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A CONVENIENT METHOD FOR THE SYNTHESIS OF C-10 ALKYLATED DOCETAXEL ANALOGS USING *TRIS*-(TRIMETHYLSILYL)SILANE AS A RADICAL MEDIATOR

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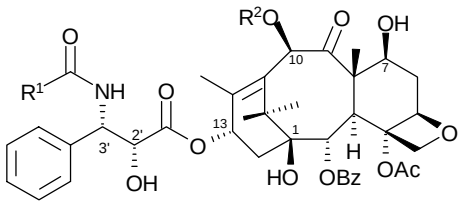
Abstract - Radical coupling has been investigated as a method for preparing Docetaxel analogs substituted at the C-10 position. C-10-Xanthate derivatives of 7-*O*-TES-10-deacetylbaccatin III were coupled with acrolein using organosilanes as radical mediators. Among the organosilanes that were investigated, *tris*(trimethylsilyl)silane gave the best results. This method provides C-10 alkylated baccatin III in good yield, and avoids the use of potentially toxic tributyltin hydride.

Paclitaxel (**1**, Taxol®)[1] has been used clinically for the treatment of ovarian cancer and has shown significant effects. On the other hand, docetaxel (**2**, Taxotere®)[2] has been used most often for the treatment of breast and lung cancers (Figure 1). Because of the huge impact of the taxoids in cancer chemotherapy,[3] many groups have reported the synthesis of taxoid derivatives.[4]

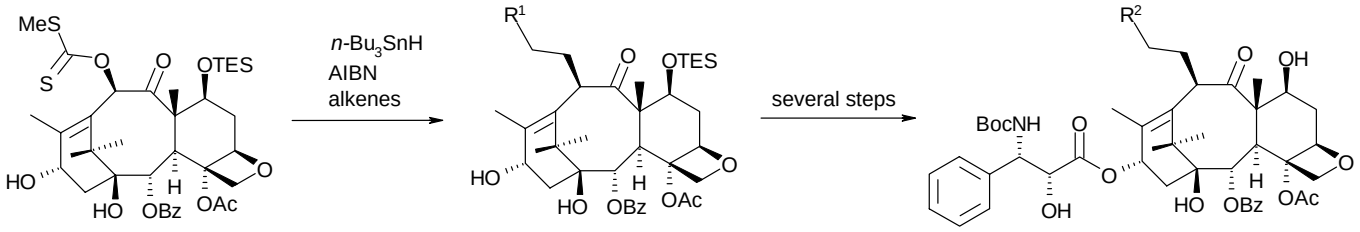
Figure 1



Paclitaxel (1: R^1 = Ph, R^2 = Ac), Docetaxel (2: R^1 = *t*-BuO, R^2 = H)

Within this extensive body of literature, we especially interested in Kingston's report describing the synthesis of the 10-deoxy analog of docetaxel (**2**), because it exhibited significantly improved *in vitro* cytotoxic activity.[5] As an extension to this promising observation, we have already described the synthesis of docetaxel analogs (**5**) which have an alkyl group at C-10 position (Scheme 1).[6] Some of these analogs showed cytotoxic activity against several cancer cell lines and were similar in potency to docetaxel. The C-10 alkylated baccatin III derivatives, which have functional groups attached to the alkyl chain in the C-10 position, can also be modified to taxoid derivatives of considerable chemical diversity.

Scheme 1



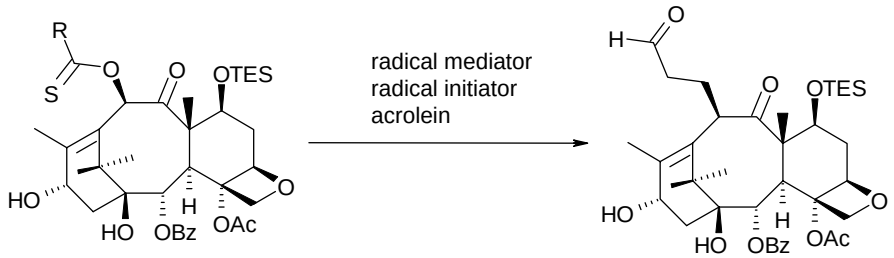
3

4: R^1 = CHO, CO_2Et, CO_2 *t*-Bu, CN, COMe

5: R^2 = CO_2Me, CO_2H, CN, Ac, NH_2, NHAc, OH,

However, the usual method of alkylation, using radical coupling with tri-*n*-butyltin hydride as a mediator has several limitations.[7] For example, (i) the experimental procedure often requires several hours for "slow injection" in order to keep the tri-*n*-butyltin hydride concentration low;[8] (ii) organotin compounds may cause environmental problems because of their toxic properties.[9] To solve these problems, we have examined organosilanes as radical mediators. Acrolein was used as the radical acceptor, because it reacts rapidly and affords a compound with a terminally functionalized C-10 alkyl substituent. The formyl group can be converted to a verify of other functional groups using well-known methods. Herein, we report a convenient method for alkylation at the C-10 position of 7-*O*-TES-10-deacetylbaccatin III, using radical coupling, with *tris*(trimethylsilyl)silane (TTMSS) as a radical mediator.

Scheme 2



3: R=SMe
6: R=OPh
7: R=pentafluorophenoxy

8

To examine the effectiveness of various organosilanes as mediators, we selected Et_3SiH,[10] Ph_2SiH,[11] and TTMSS,[7] which have been reported to work as mediators in C-C bond formation reactions proceeding *via* radical mechanisms (Table 1). Attempts to substitute Et_3SiH or Ph_2SiH_2 for *n*-Bu_3SnH resulted in failure or in a low yield, respectively (entries 2-5). However, using TTMSS the target compound (**8**) was successfully produced and moreover, in higher yield than when *n*-Bu_3SnH was used in benzene (entry 6). After some experimentation, we found the most convenient procedure, in which all of the materials were added simultaneously then heated to reflux, avoiding the troublesome "slow injection" method. The low solubility of 3 in benzene precludes direct scale up (entries 6, 7), but this problem was successfully overcome when we substituted dioxane for benzene (entries 10, 11).

Table 1: Alkylation at C-10 Position of baccatin III

entry	S.M. [a] (mmol)	mediator	initiator	solvent	temp (^oC)	yield (%)[c]	procedure [d]
1	**3** (0.04)	*n*-Bu_3SH	AIBN[b]	toluene	80-120	39	a
2	**3** (0.04)	Et_3SiH	AIBN	toluene	80-120	0	a
3	**3** (0.04)	Et_3SiH	$(PhCOO)_2O$	toluene	80-120	0	a
4	**3** (0.04)	Ph_2SiH_2	AIBN	toluene	80-120	10	a
5	**3** (0.04)	Ph_2SiH_2	$(PhCOO)_2O$	toluene	80	20	a
6	**3** (0.04)	TTMSS	AIBN	benzene	80	69	b
7	**3** (4.0)	TTMSS	AIBN	benzene	80	35	b
8	**6** (0.04)	TTMSS	AIBN	toluene	80	36	b
9	**7** (0.04)	TTMSS	AIBN	toluene	80	18	b
10	**3** (4.2)	TTMSS	AIBN	dioxane	80	50	b
11	**3** (46.7)	TTMSS	AIBN	dioxane	80	50	b

a) starting material. b) 2,2'-azobisisobutyronitrile c) isolated yield d) procedure a: To a solution (0.65 mL) of starting material, acrolein (0.4 mmol) and the initiator (0.008 mmol), a solution (0.2 mL) of the radical mediator (0.08 mmol) was added very slowly at 80 ^oC, then heated to 120 ^oC. procedure b: All of the materials were added simultaneously then heated.

The relative stereochemistry of the alkyl group at C-10 position was confirmed to be the β orientation by comparing the ^1H-NMR spectrum of **8** with that of **8** synthesized by using *n*-Bu_3SnH as mediator.[12]

In conclusion, C-10-alkylated baccatin III was prepared in good yield using TTMSS as a radical mediator. The use of TTMSS provides an efficient and eco-friendly means of introducing C-10 substituent, and avoids the "slow injection" method. In addition, we found dioxane can replace benzene as the reaction solvent so that scale-up of the synthesis of C-10-alkylated baccatin III became feasible. Investigation of the synthesis of further 10-substituted baccatin III derivatives will be reported in the near future.

EXPERIMENTAL

Melting point was found using a Yanaco PM-S3 apparatus and are not corrected. IR spectrum was obtained on a Hitachi 270-300 IR spectrophotometer. Mass spectrum was recorded on a JEOL JMS-

HX-100 spectrometer. ^{1}H-NMR spectrum was taken at 400 MHz with a JEOL JNM-EX400 spectrometer; all values are reported in ppm (δ) downfield from $(CH_3)_4Si$. Elemental analysis was obtained on a Heraeus CHN-O-Rapid instrument. Merck Silica gel (230-400 mesh) was used for column chromatography.

7-*O*-TES-10-formylethyl-10-deacetylbaccatin III (8)

Entry 11: A mixture of **3** (35.0 g, 46.7 mmol), acrolein (34.6 mL, 0.47 mol), TTMSS (43.0 mL, 0.14 mol), and AIBN (1.5 g, 9.3 mmol) were dissolved in 350 mL of dioxane, and the mixture was heated to 80 ^oC under a nitrogen atmosphere. With continuous stirring for 15 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using $CHCl_3$: acetone (20:1) as an eluent to give **8** (16.5 g, 50%) as an amorphous foam; mp: 135-140 °C; IR (KBr): 3540, 3068, 2952, 2880, 2732, 1914, 1722, 1604, 1584, 1452, 1394, 1368, 1316, 1270, 1240, 1176, 1110, 1068, 988 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.57 (6H, m), 096 (9H, s), 1.05 (3H, s), 1.12 (3H, s), 1.63 (3H, s), 1.94 (3H, s), 1.08-2.40 (8H, m), 2.29 (3H, s), 3.82 (1H, m, H-10), 4.02 (1H, d, *J* = 7.1 Hz, H-3), 4.16 (1H, d, *J* = 8.3 Hz, H-20a), 4.30 (1H, d, *J* = 8.3 Hz, H-20b), 4.54 (1H, dd, *J* = 10.8, 6.6 Hz, H-7), 4.85 (1H, m, H-13), 4.96 (1H, d, *J* = 9.0 Hz, H-5), 5.60 (1H, d, *J* = 7.1 Hz, H-2), 7.47 (2H, s), 7.60 (1H, m), 8.10 (2H, m), 9.80 (1H, s); MS (FAB); 699 (M^++1); Anal. Calcd for $C_{38}H_{54}O_{10}Si \cdot 2.5H_2O$: C, 61.35; H, 7.99. Found: C, 61.05; H, 7.69.

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12. The orientation of C-10 alkyl group was determined as β orientation in the previous report.[6]