convergence behavior for normal mode vectors. As is well known, the eigenvectors are harder to be converged than the eigenvalues. It requires about 20 iteration steps to achieve 5% γ error tolerance for the average error of the 100 target modes; about 26 steps for the largest error; and about 26 steps for the first non-zero frequency mode. All 100 modes are converged with $\gamma < 3 \times 10^{-4}$, being the error of the 100th mode the largest after 61 steps.

As demonstrated above, the present iterative approach is able to yield exact normal mode solutions in an iterative manner through diagonalization of many small-size matrices (about one tenth of the whole matrix) in low-frequency regime, which would be useful in studying biological functions of protein molecules.

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Synthesis and Biological Evaluation of C-2 Modified Taxol Analogs

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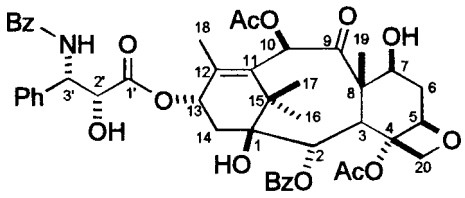
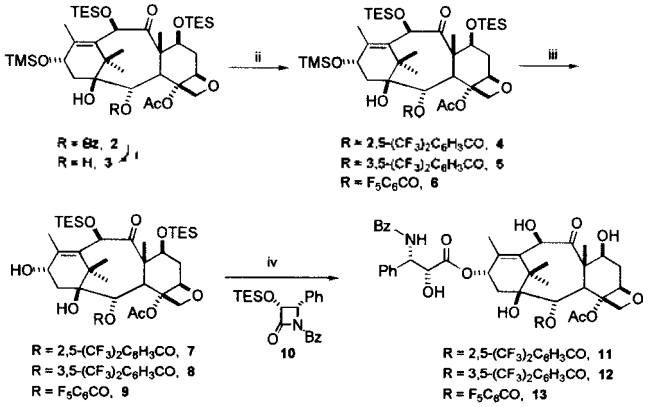
Paclitaxel[1] (Taxol), **1** a complex diterpene isolated from the bark of the western yew[2] (*Taxus brevifolia*), is one of the most potent anticancer agent developed in the last decade for the treatment of ovarian and breast.[3] Of particular interest are structure-activity relationships associated with the highly functionalized terpenoid skeletal system. In general, the northern hemisphere functionalities C-7[4] and C-10[5] have little effect on biological activity, whereas functionalities to southern hemisphere C-2,[6] C-4,[7] and C-13 ester have a marked impact. Among these functionalities, we were interested in preparing new C-2 analogs and evaluating their activities.



Taxol, **1**

In a previous report,[8] we described a selective reduction of fully protected 10-deacetylbaccatin (III) **2** using Red-Al. We felt that intermediate **3** would be suitable for furnishing new C-2 ester analogs. In this communication, we outline the preparation of a series of C-2 modified new taxol analogs and their *in vitro* activity results. Attachment of new C-2 analogs has always been problematic because of easy formation of THF ring[9] between C-2 and C-20 in either basic or acidic media. Thus, upon treatment of diol **3** with 2 equivalents of LHMDS and substituted benzoyl chlorides at low temperature (−78 °C), new C-2 analogs **4**, **5**, and **6** were obtained. Partial desilylation afforded 7,10-TES baccatin derivatives **7**, **8**, and **9** which coupled[10] with optically active β-lactam **10** to give new C-2 ester analogs.



Reagents and Conditions : i) Red-Al, THF, 0 °C, (92.4%); ii) LHMDS, THF, -78 °C,then, 2,5-$(CF_3)_2C_6H_3COCl$, 4(87.5%), 3,5-$(CF_3)_2C_6H_3COCl$, 5(89.5%), F_5C_6COCl, 6(84.6%); iii) pyr., 48% HF, CH_3CN, 7(94.5%), 8(91.4%), 9(87.6%); iv) LHMDS, THF, -45 °C,10, then, pyr., 48% HF, CH_3CN, 11(80.1%), 12(78.5%), 13(72.7%)

	Cytotoxicity ED_{50} (μg/mL)[a]		
Compd	MCF-7[b]	sk -ov- 3[c]	A549[d]
1	0.00001	0.0008	0.00018
11	0.000009	0.001	0.0015
12	0.01	0.0055	0.07
13	>0.01	>0.01	>0.01

[a] ED_{50} is the concentration of compound that cause a 50% reduction in absorbance at 540 nm relative to untreated cells using SRB assay. [b,c,d] MCF-7, sk-ov-3, A549 are human breast, ovarian, lung cancer cell line, respectively.

After final deprotection, desired taxol analogs **11, 12**, and **13**[11] were obtained in good yield.

The three C-2 modified analogs were evaluated against human breast (MCF-7), human ovarian (sk-ov-3), and human lung (A549) cell lines. For comparison, taxol was also evaluated. Both analogs **12** and **13** were substantially less active than taxol **1** *in vitro* assay. On the other hand, activities of **11** are equivalent to that of taxol **1** in the same assay.

Although these results obtained in this study are not promising, we believe that continuing studies will yield further insights into the chemistry and bioactivity of this fascinating molecule. New taxol analogs and their evaluation study are under investigation in our laboratory.

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11. **11**. mp 152-154 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09 (s, 3H, Me16), 1.20 (s, 3H, Me17), 1.73 (s, 3H, Me19), 1.75 (s, 3H, Me18), 1.87 (m, 1H, H6β), 2.18 (s, 3H, 4Ac), 2.27 (m, 1H, H14β), 2.53 (m, 2H, H6α, H 14α), 3.61 (d, *J*=6.3 Hz, 1H, 2(OH), 3.89 (d, *J*=7.2 Hz, 1H, H3), 4.29-4.08 (m, 3H, H7, H20α, H20β), 4.71 (m, 1H, H2'), 4.90 (dd, *J*=1.2, 8.7 Hz, 1H, H5). 5.16 (s, 1H, H10), 5.61 (d, *J*=7.2 Hz, 1H, H2), 5.69 (dd, *J*=2.1, 9.0 Hz, 1H, H3'), 6.12 (dd, *J*=8.4, 8.4 Hz, 1H, H13), 6.99 (d, *J*=8.7 Hz, 1H, NH), 7.41 (m, 8H, ArH), 7.71 (m, 2H, ArH), 7.94 (d, *J*=8.4 Hz, 1H, ArH), 7.99 (d, *J*=8.4 Hz, 1H, ArH), 8.48 (s, 1H, ArH); **12**. mp 152-154 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.10 (s, 3H, Me16), 1.19 (s, 3H, Me17), 1.73 (s, 3H, Me19), 1.76 (s, 3H, Me18), 1.83 (m, 1H, H6β), 2.27 (s, 3H, 4Ac), 2.34 (m, 2H, H 14α, H14β), 2.54 (m, 1H, H6α), 3.63 (m, 1H, 2(OH), 3.92 (d, *J*=6.9 Hz, 1H, H3), 4.35-4.06 (m, 3H, H7, H 20α, H20β), 4.74 (m, 1H, H2'), 4.93 (dd, *J*=1.7, 9.3 Hz, 1H, H5). 5.17 (s, 1H, H10), 5.63 (d, *J*=7.1 Hz, 1H, H2), 5.70 (dd, *J*=2.7, 9.1 Hz, 1H, H3'), 6.12 (dd, *J*=8.3, 8.3 Hz, 1H, H13), 6.99 (d, *J*=8.6 Hz, 1H, NH), 7.47-7.33 (m, 8H, ArH), 7.67 (m, 2H, ArH), 8.09 (s, 1H, ArH), 8.59 (s, 2H, ArH); **13**. mp 156-158 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.08 (s, 3H, Me16), 1.20 (s, 3H, Me17), 1.71 (s, 3H, Me19), 1.75 (s, 3H, Me18), 1.83 (m, 1H, H 6β), 2.16 (s, 3H, 4Ac), 2.28 (m, 2H, H14α, H14β), 2.55 (m, 1H, H6α), 3.68 (m, 1H, 2(OH), 3.84 (d, *J*=7.2 Hz, 1H, H3), 4.07 (d, *J*=6.9 Hz, 1H, H20α), 4.27 (dd, *J*=6.1, 10.2 Hz, 1H, H7), 4.70 (m, 1H, H2'), 4.89 (dd, *J*=1.6, 9.1 Hz, 1H, H5), 5.14 (s, 1H, H10), 5.67 (m, 2H, H2, H 3'), 6.11 (dd, *J*=8.7, 8.7 Hz, 1H, H13), 7.06 (d, *J*=8.4 Hz, 1H, NH), 7.53-7.29 (m, 8H, ArH), 7.76 (d, *J*=7.5 Hz, 2H, ArH).