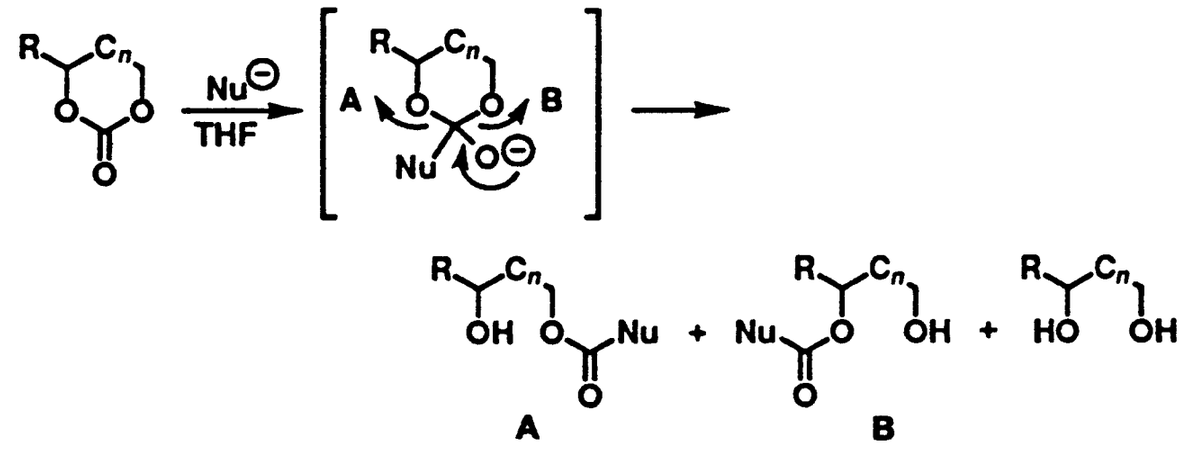
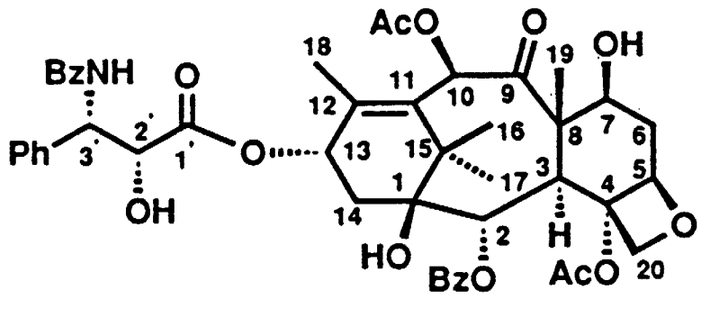


Scheme 1.

Synthesis of C-2 Taxol Analogues**

Kyriacos Costa Nicolaou,* Elias A. Couladouros, Phillipe G. Nantermet, Joanne Renaud, Rodney Kiplin Guy, and Wolfgang Wrasidlo

Taxol (**1**)[1, 2] is currently of substantial interest due to its exceptional chemistry,[3] biology,[3a, 4] and medical applications.[3, 4] Researchers in both academic and industrial laboratories have been devoting considerable time and effort to the



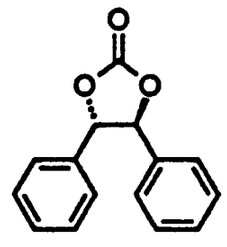
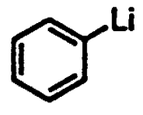
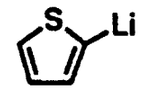
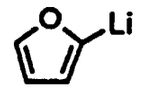
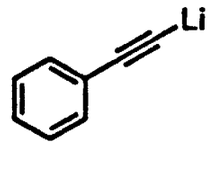
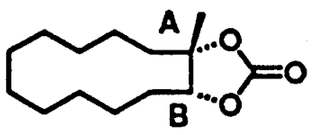
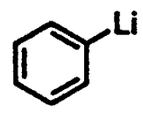
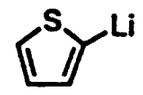
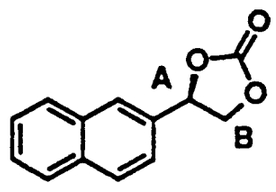
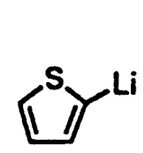
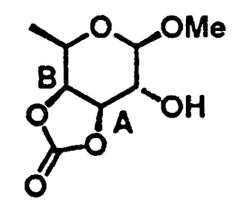
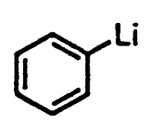
1 Taxol

design, synthesis, and biological evaluation of taxol analogues[3, 5] with the aim of attaining pharmacological properties superior to those exhibited by the parent compound. In this communication we report a general method for the regioselective functionalization of cyclic carbonates by nucleophilic ring opening and its application in the synthesis of a series of new taxoids functionalized at C-2; a family of compounds hitherto difficult to obtain.[6]

A key observation made during the total synthesis of taxol (**1**)[2a] involved the opening of a five-membered cyclic carbonate with PhLi. This reaction proceeded with exquisite regio- and chemoselection and gave a high yield of the desired product. The addition of nucleophiles to carbonates to provide esters has seen only rare use[7] and reports of such regioselective manipulation of a cyclic carbonate are rather scarce.[8] Expanding the scope of this reaction and demonstrating its wide applicability in the taxol field were the objectives of this program.

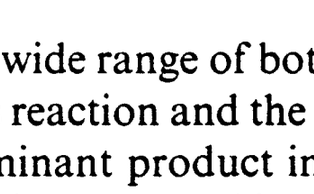
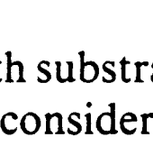
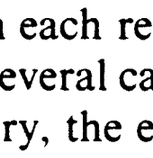
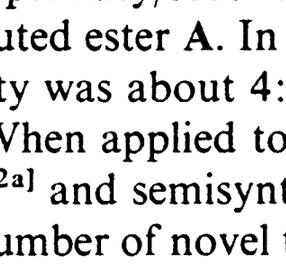
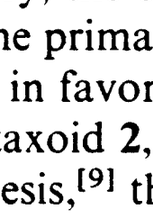
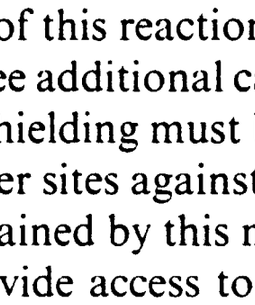
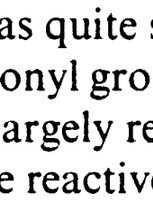
Scheme 1 shows the general strategy for the regioselective functionalization of cyclic carbonates by ring opening with nucleophilic reagents. The examples listed in Table 1 demonstrate

Table 1. Regioselective synthesis of esters through nucleophilic addition to cyclic carbonates.

Entry	Carbonate	Nucleophile	No. of equivalents	T [°C]	t [min]	Yield [%] (A:B:diol)
1a			1.5	−100	25	70:0:26
			1.25	−78	30	78 [a]:0:15
1b			1.3	−78	30	98:0:0
1c			1.1	0	15	87:0:0
1d			1.5	−78, then −45	60 30	100:0:0
2a			1.5	−78	30	85:0:12
2b			1.3	−78	30	94:0:3
3			1.5	−78	30	67:17:0
4			3.5	−78	30	93 [a]:0:0

[a] Yield based on 70–90% conversion.

Table 2. Regioselective synthesis of taxoids through nucleophilic addition to cyclic carbonates.

Entry	Carbonate	Nucleophile	No. of equivalents	T [°C]	t [min]	Yield [%] (A:B:diol)
1			1.5	−78	30	85:0:12
2			1.3	−78	30	94:0:3
3			1.5	−78	30	67:17:0
4			3.5	−78	30	93 [a]:0:0

[a] Yield based on 70–90% conversion.

the wide range of both substrates and nucleophiles that undergo this reaction and the considerable selectivities attained. The predominant product in each reaction was the ester; the only side product detected in several cases was the diol. In all cases except the primary/secondary, the exclusive product was the less substituted ester **A**. In the primary/secondary cases, the regioselectivity was about 4:1 in favor of **A**.

When applied to taxoid **2**, available from both total synthesis[2a] and semisynthesis,[9] this ring-opening process produced a number of novel taxoids **3** (Table 2). The remarkable selectivity of this reaction was quite striking, particularly in view of the three additional carbonyl groups present in the substrate **2**. Steric shielding must be largely responsible for the protection of the latter sites against the reactive nucleophiles employed. Products obtained by this method are particularly interesting in that they provide access to taxols with additional functionalities at C-2.

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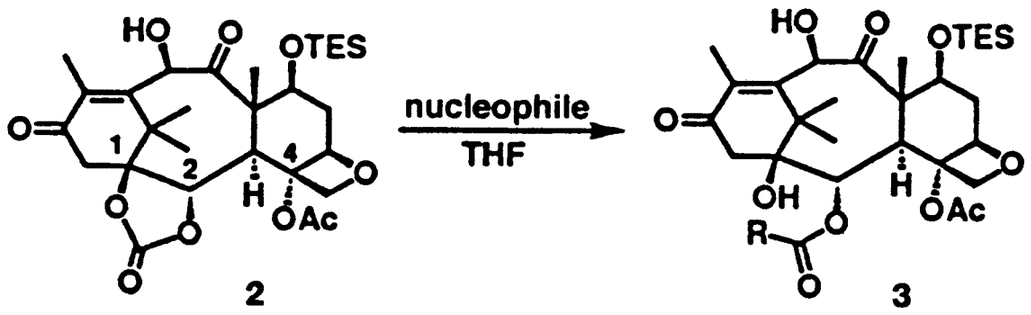
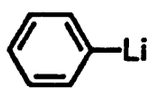
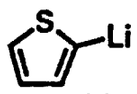
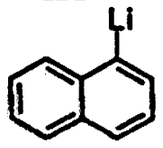
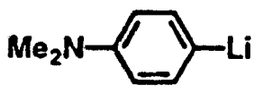
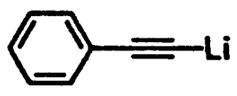
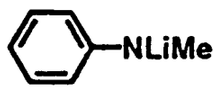


TES=Triethylsilyl

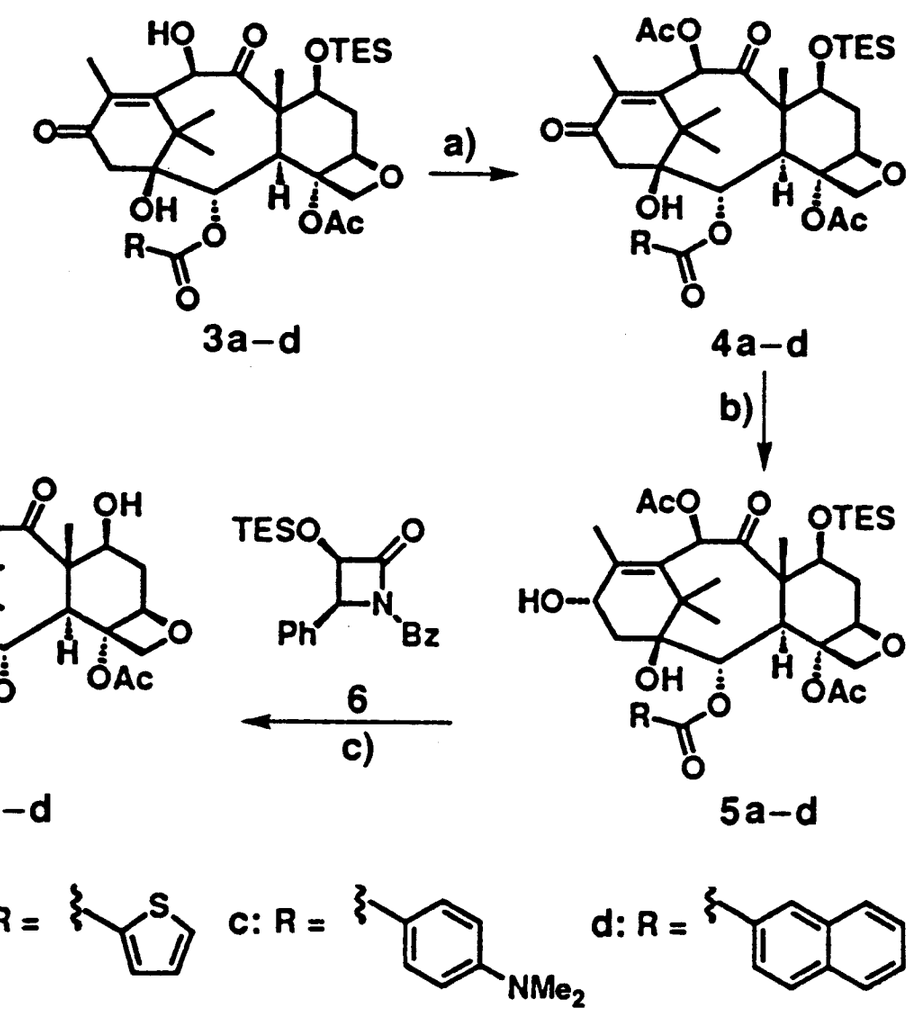
Table 2. Nucleophilic ring opening of cyclic carbonates to give C-2 taxol analogues **3**.

Entry	Nucleophile RX	No. of equivalents	*t* [min]	*T* [°C]	Yield [%]
1		1.1	30	−78	72 [a]
2		15	90	−78	74 [b]
3		20	90	−20	60 [b]
4		20	10	0	60 [a, c]
5		10	30	−78	85
6		15	10	−78	78
7		15	30	−78	96 [b]
8		15	10	−78	89
9		5	30	−78	42 [a]
10		15	30	−78	95 [d]
11		20	15	25	92
12		10	60	25	93 [d]

[a] Reaction also produced variable amounts of the C-4 hydroxy and C1-C2 dihydroxy compounds. [b] Yield based on 50–80% conversion. [c] Yield based on desilylated acetylenic compound obtained after workup. [d] 10–20% conversion only.

This position has been recognized as important for biological activity.[3] To explore such structure–activity relationships we have undertaken the conversion of compounds **3a–d** to taxoids (**7a–d**).

Several compounds of type **3** have previously been converted to taxoids.[2a] Thus acetylation of **3a–d** (Scheme 2) provided



Scheme 2. Synthesis of novel taxoids **7** [11]. a) Ac_2O/CH_2Cl_2 (1/4), Et_3N (5 equiv), 4-dimethylaminopyridine (cat.), 75–85%; b) $NaBH_4$ (10 equiv), MeOH, 0 → 25 °C, 80–90%; c) 1. $NaN(SiMe_3)_2$ (2.5 equiv), **6** (2 equiv), THF, 0 °C; 2. HF · py, THF, 25 °C, 65–85%. TES = triethylsilyl.

the corresponding 10-acetyl compounds **4** in high yield. Stereocontrolled sodium borohydride reduction of the enone carbonyl of compounds **4** led to the desired 13-α-hydroxyl compounds **5a–d** in excellent yields. Finally, coupling of these baccatin III analogues with the side-chain β-lactam **6** using Ojima's protocol,[10] followed by deprotection resulted in the formation of the new taxoids **7a–d** in high overall yields (Scheme 2).

Preliminary biological evaluation of selected compounds from this series (Table 3) revealed cytotoxicities comparable to that of taxol for the thiophene analogue **7b** and the furanyl analogue **7a**, a cytoxicity considerably less than that of taxol for the *p*-dimethylaminophenyl taxoid **7c**, and essentially no activity for the naphthalene compound **7d**. These results suggest rather well-defined demands by the taxol receptor for the C-2 ester group.[6]

The chemistry described above opens a practical approach to previously inaccessible C-2 taxol analogues and provides new opportunities for drug design and development in the taxol field. Studies directed at further refinement of the characteristics of the binding domain for taxol are currently underway in this laboratory.

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Table 3. Cytotoxicities of C-2 taxol analogues **7** [a].

Cell type	Cell line	**1**	**7a**	**7b**	**7c**	**7d**
Human T-cell leukemia	MOLT-4	5.3×10^{-10}	4.5×10^{-8}	3.7×10^{-9}	2.2×10^{-6}	$>1\times10^{-4}$
Mouse leukemia	L1210	1.1×10^{-9}	4.7×10^{-7}	1.8×10^{-8}	1.6×10^{-6}	2.9×10^{-5}
Melanoma	SK-MEL 28	2.8×10^{-9}	8.4×10^{-8}	1.2×10^{-8}	1.2×10^{-4}	$>1\times10^{-4}$
Lung adenocarcinoma	UCLA-P3	2.7×10^{-9}	6.9×10^{-8}	9.3×10^{-9}	9.8×10^{-6}	$>1\times10^{-4}$
Human promyelocytic leukemia	HL-60	1.8×10^{-9}	2.5×10^{-8}	1.2×10^{-8}	1.3×10^{-5}	$>1\times10^{-4}$
Human prostate adenocarcinoma	PC-3	5.6×10^{-9}	1.0×10^{-7}	1.8×10^{-8}	3.4×10^{-5}	$>1\times10^{-4}$
Human ovarian carcinoma	OVCAR-3	6.9×10^{-9}	9.9×10^{-9}	5.8×10^{-9}	1.1×10^{-5}	$>1\times10^{-4}$
Human perirenal cell carcinoma	786-O	9.8×10^{-9}	5.2×10^{-6}	4.3×10^{-7}	5.0×10^{-5}	$>1\times10^{-4}$

[a] Data were obtained in the concentration range from 1×10^{-13} to 1×10^{-4} M by 1:10 direct aqueous dilutions of dimethylsulfoxide solutions of the compounds.

  0570-0833/94/1515-1582 $ 10.00+.25/0

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[11] Selected physical data of the compounds **3b**, **4b**, **5b**, and **7b**.—**3b**: Amorphous solid; $R_f = 0.56$ (silica, ethyl acetate/hexanes 1/1); IR (film): $\tilde{\nu}$ = 3403, 2945, 2881, 1717, 1669, 1520, 1413, 1360, 1248, 1078 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.84 (dd, J = 1.0, 3.5 Hz, 1H, thiophene), 7.64 (dd, J = 1.0, 5.0 Hz, 1H, thiophene), 7.14 (dd, J = 3.5, 5.0 Hz, 1H, thiophene), 5.53 (d, J = 6.5 Hz, 1H, 2-H), 5.29 (d, J = 2.5 Hz, 1H, 10-H), 4.90 (br d, J = 7.5 Hz, 1H, 5-H), 4.44 (A of AB, d, J = 8.5 Hz, 1H, 20-H), 4.35 (dd, J = 6.5, 10.5 Hz, 1H, 7-H), 4.29 (d, J = 2.5 Hz, 10-OH), 4.19 (B of AB, d, J = 8.5 Hz, 1H, 20-H), 3.90 (d, J = 6.5 Hz, 1H, 3-H), 2.89 (A′ of A′B′, d, J = 19.5 Hz, 1H, 14-H), 2.62 (B′ of A′B′, d, J = 19.5 Hz, 1H, 14-H), 2.43–2.49 (m, 1H, 6-H), 2.15 (s, 3H, OAc), 2.07 (s, 3H, 18-CH_3), 1.85–1.91 (m, 1H, 6-H), 1.73 (s, 1H, 1-OH), 1.54 (s, 3H, 19-CH_3), 1.21 (s, 3H, 16-CH_3), 1.13 (s, 3H, 17-CH_3), 0.91 (t, J = 8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.49–0.56 (m, 6H, $Si(CH_2CH_3)_3$); FAB-HRMS ($C_{33}H_{46}O_{10}SSi$ [M + H^+]): calcd: 663.2659; found: 663.2655.—**4b**: Amorphous solid; $R_f = 0.56$ (silica, ethyl acetate/hexanes 1/1); IR (film): $\tilde{\nu}$ = 3456, 2956, 1711, 1669, 1525, 1413, 1376, 1264, 1227, 1073 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.84 (dd, J = 1.5, 4.0 Hz, 1H, thiophene), 7.63 (dd, J = 1.5, 5.0 Hz, 1H, thiophene), 7.13 (dd, J = 4.0, 5.0 Hz, 1H, thiophene), 6.56 (s, 1H, 10-H), 5.58 (d, J = 6.5 Hz, 1H, 2-H), 4.90 (br d, J = 8.0 Hz, 1H, 5-H), 4.44 (dd, J = 7.0, 10.5 Hz, 1H, 7-H), 4.42 (A of AB, d, J = 8.5 Hz, 1H, 20-H), 4.18 (B of AB, d, J = 8.5 Hz, 1H, 20-H), 3.85 (d, J = 6.5 Hz, 1H, 3-H), 2.91 (A′ of A′B′, d, J = 19.5 Hz, 1H, 14-H), 2.64 (B′ of A′B′, dd, J = 1.0, 19.5 Hz, 1H, 14-H), 2.48–2.55 (m, 1H, 6-H), 2.20 (s, 3H, OAc), 2.15 (s, 3H, OAc), 2.14 (s, 3H, 18-CH_3), 1.83–1.88 (m, 1H, 6-H), 1.65 (s, 3H, 19-CH_3), 1.23 (s, 3H, 16-CH_3), 1.16 (s, 3H, 17-CH_3), 0.88 (t, J = 8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.53–0.59 (m, 6H, $Si(CH_2CH_3)_3$); FAB-HRMS ($C_{35}H_{48}O_{11}SSi$ [M + Cs^+]): calcd: 837.1741; found: 837.1736.—**5b**: Amorphous solid; $R_f = 0.34$ (silica, ethyl acetate/hexanes 1/1); IR (film): $\tilde{\nu}$ = 3478, 2945, 2892, 1717, 1519, 1365, 1238, 1083 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.85 (dd, J = 1.5, 3.5 Hz, 1H, thiophene), 7.61 (dd, J = 1.5, 5.0 Hz, 1H, thiophene), 7.12 (dd, J = 3.5, 5.0 Hz, 1H, thiophene), 6.43 (s, 1H, 10-H), 5.51 (d, J = 7.0 Hz, 1H, 2-H), 4.94 (br d, J = 7.5 Hz, 1H, 5-H), 4.78–4.83 (m, 1H, 13-H), 4.45 (dd, J = 7.5, 10.5 Hz, 1H, 7-H), 4.41 (A of AB, d, J = 8.0 Hz, 1H, 20-H), 4.19 (B of AB, d, J = 8.0 Hz, 1H, 20-H), 3.82 (d, J = 7.0 Hz, 1H, 3-H), 2.48–2.54 (m, 1H, 6-H), 2.24 (s, 3H, OAc), 2.21–2.26 (m, 2H, 14-CH_2), 2.16 (d, J = 1.0 Hz, 3H, 18-CH_3), 2.15 (s, 3H, CH_3), 2.00 (d, J = 5.0 Hz, 1H, OH), 1.85–1.89 (m, 1H, 6-H), 1.66 (s, 1H, 19-CH_3), 1.58 (s, 1H, 1-OH), 1.15 (s, 3H, 16-CH_3), 1.02 (s, 3H, 17-CH_3), 0.90 (t, J = 8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.55–0.59 (m, 6H, $Si(CH_2CH_3)_3$); FAB-HRMS ($C_{35}H_{50}O_{11}SSi$ [M + Cs^+]): calcd: 839.1897; found: 839.1893.—**7b**: Amorphous solid; $R_f = 0.44$ (silica, ethyl acetate/hexanes 3/1); IR (film): $\tilde{\nu}$ = 3417, 2929, 1715, 1649, 1521, 1460, 1417, 1368, 1247, 1076 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.90 (dd, J = 1.0, 4.0 Hz, 1H, thiophene), 7.73 (d, J = 7.0 Hz, 2H, NBz), 7.63 (dd, J = 1.0, 5.0 Hz, 1H, thiophene), 7.32–7.51 (m, 8H, Ar), 7.14 (dd, J = 4.0, 5.0 Hz, 1H, thiophene), 6.96 (d, J = 9.0 Hz, 1H, NH), 6.24 (s, 1H, 10-H), 6.19 (br t, 1H, J = 9.0 Hz, 13-H), 5.75 (dd, J = 2.5 Hz, 9.0 Hz, 1H, 3′-H), 5.55 (d, J = 7.0 Hz, 1H, 2-H), 4.94 (br d, J = 8.0 Hz, 1H, 5-H), 4.76 (dd, J = 2.5, 5.0 Hz, 1H, 2′-H), 4.41 (A of AB, d, J = 8.5 Hz, 1H, 20-H), 4.32–4.40 (m, 1H, 7-H), 4.24 (B of AB, d, J = 8.5 Hz, 1H, 20-H), 3.73 (d, J = 7.0 Hz, 1H, 3-H), 3.52 (d, J = 5.0 Hz, 1H, 2′-OH), 2.50–2.56 (m, 1H, 6-H), 2.44 (d, J = 4.0 Hz, 1H, 7-OH), 2.35 (s, 3H, OAc), 2.29 (d, J = 9.0 Hz, 2H, 14-CH_2), 2.22 (s, 3H, OAc), 1.84–1.90 (m, 1H, 6-H), 1.76 (s, 3H, 18-CH_3), 1.66 (s, 3H, 19-CH_3), 1.23 (s, 3H, 16-CH_3), 1.10 (s, 3H, 17-CH_3); FAB-HRMS ($C_{45}H_{49}NO_{14}S$ [M + Cs^+]): calcd: 992.1928; found: 992.1952 (the experimental error (0.0024) lies within the accepted limits.).

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