Pergamon

Tetrahedron Letters 40 (1999) 3581–3582

TETRAHEDRON LETTERS

An Enantiocontrolled Synthesis of the Masked Taxol C-13 Side Chain, Oxazoline Carboxylic Acid

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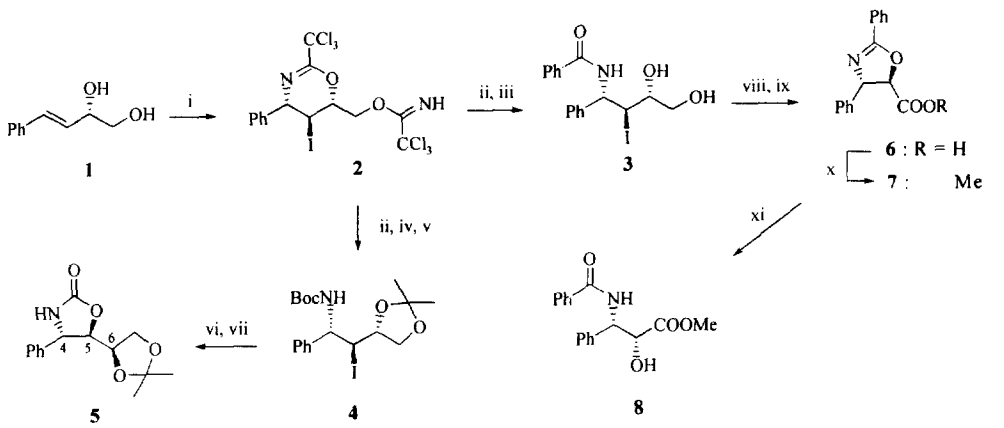
Received 18 January 1999; revised 9 March 1999; accepted 12 March 1999

Abstract : Oxazoline carboxylic acid **6** as the taxol side chain precursor has been efficiently synthesized *via* the intramolecular iodoamidation of allylic trichloroacetimidate derived from *trans*-olefinic diol **1**.

A prominent antitumor agent taxol, which is arduously extracted in small quantities from the Pacific yew's bark, is composed of the C-13 side chain N-benzoyl-(2*R*,3*S*)-phenylisoserine and the taxane skeleton baccatin III.[1,2] Although the economical preparation of baccatin III is unlikely to be attained by chemical synthesis, 10-deacetylbaccatin III can be extracted from the fresh needles of the European yew in high yield, which are restorable to serve as its continual source.[2] Therefore, the economical supply of taxol relies on the efficient synthesis of the side chain. A number of synthetic routes to the side chain have been explored.[3] In this paper we describe a new efficient synthesis of the taxane side chain precursor **5**, which can be directly coupled with 7-(triethylsilyl)baccatin III due to the masked hydroxyl group, *via* a stereo- and regio-selective intramolecular iodoamidation of allylic trichloroacetimidate.[4]

The synthesis of the precursor **6** began with *trans*-olefinic diol **1**, $[\alpha]_D^{26}$ +34.9 (*c* 0.87, $CHCl_3$), prepared from D-glyceraldehyde acetonide[5] *via* a three-step sequence of olefination, isomerization by a radical process[6] and acidic hydrolysis. **1** was exposed to trichloroacetonitrile in the presence of DBU and the following *in situ* cyclization of the generated bis(trichloroacetimidate) was conducted with IBr *via* 6-endo mode in a highly stereoselective manner.[4] The resulting dihydro-1,3-oxazine **2** was completely hydrolyzed and then monobenzoylated to produce iodo amide **3**, mp 127.5 – 128.5 °C, $[\alpha]_D^{26}$ -2.3(*c* 0.70, MeOH), in 69% overall yield, of which any appreciable amounts of stereo- and regio-isomers could not be isolated. The assigned structure of **3** was supported by the following transformation. **2** was hydrolyzed, and then protected as carbamate and acetonide in sequence to afford iodide **4** in 79% yield from **1**. **4** was treated with TBSOTf[7] and the resulting silyl carbamate was cyclized to give oxazolidinone **5** in 91% yield, of which the stereochemistry was corroborated by the coupling constant ($J_{H4, H5}$ = 5.7 Hz) and NOE experiments (4.4 % for Ph-H_5 and 2.3% for H_4 – H_6). The *vic*-diol group of **3** was oxidatively cleaved with sodium periodate and subsequently oxidized with sodium chlorite[8] to furnish oxazoline carboxylic acid **6**, mp 268-269 °C, $[\alpha]_D^{27}$ -23.0 (*c* 0.60, MeOH), in 79% overall yield, which had been utilized in the preparation of taxol.[9,10] Since sodium borohydride reduction of the aldehyde generated from the oxidative cleavage of **3** provided amido iodo alcohol, the oxazoline ring of **6** must be formed in the sodium chlorite oxidation stage. Carboxylic acid **6** was converted into the known oxazoline methyl ester **7**, $[\alpha]_D^{26}$+18.0 (*c* 0.65, $CHCl_3$) {lit.,[11] $[\alpha]_D^{20}$ +13 (*c* 1, $CHCl_3$)}, quantitatively. On the other hand, the acid **6** was subjected to methanolic HCl, and then refluxed after addition of a little water. Finally, the probable intermediate O-benzoyl-(2*R*,3*S*)-phenylisoserine methyl

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00577-8



Reagents : i) Cl_3CCN, DBU, MeCN, -30 °C; IBr, K_2CO_3, -30 ~ -10 °C. ii) 6N HCl, MeOH, rt. iii) PhCOCl, $NaHCO_3$, MeOH, 0 °C. iv) Boc_2O, $NaHCO_3$, MeOH, -10 °C. v) *p*-TsOH, acetone, rt. vi) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C. vii) *n*-Bu_4NF, THF, rt. viii) $NaIO_4$, acetone, H_2O, rt. ix) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, Bu'OH, H_2O, rt. x) CH_2N_2, MeOH, 0 °C. xi) AcCl (cat.), MeOH, rt ; H_2O (a few drops), reflux; aq. $NaHCO_3$, rt.

ester was treated with saturated aqueous sodium bicarbonate for the migration of the benzoyl group from oxygen to nitrogen to afford N-benzoyl-(2*R*,3*S*)-phenylisoserine methyl ester **8**, mp 183-184 °C, $[\alpha]_D^{26}$ -48.9 (*c* 0.93, MeOH) {lit.,[11] $[\alpha]_D^{20}$ -49 (*c* 1, MeOH)}, in 94% overall yield.[12]

Acknowledgement : This work was supported by Creative Research Initiatives of the Korean Ministry of Science and Technology.

References and Notes

1. Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A.T. *J. Am. Chem. Soc.* **1971**, *93*, 2325-2327; *Chem. Ind.* **1993**, 41.
2. Denis, J.-N.; Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F.;Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917-5919.
3. Mukai, C.; Kim, I. J.; Hanaoka, M. *Tetrahedron: Asymmetry*, **1992**, *3*, 1007-1010; Ojima, I.;Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron*, **1992**, *48*, 6985-7012; Georg, G. I.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. *Bioorg. Med. Chem. Lett.* **1993**, *3*. 2467-2470; Bonini, C.; Righi, G. *J. Chem. Soc. Chem. Commun.* **1994**, 2767-2768; Hanessian, S.; Sancéau, J.-Y. *Can. J. Chem.* **1996**, *74*, 621-624 and references cited therein; Li, G.; Sharpless, K. B. *Acta Chemica Scandinavica*, **1996**, *50*, 649-651; Jost, S.; Gimbert Y.; Greene, A. E. ; Fotiadu, F. *J. Org. Chem.* **1997**, *62*, 6672-6677.
4. *Cf.* Kang, S. H.; Lee, S. B. *J. Chem. Soc. Chem. Commun.* **1998**, 761-762; Kang, S. H.; Jun, H.-S. *J. Chem. Soc. Chem. Commun.* **1998**, 1929-1930; Kang, S. H.; Kim, J. S.; Youn, J.-H. *Tetrahedron Lett.* **1998**, *39*, 9047-9050.
5. Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron*, **1986**, *42*, 447-488.
6. Schwarz, M.; Gramminski, G. F.; Waters, R. M. *J. Org. Chem.* **1986**, *51*, 260-263.
7. Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543-5546.
8. Bal, B. S.; Childers, W. E.; Pinnik, H. W. *Tetrahedron*, **1981**, *37*, 2091-2096.
9. Kingston, D. G.; Chaudhary, A. G.; Gunatilaka, A. A. L.; Middleton, M. L. *Tetrahedron Lett.* **1994**, *35*, 4483-4484.
10. *Spectroscopic data* for **6** : ^{1}H NMR (200MHz, CD_3OD) δ 4.85 (1H, d, J 6.4), 5.31 (1H, d, J 6.4), 7.12-7.33 (5H, m), 7.33-7.56 (3H, m) and 7.93-7.97 (2H, m). ^{13}C NMR (50.3 MHz, $CDCl_3/CD_3OD$ =10/1) δ 73.8, 85.0, 126.1, 126.5, 127.3, 128.0 (2 carbons), 128.2, 131.6, 141.7, 164.8 and 176.6.
11. Gou, D.-M.; Liu, Y.-C.; Chen, C.-S. *J. Org. Chem.* **1993**, *58*, 1287-1289.
12. Bunnage, M. E.; Davis, S. G.; Goodwin, C. J. *J. Chem. Soc. Perkin Trans. 1*, **1993**, 1375-1376.