Synthesis and Biological Evaluation of 2′-Methyl Taxoids Derived from Baccatin III and 14*β*-OH-Baccatin III 1,14-Carbonate

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Abstract: A series of 2′-methyl taxoids were synthesized and essayed for growth inhibition experiments conducted in human ovarian cancer cell line A2780wt and its counterparts A2780cis, A2780tax, and A2780adr, resistant to cisplatin, paclitaxel, and doxorubicin, respectively, to test the effect of this substituent on the antitumor activity. Additional experiments were performed on MCF-7 human breast cancer cell line and MCF7-R resistant to doxorubicin. In several cases these taxoids were more active than paclitaxel showing subnanomolar IC_{50} values.

Introduction. The naturally occurring taxoids, paclitaxel and docetaxel, exhibit outstanding therapeutic activity against solid tumors.[1] Clinical use of these agents, however, demonstrates that these drugs have various undesirable side effects including peripheral neuropathies. Moreover, therapy often leads to the development of multidrug resistance (MDR), one of the most common mechanisms of drug resistance.[2] MDR induced by taxoid treatment may be mediated by a number of mechanisms, including overexpression of the energy-dependent drug-transporter P-glycoprotein that acts as an efflux system for a number of xenobiotics, thereby reducing their intratumor cell concentration and effectiveness.[3] Therefore, modifications of the diterpene moiety and the isoserine appendants of taxoids were investigated to improve the pharmacological profile of this class of agents.[4] The literature reports a series of new taxanes which were synthesized from 14*β*-OH-10-deacetyl-baccatin III (14*β*-OH-DAB, Chart 1), a naturally occurring synthon isolated from the needles of *Taxus wallichiana Zucc*.[5] Among these compounds, the taxoids derived from 14*β*-OH-baccatin III 1,14-carbonate display improved pharmacological properties,

Chart 1. 14*β*-OH-DAB and Ortataxel

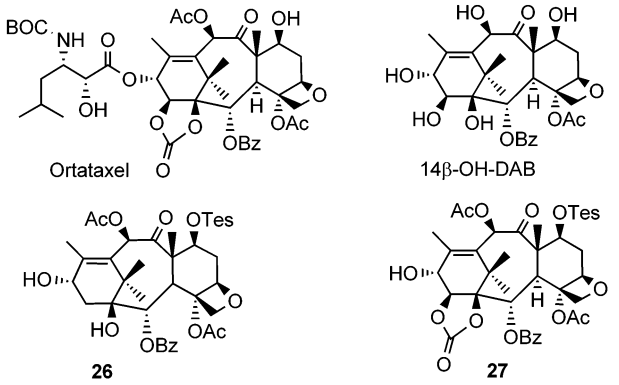
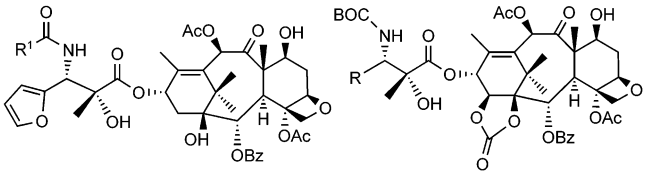


Chart 2. Compounds **1**−**5**



1: $R^1 = C_6H_5$; **2**: $R^1 = Me_3CO$

3: R = 2-furyl; **4**: $R = C_6H_5$; **5**: $R = CF_3$

including increased oral bioavailability as compared to paclitaxel and docetaxel, and a greater ease of formulation. Moreover, several of these newly synthesized taxanes revealed remarkable increases in cytotoxicities in cell lines which express MDR, such as doxorubicin-resistant human breast cancer cell lines. One of these new taxanes, Ortataxel (BAY59-8862, IDN5109), exhibited 2 orders of magnitude better cytotoxicity than paclitaxel against drug-resistant cells, and it has been selected for clinical development.[6] Additional in vitro assays have shown that the analogues of paclitaxel and docetaxel with an additional methyl substituent at the C-2′ position display higher cytotoxic activity compared to the parent compounds when evaluated in vitro assays using HCT116 human colon carcinoma cell lines.[7−9] The enhanced potency is probably due to a reduction in the degree of freedom of rotation at the C′2−C′3 bond or of some additional hydrophobic interactions between the 2′-methyl and the microtubule binding sites. For this reason, we started with a research program of synthesis and in vitro studies of a small library of 2′-methyl taxanes (Chart 2). Two compounds are derivatives of baccatin III. The heteroaromatic 2-furyl group was selected at the 3′ position of the appendant of the two taxanes which differed in the type of substituent at the nitrogen atom: a benzoyl group (compound **1**), or a BOC (**2**).[10] We have also synthesized three derivatives of 14*β*-OH-baccatin III 1,14-carbonate carrying a BOC group at the nitrogen atom. These compounds beared a 2-furyl (**3**), a phenyl (**4**), and a trifluoromethyl (**5**). All taxoids bear the acetyl group at C-10 because it has been observed that the presence of a substituent at this position is essential for modulation of P-gp, hence to overcome MDR in vitro.[5a] Compounds **1**−**5** were tested in a panel of ovarian carcinoma cell lines and several have demonstrated increased activity as compared to

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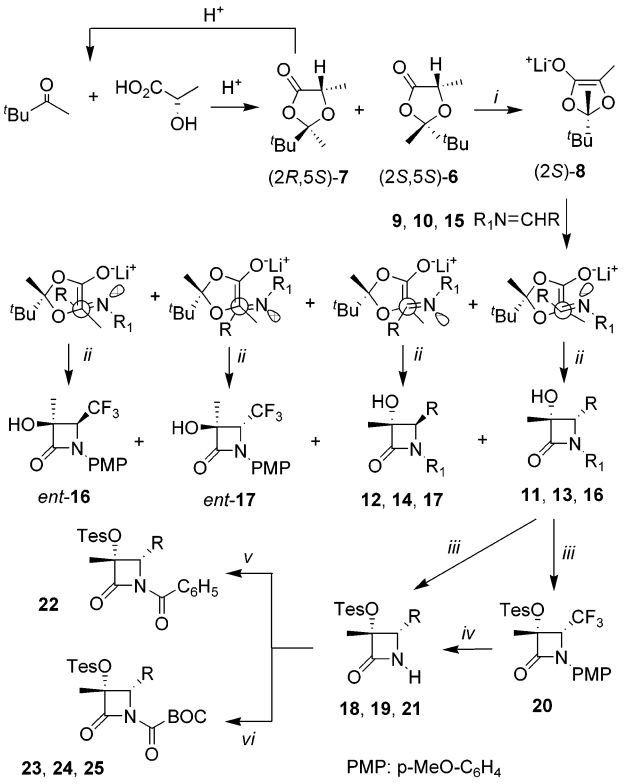
Scheme 1[a]



9: R = 2-Furyl, R^1 = Me_3Si; **10**: R = C_6H_5, R^1 = Me_3Si; **15**: R = CF_3, R^1 = PMP;
11, **12**, **18**: R = 2-Furyl, R^1 = H; **13**, **14**, **19**: R = C_6H_5, R^1 = H;
15, **16**, **17**, **20**: R=CF_3, R^1 = PMP; **21**: R = CF_3, R^1 = H;
22: R = 2-Furyl; **23**: R = 2-Furyl; **24**: R = C_6H_5; **25**: R = CF_3

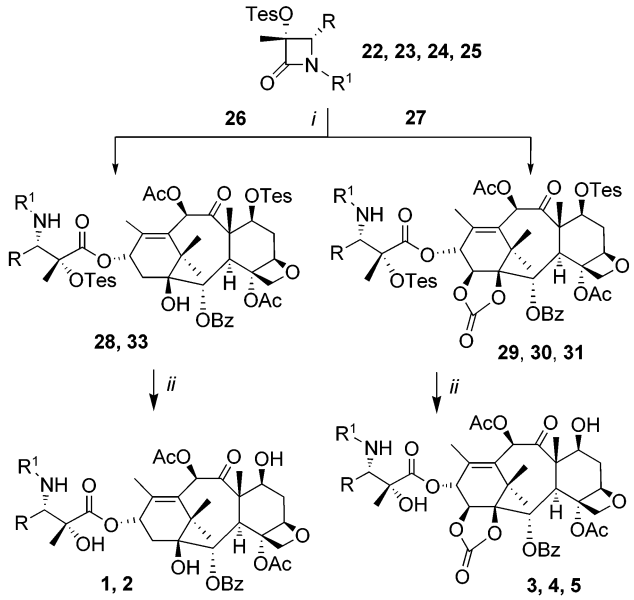
[a] Reagents: (i) LDA or LiHMDS/THF/HMPA (85:15)/−78 °C; (ii) *t*BuMeC=O; (iii) TesCl/imidazole; (iv) CAN; (v) C_6H_5COCl/$NaHCO_3$; (vi) BOC_2O/DMAP.

paclitaxel in multidrug resistant ovarian (and breast) tumor cell lines. The possibility to identify new cytotoxic agents active on wild-type, and more importantly on resistant cell lines, has been explored in order to improve the therapeutic outcome of taxane treatment on cancer.

Results and Discussion. A. Synthesis of New Taxoids. The addition of baccatin derivatives to 1-acyl-*β*-lactams,[11] or *N*,*O*-protected isoserinic acids (usually as oxazolidine derivatives),[12] are well established protocols for the semisynthesis of taxoids. The C7-OH group of the diterpene moiety must be protected to avoid the epimerization of this stereocenter.[13] We have used the *β*-lactam protocol for the synthesis of taxoids **2**-**5** bearing a BOC group at the C3′-nitrogen atom. Instead, the oxazolidine route was used for the synthesis of the *N*-benzoyl analogue **1**. Some years ago, we developed a versatile protocol for the asymmetric synthesis of trisubsituted 3-hydroxy-*β*-lactams which uses readily available aldimines and (2*S*)-α-hydroxy carboxylic acids as starting reagents.[14] This strategy is attractive because can tolerate a range of substituents at the 3- and 4-position of the resulting 3-hydroxy *β*-lactams. Accordingly, the (2*S*)-lactic acid was converted into a diastereomeric mixture of 2-*tert*-butyl-2, 5-dimethyl-[1,3]-dioxolan-4-ones (2*S*,5*S*)-**6** and (2*R*,5*S*)-**7** by acetalization with pinacolone (Scheme 1). The major (2*S*,5*S*)-isomer was isolated as a 96:4 (2*S*,5*S*)/(2*R*,5*S*) mixture.[15] The dioxolanone was converted into the lithium enolate (2*S*)-**8** (2*S*/2*R* = 96:4) by annihilation of the stereogenic center at C-5 with a base, such as LDA or lithium bis-(trimethylsilyl)amide (LHMDS). The addition of the enolate (2*S*)-**8** to the 2-furyl-*N*-trimethylsilylimine **9**, cyclization, removal of the auxiliary center, and desilylation provided mixtures of the *β*-lactams (3*R*,4*S*)-**11** (major isomer) and (3*R*,4*R*)-**12** (minor). Similarly, the phenyl-*N*-trimethylsilylimine **10** gave (3*R*,4*S*)-**13** (major) and (3*R*,4*R*)-**12** (minor) (Table 1S, Supporting Information). The (3*R*,4*S*) stereochemistry of the major isomers **11** and **13** was that required for the taxoid appendants. Enantioselective HPLC analysis showed that **11** and **13** were obtained as enantiomeric couples in a ratio (3*R*,4*S*)/(3*S*,4*R*) = 96:4 (ee = 92%). This result indicated that the cycloaddition occurred under total facial-diastereocontrol because the obtained 92% ee corresponds to that expected on the basis of the diastereomeric excess (de) of the starting lactone **6**. The addition of (2*S*)-**8** to trifluoromethyl-*N*-*p*-methoxyphenyl-imine **15** gave a 4:1 diastereomeric mixture of *β*-lactams (3*R*,4*R*)-**16** and (3*R*,4*S*)-**17**. Differently to that obtained for compounds **11**−**14**, the addition of **15** to the enolate lacked stereochemical control at the C5 carbon atom. In fact, the ^{1}H NMR analysis in the presence of the chiral shift reagent Yt(hfc)$_3$ showed that both diastereomeric *β*-lactams were obtained with an enantiomeric excess (ee) of 54%. The steric interaction of the small trifluoromethyl substituent of the imine with the *tert*-butyl substituent does not preclude the attack of the enolate to the imine from the more hindered face, causing the formation of minor amounts of the enantiomeric *β*-lactams *ent*-**16** and *ent*-**17**.[16] The *β*-lactams **11** and **13** and the mixture of **16** and *ent*-**16** were protected as triethylsilyl ethers (OTes) by treatment with Et_3SiCl and imidazole to afford compounds **18** (R = 2-furyl), **19** (R = C_6H_5), and **20** (R = CF_3). The C_6H_4-*p*-OMe group of **20** was oxidatively cleaved with cerium ammonium nitrate (CAN) to yield the NH free *β*-lactam **21**. Schotten−Baumann *N*-benzoylation of the *β*-lactam **18** gave the 1-benzoyl-protected *β*-lactam (3*R*,4*S*)-**22** (R = 2-furyl). Instead, the treatment of **18**, **19**, and **21** with di-*tert*-butyl dicarbonate/DMAP gave the 1-BOC-protected *β*-lactams **23** (R = 2-furyl), **24** (R = C_6H_5), and a 77:23 mixture of **25**/*ent*-**25** (R = CF_3).

The esterification of **23** with metalated 7-Tes-baccatin III (**26**, Chart 1) gave the 2′-methyl-taxoid **28** (Scheme 2 and Table 2S, Supporting Information). The reactions of metalated 7-Tes-14*β*-OH-baccatin III 1,14-carbonate (**27**, Chart 1) and *β*-lactams **23** and **24** gave compounds **29** (R = 2-furyl) and **30** (R = C_6H_5), while the coupling with the 77:23 mixture of **25**/*ent*-**25** occurred with kinetic resolution, probably due to the very low reaction temperature (−50 °C). In fact, only compound **31** was detected by ^{1}H NMR in the crude reaction mixture. The high level of kinetic resolution in the coupling reactions of enantiomeric mixtures of (3*R*,4*S*)- and (3*S*,4*R*)-*β*-lactams and metalated baccatin III at low temperatures was noticed by Holton.[17] The origin of the kinetic resolution of racemic mixtures of (3*R*,4*R*)- and (3*S*,4*S*)-CF_3-*β*-lactams was explained on the basis that only the (3*R*,4*R*)-isomer can adopt a relative orientation, with respect to the metalated baccatin, which results in a minimization of steric interactions for this orientation.[18] Thus, the total kinetic resolution of the 77:23 mixture

Scheme 2[a]



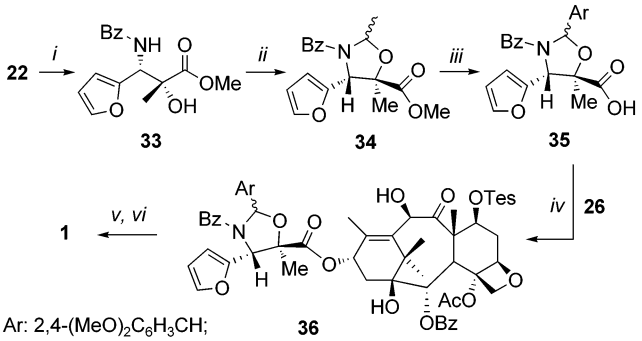
23, **28**, **29**, **2**, **3**: R = 2-furyl, R^1 = BOC; **22**, **33**, **1**: R = C_6H_5, R^1 = Bz;
24, **30**, **4**: R = C_6H_5, R^1 = BOC; **25**, **31**, **5**: R = CF_3, R^1 = BOC

[a] Reagents: (i) NaHMDS/THF/−40 °C; (ii) HF/pyridine/MeCN/25 °C.

of (3*R*,4*R*)/(3*S*,4*S*)-**25** by the chiral metal alkoxide of **27** yielded the taxoid **31** with desired (*R*)-configuration at the C-2′ and C-3′ positions. The metalation of the C13-OH of **26** and **27** was carried out with NaHMDS as the base.[9] The pivotal role of the counterion of the base (Na^+ vs Li^+) was apparent when **27** was the partner of the *β*-lactams. In fact, Na^+ was the key ingredient for the formation of the 2′-methyl taxoids **3**−**5** since much lower yields were observed (<10%) when LiHMDS was used. A similar effect, but less impressive, is also reported in the literature with the baccatin derivative **26**.[9] The 2′-methyl-taxoids **28**-**31** were desilylated by treatment with HF/pyridine to yield compounds **2**-**5**. The esterification of metalated **26** with the *N*-benzoyl-*β*-lactam **22** gave **33** in only 10% (Table 1S). The 13-*O*-benzoyl-7-Tes-baccatin III was recovered as the major product. This result was unexpected considering that the reaction of **26** with the *N*-BOC analogue of **22** gave the corresponding taxoid in much higher yields (55%).[9] The desylilation of **33** with HF/pyridine yielded compound **1**. For this reason, the synthesis of **1** via *N*,*O*-protected isoserine route was attempted. We have already reported the synthesis of the oxazolidine derivative **34**, as a 4:1 mixture of epimers at C5, from the ester **33**.[19] LiOH induced hydrolysis of **34** afforded the carboxylic acid **35**. Alternatively, **33** was also prepared by methanolysis of *β*-lactam **22** (Scheme 3). The esterification of the acid **35** with **26**, in the presence of dicyclohexylcarbodiimide and DMAP, failed. Instead, the variant protocol which uses di-2-pyridyl thionocarbonate as the dehydrating agent gave a mixture of epimeric taxoids **36** in moderate amounts (Table 2S). This mixture was subjected to sequential desilylation and *N*,*O*-deprotection to yield **1**.

B. Growth Inhibition Effects of Taxoids 1−5. Our initial goal was to evaluate the effect of the restriction in the degree of freedom of rotation at the C′2−C′3 bond on the cytotoxic activity of the 2′-methyl-substituted

Scheme 3[a]



[a] Reagents: (i) MeOH/imidazole; (ii) 2,4-$(MeO)_2C_6H_3CH(OMe)_2$, PPTS; (iii) LiOH/H_2O; (iv) (2-pyridyl$O)_2C$═S/DMAP; (v) HF/pyridine/MeCN; (vi) AcCl/MeOH.

Table 1. In Vitro Profile (IC_{50}, nM)[a] for Compounds **1**−**5**, Taxol, IDN5109, in A2780, A2780cis, A2780adr, and A2780tax Cell Lines

compound[a]	A2780	A2780CIS (*R*/*S*)	A2780ADR (*R*/*S*)	A2780TAX (*R*/*S*)
Taxol	5.3	4.6 (0.9)	2688 (507)	4498 (849)
Ortataxel	4.8	3.6 (0.7)	63 (13)	56 (12)
1	3.1	2.9 (0.9)	61.4 (20)	420 (135)
2	2.9	3.3 (1.1)	41.3 (14)	312 (107)
3	5.9	2.5 (0.4)	27.1 (4)	30.9 (5)
4	2.5	1.7 (0.7)	52.9 (21)	299 (118)
5	4.6	2.8 (0.6)	79.3 (17)	285 (61)

[a] The concentration of compound which inhibits 50%.

compounds **1**−**5**. For this reason, the in vitro growth inhibition experiments were conducted in the A2780wt ovarian cell line, a model that demonstrated excellent sensitivity to paclitaxel and in the counterpart A2780cis cell line resistant to cisplatin, which is characterized by a MDR-independent mechanism. In addition, the citotoxicity was also tested against A2780adr and A2780tax cell lines resistant to doxorubicin and paclitaxel, respectively. Both these cell lines exhibit an MDR phenotype with P-glycoprotein overexpression. The results, expressed as IC_{50} values, are reported in Table 1. The potency differential in the resistant vs sensitive cell line is expressed as a ratio of their IC_{50} values (*R*/*S* ratio). High in vitro potency against both the sensitive and the resistant cell lines is expressed by a low *R*/*S* ratio. To better appreciate compounds properties, the ratio with respect to the paclitaxel activity was also calculated by dividing the IC_{50} obtained in each cell line over the IC_{50} of paclitaxel in the same cells (Figure 1, Supporting Information). Values lower than 1 indicates an activity higher than that of paclitaxel. The newly developed analogues are very potent cytotoxic compounds especially in resistant cell lines. Compound **1** is several times more active than paclitaxel in A2780tax and A2780adr and cell lines that overexpress P-gp. Compound **2** is slightly less active than **1** in the P-gp negative cell lines, but it is more potent in A2780tax and A2780adr cells. Cytotoxicity of carbonates **3**, **4**, and **5** were similar to paclitaxel in A2780wt and A2780 cis. However, all the carbonates (**3**−**5**) were more active than paclitaxel in P-gp positive cell lines. The most potent antitumor agent was the taxoid **3**. In sensitive and *cis*-platinum resistant cell lines, **3** and paclitaxel produced similar results, while in taxol and doxorubicin resistant cell lines the new analogue is more than 2 orders of magnitude more active than paclitaxel and also

Table 2. In Vitro Profile (IC_{50}, nM) for Compound **3**, Taxol,[a] Docetaxel,[a] Idn5109,[a] and **37**[a] in MCF7 and MCF7-R Cell Lines

	Taxol[a]	Docetaxel[a]	IDN5109[a]	**3**[b]	**37**[a]
MCF7	1.7	1.0	1.1	1.7 (0.54)	0.5
MCF7-R	299	235	36	16 (7.8)	49
(*R*/*S*)	176	235	33	9.4 (14)	96

[a] See ref 5a. [b] Duplicate experiment in parentheses.

more active than Ortataxel. On the basis of these findings, we have focused our attention on compound **3** which was tested in additional cytotoxic experiments on human breast cell lines, MCF-7 and its counterpart MCF7-R resistant to doxorubicin. The obtained results confirmed the previous ones. The activity of **3** is comparable to that of paclitaxel in the sensitive MCF7 cell line, while it was almost 20-fold more active than paclitaxel against the resistant MCF7-R (Table 2). Moreover, this compound was more potent than its 2′-demethyl derivative **37**[5a] (Chart 3, Supporting Information) and Ortataxel (IDN5109)[5a] in both the sensitive and the Pgp positive, multidrug resistant cell lines, associated with a lower *R*/*S* value.

Conclusions. Our results clearly outlined the beneficial effect of the additional methyl substituent, hence of the conformational restriction in the rotation around the C2′−C′3 bond, on the cytotoxicity of the sensitive cell lines A2780 and MCF7, and their resistant counterparts. For this reason, the taxoids here tested are characterized by low differential potencies, hence are potential candidates to develop new drugs able to overcome the resistant phenotype. However, mechanisms through which this overcoming is obtained merit further investigations. Also, further experiments are actively underway to elucidate the in vivo antitumor activities of these new molecules.

Supporting Information Available: Experimental details for the new compounds, Tables 1S and 2S, Figure 1, and Chart 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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