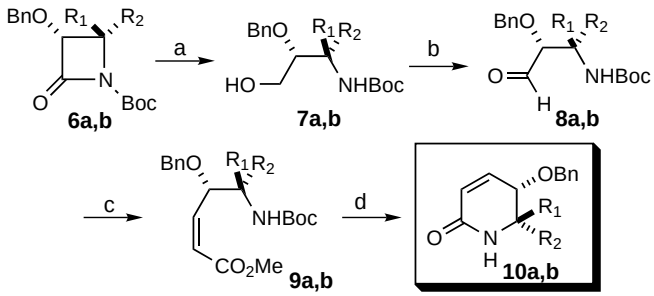
PII: S0040-4039(01)00470-1



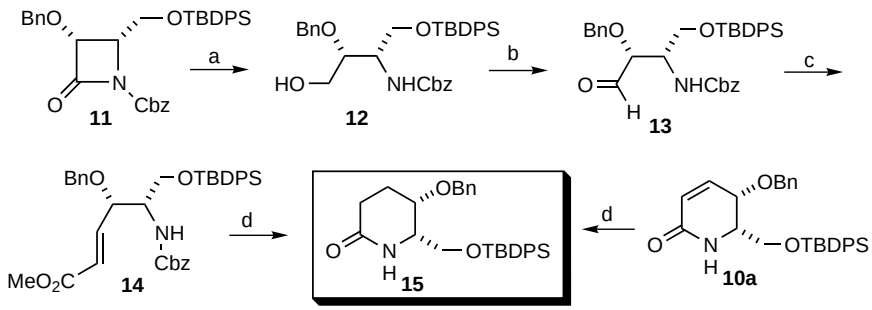
Scheme 2. (a) TsOH, THF–H_2O, heat, 12 h; $NaIO_4$, MeOH–THF–H_2O, rt, 12 h (90%); (b) $NaBH_4$, MeOH, 0°C, 2 h; TBDPSCl, imidazole, DMF, rt, 24 h; (**4a**: 90%, **4b**: 81%); (c) $(NH_4)_2Ce(NO_3)_6$, CH_3CN–H_2O, 0°C, 30 min; $(Boc)_2O$, cat. DMAP, CH_3CN, 4 h (**6a**: 82%, **6b**: 66%); (d) 40% aq. $(CH_3)_2NH$, benzene, rt, 48 h, (96%).

addition reaction, as shown in Scheme 3. Thus, **6a** was reduced to 3-*N*-Boc-amino alcohol **7a** almost quantitatively by $LiAlH_4$ in THF at 0°C for 20 min. Oxidation of 3-*N*-Boc-amino alcohol **7a** by IBX (2-iodoxybenzoic acid)[10] in DMSO for 3 h at rt cleanly produced highly pure 3-*N*-Boc-amino aldehyde **8a** and it was used in the next step without further purification. Aldehyde **8a** was dissolved in dry MeOH[11,12] and treated with methyl (triphenylphosphoranylidene)acetate at rt to give a 7:1 mixture of *Z*-α,β-unsaturated ester **9a** as the major product and its *E*-isomer in 81% overall yield from **7a**. These two isomers were easily separated by flash chromatography and identified by chemical shifts and coupling constants of olefinic protons [6.28 ppm (dd, $J=11.8$, 8.9 Hz) and 5.99 ppm (dd, $J=11.8$, 1.0 Hz) for the *Z*-isomer of **9a**, and 6.96 ppm (dd, $J=15.8$, 5.1 Hz) and 6.08 ppm (dd, $J=15.8$, 1.2 Hz) for the *E*-isomer of **9a**]. Finally, *Z*-*N*-Boc amino ester **9a** was subjected to removal of *N*-Boc protection under mild conditions (TMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 1 h)[13] and in turn cyclized with catalytic DMAP in toluene to give the desired 5,6-*cis*-disubstituted-5,6-dihydro-2(1*H*)-pyri-



a(*cis*): R_1=H, R_2=$CH_2OTBDPS$
b(*trans*): R_1=$CH_2OTBDPS$, R_2=H

Scheme 3. (a) $LiAlH_4$, THF, 0°C, 30 min, (**7a**: 87%, **7b**: 95%); (b) IBX, DMSO, rt, 3 h, (**8a**: 93%, **8b**: 95%); (c) $Ph_3P{=}CHCO_2Me$, MeOH, rt, 12 h, (**9a**: 87%, *E*:*Z*=1:7, **9b**: 81%, *E*:*Z*=1:4); (d) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 1 h, then cat. DMAP, toluene, reflux, 1 h, (**10a**: 95%, **10b**: 89%).



Scheme 4. (a) $NaBH_4$, MeOH, 0°C, 2 h, (90%); (b) IBX, DMSO, rt, 3 h, (89%); (c) $Ph_3P{=}CHCO_2Me$, benzene, reflux, 5 h, (88%, *E*:*Z*=11:1); (d) H_2–Pd/C, EtOAc, rt, 12 h (96%).

done **10a**[14] in excellent yield from **9a**. 5,6-*trans*-Disubstituted-5,6-dihydro-2(1*H*)-pyridone **10b** was also prepared from 3,4-*trans*-*N*-Boc-2-azetidinone **6b** through essentially the same procedure for **6a** to **10a**.[14]

Next we investigated the synthesis of 3,4,5,6-tetrahydro-2(1*H*)-pyridone **15**. Although hydrogenation of 5,6-*cis*-disubstituted-5,6-dihydro-2(1*H*)-pyridone **10a** under Pd/C catalyst afforded 3,4,5,6-tetrahydro-2(1*H*)-pyridone **15**, we have found more efficient synthetic route to 3,4,5,6-tetrahydro-2(1*H*)-pyridone **15** from *N*-Cbz-2-azetidinone **11** as shown in Scheme 4.

Thus, *N*-Cbz-2-azetidinone **11** was converted to 3-*N*-Cbz-amino aldehyde **13** via 3-*N*-Cbz-amino alcohol **12** and treatment of methyl (triphenylphosphoranylidene)acetate in MeOH or benzene afforded 5-*N*-Cbz amino-*Z*- or *E*-2,3-unsaturated ester **14**. Hydrogenation of unsaturated ester **14** in the presence of Pd/C catalyst for saturation of olefininc bond and removal of *N*-Cbz group produced directly 3,4,5,6-tetrahydro-2(1*H*)-pyridone **15**[14] with concomitant cyclization of intermediate 5-amino ester in excellent yields. The efficiency of the steps employed in the present work as well as easy access of starting chiral 2-azetidinones with different substitutents would provide a new efficient method for various chiral 5,6-dihydro-2-pyridones and 3,4,5,6-tetrahydro-2-pyridones. The application of the present work to the preparation of various piperidine and indolizidine alkaloids and azasugars are underway and will be reported in due course.

In summary, we have developed an efficient method for the synthesis of chiral 5,6-dihydro-2(1*H*)-pyridones and 3,4,5,6-tetrahydro-2(1*H*)-pyridones which can be served as valuable chiral intermediates for different piperidine and indolizidine alkaloids and azasugars from easily accessible 2-azetidinones having preadjusted substituents and stereochemistry through the reductive ring opening of 2-azetidinones followed by *Z*-selective installation of acetate moiety and re-cyclization to 2-pyridones.

Acknowledgements

We would like to thank the Ministry of Science and Technology of Korea for financial support.

References

1. For piperidine and indolizidine alkaloids, see: (a) Elbein, A. D.; Molyneux, R. In *Alkaloids*; *Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley and Sons: New York, 1987; Vol. 5; (b) Michael, J. P. *Nat. Prod. Rep*. **1999**, *16*, 675; (c) O'Hagen, D. *Nat. Prod. Rep*. **1997**, *14*, 637; (d) Michael, J. P. *Nat. Prod. Rep*. **1997**, *14*, 619.
2. For polyhydroxylated piperidines (azasugars), see: (a) Stutz, A. E. *Iminosugars as Glycosidase Inhibiyors*; Wiley-VCH: Weinheim, 1998; (b) Sears, P.; Wong, C. H. *Angew. Chem., Int. Ed*. **1999**, *38*, 2300; (c) Jacob, G. S. *Curr. Opin. Struct. Biol*. **1995**, *5*, 605; (d) Hughes, A. B.; Rudge, A. J. *Nat. Prod. Rep*. **1994**, *11*, 135.
3. For some representative examples of previous work, see: (a) Mehta, G.; Mohal, N. *Tetrahedron Lett*. **2000**, *41*, 5741; (b) Sun, H.; Millar, K. M.; Yang, J.; Abboud, K.; Horenstein, B. A. *Tetrahedron Lett*. **2000**, *41*, 2801; (c) Ma, D.; Sun, H. *Org. Lett*. **2000**, *2*, 2503; (d) Yokoyama, H.; Otaya, K.; Kobayashi, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Org. Lett*. **2000**, *2*, 2427; (e) Davis, F. A.; Chao, B.; Fang, T.; Szewczyk, J. M. *Org. Lett*. **2000**, *2*, 1041; (f) Bailey, P. D.; Millwood, P. A.; Smith. P. D. *J. Chem. Soc., Chem. Commun*. **1998**, 633; (g) Yoda, H.; Kawauchi, M.; Takabe, K. *Synlett* **1998**, 137; (h) Goti, A.; Cardona, F.; Brandi, A. *Synlett* **1996**, 761; (i) Toyooka, N.; Yoshida, Y.; Momose, T. *Tetrahedron Lett*. **1995**, *36*, 3715; (j) Altenbach, H.-J.; Himmeldirk, K. *Tetrahedron: Asymmmetry* **1995**, *6*, 1077; (k) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem*. **1995**, *60*, 398; (l) Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem*. **1994**, *59*, 3575; (m) Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L.; Ulgheri, F. *J. Org. Chem*. **1993**, *58*, 3397.
4. For some reviews on β-lactam antibiotics, see: (a) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B.; Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 1–3; (b) *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Brown, A. G., Roberts, S. M., Eds.; The Royal Society of Chemistry: Burling House, London, 1984; (c) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman and Hall: London, 1992.
5. (a) Georg, G. I.; Rabikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1992; p. 295; (b) Hart, D. J.; Ha, D. C. *Chem. Rev*. **1989**, *89*, 1447.
6. (a) Ojima, I. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1992; p. 197; (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; p. 279; (c) Ha, D.-C.; Kang, S.; Chung, C.-M.; Lim, H.-K. *Tetrahedron Lett*. **1998**, *39*, 7541; (d) Ojima, I. *Acc. Chem. Res*. **1995**, *28*, 383; (e) Palomo, C.; Cossio, F. P.; Cuevas, C.; Odriozola, J. M.; Ontoria, J. M. *Tetrahedron Lett*. **1992**, *33*, 4827; (f) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755.
7. Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hegde, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem*. **1988**, *53*, 4227.
8. Alcaide, B.; Martin-Cantalejo, Y.; Perez-Castells, J.; Sierra, M. A. *J. Org. Chem*. **1996**, *61*, 9156.
9. Alcaide, B.; Aly, M. F.; Rodriguez-Vicente, A. *Tetrahedron Lett*. **1998**, *39*, 5865.
10. Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem*. **1995**, *60*, 7272.
11. Sanchez-Sancho, F.; Valverde, S.; Herradon, B. *Tetrahedron: Asymmetry* **1996**, *7*, 3209.
12. Recently, the highly *Z*-selective Honer–Wadsworth–Emmons reaction of aldehyde was also reported: Ando, K. *J. Org. Chem*. **1998**, *63*, 8411.
13. Sakaitani, M.; Ohfune, Y. *J. Org. Chem*. **1990**, *55*, 870.

14. Compound **10a**: $[\alpha]_D^{22}=+109.2°$ ($c=1.31$, $CHCl_3$); IR (NaCl): ν 3220, 1684, 1618, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (m, 5H), 7.26 (m, 10H), 6.61 (dd, 1H, $J=4.4$ Hz), 6.06 (d, 1H, $J=9.8$ Hz), 6.03 (br s, 1H), 4.50 (d, 1H, $J=11.7$ Hz), 4.40 (d, 1H, $J=11.7$ Hz), 4.07 (t, 1H), 3.95 (t, 1H), 3.85 (dd, 1H, $J=4.4$, 10.2 Hz), 3.75 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.54, 138.73, 137.28, 135.41, 132.77, 129.83, 128.33, 127.78, 127.53, 127.06, 70.84, 68.06, 62.50, 60.26, 55.81, 26.71, 19.05, 14.09; HRMS calcd for $C_{29}H_{33}NO_3Si$ 472.2307 (MH^+), found 472.2331. Compound **10b**: $[\alpha]_D^{22}=+34.68°$ ($c=1.13$, $CHCl_3$); IR (NaCl): ν 3213, 1686, 1620, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.60 (m, 5H), 7.26 (m, 10H), 6.57 (dd, 1H, $J=2.8$, 10.2 Hz), 5.95 (dd, 1H, $J=1.6$, 9.9 Hz), 5.74 (br s, 1H), 4.58 (d, 1H, $J=11.8$ Hz), 4.43 (d, 1H, $J=11.6$ Hz), 4.09 (t, 1H, $J=2.8$, 4.5 Hz), 3.76 (m, 2H), 3.72 (d, 1H, $J=4.5$ Hz), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.47, 145.72, 140.09, 137.07, 135.52, 132.62, 130.14, 128.50, 127.88, 127.78, 127.71, 124.94, 71.16, 70.79, 56.09, 26.82, 19.14; HRMS calcd for $C_{29}H_{33}NO_3Si$ 472.2307 (MH^+), found 472.2314. Compound **15**: $[\alpha]_D^{22}$ +7.9° (c, 0.503, $CHCl_3$); IR (NaCl): ν 3205, 1668, 1471, 1439, 1113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66–7.60 (m, 5H), 7.50–7.06 (m, 10H), 6.02 (s, 1H), 4.53 (d, 1H, $J=12$ Hz), 4.30 (d, 1H, $J=11.8$ Hz), 3.73–3.66 (m, 3H), 3.62–3.56 (m, 1H), 2.51 (dd, 1H, $J=6.3$, 11.6 Hz), 2.39 (dd, 1H, $J=2.8$, 6.3 Hz), 1.82–1.72 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.17, 137.66, 135.51, 135.47, 132.92, 132.73, 129.88, 128.36, 128.02, 127.84, 127.80, 127.71, 127.37, 70.33, 69.71, 64.50, 58.04, 57.92, 26.79, 23.42, 19.13; HRMS calcd for $C_{29}H_{35}NO_3Si$ 474.2464 (MH^+), found 474.2474.