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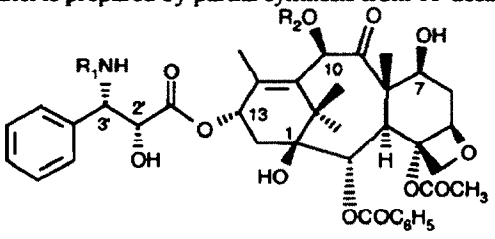
2-Monosubstituted-1,3-Oxazolidines as Improved Protective Groups of N-Boc-Phenylisoserine in Docetaxel Preparation

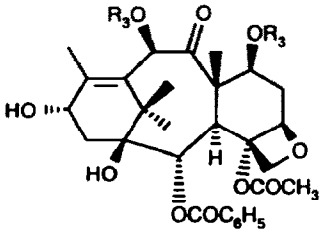
Eric Didier*, Elie Fouque, Isabelle Taillepied and Alain Commerçon

Rhône-Poulenc Rorer S.A.- Centre de Recherches de Vitry-Alfortville
13, Quai Jules Guesde - BP14 - 94403 Vitry-sur-Seine (France)

Abstract: A new route for semisynthetic docetaxel, **1**, is described using 2-monosubstituted-4-phenyl-1,3-oxazolidine-5-carboxylic acids in esterification of 7,10-O-diTroc-10-desacetylbaccatin III (**4**). Subsequent deprotection of esters **10(+10')** afforded title compound **1** without removal of the Boc group.

Docetaxel (Taxotere®) **1**, like the structurally related natural product paclitaxel (Taxol®) **2**, belongs to a new class of antitumor drugs able to interfere with the microtubule-tubulin system[1]. These two taxoids are now well-established as clinically active anticancer agents[2]. Paclitaxel can be extracted from yew bark[3] while docetaxel is prepared by partial synthesis from 10-desacetylbaccatin III **3** obtained from yew needles[4].

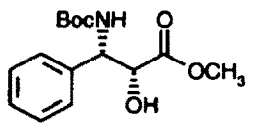




1, R_1=tBuOCO, R_2=H (docetaxel)
2, R_1=C_6H_5CO, R_2=Ac (paclitaxel)

3, R_3=H (10-desacetylbaccatin III)
4, R_3=Troc (Cl_3CCH_2COO)

In a previous paper[5], we showed that (4S,5R)-N-Boc-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid **6**, obtained from (2R,3S)-N-(*tert*-butoxycarbonyl)-3-phenylisoserine methyl ester **5**[6] by cyclization with 2-methoxypropene and subsequent saponification, afforded upon coupling with the O-diprotected baccatin III derivative **4**[4] the corresponding ester in high yields without epimerization at C-2'. Subsequent cleavage of the oxazolidine ring by formic acid at room temperature resulted in an undesired concomitant removal of the Boc group at the nitrogen atom to give product **7** rather than **1**.



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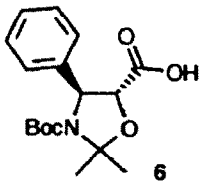

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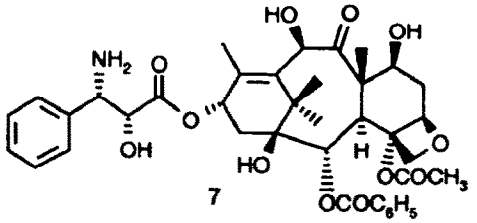

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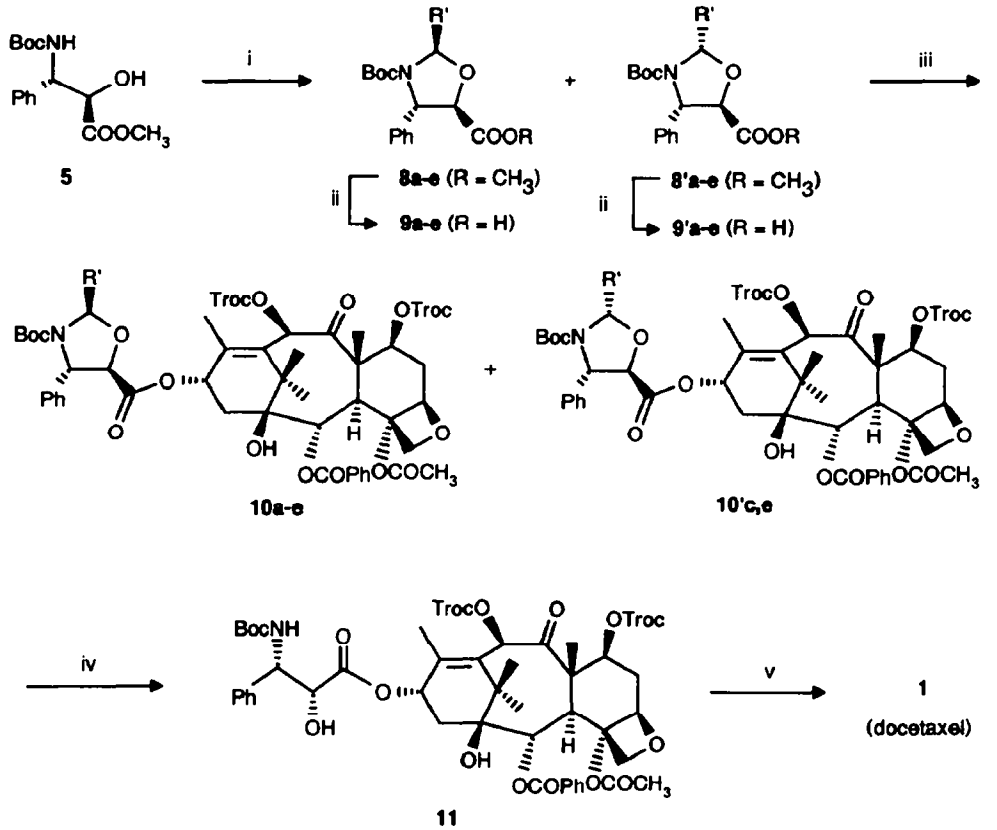
In order to retain the Boc moiety, we investigated a large number of other smooth acidic conditions[7] but none afforded a chemoselective opening of the oxazolidine ring. These results led us to examine other oxazolidine-type protections. Conveniently 2-modified oxazolidines appeared to be suitable candidates.

As depicted in Scheme 1, cyclic N,O-acetalization of compound **5** with selected aldehydes or dimethylacetals in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) afforded the corresponding 2-monosubstituted-1,3-oxazolidine methyl esters **8a-e** and **8'a-e** as mixtures of diastereomers in 40-80% yield[8]. In several cases, under kinetic control[9] (entries **a**, **b** and **d**, Table 1), the reaction gave diastereomeric excesses higher than 70%, allowing the isolation of the major diastereomers **8a**, **8b** and **8d** in 50-74% yields after a single crystallization from the crude reaction products. A diastereomeric excess of 40% was obtained for compound **8e** while a quasi-equimolar diastereomeric mixture of **8c** and **8'c** was obtained under thermodynamic control. The configuration of diastereomer **8b** at the 2-position was shown to be *R* by NOE experiments. Further ^{1}H-NMR correlations confirmed the same configuration for compounds **8a** and **8d**.



Scheme 1

Reagents; i) **8a**: 5, $PhCH(OCH_3)_2$ (1.1eq.), PPTS (cat.), toluene, 80°C (dist. 2h), cryst. in diisopropylether; **8b**: 5, 4-OMe-$PhCH(OCH_3)_2$ (1.1eq.), PPTS (cat.), toluene (dist. 0.5h), cryst. toluene/cyclohexane; **8c+8'c**: 5, 2,4-$(OMe)_2$-PhCHO (1.05eq.), PPTS (cat.), toluene (dist. 24h, Dean Stark); **8d**: 5, 3,4-$(OMe)_2$-$PhCH(OCH_3)_2$ (1.02eq.), PPTS (cat.), toluene (dist. 0.5h), cryst. in diisopropylether; **8e+8'e**: 5, $CH(OCH_3)_3$ (1eq.), PPTS (cat.), toluene (dist. 2h), cryst. in n-hexane. ii) KOH or $LiOH{\cdot}H_2O$ (1.1eq), MeOH, H_2O, HCl 1N, >90% for **9a,b,d** and **9e+9'e**, 74% for **9c+9'c**. iii) **10a**: 4, **9a** (3eq.), DCC (3eq.), DMAP (0.2eq.), toluene, 25°C (24h), flash chromatography in n-hexane/AcOEt: 1/1, 75%; **10b**: 4, **9b** (1.7eq.), DCC (1.06eq.), DMAP (0.2eq.), toluene, 25°C (2h); **10c+10'c**: 4, **9c+9'c** (3eq.), DCC (3eq.), DMAP (0.2eq.), toluene, 25°C (5h); **10d**: 4, **9d** (1.3eq.), DCC (1.3eq.), DMAP (0.2eq.), toluene, 0°C (1h); **10e+10'e**: 4, **9e+9'e** (2eq.), DCC (2eq.), DMAP (0.2eq.), toluene, 25°C (4h); iv) CH_3SO_3H (1.2eq.) or PTSA (1 eq.), MeOH, 25°C, (1-48h); from **10e+10'e**: aq. HCl (37%) (1.3eq.), AcOEt, 25°C (20h); v) Zn (11eq.), AcOH (40 eq.), AcOEt, 3h, 30°C, 95% by HPLC.

Table 1

Entry	R'	Compounds 8+8'		Compound 11	
		Yield (%)	d.e. (%) by HPLC[a]	Yield from 4 (%) by HPLC[a]	Conditions
a	Ph	65 (**8a**)	>97	50	MSA, MeOH, r.t., 48h
b	4-MeO-Ph	74 (**8b**)	>99	92	PTSA, MeOH, r.t., 1h
c	2,4-$(MeO)_2$-Ph	80 (**8c+8'c**)	<5	88	MSA, MeOH, r.t., 4h
d	3,4-$(MeO)_2$-Ph	50 (**8d**)	>97	86	MSA, MeOH, r.t., 2h
e	MeO	40 (**8e+8'e**)	30[b]	53	37% aq.HCl, AcOEt, r.t., 1h

[a] External standardization [b] Measured by ^{1}H-NMR;

Alkaline hydrolysis of the methyl esters **8a,b,d** and **8c+8'c** to give the corresponding carboxylic acids **9a,b,d** and **9c+9'c** was carried out in nearly quantitative yields under standard conditions while that of 2-methoxy-oxazolidines **8e+8'e** and acidification to pH=5 resulted partly in deprotection of the oxazoline ring due to its high lability in an acidic medium (16% of the corresponding NH-Boc-hydroxy acid followed by HPLC).

The coupling of carboxylic acids **9(+9')** with the O-diprotected baccatin derivative **4** afforded the corresponding esters **10(+10')** in nearly quantitative yield and without detectable epimerization at C-5 on the oxazolidine ring. Only in the case of **9a**, coupling remained incomplete after 24h and ester **10a** was obtained in 75% yield after chromatography. Esterification of **9e+9'e** was carried out on a crude mixture containing about 16% of the corresponding NH-Boc-hydroxy acid (*vide supra*).

Acid-mediated oxazolidine cleavage of the crude esters **10(+10')** was carried out with methanesulfonic acid (MSA) or *p*-toluenesulfonic acid (PTSA) in methanol at room temperature (see Table I). Derivative **10a** was very slowly and incompletely deprotected even after 48 h reaction with MSA. Deprotection of **10e+10'e** with aq. HCl (37%) in AcOEt at room temperature afforded within 1 hour the 2'-O-formyl intermediate which gave very slowly and incompletely product **11** in 53% yield from **4** after 20h.

Deprotection of the 2,2,2-trichloroethoxycarbonyl (Troc) groups from **11** was carried out by the standard procedure to give docetaxel **1** in 95% yield.

These results demonstrate that oxazolidines bearing 4-methoxy-phenyl and 3,4-dimethoxy-phenyl substituents at the 2-position are the most suitable protective groups for retaining the Boc moiety under acidic cleavage. This methodology has proved general and easily applicable to the preparation of docetaxel analogs having modified phenylisoserine side-chains.

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References and notes:

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8. All new compounds exhibit IR, ^{1}H-NMR spectra and mass spectra in agreement with the structure indicated. As examples, we report herein the ^{1}H-NMR data of docetaxel precursors in the 2-(2,4-dimethoxy-phenyl)-oxazolidine series (analytical samples).
8c+8'c: foam, ^{1}H-NMR (250 MHz, DMSO-d_6): δ 1.00 (s, $C(CH_3)_3$ **8c**), 1.22 (s, $C(CH_3)_3$ **8'c**), 3.55 (bs, OCH_3 **8c**), 3.75-3.85 (m, OCH_3), 4.64 (d, J=4.5Hz, H(5) **8c**), 5.01(d, J=2.5Hz, H(5) **8'c**), 5.21 (d, J=2.5Hz, H(4) **8'c**), 5.26 (d, J=4.5Hz, H(4) **8c**), 6.46 (dd, J=7.5Hz and 1.5Hz, H(C_6H_5) **8'c**), 6.52 (s, H(2) **8'c**), 6.50-6.65 (m, H(2) **8c** + H(C_6H_5)), 7.00 (d, J=7.5Hz, H(C_6H_5) **8'c**), 7.10 (d, J=7.5Hz, H(C_6H_5) **8c**), 7.30-7.55 (m, C_6H_5).
9c+9'c: foam, ^{1}H-NMR (200 MHz, DMSO-d_6, 393°K): δ 1.00 (s, $C(CH_3)_3$ **9c**), 1.25 (s, $C(CH_3)_3$ **9'c**), 3.75-3.85 (m, OCH_3), 4.43 (d, J=5Hz, H(5) **9c**), 4.77 (d, J=2Hz, H(5) **9'c**), 5.21 (d, J=5Hz, H(4) **9'c**), 5.21 (d, J=5Hz, H(4) **9c**), 6.42 (dd, J=7.5 and 1.5Hz, H(C_6H_5) **9'c**), 6.49 (s, H(2) **9'c**), 6.45-6.60 (m, H(2) **9c** + H(C_6H_5)), 7.02 (d, J=7.5Hz, H(C_6H_5) **9'c**), 7.15 (d, J=7.5Hz, H(C_6H_5) **9c**), 7.25-7.50 (m, C_6H_5).
10c: foam, ^{1}H-NMR (400 MHz, $CDCl_3$, 323°K): δ 1.10 (s, 9H, $C(CH_3)_3$), 1.16 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.66 (s, 1H, OH), 1.82 (s, 3H, CH_3), 2.00 (s, 3H, $COCH_3$), 2.00 (m, 1H, 1H of CH_2), 2.12 (dd, J=15 and 9Hz, 1H, 1H of CH_2), 2.24 (dd, J=15 and 9Hz, 1H, 1H of CH_2), 2.6 (m, 1H, 1H of CH_2), 3.82 (d, J=7Hz, 1H, CH), 3.82 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.12 (d, J=8Hz, 1H, 1H of CH_2), 4.26 (d, J=8Hz, 1H, 1H of CH_2), 4.55 (d, J=4Hz, H, CH), 4.62(d, J=12Hz, 1H, 1H of CH_2), 4.78 (ab, J=11Hz, 2H, CH_2), 4.89 (d, J=10Hz, 1H, CH), 4.89 (d, J=12Hz, 1H, 1H of CH_2), 5.46 (bd, J=4Hz, 1H, CH), 5.50 (dd, J=11 and 7Hz, 1H, CH), 5.65 (d, J=7Hz, 1H, CH), 6.05 (t, J=9Hz, 1H, CH), 6.16 (s, 1H, CH), 6.50 (m, 2H, H(C_6H_5)), 6.72 (bs, 1H, CH), 7.22 (d, J=7.5Hz, 1H, H(C_6H_5)), 7.30-7.50 (m, 5H, C_6H_5), 7.48 (t, J=7.5Hz, 2H, H(C_6H_5)), 7.63 (t, J=7.5Hz, 1H, H(C_6H_5)), 8.03 (d, J=7.5Hz, 2H, H(C_6H_5)).
10'c: foam, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.20 (s, 3H, CH_3), 1.25 (s, 9H, $C(CH_3)_3$), 1.30 (s, 3H, CH_3), 1.76 (s, 1H, OH), 1.85 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.05 (m, 1H, 1H of CH_2), 2.17 (s, 3H, $COCH_3$), 2.26 (dd, J=15 and 9Hz, 1H, 1H of CH_2), 2.34 (dd, J=15 and 9Hz, 1H, 1H of CH_2), 2.60 (m, 1H, 1H of CH_2), 3.82 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.95 (d, J=7Hz, 1H, CH), 4.14 (d, J=8Hz, 1H, 1H of CH_2), 4.30 (d, J=8Hz, 1H, 1H of CH_2), 4.62 (d, J=12Hz, 1H, 1H of CH_2), 4.90 (limit ab, 2H, CH_2), 4.90 (m, 1H, CH), 4.92 (m, 1H, CH), 4.92 (d, J=12Hz, 1H, 1H of CH_2), 5.36 (d, J=2Hz, 1H, CH), 5.63 (dd, J=11 and 7Hz, 1H, CH), 5.70 (d, J=7Hz, 1H, CH), 6.28 (s, 1H, CH), 6.34 (t, J=9Hz, 1H, CH), 6.43 (dd, J=7.5 and 1.5Hz, 1H, H(C_6H_5)), 6.51 (d, J=1.5Hz, 1H, H(C_6H_5)), 6.69 (s, 1H, CH), 7.16 (d, J=7.5Hz, 1H, H(C_6H_5)), 7.35-7.50 (m,3H, H(C_6H_5)), 7.48 (t, J=7.5Hz, 2H, H(C_6H_5)), 7.57 (d, J=7.5Hz, 2H, H(C_6H_5)), 7.63 (t, J=7.5Hz, 1H, H(C_6H_5)), 8.04 (d, J=7.5Hz, 2H, H(C_6H_5)).
9. Kinetic control was performed by adding a toluene solution of aldehyde or dimethylacetal derivative within 5-15 minutes to a refluxing toluene solution of substrate **5** and PPTS (10%) with simultaneous azeotropic distillation of methanol or water. The total refluxing period did not take more than 0.5-2h.

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