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# Expeditious Semisynthesis of Docetaxel Using 2-Trichloromethyl-1,3-Oxazolidine as Side-Chain Protection

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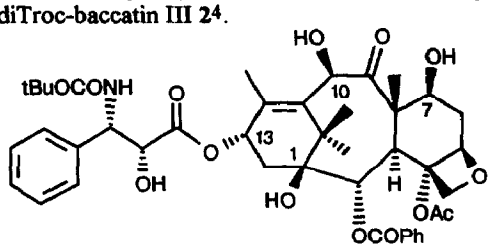
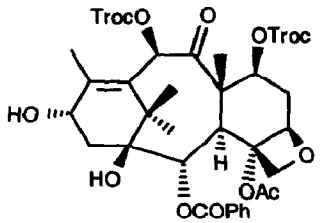
**Abstract:** Chloral reacts with phenylisoserine and N-Boc-phenylisoserine methyl esters to give N-unprotected 2-trichloromethyl-1,3-oxazolidines 4+4'. The corresponding oxazolidinecarboxylic acids 5+5' were esterified by 10-desacetyl-7,10-diTroc-baccatin III. Concomitant deprotection of the Troc and 2-trichloromethylmethylene groups was achieved under reducing conditions (Zn, AcOH). The recovered product 7 was acylated with di-*tert*-butyldicarbonate to give docetaxel 1.

In another paper[1] we described a significant improvement in the semisynthesis of anticancer agent docetaxel 1[2] using 2-(4-methoxy-phenyl) and 2-(2,4-dimethoxy-phenyl) oxazolidines as protective groups of N-Boc-phenylisoserine rather than the corresponding 2,2-dimethyl-oxazolidine protection[3]. These 2-monoalkyl-oxazolidine-type protections were easily cleaved without removal of the Boc group.

In this paper we report an unprecedented protection of phenylisoserine and phenylisoserinates by trichloroacetaldehyde (chloral) and its use in an expeditious semisynthesis of docetaxel from 10-desacetyl-7,10-diTroc-baccatin III 2[4].




1 (docetaxel)



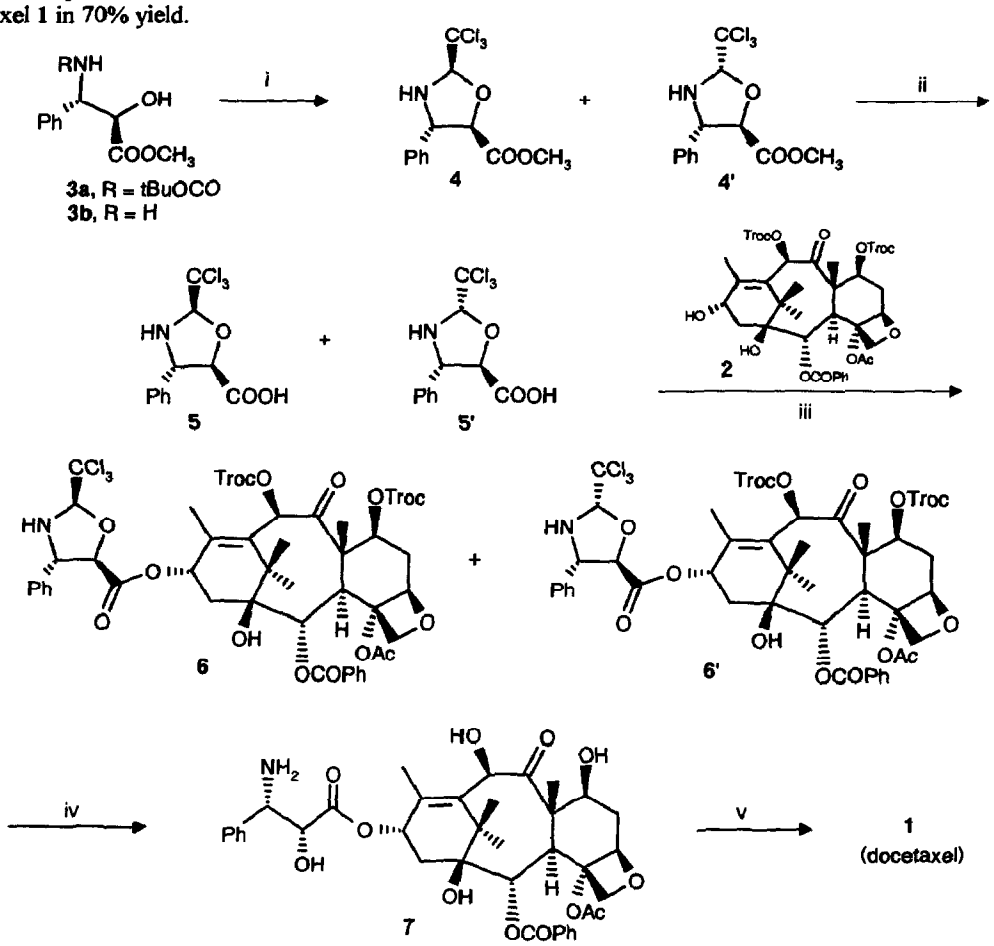

2, Troc = $Cl_3CCH_2COO$-

Trichloroacetaldehyde (chloral) has been reported in the literature to react with β-aminoalcohols[5] or α -aminoacids[6] to give 2-trichloromethyl-oxazolidines and 2-trichloromethyl-5-oxazolidinones respectively. In our search for new oxazolidine-type protections of phenylisoserine, 2-trichloromethyl-oxazolidine appeared to be a suitable cyclic protection which might be cleaved under reducing conditions along with the O-diTroc protective groups on the baccatin moiety[7]. Thus we attempted the reaction of methyl phenylisoserinate **3a** with chloral[8].

Cyclization of **3a**[3] with trichloroacetaldehyde (20 eq.) in the presence of pyridinium *p*-toluenesulfonate (PPTS) in refluxing toluene afforded the oxazolidine derivatives **4+4'** but with removal of the Boc group (91% yield; 30% d.e.; the configuration of the major diastereomer at the 2-position was shown to be *S* by X-ray crystallographic analysis). By treatment with lithium hydroxide in methanol, esters **4+4'** gave in nearly quantitative yield the corresponding acids **5+5'** (same ratio of diastereomers). We subsequently found that we could directly obtain esters **4+4'** (35% d.e.) by reaction of methyl phenylisoserinate **3b**[9] with chloral using the same cyclization conditions.

Coupling reaction of carboxylic acids **5+5'** with the O-diprotected baccatin derivative **2** afforded the corresponding esterification products **6+6'** in nearly quantitative yield (hydroxyl at C-1 is known to be unreactive as is the weakly basic oxazolidine nitrogen). No epimerization at C-5 on the oxazolidine ring was detected under esterification conditions. Simultaneous cleavage of 2-trichloromethyl-oxazolidine ring and of the Troc protective groups on the baccatin core occurred in 65% yield from **6+6'** with zinc in AcOH/AcOEt

at room temperature. The recovered amino-derivative 7 was acylated using standard procedure[3] to give docetaxel 1 in 70% yield.




Reagents: i) from **3a**: 2, $CCl_3CHO$ (20eq.), PPTS (cat.), toluene (dist. 0.5h), flash chromatography in AcOEt/cyclohexane 1/3, 91% (30% d.e. by NMR); from **3b**: $CCl_3CHO$ (4eq.), PPTS (cat.), toluene at reflux (Dean Stark, 1.5h), 96% (35% d.e. by HPLC); ii) LiOH·$H_2O$ (1.1eq), MeOH, $H_2O$, HCl 1N, >90%; iii) 2, 5+5' (1.8eq.), DCC (1.03eq.), DMAP (0.2eq.), toluene, 25°C (3h.); iv) 6+6', Zn (10eq.), AcOH (40eq.), AcOEt, 25°C (16h), 65% by HPLC from 2; v) 7, Di-*tert*-butyl dicarbonate (1.2eq.), MeOH, 25°C (15h), 70% by HPLC.

**References and notes:**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2. For a recent review on docetaxel, see: Lavelle F., Guéritte-Voegelein F., Guénard D., *Bull. Cancer*, **1993**, *80*, 326-338.
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6. Dane E., Heiss R., Schäfer H., *Angew. Chem.*, **1959**, *71*, 339.
7. Cleavage of trichloromethylacetals of 1,2-diols with zinc in acetic acid has been reported; see: Overman L.E., Campbell C. B., *J. Org. Chem.*, **1974**, *39*, 1474-1481.
8. All new compounds exhibit IR, $^1$H-NMR and mass spectra in agreement with the structure indicated.
9. Compound **3b** can be prepared in 75% yield by deprotection of **3a** in formic acid at room temperature.


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