SYNTHESIS OF TAXOIDS I. REGIOSELECTIVE LEWIS ACID-MEDIATED RING-OPENING OF ARYL ORTHOACETATES†

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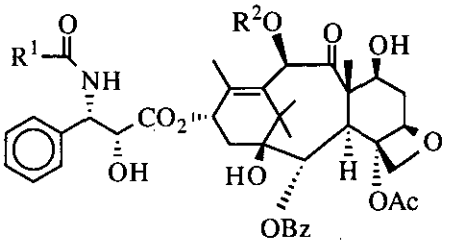
Abstract —— The reaction of aryl orthoacetates with acetyl bromide readily proceeded regioselectively to afford the desirable aryl bromides in the presence of tin(II) or zinc bromide as a catalyst. The synthesis of some docetaxel derivatives is also described by using this improved process

Paclitaxel (**1**), isolated from the bark of *Taxus brevifolia*,[1] is regarded as one of the most promising anticancer agent,[2] especially for the treatment of ovarian, breast and lung cancer.[3] Paclitaxel (**1**) is an antimitotic agent with a unique mode of action, promoting the assembly of stable microtubles.[4] Docetaxel (**2**), a semisynthetic analog of paclitaxel,[5] is two times as active as paclitaxel (**1**) in an *in vitro* tubulin assay as an inhibitor of microtuble depolymerization.[6]



1 R^1 = Ph, R^2 = Ac (Paclitaxel)

2 R^1 = *tert*-BuO, R^2 = H (Docetaxel)

† This paper is dedicated to Dr. Shigeru Oae, Professor Emeritus of Tsukuba University, on the occasion of his 77th birthday, and with gratitude for his many contributions in organic chemistry.

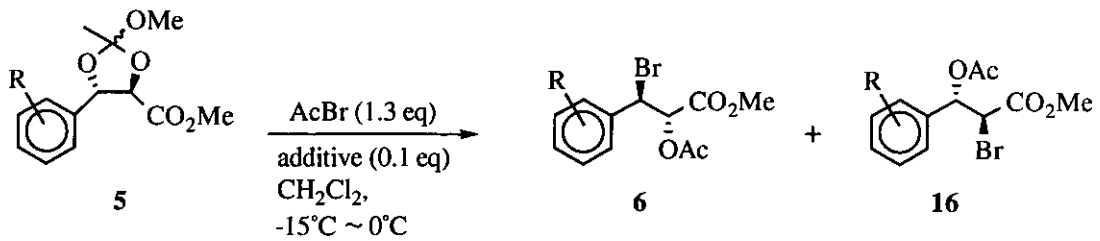
Investigations by several groups have provided extensive data on structure-activity relationships of the C-13-3'-phenylisoserine side chain.[7] As the role of the C-13 side chain in the biological activity of taxoid became evident, enantioselective synthesis of the C-13 side chain has been the focus of many investigators.[8] Among the numerous papers,[8] Sharpless's method[9] was considered to be more efficient and adaptable for industrial scale production, which proceeded through the asymmetric dihydroxylation (**AD**) reaction.[10] However, they mentioned that the reaction of cyclic orthoacetate (**5a**) with acetyl bromide (AcBr) afforded the bromoacetate (**6a**) with an appreciable amounts of the unwanted regioisomer (**16a**) (>14%),[9,11] which have been major obstacle in the synthesis of taxoid side chain (see Scheme 1 and Table1).

As an ongoing part of our work on taxoid, we would like to describe herein an improved Sharpless's method, namely an efficient regioselective synthesis of the bromoacetate (**6a**), and also describe the synthesis of some docetaxel derivatives using this improved process. A decade ago, we reported that tin compounds such as $SnBr_2$ were found to exhibit excellent catalytic activity for cis-opening of the epoxide.[12,13] Consequenty, Lewis acid would be expected to control the reaction of **5a** to bromoacetate regiochemically. We examined some Lewis acids as a catalyst on this reaction to obtain better regioselectivity (Table 1). The regiochemistry and the ratio of the isomeric bromoacetates formed were determined by analysis of the ^{1}H-nmr spectra of the bromoacetates (**6** and **16**) (see Experimental Section). Typical Lewis acids such as $BF_3 \cdot Et_2O$ and $TiBr_4$ were ineffective to the reaction. Fortunately, mild Lewis acids such as $ZnBr_2$ and $SnBr_2$ were found to exhibit excellent catalytic activity and the bromoacetate (**6a**) was obtained in excellent yield as a sole product without the undesired regioisomer (**16a**) and stereoisomer. Furthermore, we examined the effect of some fluoro-substituents on the benzene ring of cyclic orthoacetate and the results are summarized in Table 1. In the case of without Lewis acid, the ratio of **6/16** was small ($\leq$5) and the regioselectivity of ring opening of these cyclic orthoacetates (**5**) was influenced by fluoro-substituted position on benzene ring and the ratios tend to decrease in order of the electron-withdrawing ability. * On the contrary, in the presence of mild Lewis acid such as $SnBr_2$ or $ZnBr_2$, the reaction proceeded smoothly and the selectivity was dramatically improved (entries **4**, **5**, **7** and **9**) and the desired bromoacetates (**6**) were obtained predominantly except 3-fluoro derivative (entry **11**).

Finally, some taxoid analogues (**15a, b, c** and **d**) were synthesized as shown in Scheme 1. Typical procedure is as follows : the methyl cinnamates (**3**) were subjected to the AD process (**AD-α**)[9,10] at room temperature to give

*Without Lewis acid, the reaction of 2-nitro- or 2-methoxy-substituted derivatives (**5**) with AcBr afforded the ratios, 1.2 and 11 respectively (the ratio of **6/16**), which also support this substituent effect.[14]

Table 1. Reaction of the aryl orthoacetates with acetyl bromide in dichloromethane.



5 **6** **16**

a: R = H
b: R = 4-F
c: R = 2,4-F
d: R = 3-F

Entry	Substrate	R	Additive	Products Yield (**6+16**)* (%)	Ratio (**6/16**)
1	**5a**	H	—	94	5
2	**5a**	H	$BF_3 \cdot Et_2O$	44	6
3	**5a**	H	$TiBr_4$	94	5
4	**5a**	H	$ZnBr_2$	94	>100**
5	**5a**	H	$SnBr_2$	80	>100**
6	**5b**	4-F	—	89	5
7	**5b**	4-F	$ZnBr_2$	91	>100**
8	**5c**	2,4-F	—	95	1.5
9	**5c**	2,4-F	$SnBr_2$	76	20
10	**5d**	3-F	—	93	2.4
11	**5d**	3-F	$SnBr_2$	78	4.6

* Isolated yield.
** Regioisomer (**1 6**) was not detected by 300 MHz ^{1}H-nmr spectrum.

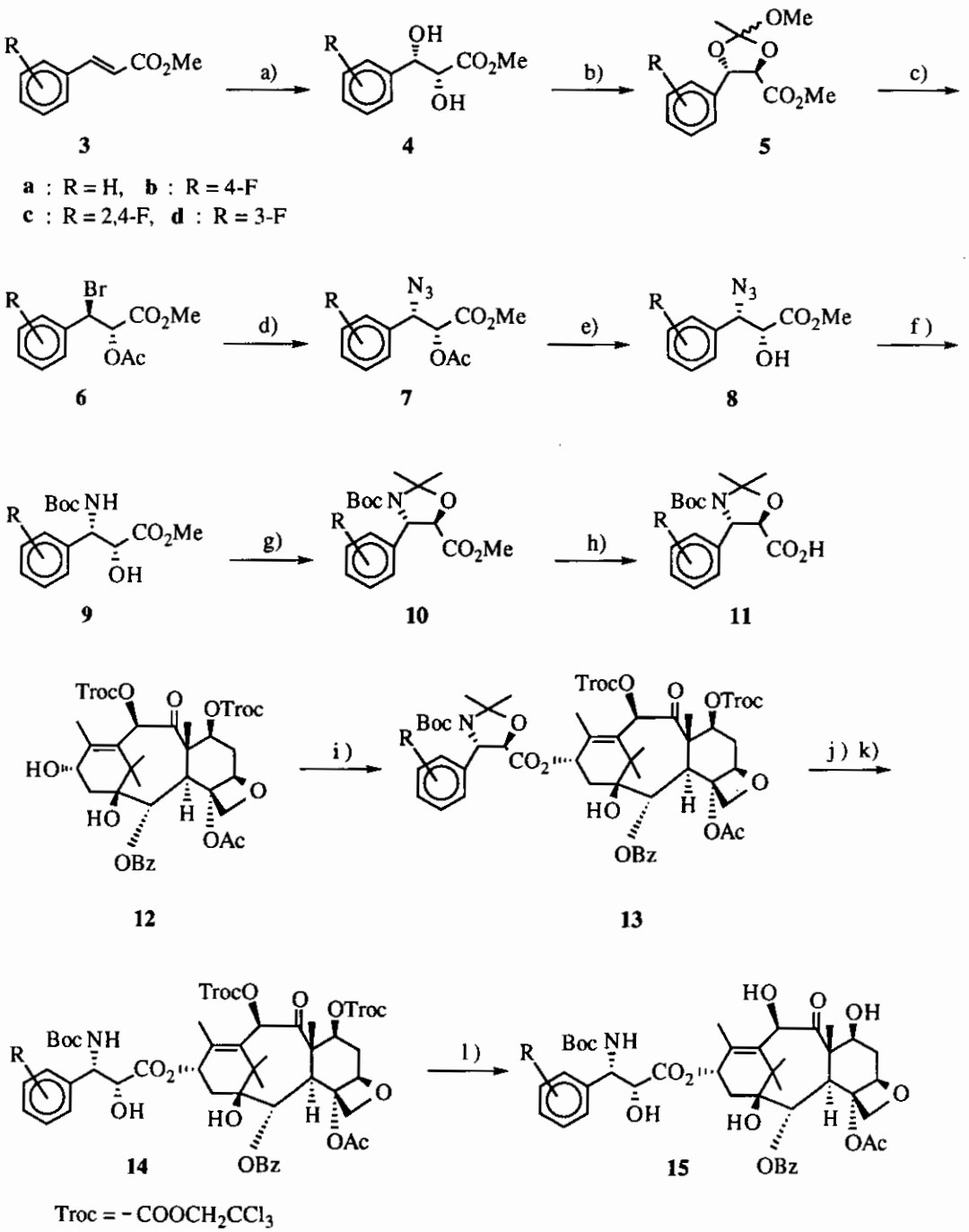
enantio pure (2*R*, 3*S*)-diols (**4**) in good yields (**a**, 72%; **b**, 72%; **c**, 71% and **d**, 67%). The diols (**4**) were converted to the cyclic orthoacetates (**5**) by reaction with trimethyl orthoacetate in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) at room temperature (almost quantitative yield), which were treated with AcBr in the presence of a catalytic amount of $SnBr_2$ or $ZnBr_2$ in CH_2Cl_2 to afford the bromoacetates (results see Table 1). Then, the bromoacetates (**6**) were reacted with sodium azide in dimethyl formamide (DMF) at 40°C to yield the acetoxy azido esters (**7**) in good yields (**a**, 78%; **b**, 82%; **c**, 75% and **d**, 67%). Compounds (**7**), on hydrolysis using K_2CO_3 in methanol, gave the hydroxy azido esters (**8**) in good yields (**a**, 87%; **b**, 80%; **c**, 73% and **d**, 91%). Then, the azido esters (**8**) were subjected to hydrogenation with 10% Pd-C under 1 atm of hydrogen in the presence of di-*tert*-butyl dicarbonate ($(Boc)_2O$) in AcOEt, giving *N*-*tert*-butoxycarbonyl-3-phenylisoserines (**9**) in excellent yields (**a**, 91%; **b**, 93%; **c**, 91% and **d**, 94%). Cyclic protection of **9** developed by Commerçon *et al.*,[15] was carried out with isopropenyl methyl ether in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) to give the oxazolidines (**10**) (**a**, 79%; **b**, 84%; **c**, 74% and **d**, 79%). Saponification led quantitatively to acids (**11**). Esterification of the 7,10-di-O-(2,2,2-trichloro-ethoxycarbonyl)-10-deacetyl baccatin III (**12**) using acids (**11**) gave **13** under standard condition in excellent yields (**a**, 94%; **b**, 99%; **c**, 91% and **d**, 90%). Deprotection of the oxazolidine-type protection under acidic condition followed by N-acylation of the intermediate phenylisoserinates with $(Boc)_2O$ afforded **14** (**a**, 75%; **b**, 37%; **c**, 43% and **d**, 35%). The final reductive deprotection was performed with zinc powder in acetic acid to give **15** in moderate yields (**a**, 82%; **b**, 46%; **c**, 50% and **d**, 67%).

Evaluation for antitumor activity of new compounds (**15**) will be submitted to an appropriate journal together with that of novel compounds which have been synthesizing in progress.

EXPERIMENTAL

Melting points were determined with a Büchi 535 digital melting point apparatus. All melting points are uncorrected. Ir spectra were obtained with a Analect FT-Ir spectrophotometer. ^{1}H-nmr were measured with a Varian Gemini-300 spectrometer. Ms were recorded with a Hitachi RMU-6 or JEOL JMS-HX 100 mass spectrometer. Optical rotations were measured with a Horiba SEPA-200 high sensitive polarimeter. Silica gel (SiO_2) 60K-230 (230-430 mesh) (Katayama) was used for column chromatography. In general, reactions were carried out in dry solvents under argon atmosphere. Physical data of derivatives (**4a**~**15a**) were identified with literature data.[9,15,16]

Scheme 1



a) AD-α, b) $MeC(OMe)_3$, TsOH(cat.), CH_2Cl_2 c) AcBr, $ZnBr_2$ (0.1 eq) or $SnBr_2$ (0.1 eq), CH_2Cl_2 d) NaN_3, DMF e) K_2CO_3, MeOH f) H_2/10% Pd-C, $(Boc)_2O$, AcOEt g) isopropenyl methyl ether, PPTS (cat.) toluene h) LiOH, MeOH, H_2O then H_3^+O i) **11** (1.5 eq), DCC (1.6 eq), DMAP (0.5 eq), toluene j) HCO_2H k) $(Boc)_2O$, $NaHCO_3$, THF l) Zn, AcOH, MeOH

Typical procedure for the synthesis of Methyl (2*R*,3*S*)-2-Acetoxy-3-bromo-3-phenyl-propionate (6a): To a solution of **5a** (29.2 g; 116 mmol) and $ZnBr_2$ (2.60 g; 11.6 mmol) in dichloromethane (CH_2Cl_2) (300 ml) was added dropwise acetyl bromide (11.2 ml; 150 mmol) at -15°C. The mixture was continued to stir for 1 h at -15°C. Then the mixture was warmed to 0°C, and continued to stir for 2 h. After water (240 ml) was added, the mixture was allowed to ambient temperature. The organic layer was separated and washed with brine, and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the crude product was purified by column chromatography on SiO_2 using ethyl acetate/hexanes (1:4) as an eluent to give **6a** (22.6 g, Y = 94%).

The ratio of **6a/16a** was determined by ^{1}H-nmr analysis of crude product. The comparison of **6a** with **16a** was described as follow.

6a: ^{1}H-Nmr ($CDCl_3$)δ: 2.10 (3H, s, Ac), 3.71 (3H, s, CO_2Me), 5.34 (1H, d, J = 6.4 Hz, 3-H), 5.65 (1H, d, J = 6.4 Hz, 2-H), 7.3-7.5 (5H, m, Ph).

16a: ^{1}H-Nmr ($CDCl_3$)δ: 2.02 (3H, s, Ac), 3.82 (3H, s, CO_2Me), 4.50 (1H, d, J = 9.9 Hz, 2-H), 6.12 (1H, d, J = 9.9 Hz, 3-H), 7.3-7.5 (5H, m, Ph).

Bromo acetates (6b, 6c and 6d) were obtained in the same manner as described for the preparation of **6a**.

6b: Ir (Neat): 1750 cm^{-1}. FAB-ms m/z: 319, 321 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 2.13 (3H, s, Ac), 3.70 (3H, s, CO_2Me), 5.35 (1H, d, J = 6.1 Hz, 3-H), 5.63 (1H, d, J = 6.1 Hz, 2-H), 7.02 (2H, m, Ar-H), 7.45 (2H, m, Ar-H).

6c: Ir (Neat): 1760 cm^{-1}. FAB-ms m/z: 337, 339 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 2.15 (3H, s, Ac), 3.73 (3H, s, CO_2Me), 5.59 (1H, d, J = 6.0 Hz, 3-H), 5.67 (1H, d, J = 6.0 Hz, 2-H), 6.75-6.95 (2H, m, Ar-H), 7.67 (1H, m, Ar-H).

6d: Ir (Neat): 1750 cm^{-1}. FAB-ms m/z: 319, 321 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 2.14 (3H, s, Ac), 3.71 (3H, s, CO_2Me), 5.33 (1H, d, J = 5.9 Hz, 3-H), 5.62 (1H, d, J = 5.9 Hz, 2-H), 6.98-7.06 (1H, m, Ar-H), 7.18-7.39 (3H, m, Ar-H).

The comparison of ^{1}H-nmr (**16b**, **16c** and **16d**) was described as follow.

16b: ^{1}H-Nmr ($CDCl_3$)δ: 2.02 (3H, s, Ac), 3.82 (3H, s, CO_2Me), 4.47 (1H, d, J = 9.8 Hz, 2-H), 6.10 (1H, d, J = 9.8 Hz, 3-H), 7.07 (2H, m, Ar-H), 7.39 (2H, m, Ar-H).

16c: ^{1}H-Nmr ($CDCl_3$)δ: 2.04 (3H, s, Ac), 3.82 (3H, s, CO_2Me), 4.66 (1H, d, J = 9.8 Hz, 2-H), 6.30 (1H, d, J = 9.8 Hz, 3-H), 6.75-6.95 (2H, m, Ar-H), 7.40 (1H, m, Ar-H).

16d: ^{1}H-Nmr ($CDCl_3$)δ: 2.04 (3H, s, Ac), 3.82 (3H, s, CO_2Me), 4.46 (1H, d, J = 9.8 Hz, 2-H), 6.09 (1H, d, J = 9.8 Hz, 3-H), 7.08-7.14 (1H, m, Ar-H), 7.18-7.39 (3H, m, Ar-H).

Methyl (2*R*,3*S*)-2,3-Dihydroxy-3-(2,4-difluorophenyl)propionate (4c): To a solution of $K_3Fe(CN)_6$ (64.8 g; 197 mmol), K_2CO_3 (27.2 g; 197 mmol) and $(DHQ)_2PHAL$ (511 mg; 0.656 mmol) in *t*-BuOH-water (1:1, 650 ml) was added osmium tetroxide (34 mg; 0.134 mmol) with stirring. To the mixture was added **3c** (13.0 g; 65.6 mmol). The mixture was stirred at room temperature for 18 h. To the reaction mixture was added Na_2SO_3 (98 g), and the mixture was stirred at room temperature for 30 min. The mixture was diluted with ethyl acetate and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with brine, and dried over Na_2SO_4. After the solvent was removed, the residue was purified by column chromatography on SiO_2 using ethyl acetate/hexanes (1:1) as an eluent and recrystallized from dichloromethane-hexanes to give **4c** (10.85 g, Y = 71% and > 99% ee) as colorless needles. The ee was determined by hplc analysis of bis acetate derivatives. (Opti-Pak XC (3.9 × 300 mm I.D.), rt, 5% *i*-PrOH in hexane, 1.0 ml/ min.) Retention time of (2*R*,3*S*) isomer was 8.45 min and (2*S*,3*R*) isomer was 6.03 min. mp 86.5~87.5°C. $[\alpha]_D^{20}$ + 10.1° (c 1.03, $CHCl_3$). Ir (Nujol): 3440, 3360, 1750 cm^{-1}. FAB-ms m/z: 233 (MH^+). ^{1}H-Nmr ($CDCl_3$) δ: 2.89 (1H, d, J = 7.2 Hz, D_2O exchangeable, 3-OH), 3.22 (1H, d, J = 5.9 Hz, D_2O exchangeable, 2-OH), 3.85 (3H, s, CO_2Me), 4.35 (1H, dd, J = 3.0, 5.9Hz, 2-H), 5.29 (1H, dd, J = 3.0, 7.2 Hz, 3-H), 6.81 (1H, m, Ar-H), 6.92 (1H, m, Ar-H), 7.52 (1H, m, Ar-H).

4a, **4b** and **4d** were obtained in the same manner.

4b: mp 69.5~70.5°C. $[\alpha]_D^{20}$+9.4° (c 1.00, $CHCl_3$). Ir (Nujol): 3330, 1745 cm^{-1}. FAB-ms m/z: 237 (M^++Na). ^{1}H-Nmr ($CDCl_3$)δ: 2.77 (1H, d, J = 7.0 Hz, D_2O exchangeable, 3-OH), 3.15 (1H, d, J = 5.9 Hz, D_2O exchangeable, 2-OH), 3.81 (3H, s, CO_2Me), 4.33 (1H, dd, J = 3.0, 5.9 Hz, 2-H), 4.99 (1H, dd, J = 3.0, 7.0 Hz, 3-H), 7.06 (2H, m, Ar-H), 7.38 (2H, m, Ar-H).

4d: mp 78.0~80.0°C. $[\alpha]_D^{20}$+8.3° (c 1.02, $CHCl_3$). Ir (Nujol): 3560, 1745 cm^{-1} FAB-ms m/z: 215 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 2.85 (1H, br d, J = 4.5 Hz, D_2O exchangeable, 2-OH), 3.18 (1H, d, J = 5.8 Hz, D_2O exchangeable, 3-OH), 3.84 (3H, s, CO_2Me), 4.37 (1H, dd, J = 2.8, 4.9 Hz, 2-H), 5.02 (1H, br s, 3-H), 7.01 (1H, m, Ar-H), 7.13-7.18 (2H, m, Ar-H), 7.34 (1H, m, Ar-H).

General procedure for the synthesis of cyclic orthoacetates (5): To a solution of **4** (46.7 mmol) in CH_2Cl_2 (100 ml) were added *p*-TsOH•H_2O (140 mg, 0.74 mmol) and trimethyl orthoacetate (7.30 g, 60.7 mmol) with stirring at 0°C, then the mixture was allowed to ambient temperature and stirred for 2.5 h. The

reaction mixture was diluted with $CHCl_3$, washed aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on SiO_2 using ethyl acetate/hexanes (1:5) as an eluent to give **5** as the mixture of two diastereomers. **5** was used in the next step without further purification.

General procedure for the synthesis of 2-acetoxy-3-azidopropionates (7): To a solution of **6** (43.6 mmol) in DMF (120 ml) was added NaN_3 (5.68 g, 87.4 mmol). The mixture was stirred at 40°C for 2.5 h. The mixture was poured into ice-water and extracted with $CHCl_3$. The organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on SiO_2 using ethyl acetate/hexanes (1:4) as an eluent to give **7** as an oil.

7b: Ir (Neat): 2110, 1750 cm^{-1}. FAB-ms m/z: 282 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 2.14 (3H, s, Ac), 3.70 (3H, s, CO_2Me), 5.06 (1H, d, J = 5.0 Hz, 3-H), 5.20 (1H, d, J = 5.0 Hz, 2-H), 7.09 (2H, m, Ar-H), 7.35 (2H, m, Ar-H).

7c: Ir (Neat): 2120, 1760 cm^{-1}. FAB-ms m/z: 300 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 2.12 (3H, s, Ac), 3.76 (3H, s, CO_2Me), 5.30 (1H, d, J = 4.8 Hz, 3-H), 5.41 (1H, d, J = 4.8 Hz, 2-H), 6.87 (1H, m, Ar-H), 6.95 (1H, m, Ar-H), 7.46 (1H, m, Ar-H).

7d: Ir (Neat): 2100, 1750 cm^{-1}. FAB-ms m/z: 282 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 2.14 (3H, s, Ac), 3.72 (3H, s, CO_2Me), 5.07 (1H, d, J = 4.9 Hz, 3-H), 5.24 (1H, d, J = 4.9 Hz, 2-H), 7.03-7.15 (3H, m, Ar-H), 7.37 (1H, m, Ar-H).

General procedure for the synthesis of 3-azido-2-hydroxypropionates (8): A solution of **7** (33.8 mmol) in MeOH (60 ml) was added dropwise to a suspension of K_2CO_3 (5.13 g, 37.2 mmol) in MeOH (140 ml) at 0°C. The mixture was stirred for 20 min. Acetic acid (16 ml) was added dropwise to the mixture and the mixture was filtered off. The filtrate was concentrated *in vacuo*. To the residue were added ethyl acetate and water. The organic layer was separated and washed with brine, and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on SiO_2 using ethyl acetate/hexanes (1:4) as an eluent to give **8** as a solid.

8b: Ir (Nujol): 3500, 2100, 1750, 1735 cm^{-1}. FAB-ms m/z: 240 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 3.12 (1H, br d, J = 5.6 Hz, D_2O exchangeable, 2-OH), 3.85 (3H, s, CO_2Me), 4.36 (1H, dd, J = 2.9, 5.6 Hz, 2-H), 4.84 (1H, d, J = 2.9 Hz, 3-H), 7.10 (2H, m, Ar-H), 7.46 (2H, m, Ar-H).

8c: Ir (Neat): 3480, 2120, 1750 cm^{-1}. FAB-ms m/z: 258 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 3.15 (1H, d, J = 6.7 Hz,

D_2O exchangeable, 2-OH), 3.89 (3H, s, CO_2Me), 4.38 (1H, dd, J=2.7, 6.7 Hz, 2-H), 5.22 (1H, d, J = 2.7 Hz, 3-H), 6.87 (1H, m, Ar-H), 6.96 (1H, m, Ar-H), 7.65 (1H, m, Ar-H).

8d: Ir (Neat): 3480, 2100, 1740 cm^{-1}. FAB-ms m/z: 240 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 3.13 (1H, br d, J = 6.2 Hz, D_2O exchangeable, 2-OH), 3.86 (3H, s, CO_2Me), 4.38 (1H, m, 2-H), 4.86 (1H, d, J = 2.7 Hz, 3-H), 7.07 (1H, m, Ar-H), 7.19-7.24 (2H, m, Ar-H), 7.38 (1H, m, Ar-H).

General procedure for the synthesis of *N*-(*tert*-butoxycarbonyl)-3-penylisoserine Methyl esters (9): To a solution of **8** (24.5 mmol) in ethyl acetate (60 ml) were added $(Boc)_2O$ (6.42 g, 29.4 mmol) and 10% Pd-C (1.2 g). The mixture was hydrogenated under atmospheric pressure of hydrogen at room temperature for 3.5 h. The catalyst was removed by filtration and washed with ethyl acetate. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 using ethyl acetate/hexanes (1:2) as an eluent to give **9** as a powder.

9b: Ir (Nujol): 3480, 3370, 1735, 1680 cm^{-1}. FAB-ms m/z: 314 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 1.41(9H, s, Boc), 3.15 (1H, d, J = 4.3 Hz, D_2O exchangeable, 2-OH), 3.85 (3H, s, CO_2Me), 4.43 (1H, dd, J = 1.8, 4.3 Hz, 2-H), 5.18 (1H, br d, J = 10.3 Hz, 3-H), 5.35 (1H, br d, J = 10.3 Hz, 3-NH), 7.04 (2H, m, Ar-H), 7.35 (2H, m, Ar-H).

9c: Ir (Nujol): 3500, 3380, 1740, 1680 cm^{-1}. FAB-ms m/z: 332 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 1.41 (9H, s, Boc), 3.16 (1H, d, J = 4.3 Hz, D_2O exchangeable, 2-OH), 3.86 (3H, s, CO_2Me), 4.42 (1H, m, 2-H), 5.39-5.48 (2H, m, 3-H and 3-NH), 6.8-6.9 (2H, m, Ar-H), 7.33 (1H, m, Ar-H).

9d: Ir (Nujol): 3500, 3370, 1730, 1685 cm^{-1}. FAB-ms m/z: 314 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 1.42 (9H, s, Boc), 3.18 (1H, d, J = 4.1 Hz, D_2O exchangeable, 2-OH), 3.85 (3H, s, CO_2Me), 4.46 (1H, m, 2-H), 5.20 (1H, d, J = 9.6 Hz, 3-H), 5.39 (1H, d, J = 9.6 Hz, 3-NH), 6.98 (1H, m, Ar-H), 7.09 (1H, m, Ar-H), 7.15 (1H, d, J = 7.8 Hz, Ar-H), 7.32 (1H, m, Ar-H).

General procedure for the synthesis of oxazolidines (10): To a solution of **9** (14.4 mmol) in benzene (200 ml) were added isopropenyl methyl ether (2.09 g, 29 mmol) and PPTS (362 mg, 1.44 mmol). The mixture was stirred at room temperature for 30 min and then stirred at 90°C. After 30 min, the mixture was cooled to room temperature and isopropenyl methyl ether (2.09 g, 29 mmol) was added. The reaction mixture was stirred at 90°C again. After 1 h, the mixture was concentrated *in vacuo*, and the residue was purified by column chromatography on SiO_2 using ethyl acetate/hexanes (1:10) as an eluent to give **10** as an oil.

10b: Ir (Neat): 1760, 1740, 1700 cm^{-1}. FAB-ms m/z: 354 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 1.19 (9H, s, Boc),

1.68 (3H, s, Me), 1.77 (3H, s, Me), 3.81 (3H, s, CO_2Me), 4.45(1H, d, J = 5.5 Hz, 2-H), 5.10 (1H, m, 3-H), 7.04 (2H, m, Ar-H), 7.31 (2H, m, Ar-H).

10c: Ir (Neat): 1760, 1740, 1700 cm^{-1}. FAB-ms m/z: 372 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 1.19 (9H, s, Boc), 1.69 (3H, s, Me), 1.76 (3H, s, Me), 3.80 (3H, s, CO_2Me), 4.47 (1H, d, J = 5.8 Hz, 2-H), 5.36 (1H, m, 3-H), 6.82 (1H, m, Ar-H), 6.90 (1H, m, Ar-H), 7.30 (1H, m, Ar-H).

10d: Ir (Neat): 1760, 1740, 1700 cm^{-1}. FAB-ms m/z: 354 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 1.19 (9H, s, Boc), 1.69 (3H, s, Me), 1.77 (3H, s, Me), 3.82 (3H, s, CO_2Me), 4.46 (1H, d, J = 5.1 Hz, 2-H), 5.10 (1H, m, 3-H), 6.95-7.07 (2H, m, Ar-H), 7.12 (1H, d, J = 7.7 Hz, Ar-H), 7.27-7.35 (1H, m, Ar-H).

General procedure for the synthesis of carboxylic acids (11): To a solution of **10** (14.0 mmol) in MeOH (100 ml) was added LiOH (410 mg, 17.1 mmol) in water (50 ml) with stirring at 0°C, then the mixture was allowed to room temperature and stirred for 1 h. MeOH was removed *in vacuo*. The pH of the residue was adjusted *ca* 2 by adding 10% HCl in an ice bath. The mixture was extracted with $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo*, to give **11** as a viscous oil. **11** was used in the next step without further purification.

General procedure for the coupling reaction of 7, 10-di-O-trichloroethoxycarbonyl-10-deacetyl baccatin III (12) with 11: To a solution of **12** (7.5 mmol) and **11** (11.2 mmol) in toluene (150 ml) were added DCC (2.46 g, 11.9 mmol) and DMAP (452 mg, 3.7 mmol). The mixture was stirred at 80°C for 1.5 h. The precipitate was removed by filtration and filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 using ethyl acetate/hexanes (1:4) as an eluent to give **13** as a form.

13b: Ir (Nujol): 3520, 1760, 1720, 1700 cm^{-1}. FAB-ms m/z: 1214 (MH^+), 1216, 1218. ^{1}H-Nmr ($CDCl_3$)δ: 1.19 (9H, s, Boc), 1.28 (6H, s, 15-diMe), 1.71 (1H, s, D_2O exchangeable, 1-OH), 1.75 (3H, s, Me), 1.80 (3H, s, Me), 1.83 (3H, s, 8-Me), 2.00 (3H, s, Ac), 2.05 (3H, d, J = 1.2 Hz, 12-Me), 2.09 (1H, m, 6-H), 2.20 (2H, m, 14-H), 2.61 (1H, m, 6-H), 3.90 (1H, d, J = 6.8 Hz, 3-H), 4.12 (1H, d, J = 8.3 Hz, 20-H), 4.30 (1H, d, J = 8.3 Hz, 20-H), 4.44 (1H, d, J = 6.6 Hz, 2'-H), 4.60 (1H, d, J = 11.8 Hz, Troc), 4.78 (2H, s, Troc), 4.91 (1H, d, J = 11.8 Hz, Troc), 4.93 (1H, m, 5-H), 5.10 (1H, m, 3'-H), 5.58 (1H, dd, J = 7.0, 10.8 Hz, 7-H), 5.68 (1H, d, J = 6.8 Hz, 2-H), 6.25 (1H, s, 10-H), 6.29 (1H, m, 13-H), 7.08 (2H, m, 3'-Ar-H), 7.33 (2H, m, 3'-Ar-H), 7.51 (2H, m, 2-Ar-H), 7.64 (1H, m, 2-Ar-H), 8.04 (2H, m, 2-Ar-H).

13c: Ir (Nujol): 3500, 1760, 1740, 1700 cm^{-1}. FAB-ms m/z: 1232 (MH^+), 1234, 1236. ^{1}H-Nmr ($CDCl_3$)δ: 1.19 (9H, s, Boc), 1.26 (6H, s, 15-diMe), 1.71 (1H, s, D_2O exchangeable, 1-OH), 1.75 (3H, s, Me), 1.79

(3H, s, Me), 1.84 (3H, s, 8-Me), 2.04 (3H, s, 12-Me), 2.05 (3H, s, Ac), 2.06 (1H, m, 6-H), 2.23 (2H, m, 14-H), 2.61 (1H, m, 6-H), 3.91 (1H, d, J = 7.0 Hz, 3-H), 4.12 (1H, d, J = 8.5 Hz, 20-H), 4.31 (1H, d, J = 8.5 Hz, 20-H), 4.49 (1H, d, J = 6.3 Hz, 2'-H), 4.60 (1H, d, J = 11.7 Hz, Troc), 4.79 (2H, s, Troc), 4.91 (1H, d, J = 11.7 Hz, Troc), 4.93 (1H, m, 5-H), 5.40 (1H, m, 3'-H), 5.56 (1H, m, 7-H), 5.68 (1H, d, J = 7.0 Hz, 2-H), 6.25 (1H, s, 10-H), 6.28 (1H, m, 13-H), 6.84 (1H, m, 3'-Ar-H), 6.97 (1H, m, 3'-Ar-H), 7.35 (1H, m, 3'-Ar-H), 7.50 (2H, m, 2-Ar-H), 7.64 (1H, m, 2-Ar-H), 8.05 (2H, m, 2-Ar-H).

13d: Ir (nujol): 3500, 1760, 1730, 1705 cm^{-1}. FAB-ms m/z: 1214 (MH^+), 1216, 1218. ^{1}H-Nmr ($CDCl_3$)δ: 1.19 (12H, br s, Boc and 15-Me), 1.28 (3H, s, 15-Me), 1.71 (1H, s, D_2O exchangeable, 1-OH), 1.75 (3H, s, Me), 1.81 (3H, s, Me), 1.84 (3H, s, 8-Me), 1.85 (1H, m, 6-H), 2.07 (3H, s, 12-Me), 2.08 (3H, s, Ac), 2.22 (2H, m, 14-H), 2.63 (1H, m, 6-H), 3.89 (1H, d, J = 7.0 Hz, 3-H), 4.10 (1H, d, J = 8.4 Hz, 20-H), 4.27 (1H, d, J = 8.4 Hz, 20-H), 4.45 (1H, d, J = 6.3 Hz, 2'-H), 4.60 (1H, d, J = 11.8 Hz, Troc), 4.72 (1H, d, J = 11.8 Hz, Troc), 4.79 (1H, d, J = 11.8 Hz, Troc), 4.91 (1H, d, J = 11.8 Hz, Troc), 4.92-4.95 (1H, m, 5-H), 5.18 (1H, br s, 3'-H), 5.59 (1H, dd, J = 7.1, 10.8 Hz, 7-H), 5.68 (1H, d, J = 7.0 Hz, 2-H), 6.26 (1H, s, 10-H), 6.26-6.32 (1H, m, 13-H), 7.03-7.09 (2H, m, 3'-Ar-H), 7.15 (1H, d, J = 7.5 Hz, 3'-Ar-H), 7.35 (1H, m, 3'-Ar-H), 7.49 (2H, m, 2-Ar-H), 7.63 (1H, m, 2-Ar-H), 8.04 (2H, m, 2-Ar-H).

General procedure for the synthesis of 14: A mixture of **13** (7.35 mmol) and formic acid (100 ml) was stirred at room temperature for 16 h. The mixture was concentrated *in vacuo*. The residue was dissolved in a small amount of ethanol and iPr$_2$O was added to the mixture. The resulting precipitate was collected by filtration and dried *in vacuo*. The solid was dissolved in THF (150 ml). To the solution were added $NaHCO_3$ (1.50 g, 17.8 mmol) and $(Boc)_2O$ (2.60 g, 11.9 mmol) with stirring at 0°C, then the mixture was allowed to ambient temperature and stirred for 16 h. The preciptate was removed by filtration and the solvent was evaporated. The residue was dissolved in ethyl acetate and washed with water and brine, and dried over Na_2SO_4. After the solvent was removed, the residue was purified by column chromatography on SiO_2 using ethyl acetate/hexanes (1:3) as an eluent to give **14** as a form.

14b: Ir (Nujol): 3400, 1760, 1730 cm^{-1}. FAB-ms m/z: 1174 (MH^+), 1176, 1178. ^{1}H-Nmr ($CDCl_3$)δ: 1.21 (3H, s, 15-Me), 1.28 (3H, s, 15-Me), 1.35 (9H, s, Boc), 1.73 (1H, s, D_2O exchangeable, 1-OH), 1.80 (1H, m, 6-H), 1.86 (3H, s, 8-Me), 1.96 (3H, s, 12-Me), 2.10 (2H, m, 14-H), 2.36 (3H, s, Ac), 2.60 (1H, m, 6-H), 3.41 (1H, d, J = 5.1 Hz, D_2O exchangeable, 2'-OH), 3.91 (1H, d, J = 7.0 Hz, 3-H), 4.18 (1H, d, J = 8.7 Hz, 20-H), 4.34 (1H, d, J = 8.7 Hz, 20-H), 4.59 (1H, m, 2'-H), 4.60 (1H, d, J = 11.8 Hz, Troc), 4.78 (2H, s,

Troc), 4.91 (1H, d, J = 11.8 Hz, Troc), 4.96 (1H, m, 5-H), 5.26 (1H, br s, 3'-NH), 5.36 (1H, m, 3'-H), 5.54 (1H, m, 7-H), 5.70 (1H, d, J = 7.0 Hz, 2-H), 6.23 (1H, m, 13-H), 6.25 (1H, s, 10-H), 7.05-7.40 (4H, m, 3'-Ar-H), 7.50 (2H, m, 2-Ar-H), 7.63 (1H, m, 2-Ar-H), 8.10 (2H, m, 2-Ar-H).

14c: Ir (Nujol): 3440, 1760, 1720 cm^{-1}. FAB-ms m/z: 1192 (MH^+), 1194, 1196. ^{1}H-Nmr ($CDCl_3$)δ: 1.21 (3H, s, 15-Me), 1.29 (3H, s, 15-Me), 1.32 (9H, s, Boc), 1.75 (1H, s, D_2O exchangeable, 1-OH), 1.86 (3H, s, 8-Me), 2.02 (3H, s, 12-Me), 2.10 (1H, m, 6-H), 2.38 (2H, m, 14-H), 2.44 (3H, s, Ac), 2.60 (1H, m, 6-H), 3.33 (1H, m, D_2O exchangeable, 2'-OH), 3.93 (1H, d, J = 7.0 Hz, 3-H), 4.19 (1H, d, J = 8.2 Hz, 20-H), 4.35 (1H, d, J = 8.2 Hz, 20-H), 4.57 (1H, m, 2'-H), 4.61 (1H, d, J = 11.8 Hz, Troc), 4.78 (2H, s, Troc), 4.91 (1H, d, J = 11.8 Hz, Troc), 4.97 (1H, m, 5-H), 5.36 (1H, m, 3'-H), 5.57 (2H, m, 7-H and 3'-NH), 5.71 (1H, d, J = 7.0 Hz, 2-H), 6.26 (1H, s, 10-H), 6.28 (1H, m, 13-H), 6.88 (1H, m, 3'-Ar-H), 6.94 (1H, m, 3'-Ar-H), 7.39 (1H, m, 3'-Ar-H), 7.50 (2H, m, 2-Ar-H), 7.62 (1H, m, 2-Ar-H), 8.11 (2H, m, 2-Ar-H).

14d: Ir (Nujol): 3430, 1760, 1730 cm^{-1}. FAB-ms m/z: 1174 (MH^+), 1176, 1178. ^{1}H-Nmr ($CDCl_3$)δ: 1.21 (3H, s, 15-Me), 1.28 (3H, s, 15-Me), 1.35 (9H, s, Boc), 1.73 (1H, s, D_2O exchangeable, 1-OH), 1.86 (3H, s, 8-Me), 1.98 (3H, s, 12-Me), 2.05 (1H, m, 6-H), 2.31-2.34 (2H, m, 14-H), 2.39 (3H, s, Ac), 2.63 (1H, m, 6-H), 3.42 (1H, d, J = 4.9 Hz, D_2O exchangeable, 2'-OH), 3.91 (1H, d, J = 7.2 Hz, 3-H), 4.18 (1H, d, J = 8.3 Hz, 20-H), 4.33 (1H, d, J = 8.3 Hz, 20-H), 4.60 (1H, d, J = 11.8 Hz, Troc), 4.63 (1H, m, 2'-H), 4.76 (1H, d, J = 11.7 Hz, Troc), 4.79 (1H, d, J = 11.7 Hz, Troc), 4.91 (1H, d, J = 11.8 Hz, Troc), 4.96 (1H, m, 5-H), 5.26 (1H, m, 3'-NH), 5.39 (1H, d, J = 9.4 Hz, 3'-H), 5.54 (1H, dd, J = 7.3, 10.6 Hz, 7-H), 5.70 (1H, d, J = 7.2 Hz, 2-H), 6.24 (1H, m, 13-H), 6.25 (1H, s, 10-H), 7.03 (1H, m, 3'-Ar-H), 7.13 (1H, m, 3'-Ar-H), 7.18 (1H, d, J = 8.1 Hz, 3'-Ar-H), 7.37 (1H, m, 3'-Ar-H), 7.51 (2H, m, 2-Ar-H), 7.63 (1H, m, 2-Ar-H), 8.10 (2H, m, 2-Ar-H).

General procedure for the synthesis of 15: To a solution of **14** (2.73 mmol) in MeOH-AcOH (4:1, 120 ml) was added Zn (5.40 g, 82.6 mmol). The mixture was stirred at 60°C for 1 h. Zn was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, and the organic layer was washed with cold 1% aqueous HCl, cold aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. After the solvent was removed, the residue was purified by column chromatography on SiO_2 using ethyl acetate/hexanes (2:3) as an eluent to give **15** as an amorphous powder.

15b: Ir (Nujol) 3440, 1710 cm^{-1}. FAB-ms m/z: 826 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 1.13 (3H, s, 15-Me), 1.24 (3H, s, 15-Me), 1.34 (9H, s, Boc), 1.73 (1H, s, D_2O exchangeable, 1-OH), 1.75 (1H, d, J = 7.0 Hz, D_2O

exchangeable, 7-OH), 1.76 (3H, s, 8-Me), 1.83 (1H, m, 6-H), 1.86 (3H, d, J = 1.1 Hz, 12-Me), 2.29 (2H, m, 14-H), 2.36 (3H, s, Ac), 2.58 (1H, m, 6-H), 3.49 (1H, d, J = 5.1 Hz, D_2O exchangeable, 2'-OH), 3.92 (1H, d, J = 7.0 Hz, 3-H), 4.19 (1H, d, J = 8.4 Hz, 20-H), 4.22 (1H, m, 7-H), 4.23 (1H, d, J = 1.7 Hz, D_2O exchangeable, 10-OH), 4.32 (1H, d, J = 8.4 Hz, 20-H), 4.58 (1H, m, 2'-H), 4.94 (1H, m, 5-H), 5.21 (1H, d, J = 1.7 Hz, 10-H), 5.25 (1H, m, 3'-H), 5.43 (1H, br d, J = 9.0 Hz, 3'-NH), 5.68 (1H, d, J = 7.0 Hz, 2-H), 6.24 (1H, m, 13-H), 7.08 (2H, m, 3'-Ar-H), 7.38 (2H, m, 3'-Ar-H), 7.49 (2H, m, 2-Ar-H), 7.61 (1H, m, 2-Ar-H), 8.10 (2H, m, 2-Ar-H).

15c: Ir (Nujol) 3440, 1720 cm^{-1}. FAB-ms m/z: 844 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 1.13 (3H, s, 15-Me), 1.26 (3H, s, 15-Me), 1.31 (9H, s, Boc), 1.60 (1H, d, J = 7.0 Hz, D_2O exchangeable, 7-OH), 1.73 (1H, s, D_2O exchangeable, 1-OH), 1.76 (3H, s, 8-Me), 1.85 (1H, m, 6-H), 1.93 (3H, d, J = 1.4 Hz, 12-Me), 2.2-2.4 (2H, m, 14-H), 2.43 (3H, s, Ac), 2.59 (1H, m, 6-H), 3.38 (1H, br d, J = 4.0 Hz, D_2O exchangeable, 2'-OH), 3.93 (1H, d, J = 7.0 Hz, 3-H), 4.20 (1H, d, J = 8.4 Hz, 20-H), 4.22 (2H, m, 7-H and 10-OH), 4.33 (1H, d, J = 8.4 Hz, 20-H), 4.56 (1H, m, 2'-H), 4.96 (1H, m, 5-H), 5.21 (1H, d, J = 1.8 Hz, 10-H), 5.39 (1H, m, 3'-H), 5.53 (1H, br d, J = 9.2 Hz, 3'-NH), 5.69 (1H, d, J = 7.0 Hz, 2-H), 6.29 (1H, m, 13-H), 6.87 (1H, m, 3'-Ar-H), 6.93 (1H, m, 3'-Ar-H), 7.38 (1H, m, 3'-Ar-H), 7.50 (2H, m, 2-Ar-H), 7.60 (1H, m, 2-Ar-H), 8.12 (2H, m, 2-Ar-H).

15d: Ir (Nujol): 3420, 1710 cm^{-1}. FAB-ms m/z: 826 (MH^+). ^{1}H-Nmr ($CDCl_3$)δ: 1.13 (3H, s, 15-Me), 1.24 (3H, s, 15-Me), 1.34 (9H, s, Boc), 1.58 (1H, d, J = 7.0 Hz, D_2O exchangeable, 7-OH), 1.70 (1H, s, D_2O exchangeable, 1-OH), 1.76 (3H, s, 8-Me), 1.87 (3H, s, 12-Me), 1.88 (1H, m, 6-H), 2.25-2.28 (2H, m, 14-H), 2.37 (3H, s, Ac), 2.59 (1H, m, 6-H), 3.46 (1H, d, J = 5.3 Hz, D_2O exchangeable, 2'-OH), 3.92 (1H, d, J = 7.4 Hz, 3-H), 4.18-4.25 (3H, m, 20-H, 7-H and 10-OH), 4.31 (1H, d, J = 8.4 Hz, 20-H), 4.60 (1H, br s, 2'-H), 4.94 (1H, m, 5-H), 5.21 (1H, d, J = 1.6 Hz, 10-H), 5.26 (1H, m, 3'-H), 5.45 (1H, br d, J = 9.0 Hz, 3'-NH), 5.68 (1H, d, J = 7.0 Hz, 2-H), 6.24 (1H, m, 13-H), 7.02 (1H, m, 3'-Ar-H), 7.12 (1H, m, 3'-Ar-H), 7.16 (1H, d, J = 7.9 Hz, 3'-Ar-H), 7.36 (1H, m, 3'-Ar-H), 7.50 (2H, m, 2-Ar-H), 7.61 (1H, m, 2-Ar-H), 8.10 (2H, m, 2-Ar-H).

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