2-[(Hydroxyimino)methyl]-1-methylquinolinium Triiodide (12). A solution of 94 mg (0.30 mmol) of the oxime methiodide **3a** in 7.0 mL of MeOH was vigorously stirred with a solution of 91 mg (0.36 mmol) of I_2 in 6.0 mL of 20% aqueous KI solution at room temperature. After 1 h at room temperature, the solid obtained was filtered, dried, and crystallized from absolute EtOH, yielding 88 mg (52%) of triiodide **12** as brown, shiny crystals: mp 171–173 °C; IR (KBr) 3300 (OH), 1595 (C=N), 1005 (=NOH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.55 (s, 1 H, NCH_3), 7.9–9.2 (m, 7 H, Ar H, CH=N), 13.55 (s, 1 H, =NOH). Anal. Calcd for $C_{11}H_{11}I_3N_2O$: C, 23.26; H, 1.95; I, 67.03; N, 4.93. Found: C, 23.49; H, 1.98; I, 66.73; N, 4.97.

Reaction of 1,2-Dimethylquinolinium Iodide (13) with Hydroxylamine Hydrochloride. To a solution of 86 mg (0.30 mmol) of 1,2-dimethylquinolinium iodide (**13**) in 1.14 mL of H_2O were added 1.14 mL of concentrated aqueous HCl solution and 63 mg (0.90 mmol) of hydroxylamine hydrochloride. The mixture was refluxed for 90 min, cooled to room temperature, and the solid obtained was filtered, washed with H_2O, and dried. Crystallization from MeOH yielded 9 mg (17%) of dark brown crystals, mp 141–143 °C. The compound was identical in all respects with an authentic sample of 1,2-dimethylquinolinium triiodide (**14**) prepared according to the literature method:[14] IR (KBr) 1615, 1525 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.08 (s, 3 H, CH_3 at C_2), 4.45 (s, 3 H, CH_3N), 7.9–9.2 (m, 6 H, Ar H).

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Registry No. 3a, 83484-86-0; **5**, 5470-96-2; **6**, 1131-68-6; **7**, 103068-53-7; **8**, 88612-18-4; **10**, 103068-54-8; **11**, 103068-55-9; **12**, 103068-56-0; **13**, 876-87-9; **14**, 103068-57-1; **15**, 103068-58-2; **16**, 23216-56-0; **17**, 41106-14-3; **18**, 7727-09-5; 2-dibromomethylquinoline, 53867-81-5.

Supplementary Material Available: Full details of synthesis, transformations and spectroscopic characterization of **7** (5 pages). Ordering information is given on any current masthead page.

Modified Taxols. 3. Preparation and Acylation of Baccatin III

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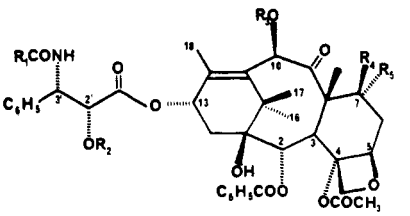
In the previous paper in this series we discussed various oxidation reactions of taxol **1a** and the products resulting therefrom.[1] In this paper we turn our attention to the preparation and reactions of baccatin III (**2**), the diterpenoid nucleus of taxol.

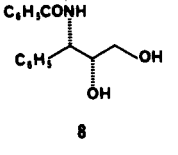
A key component of our studies on structure–activity relationships in the taxol area is the preparation of taxol analogues with modified C-13 ester side chains. One way of preparing these analogues is by the preparation of an appropriate side chain and its attachment to the C-13 position of baccatin III (**2**) (Chart I). Baccatin III, however, is only available in low yield by isolation from the yew *Taxus baccata*,[2] and we thus desired to develop a method to convert the more readily available taxol **1a** into baccatin-III. Any method developed for taxol would be applicable to cephalomannine (**1b**)[3] also and would thus provide a source of pure baccatin III from the difficultly separable mixture of taxol and cephalomannine obtained from *T. brevifolia*.[4]

Chart I

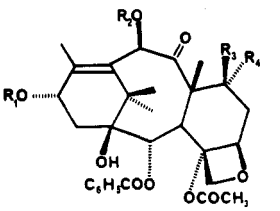


a series $R_1 = C_6H_5$; b series $R_1 = CH_3CH{=}C(CH_3)$

1	$R_2 = R_5 = H$	$R_3 = CH_3CO$	$R_4 = OH$	
3	$R_2 = R_3 = R_5 = H$	$R_4 = OH$		
6	$R_2 = R_4 = H$	$R_3 = CH_3CO$	$R_5 = OH$	
9	$R_2 = R_3 = CH_3CO$	$R_4 = OH$	$R_5 = H$	
14	$R_2 = R_3 = R_4 = H$	$R_5 = OH$		



8



2	$R_1 = R_4 = H$	$R_2 = CH_3CO$	$R_3 = OH$	
4	$R_1 = R_2 = R_4 = H$	$R_3 = OH$		
5	$R_1 = R_2 = R_3 = H$	$R_4 = OH$		
7	$R_1 = R_3 = H$	$R_2 = CH_3CO$	$R_4 = OH$	
10	$R_1 = R_2 = CH_3CO$	$R_3 = OH$	$R_4 = H$	
11	$R_1 = R_4 = H$	$R_2 = CH_3CO$	$R_3 = CH_3COO$	
12	$R_1 = R_4 = H$	$R_2 = CH_3CO$	$R_3 = CCl_3CH_2OCOO$	
13	$R_1 = R_2 = CH_3CO$	$R_3 = CCl_3CH_2OCOO$	$R_4 = H$	
15	$R_1 = R_2 = CH_3CO$	$R_3 = CH_3COO$	$R_4 = H$	

Preparation of baccatin III from taxol has not previously been reported, but cephalomannine was converted to baccatin III by methanolysis in the presence of sodium bicarbonate.[3] This reaction only gave a 19% yield of baccatin III, however, with the remaining products being identified as 10-deacetylcephalomannine (**3b**), 10-deacetylbaccatin III (**4**), and 10-deacetylbaccatin V (**5**).

A noteworthy feature of the methanolysis reaction described above is that all of the products except baccatin III have undergone methanolysis of the C-10 acetate function. In earlier work we had shown that the C-10 acetate function is sterically very hindered, since acetylation of a crude mixture derived from *T. brevifolia* yielded a diacetate of 10-deacetyltaxol.[5] We thus surmised that the use of a bulky base would suppress deacetylation at C-10 and yield a higher proportion of baccatin III. It was

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(2) (a) Chan, W. R.; Halsall, T. G.; Hornby, G. M.; Oxford, A. W.; Sabel, W.; Bjomer, K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc., Chem. Commun.* **1966**, 923–925. (b) Della Casa de Marcano, D. P.; Halsall, T. G.; Hornby, G. M. *Ibid.* **1970**, 216–217. (c) Della Casa de Marcano, D. P.; Halsall, T. G. *Ibid.* **1975**, 365–366. (d) Sénilh, V.; Blechert, S.; Colin, M.; Guénard, D.; Picot, F.; Potier, P.; Varenne, P. *J. Nat. Prod.* **1984**, *47*, 131–137.

(3) Miller, R. W.; Powell, R. G.; Smith, C. R., Jr.; Arnold, E.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 1469–1474.

(4) Dr. F. E. Boettner (Polysciences, Inc.) has recently informed us that he has developed an improved method to separate taxol and cephalomannine.

(5) Kingston, D. G. I.; Hawkins, D. R.; Ovington, L. *J. Nat. Prod.* **1982**, *45*, 466–470.

0022-3263/86/1951-3239$01.50/0

recognized that epimerization of the C-7 hydroxyl group to give baccatin V (7) would be a problem, but there were indications in the literature that the conversion of baccatin III to baccatin V was reversible,[3] and we thus hoped to effect an equilibration and separation of isomers in a subsequent step.

Reaction of a mixture of taxol **1a** and cephalomannine **1b** with triethylamine in methanol under various conditions yielded a complex mixture of products. Solvolysis in isopropyl alcohol, however, using either triethylamine or sodium isopropoxide as base, gave much cleaner reactions. Solvolysis with triethylamine in isopropyl alcohol yielded a mixture of unreacted taxol/cephalomannine (**1a**/**1b**) and 7-epitaxol/7-epicephalomannine (**6a**/**6b**) with no evidence of deacylation either to baccatin III (**2**) or 10-deacetyltaxol/10-deacetylcephalomannine (**3a**). Solvolysis in dry 0.01 M sodium isopropoxide in isopropyl alcohol, however, yielded 7-epitaxol/7-epicephalomannine (**6a**/**6b**) (22%), unreacted taxol/cephalomammine (**1a**/**1b**) (13%), baccatin V (**7**) (37%), and baccatin III (**2**) (12%), as judged by HPLC. Continued reaction led to an increase in the amount of baccatin V and a decrease in the amount of baccatin III produced. This result indicated that the equilibrium between baccatin III and baccatin V favored baccatin V under these conditions, and this fact made it unlikely that a good yield of baccatin III could ever be obtained under solvolytic conditions.

We next turned to reductive conditions to effect selective removal of the C-13 ester side chain. Our first concern was the possible side reaction of reduction of the C-9 carbonyl group, but this group is hindered by the C-16 methyl on one face and C-7 on the other face, and we never saw any reduction of it under any of the conditions we tested. The use of sodium cyanoborohydride, a reagent stable in mild acid and thus not liable to give complicating base-catalyzed reactions, gave no reaction. Sodium borohydride in isopropyl alcohol, however, converted taxol to a mixture of baccatin III (**2**), baccatin V (**7**), and the diol **8**. The formation of baccatin V could be reduced by running the reaction at 0 °C and quenching with acetic acid as soon as all the taxol had reacted, but a more convenient method was to use tetrabutylammonium borohydride in dichloromethane. Under these conditions baccatin III was obtained from taxol in 97% yield, providing for the first time a simple high-yield preparation of this important compound. Mixtures of taxol and cephalomannine could also be converted into baccatin III in good yield; the reduction in yield as compared with the reaction of taxol alone is presumably due to the presence of other substances in the partially purified taxol/cephalomannine mixture used as substrate for this reaction.

Although borohydride does not normally reduce esters, there have been previous reports of the cleavage of α-hydroxy esters by this reagent,[6] and the mechanism presumably involves complexation of the borohydride with the α-hydroxyl group followed by intramolecular delivery of hydride ion to the ester carbonyl group. Two facts confirm that this type of mechanism is taking place on taxol. In the first place, the isolation of the reduced side chain acid **8** confirms that the cleavage is reductive and not simply hydrolytic. Second, attempted reduction of 2′-acetyltaxol **9a**[7] with tetrabutylammonium borohydride in dichloromethane gave no reaction at all,[8] indicating that a free 2′-hydroxyl group is necessary for the success of the reduction.

With a supply of baccatin III now available, we investigated the acetylation of this substance. The literature contains conflicting reports, with one group claiming that acetylation yields 13-acetylbaccatin III (**10**),[3] while another group reports the formation of 7-acetylbaccatin III (**11**).[2d] Since neither group reported complete characterization data, we decided to reinvestigate this reaction.

Acetylation of baccatin III (**2**) with acetic anhydride in pyridine at room temperature yielded a single acetylation product. This product showed a signal for the C-7 proton at 5.58 ppm (dd, J = 2, 11 Hz), instead of the 4.4 ppm observed in baccatin III. Assignment of the C-7 signal at 5.58 ppm to the C-7 proton was confirmed by the observation of coupling to the C-6 proton at 1.8 ppm (2D COSY). The signal for the C-13 proton in baccatin III at 4.82 ppm (br t, J = 9 Hz) was essentially unchanged at 4.83 ppm (br t, J = 8 Hz). In all our work with taxol and its derivatives, taxanes with an intact oxetane ring all show broad triplets for the C-13 protons and multiplets or doublets of doublets for the C-7 protons. These data thus show that acetylation gave 7-acetylbaccatin III (**11**).

Preparation of 13-acetylbaccatin III (**10**) was achieved by protection of the 7-hydroxyl group of baccatin III as its 2,2,2-trichloroethyloxycarbonyl (troc) derivative **12** followed by acetylation with excess acetic anhydride, pyridine, and 4-(dimethylamino)pyridine for several hours at 75 °C to give the acetate. Deprotection of the 7-position by treatment with zinc in methanol and acetic acid then yielded 13-acetylbaccatin III (**10**). The ^{1}H NMR signal for the C-13 proton of **10** occurs at 6.16 ppm (td, J = 8, 1 Hz) very similar to that observed in taxol (6.18 ppm, br t, J = 8 Hz), and a 2D COSY experiment revealed coupling between this proton and the C-18 protons at 1.89 ppm. The signal for the C-7 proton occurs at 4.42 ppm (br t, J = 8 Hz), coupled to the C-6 proton at 1.8 ppm.

We also prepared 7,13-diacetylbaccatin III (**15**) by acetylation of baccatin III with acetic anhydride in pyridine/DMAP at 75 °C. The product showed downfield shifts for both the C-7 proton (5.60 ppm, dd) and the C-13 proton (6.18 ppm, br t) as expected, thus confirming the assignments described above.

We have determined the ^{13}C NMR spectra of compounds **10**–**13** and **15**, and the assignments are given in Table II. For compounds **10**, **12**, and **15** the assignments were confirmed by heteronuclear 2D COSY experiments; for compounds **11** and **13** assignments were made by analogy with those for **10**, **12**, and **15** and the literature spectra.[9]

These results are particularly relevant in the light of a recent publication on the partial synthesis of taxol analogues from 10-deacetylbaccatin III (**4**)[10] by reaction with cinnamoyl chloride and subsequent modification of the side chain. Taxol analogues are thus now available from partially purified taxol/cephalomannine mixtures via deacylation at C-13 and subsequent reacylation.

Experimental Section

General Methods. For the general methods used, see the previous paper in this series.[1]

(6) Plaumann, H. P.; Smith, J. C.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1980**, 354–355.

(7) Mellado, W.; Magri, N. F.; Kingston, D. G. I.; Garcia-Arenas, R.; Orr, G. A.; Horwitz, S. B. *Biochem. Biophys. Res. Commun.* **1984**, *124*, 329–336.

(8) Some reductive cleavage was observed with sodium borohydride in isopropyl alcohol, but this was much slower than with taxol itself under the same conditions and could be acounted for by initial solvolysis of the 2′-acetate group under the basic reaction conditions,[7] followed by normal reaction of the resulting taxol.

(9) Rojas, A. C.; de Marcano, D.; Méndez, B.; de Méndez, J. *Org. Magn. Reson.* **1983**, *21*, 257–260.

(10) Sénilh, V.; Guéritte, F.; Guénard, D.; Colin, M.; Potier, P. *C. R. Seances Acad. Sci., Ser. 2* **1984**, *299*, 1039–1043.

Table I. ^{1}H NMR Spectra (δ) of Baccatin III and Its Derivatives[a]

protons on	2	10	11	12	13	15
C-2	5.58 (d, 7)	5.64 (d, 7)	5.60 (d, 7)	5.62 (d, 7)	5.69 (d, 7)	5.65 (d, 7)
C-3	3.84 (d, 7)	3.81 (d, 7)	3.98 (d, 7)	4.15 (d, 7)	3.98 (d, 7)	3.95 (d, 7)
C-5	4.94 (dd, 2, 8)	4.95 (dd, 1.5, 9)	4.95 (br d, 9)	4.97 (br d, 9)	4.99 (br d, 9)	4.98 (d, 9)
C-6	2.6 (m), 2.3 (m)	1.8, 2.6 (m)	1.8, 2.6 (m)	2.6 (m), 2.3 (m)	2.63 (m), 2.3 (m)	1.8, 2.6 (m)
C-7	4.42 (m)	4.42 (br t, 8)	5.58 (dd, 2, 11)	5.60 (dd, 7, 10)	5.60 (dd, 7, 10)	5.60 (dd, 7, 10)
C-10	6.28 (s)	6.28 (s)	6.24 (s)	6.37 (s)	6.38 (s)	6.25 (s)
C-13	4.82 (br t, 9)	6.16 (td, 8, 1)	4.83 (br t, 8)	4.82 (br t, 7)	6.18 (br t, 8)	6.18 (dt, 2, 9)
C-14	2.3 (m)	2.2 (m)	2.2 (m)	2.0–2.3 (m)	2.2–2.3 (m)	2.25 (m)
C-16	1.04 (s)	1.21 (s)	1.11 (s)	1.11 (s)	1.21 (s)	1.20 (s)
C-17	1.04 (s)	1.10 (s)	1.05 (s)	1.07 (s)	1.17 (s)	1.17 (s)
C-18	1.98 (s)	1.89 (br s)	2.03 (s)	2.10 (s)	1.98 (s)	1.97 (s)
C-19	1.62 (s)	1.65 (s)	1.77 (s)	1.80 (s)	1.83 (s)	1.81 (s)
C-20	4.10 (d, 8)	4.14 (d, 8)	4.14 (d, 8.5)	4.00 (d, 8)	4.17 (d, 8)	4.15 (d, 9)
	4.26 (d, 8)	4.28 (d, 8)	4.31 (d, 8.5)	4.31 (d, 8)	4.34 (d, 8)	4.33 (d, 9)
OAc	2.20 (s)	2.30 (s)	2.27 (s)	2.28 (s)	2.16 (s)	2.04 (s)
	2.24 (s)	2.22 (s)	2.13 (s)	2.14 (s)	2.21 (s)	2.18 (s)
		2.18 (s)	2.00 (s)		2.35 (s)	2.20 (s)
						2.35 (s)
2-OBz	8.05 (dd, 2, 8)	8.05 (d, 7.5)	8.09 (d, 7)	8.08 (d, 8)	8.08 (d, 8)	8.08 (t)
	7.46 (m)	7.40 (t, 7.5)	7.59 (t, 7)	7.60 (t, 8)	7.62 (t, 8)	7.62 (m)
		7.47 (t, 7.5)	7.46 (t, 7)	7.47 (t, 8)	7.49 (t, 8)	7.48 (m)
other				4.62 (d, 12)[b]	4.65 (d, 12)[b]	
				5.02 (d, 12)[b]	5.05 (d, 12)[b]	

[a] Multiplicity and coupling constants (J in hertz) in parentheses. All spectra obtained in $CDCl_3$. [b] CH_2 protons of the 2,2,2-trichloroethyloxycarbonyl group.

Table II. ^{13}C NMR Spectra of Baccatin III Derivatives[a]

C	10	11	12	13	15
1	79.1	78.5	78.7	78.7	78.8
2	74.9[c]	76.3	76.7[c]	77.2	74.5[c]
3	45.7[c]	47.4	47.4[c]	47.1	47.3[c]
4	81.0	80.6	80.6	80.4	80.9
5	84.3[c]	83.9	83.8[c]	83.7	84.0[c]
6	35.5[c]	33.3	33.2[c]	33.2	33.4[c]
7	72.1[c]	71.6	74.4[c]	74.3	71.4[c]
8	58.5	56.0	56.2	56.1	56.1
9	203.6	202.4	201.9	201.9	202.0
10	75.7[c]	75.8	75.9[c]	75.4	75.4[c]
11	132.8	131.4	131.7	132.6	132.5
12	142.9	144.9	144.9	141.6	141.4
13	69.6[c]	67.6	67.9[c]	69.5	69.5[c]
14	35.7	38.6	38.5	35.6	35.6[c]
15	43.0	42.7	42.7	43.1	43.2
16	26.6[c]	26.6	26.6[c]	26.3	26.4[c]
17	20.7[c]	22.4	20.1[c]	22.4	20.7[c]
18	14.9[c]	15.1	15.1[c]	14.6	14.7[c]
19	9.4[c]	10.6	10.6[c]	10.6	10.8[c]
20	76.1[c]	74.4	76.3[c]	76.2	76.5
C=O of OAc	169.7	168.9	169.1	169.0	170.2
	170.1	170.5	170.7	169.7	170.2
	171.3	170.5		170.1	169.5
					168.7
CH_3 of OAc	22.5	21.0	22.4[c]	21.1	22.4
	21.5	20.7	20.7[c]	21.1	21.2
	21.2	20.0		20.7	20.7
					20.7
C=O of OBz	167.0	166.8	166.9	166.8	167.0
1-benzoyl	129.2	129.3	129.2	129.1	129.3
o-benzoyl	130.1 (2)	130.0 (2)	130.0 (2)	130.0 (2)	130.0 (2)
m-benzoyl	128.7 (2)	128.6 (2)	128.6 (2)	128.6 (2)	128.6 (2)
p-benzoyl	133.7	133.6	133.7	133.7	133.7
C=O of troc			153.2	153.1	
CH_2CCl_3			94.5	94.5	
CH_2CCl_3			77.3[c]	*b*	

[a] In ppm. [b] Peak concealed by signal for $^{13}CDCl_3$. [c] Assignments confirmed by heteronuclear COSY.

Reaction of Taxol (1a) with Sodium Borohydride. Preliminary studies showed that taxol reacted more rapidly with sodium borohydride in 2-propanol than in methanol. A 20-mg sample of **1a** in dry 2-propanol (1 mL) was treated with $NaBH_4$ (10 mg) at room temperature for 1 h. The reaction was stopped by the addition of one drop AcOH, the mixture was diluted with H_2O, and the products were extracted into CH_2Cl_2. The product mixture was purified by HPLC (RP-8 column, 250 × 10 mm, 55:45 MeOH–H_2O, 6 mL/min) to yield the diol **8**, 2.4 mg [mp 147–148 °C; ^{1}H NMR δ 3.62 (2 H, br t, J = 2.5 Hz, H-1), 4.13 (1 H, m, H-2), 5.34 (1 H, dd, J = 3.5, 8 Hz, H-3), 6.92 (1 H, d, J = 7 Hz, NH), 7.2–7.6 (8 H, m, Ar H), 7.80 (2 H, d, J = 7 Hz, *o*-PhCO); FABMS, m/z (relative intensity) 272 (MH^+, 61), 155 (52), 154 (15), 153 (17), 152 (31), 135 (42), 122 (24), 119 (100), 105 (37), 103 (50); m/z 272.1287 (MH^+; $C_{16}H_{18}NO_3$ requires 272.1313); IR 3570, 3375, 1655, 1550 cm^{-1}], baccatin III (**2**), 4.2 mg [^{1}H NMR spectrum (Table I) and K′ on HPLC identical with that of authentic material[3]], and baccatin V (**7**) 5.4 mg [^{1}H NMR spectrum and K′ on HPLC identical with that of authentic material[3]].

Preparation of Baccatin III (2) from Taxol 1a. A 100-mg sample of **1a** in dry CH_2Cl_2 (2.0 mL) was allowed to react with Bu_4NBH_4 (50 mg) for 1 h, and the reaction was quenched with 0.5 mL of AcOH. The mixture was stirred 10 min and evaporated and the product isolated by preparative TLC (6:4 EtOAc–hexane). The isolated baccatin III (**2**) was homogeneous (TLC, ^{1}H NMR); yield, 65 mg (97%).

Reaction of 2′-Acetyltaxol 9a with Tetrabutylammonium Borohydride. A 1-mg sample of **9a**[7] in dry CH_2Cl_2 (1 mL) was treated with Bu_4NBH_4 (5 mg) at 23 °C. Analysis by TLC (6:4 EtOAc–hexane) over a period of 48 h showed that no reaction occurred.

Acetylation of Baccatin III (2). A 35-mg sample of **2** in dry pyridine (1.0 mL) was incubated at room temperature with Ac_2O (0.07 mL) for 4 h. Usual workup and isolation of the products by preparative TLC (6:4 EtOAc–hexane) gave unreacted baccatin III (**2**), R_f 0.34 (18 mg), and 7-acetylbaccatin III (**11**), R_f 0.47 (13 mg). Compound **11**: FABMS, m/z (relative intensity) 651 (MNa^+, 14), 649 ($MNa^+ - H_2$, 6), 629 (MH^+, 60), 627 ($MH^+ - H_2$, 43), 569 (MH^+ – AcOH, 49), 567 (MH^+ – AcOH – H_2, 37), 551 (MH^+ – AcOH – H_2O, 28), 509 (MH^+ – 2AcOH, 15), 155 (37), 152 (23), 135 (28), 119 (74), 105 (100); IR 1770, 1745, 1700, 1395, 1260, 1200, 1145–980, 730 cm^{-1}; ^{1}H NMR, see Table I; ^{13}C NMR, see Table II.

7-(2,2,2-Trichloroethyloxycarbonyl)baccatin III (12). Baccatin III (104 mg), 4-(dimethylamino)pyridine (2.8 mg), and pyridine (0.05 mL) were dissolved in CH_2Cl_2 (1.0 mL) and treated with 2,2,2-trichloroethyl chloroformate (Aldrich) (0.05 mL, 2 equiv) at room temperature. After 40 min an additional 0.03 mL of the chloroformate was added, and the reaction was worked up in the usual way 3 min later to yield **12** as the product in greater than 95% purity (TLC and ^{1}H NMR). Flash column chromatography and recrystallization (methanol) yielded pure **12**: mp 211–213 °C; R_f (7:3 EtOAc–hexane) 0.62; FABMS m/z (relative intensity) 761 (MH^+, 66), 701 (MH^+ – AcOH, 58), 683 (20), 625 (7), 105 (100); IR 1770, 1730, 1660, 1550, 1385, 1290, 1260, 1115, 1160, 980, 720,

cm^{-1}; ^1H NMR, see Table I; ^{13}C NMR, see Table II.

13-Acetyl-7-(2,2,2-trichloroethyloxycarbonyl)baccatin III (13). Compound **12** (200 mg, 0.26 mmol), 4-(dimethylamino)-pyridine (15 mg), and acetic anhydride (0.4 mL) in dry acetonitrile (4.0 mL) was heated to 75 °C and kept at this temperature for 6 h. Usual workup and purification by preparative TLC (4:1 hexane–ethyl acetate) yielded **13** as a white solid; 0.15 g (71%); mp 239.5–241 °C dec; FABMS, m/z 803/805 (MH^+); IR 1770, 1740 cm^{-1}; ^1H NMR, see Table I; ^{13}C NMR, see Table II.

13-Acetylbaccatin III (10). Compound **13** (74 mg) was treated with Zn dust (100 mg) in MeOH–AcOH (1:1, 2.0 mL) at 40 °C for 10 min, and the reaction was worked up by filtering, evaporating the salts in vacuo, redissolving in CH_2Cl_2, and refiltering to remove Zn salts. The product **10** was obtained as a white powder (50 mg, 83%'); recrystallization (MeOH) gave mp 222.5–225 °C: $[\alpha]^{23}_D$ −59.6° (c 0.02, MeOH); FABMS, m/z (relative intensity) 651 (MNa^+, 7), 629 (MH^+, 22), 611 ($MH^+ - H_2O$, 2), 569 (MH^+ – AcOH, 11), 551 (MH^+ – AcOH – H_2O, 18), 509 (MH^+ – 2AcOH, 15), 135 (17), 119 (25), 105 (100); m/z 629.2541 (MH^+; $C_{33}H_{41}O_{12}$ requires 629.2599); IR 1760, 1740, 1725, 1670, 1570, 1390, 1295, 1120, 1090, 1060, 1000, 720 cm^{-1}; ^1H NMR, see Table I; ^{13}C NMR, see Table II.

7,13-Diacetylbaccatin III (15). A mixture of baccatin III (0.15 g, 0.51 mmol), acetic anhydride (1.5 mL), 4-(dimethylamino)-pyridine (8 mg), and pyridine (0.125 mL) was heated at 75 °C for 3 h. Workup by standard procedures and purification by PTLC yielded **15**: 0.085 g (49%); mp 234–236 °C; FABMS, m/z (relative intensity) 693 (25, MMa^+), 671(15, MH^+), 611 (12, $MH^+ - CH_3COOH$), 593 (3, $MH^+ - CH_3COOH - H_2O$), 551 (10, $MH^+ - 2CH_3COOH$), 533 (4), 525 (6), 517 (17), 459 (90), 433 (100); IR 1750, 1765 cm^{-1}; ^1H NMR, see Table I; ^{13}C NMR, see Table II.

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Fluorination of Activated Aromatic Systems with Cesium Fluoroxysulfate

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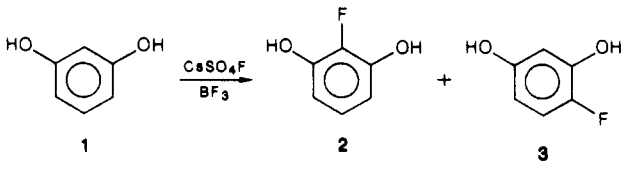
We have previously described the reactions between activated aromatics and fluoroxytrifluoromethane, CF_3OF.[1,2] The use of CF_3OF as a fluorination agent has declined because of the development of safer and more readily available hypofluorites. Rozen et al. have described the preparation and reactions of acetyl and trifluoroacetyl hypofluorites.[3] Appleman et al.[4] have reported the isolation and reactions of cesium and rubidium fluoroxysulfate, and Zupan et al.[5] have applied the use of cesium fluoroxysulfate ($CsSO_4F$) in several organic systems; both groups have reported detonations of $CsSO_4F$. Because of the ease of preparation of $CsSO_4F$, its mild reaction conditions, and its relatively long shelf life,[4,5] we conducted a study of the reaction of $CsSO_4F$ with several activated aromatic systems. This study parallels the experiments we reported several years ago with CF_3OF. We now report the new results with $CsSO_4F$ and a comparison with the previous CF_3OF studies.

In order to determine optimum reaction conditions for fluorination we chose the boron trifluoride catalyzed reaction between $CsSO_4F$ and resorcinol.[4a] The best reaction conditions proved to be an initial substrate to $CsSO_4F$ ratio of 1:1 with four drops of boron trifluoride etherate in acetonitrile solution at room temperature. Reaction time (3–12 h) was determined by substrate reactivity. Thus resorcinol (**1**) reacted with $CsSO_4F/BF_3$ for 3 h to give a mixture of 2-fluororesorcinol (**2**) and 4-fluororesorcinol (**3**).



1 2 3

$CsSO_4F/1$	% 2	% 3
1	4	21
1.3	13	40
2	25	27

The substitution ortho to the hydroxyl groups is in accord with previous results of Appleman.[4] Fluorination at the 4-position predominates over fluorination at 2-position, but the amount of the 2-substitution may be increased by increasing the amount of $CsSO_4F$. Rozen has shown that fluorination of 1,3-dimethoxybenzene with CH_3COOF produces only 4-substitution without 2-substitution and has attributed the result to steric hinderance at the 2-position.[3d] In our case, apparently the association of the $CsSO_4F$ with the phenolic hydroxyl groups permits formation of some 2-isomer **2**.[4b]

We attempted several reactions between piperonal and $CsSO_4F$, but we were unable to detect any fluorination product. Rozen, in a study of the piperonal–CH_3COOF reaction observed addition of CH_3COOF to the 1,2-bond. His results showed the dual mechanistic nature of CH_3COOF: transfer of fluorine ions and addition.[3d] We have previously shown that CF_3OF adds to the aromatic nucleus of pyrenol.[6] The addition of $CsSO_4F$ to the aromatic nucleus is apparently a much less desirable process than is the addition of CH_3COOF or CF_3OF.

Reaction of 17β-estradiol (**4**) and $CsSO_4F/BF_3$ provided a clean and simple preparation of two fluorinated isomers: 2-fluoro-17β-estradiol (**5**) and 4-fluoro-17β-estradiol (**6**). Both fluorinated isomers were useful in the study of cancer therapy with estrogens.[7,8] The present synthesis is especially attractive because the products are produced in

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