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Tetrahedron Letters 45 (2004) 8191–8194
Tetrahedron Letters

Facile synthesis of (−)-tabtoxinine-β-lactam and its (3′*R*)-isomer

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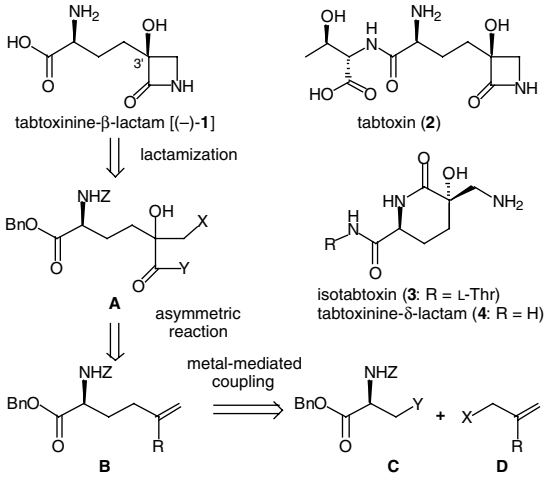
Received 28 July 2004; revised 1 September 2004; accepted 3 September 2004
Available online 21 September 2004

Abstract—A concise and high yielding synthesis of (−)-tabtoxinine-β-lactam **1**, the cause of tobacco wildfire disease, was achieved from L-serine using a zinc-mediated coupling reaction, Sharpless asymmetric dihydroxylation and lactamization of *N*-OBn amide as the key steps.

Tobacco wildfire disease, caused by infection of *Pseudomonas syringae* pv. *tabaci*, has been the most serious pest for tobacco.[1] Several toxins and related compounds were isolated from this bacteria and other *Pseudomonas* sp.[2] Tabtoxinine-β-lactam **1** was isolated as a phytopathogenic compound[2a,2b] along with its precursor tabtoxin **2**. Compound **2** is hydrolyzed by host plant aminopeptidase to give **1**, which causes chlorosis by irreversible inactivation of glutamine synthetase.[3] Recently, the tabtoxin-resistance gene (*ttr*) was cloned and transgenic tobacco cultivars have been developed.[4] In addition, a tabtoxin-resistant protein was characterized.[5] Although **2** is available by fermentation (13 mg/L),[2b] subsequent conversion to **1** by hydrolysis of the amide bond is complicated by concomitant isomerization to isotabtoxin **3** ($t_{1/2}$ = 24 h at pH 7.0).[2b] Several syntheses of (±)-**1**,[6a] (−)-**1**,[6b] its analogs,[7] **2**[8] and tabtoxinine-δ-lactam **4**[9] have been reported to date, however these not prove amenable to scale-up and further biological tests of (−)-**1** have yet to be conducted as a result. Here we describe a short, efficient, and stereoselective synthesis of both (−)-**1** and its (3′*R*)-isomer.

Scheme 1 depicts our synthetic plan. β-Lactam formation can be achieved in many different ways; precursor **A** could be (i) amino carboxylic acid (Y = OH, X = NH_2), (ii) amino ester (Y = OR, X = NH_2), (iii) amide (Y = NHR, X = leaving group), etc. The quaternary asymmetric center of **A** could be constructed by suitable asymmetric reactions of the double bond of **B**. The carbon skeleton of **B** could be prepared from L-serine derivative **C**, and C_4-fragment **D**.



Scheme 1. Related compounds and retrosynthetic analysis of (−)-**1**.

The carbon framework was constructed as shown in Scheme 2. Barton et al. reported a synthesis of **7a**, however, the yield was only 34%.[10] The synthesis started from the known iodide **5**,[11b] prepared from L-serine in four steps. Using Baldwin's radical coupling methodology,[11] this iodide was coupled with the known allylic stannane **6**[11a] to give ester **7a** in 61% yield. A variety of conditions were tried, but the yield could not be improved, so, we tried a zinc-mediated coupling reaction.[12]

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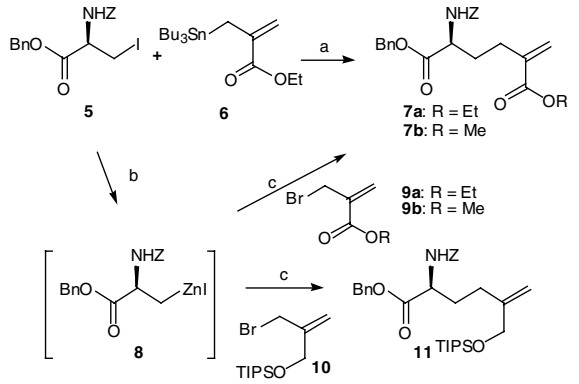
doi:10.1016/j.tetlet.2004.09.033



Scheme 2. Synthesis of the carbon skeleton **B**: (a) AIBN, toluene, 65–70 °C (61%); (b) Zn, DMF, rt 20 min; (c) CuCN·2LiCl, DMF (98% of **7a** and **7b**; 87% of **11**).

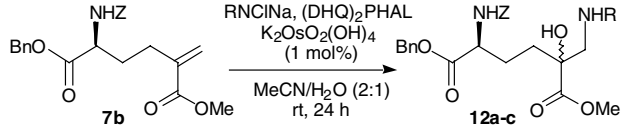
The alkyl zinc iodide **8**, prepared from **5** with active zinc, was treated with allylic bromides **9a**,[12b,13] **9b**, and **10** to afford **7a**, **7b**, and **11** in good yields, respectively.

Construction of the asymmetric quaternary center was achieved using Sharpless aminohydroxylation.[14] As shown in Table 1, a variety of nitrogen donors were used to prepare amino alcohols **12a–c**. The highest diastereomeric purity (81% de) was achieved for toluenesulfonamide (entry 5), however, the yield was only 40% (accompanied by the corresponding diol) and further conversion or deprotection of the *N*-Ts group failed.

Next we tried a Sharpless asymmetric dihydroxylation (Table 2).[15] Diastereoselectivity was low using either asymmetric catalyst (entries 1–3) for the α,β-unsaturated ester **7a**, but significantly higher for silyl ethers **11** (entries 4 and 5).[15b] This may be due to the steric bulk of the silicon group.

The next key step was closure of the β-lactam ring. Preliminary studies using model compounds suggested that condensation conditions from **15** to **17** including DCC, $MsCl/K_2CO_3$,[16] $(PyS)_2/Ph_3P$,[17] sulfonamide/Ph_3P[18] or the Mitsunobu reaction[19] would fail. The magnesium

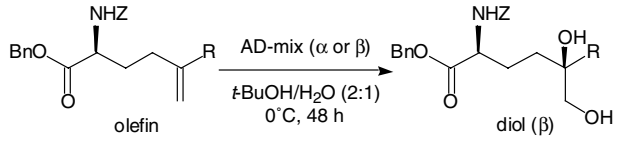
Table 1. Asymmetric aminohydroxylation[a]



Entry	N source (R)	Catalyst	Product	Yield (%)	de[b] (%)
1	Boc[c]	4 mol%	**12a**	53	69
2		—		38	11
3	EtOCO[c]	4 mol%	**12b**	64	10
4		—		55	4
5	Ts (chloramine T)	4 mol%	**12c**	40	81
6		—		64	5

[a] Absolute configuration of the hydroxy group was not determined.
[b] Diastereomeric excess (de) was determined by HPLC analysis.
[c] These reagents were generated in situ.

Table 2. Asymmetric dihydroxylation[a]

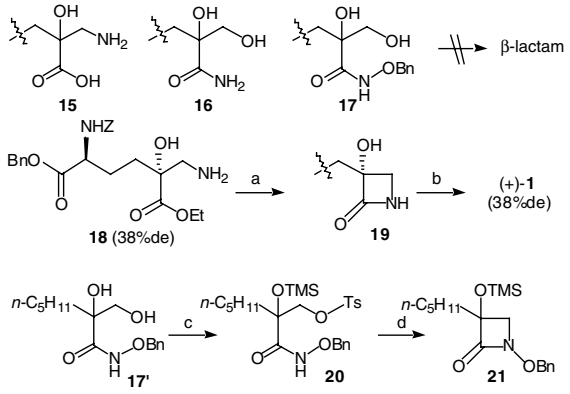


Entry	Olefin (R)	AD-mix	Diol	Yield (%)	de[b] (%)
1	**7a** (CO_2Et)	[c]	**13α**	84	6
2		β	**13β**	88	38
3		α	**13α**	78	23
4	**11** (CH_2OTIPS)	β	**14β**	85	95
5		α	**14α**	94	94

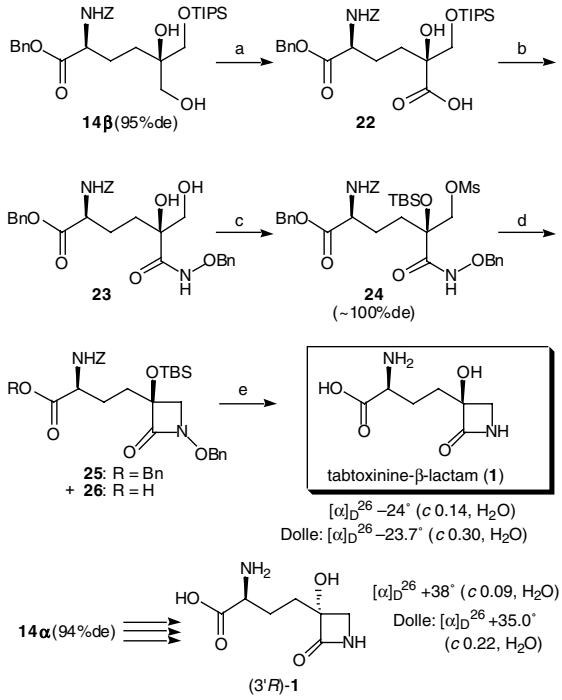
[a] Orientation of the hydroxy groups of **13** and **14** were attributed from the final products (+)-**1** and (−)-**1**, respectively.
[b] Diastereomeric excess (de) was determined by HPLC analysis using Daicel CHIRALCEL® OD column.
[c] OsO_4 (cat), NMO (2 equiv), $MeCN/H_2O$ (2:1).

amide of **18**, derived from **13β** (38% de), gave β-lactam **19**,[20] but the yield was only 30% (Scheme 3). Preliminal study of deprotection of **19** afforded (+)-**1** (38% de). We then examined substitution conditions reported by Haaf and Rüchardt.[21] Diol **17′** was converted to **20**; protection of the tertiary hydroxy group was necessary to avoid epoxy ring formation. Ring closure proceeded to give β-lactam **21** in 80% yield.

We applied this method to the total synthesis (Scheme 4). Oxidation of the primary hydroxy group of **14β** using standard conditions (Dess–Martin, IBX,[22] Swern oxidation etc.) resulted in decomposition or low yields of the aldehyde. This step was only successful with Aladro's TEMPO conditions,[23] which gave carboxylic acid **22** in one pot. This was condensed with (benzyloxy)amine to give benzyl hydroxamate and the silyl group was removed to give diol **23**. Tosylation proved troublesome: **23** underwent preferential *N*-tosylation at the hydroxamate using either TsCl/Py or $TsCl/Et_3N$. Fortunately, mesylation was successful and the resulting monomesylate crystallized. A single recrystallization was sufficient to give a diastereomerically pure sample.[24] The tertiary



Scheme 3. Model studies of β-lactam formation: (a) i. TMSCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, ii. *t*-BuMgCl, THF/CH_2Cl_2; 0 °C to rt, 12 h, iii. AcOH (30%); (b) H_2, Pd/C, EtOH (quant); (c) i. TsCl, Py, ii. TMSOTf, 2,6-lutidine (88%); (d) NaH, THF (80%).



Scheme 4. Synthesis of (−)-1 and (+)-(3′*R*)-**1**: (a) TEMPO, NaClO, $NaClO_2$, MeCN/H_2O, rt, 12 h (89%); (b) i. $NH_2OBn{\cdot}HCl$, $NaHCO_3$, HOBt, EDCI, 0 °C to rt, 12 h (95%), ii. TBAF, THF; 0 °C, 1 h (86%); (c) i. MsCl, Et_3N, $CHCl_3$, rt, 12 h, ii. recrystallization (91%), iii. TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 2 h (88%); (d) KHMDS, THF, −78 to 0 °C, 24 h (59% of **25** and 11% of **26**); (e) i. TBAF, THF, 0 °C, ii. H_2, Raney-Ni, H_2O–MeOH (1:2) (89% from **25** and 68% from **26**).

hydroxy group was protected as a TBS ether to afford **24**; a TMS group at this position was unable to withstand the conditions of the next step. β-Lactam formation was achieved using KHMDS to give **25**, with debenzylated acid **26** as a by-product. Use of NaH increased the yield of **26**.[25] TBS deprotection of **25** and **26** followed by hydrogenolysis on Raney-Ni gave (−)-**1**.[26] The product was to be diastereomerically pure and the value of specific optical rotation was in good agreement with the literature value {$[\alpha]_D^{26}$ −24 (*c* 0.14, H_2O), lit.[6c] $[\alpha]_D^{25}$ −23.7 (*c* 0.30, H_2O)}. The overall yield was 28% in 12 steps from **5** and 24% in 15 steps from L-serine.

In a similar manner as described for (−)-**1**, (3′*R*)-isomer (+)-(3′*R*)-**1** was synthesized from **14α** {$[\alpha]_D^{25}$ +38 (*c* 0.09, H_2O), lit.[6c] $[\alpha]_D^{25}$ −38.0 (*c* 0.22, H_2O)}. The overall yield was 12% from **5**.

In summary the stereoselective synthesis of (−)-tabtoxinine-β-lactam (−)-**1**, a phytopathogenic compound of tobacco wildfire disease, and its (+)-(3′*R*)-isomer was achieved using zinc-mediated coupling, Sharpless asymmetric dihydroxylation, and β-lactam formation of hydroxamate as the key steps.

Acknowledgements

We thank Dr. Yoshifumi Itoh [Akita Research Institute of Food and Brewing (ARIF)] for academic assistance. This work was partially supported by a Grant-in-aid for Scientific Research from Japan Society for the Promotion of Science (No. 14760069), The Agricultural Chemical Research Foundation, Intelligent Cosmos Foundation and The Naito Foundation.

References and notes

1. Wolf, F. A.; Foster, A. C. *Science* **1917**, *46*, 361–362.
2. (a) Woolley, D. W.; Shaffner, G.; Braun, A. C. *J. Biol. Chem.* **1955**, *215*, 485–493, and references cited therein; (b) Stewart, W. W. *Nature* **1971**, *229*, 174–178; (c) Taylor, P. A.; Schnoes, H. K.; Durbin, R. D. *Biochim. Biophys. Acta* **1972**, *286*, 107–117; (d) Durbin, R. D.; Uchytil, T. F.; Steele, J. A.; Ribeiro, R. de L. D. *Phytochemistry* **1978**, *17*, 147.
3. (a) Uchytil, T. F.; Durbin, R. D. *Experientia* **1980**, *36*, 301302; (b) Thomas, D. M.; Langston-Unkefer, P. J.; Uchytil, T. F.; Durbin, R. D. *Plant Physiol.* **1983**, *71*, 912–915, and references cited therein.
4. (a) Anzai, H.; Yoneyama, K.; Yamaguchi, I. *Mol. Gen. Genet.* **1989**, *219*, 492–494; (b) Batchvarova, R.; Nikolaeva, V.; Slavov, S.; Bossolova, S.; Valkov, V.; Atanassova, S.; Guelemerov, S.; Atanassov, A.; Anzai, H. *Theor. Appl. Genet.* **1998**, *97*, 986–989.
5. (a) Liu, J.; Le, Y.; Ye, B.; Zhen, Y.; Zhu, C.; Shen, J.; Zhang, R. *Protein Expres. Purif.* **2002**, *24*, 439–444; (b) He, H.; Ding, Y.; Bartlam, M.; Sun, F.; Le, Y.; Qin, X.; Tang, H.; Zhang, R.; Joachimiak, A.; Liu, J.; Zhao, N.; Rao, Z. *J. Mol. Biol.* **2003**, *325*, 1019–1030.
6. (a) Baldwin, J. E.; Otsuka, M.; Wallace, P. M. *J. Chem. Soc., Chem. Commun.* **1985**, 1549–1550; (b) Baldwin, J. E.; Otsuka, M.; Wallace, P. M. *Tetrahedron* **1986**, *42*, 3097–3110; (c) Doll, R. E.; Li, C.-S.; Novelli, R.; Kruse, L. I.; Eggleston, D. *J. Org. Chem.* **1992**, *57*, 128–132.
7. (a) Snyder, B. B.; Johnston, M. I. *Synth. Commun.* **1987**, *17*, 1877–1886; (b) Greenlee, W. J.; Springer, J. P.; Patchett, A. A. *J. Med. Chem.* **1989**, *32*, 165–170.
8. (a) Baldwin, J. E.; Bailey, P. D.; Gallacher, G.; Singleton, K. A.; Wallace, P. M. *J. Chem. Soc., Chem. Commun.* **1983**, 1049–1050; (b) Baldwin, J. E.; Bailey, P. D.; Gallacher, G.; Otsuka, M.; Singleton, K. A.; Wallace, P. M. *Tetrahedron* **1984**, *40*, 3695–3708.
9. Lee, D. L.; Rapoport, H. *J. Org. Chem.* **1975**, *40*, 3491–3495.
10. Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1987**, *43*, 4297–4308.
11. (a) Baldwin, J. E.; Adlington, R. M.; Birch, D. J.; Crawford, J. A.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1339–1340; (b) Adlington, R. M.; Baldwin, J. E.; Basak, A.; Kozyrod, R. P. *J. Chem. Soc., Chem. Commun.* **1983**, 944–945.
12. (a) Dexter, C. S.; Jackson, R. F. W. *J. Org. Chem.* **1999**, *64*, 7579–7585; (b) Weigand, S.; Brückner, R. *Synthesis* **1996**, 475–482.
13. Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924–926.
14. (a) Pringle, W.; Sharpless, K. B. *Tetrahedron Lett.* **1999**, *40*, 5151–5154; (b) O'Brien, P. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 326–329.
15. (a) Kolb, H. C.; Van Nioeuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547; (b) Hale, K. J.; Manaviazar, S.; Peak, S. A. *Tetrahedron Lett.* **1994**, *35*, 425–428.
16. Loewe, M. F.; Cvetovich, R. J.; Hazen, G. G. *Tetrahedron Lett.* **1991**, *32*, 2299–2302.
17. Ohno, M.; Kobayashi, S.; Iimori, T.; Wang, Y.; Izawa, T. *J. Am. Chem. Soc.* **1981**, *103*, 2405–2406.

18. Murayama, T.; Kobayashi, T.; Miura, T. *Tetrahedron Lett.* **1995**, *36*, 3703–3706.
19. Miller, M. J.; Biswas, A.; Krook, M. A. *Tetrahedron* **1983**, *39*, 2571–2575.
20. (a) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161–6163; (b) Lynch, J. K.; Hoolladay, M. W.; Ryther, K. B.; Bai, H.; Hsiao, C.-N.; Morton, H. E.; Dickmann, D. A.; Arnold, W.; King, S. A. *Tetrahedron: Asymmetry* **1998**, *9*, 2791–2794; (c) Baldwin, J. E.; Adlingston, R. M.; Gollins, D. W.; Schofield, C. J. *Tetrahedron* **1990**, *46*, 4733–4748.
21. Haaf, K.; Rüchardt, C. *Chem. Ber.* **1990**, *123*, 635–638.
22. Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.
23. Aladro, F. J.; Guerra, F. M.; Moreno-Dorado, F. J.; Bustamante, J. M.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron Lett.* **2000**, *41*, 3209–3213.
24. Determined by ^{1}H NMR analysis.
25. Nagao, Y.; Nagase, Y.; Kumagai, T.; Matsunaga, H.; Abe, T.; Shimada, O.; Hayashi, T.; Inoue, Y. *J. Org. Chem.* **1992**, *57*, 4243–4249.
26. Compound (−)-**1**: amorphous solid. IR ν_{max} (KBr) cm^{-1}: 3230 (s, O–H, N–H), 1740(s, C=O), 1620 (m), 1400 (m), 1200 (m), 940 (w), 790 (w). ^{1}H NMR δ (D_2O, 300 MHz): 1.65–2.08 (4H, m, H-1′, H-2′), 3.20 (1H, d, J = 6.6 Hz, H-4), 3.32 (1H, d, H-4), 3.68 (1H, t, H-2′). ^{13}C NMR (D_2O, 75 MHz) δ: 25.33, 30.75, 51.43, 54.93, 84.57, 174.29, 174.79. HRMS (FAB^{+}) *m/z*: calcd for $C_7H_{13}N_2O_4$, 189.0875; found: 189.0879.