PREPARATION OF USEFUL SYNTHETIC INTERMEDIATES OF TAXOL ANALOGS, CYCLOOCTENONE DERIVATIVES

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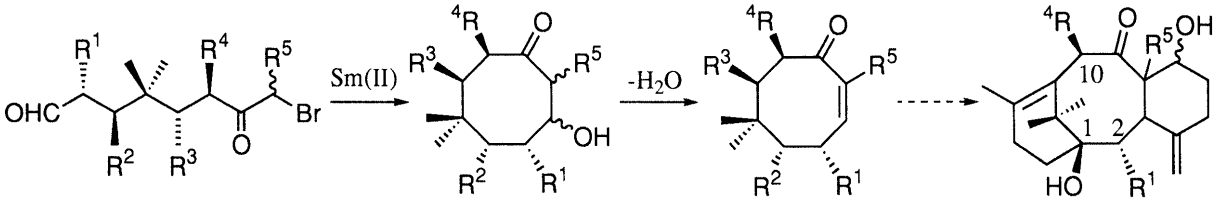
Stereoselective syntheses of ω-(α-bromoketo) octanals and nonanal with oxygenated functions and formation of the corresponding eight-membered carbocyclic aldols by subsequent samarium(II)-mediated cyclization are demonstrated. Cyclooctenones deoxygenated at the C2 or C10 position in the taxane framework are prepared by dehydration of the above aldols.

KEY WORDS cyclooctenone; samarium(II) iodide; ω-(α-bromoketo) aldehyde; deoxygenated taxane framework

Taxane diterpenes, including the antineoplastic agent Taxol, have a highly oxidized tricyclic carbon framework consisting of a central eight-membered ring and peripheral six-membered rings. In the course of our synthetic studies on Taxol, fully substituted cyclooctanone **2a**, which corresponds to the eight-membered ring structure of Taxol, was prepared in high yield by Sm(II)-mediated aldol-type cyclization[1] of an optically active acyclic ω-(α-bromoketo) octanal **1a**, as shown in Chart 1.[2] Successive construction of the tricyclic carbon framework of Taxol was achieved by using cyclooctenone **3a**, a dehydrated product of cyclooctanone **2a**, as the starting material.[3] Further asymmetric total synthesis of Taxol has recently been completed according to this synthetic strategy.[4]



1a-f **2a-f** **3a-f** **taxane framework**

Chart 1. Syntheses of Cyclooctenone Derivatives **3**. (R^1-R^5 and reaction conditions: see Table)

In order to improve the pharmacological profile of Taxol, especially solubility in water, syntheses of novel Taxol derivatives were planned using cyclooctenone intermediates deoxygenated at the C2 or C10 position of the taxane framework in the above synthetic route. In this communication, preparation of cyclooctenone derivatives deoxygenated at the C2 or C10 position in the taxane framework is described: stereoselective preparation of ω-(α-bromoketo) octanal **1b-e** and ω-(α-bromoketo) nonanal **1f**, and subsequent Sm(II)-mediated aldol-type cyclization of **1b-f**. The resulting β-hydroxycyclooctanones **2b-f** were converted to the corresponding cyclooctenones **3b-f**, respectively, *via* the dehydration process.[5]

As shown in Chart 2, preparation of ω-(α-bromoketo) octanals **1b-e** and ω-(α-bromoketo) nonanal **1f** was achieved by starting from optically active pentanol **4** or **11** *via* heptanol intermediates **7b-e**. Transformation of pentanol **11**, a precursor of octanal **1a**,[2] to heptanol **7e** was achieved *via* the formation of an (*E*)-allyl alcohol structure and subsequent hydrogenation of its double bond. (*E*)-Allyl alcohol **5** derived from **4**[6] led to the desired α-epoxide **6** with high diastereoselectivity (92% de) using *m*-chloroperoxybenzoic acid (*m*-CPBA).[7] 2,3-Epoxy alcohol **6** was converted to heptanol **7d** by the following three-step procedure: 1) regioselective reduction to 1,3-diol;[8] 2) formation of cyclic acetal; and 3) reductive cleavage of the acetal bond by diisobutylaluminum hydride (DIBAL).[9] Epoxy alcohol **6** was further transformed to cyclic carbonate **8**,[10] which was in turn hydrolyzed under alkaline conditions. Subsequent acetylation of the resulting triol with a combination of acetyl chloride and *N,N*-

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diisopropylethylamine afforded monoacetate **9**. Treatment of the vicinal diol **9** with anisaldehyde dimethylacetal and camphorsulfonic acid (CSA) resulted in 1,3-dioxane ring formation through acyl migration to the adjacent secondary hydroxyl group. Subsequent alkaline hydrolysis and benzylation of the secondary hydroxyl group gave acetal **10**, which was then reduced to heptanol **7c** with DIBAL. Heptanol **7b** was also obtained from acetal **10** by the following procedures: replacement of *tert*-butyldimethylsilyl (TBS) protection of the terminal hydroxyl group by a triethylsilyl (TES) group and reductive cleavage of cyclic acetal. Subsequent TBS protection of the resulting primary hydroxyl group and removal of the TES group afforded **7b**.

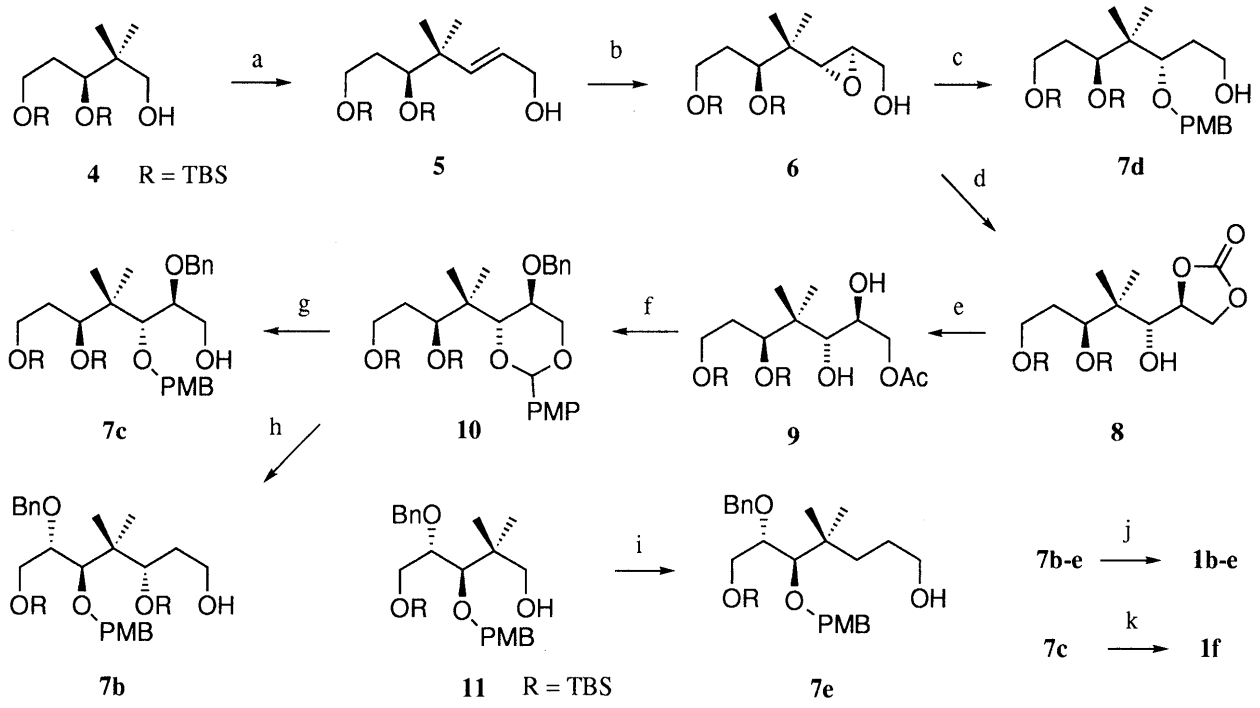

Chart 2. Synthesis of ω-(α-Bromoketo) Aldehydes **1b-f**. a) dimethylsulfoxide, oxalyl chloride, CH_2Cl_2; Et_3N (Swern oxid.) 98%; trimethyl phosphonoacetate, NaH, THF, 96%; DIBAL, CH_2Cl_2, 92% b) *m*-CPBA, CH_2Cl_2, 96% c) $LiBH_4$, BH_3, THF, 72%; 4-MeOPhCH(OMe)$_2$, 10-camphorsulfonic acid (CSA), CH_2Cl_2, 83%; DIBAL, CH_2Cl_2, 80% d) PhNCO, Et_3N, CH_2Cl_2, 98%; $EtAlCl_2$, Et_2O; $HClO_4$ aq., THF, 89% (2steps) e) 1M NaOH, MeOH, 92%; CH_3COCl, iPr_2NEt, CH_2Cl_2, 89% f) 4-MeOPhCH(OMe)$_2$, CSA, C_6H_6, 89%; 1M NaOH, MeOH, THF, 93%; BnBr, NaH, DMF, 98% g) DIBAL, CH_2Cl_2, 74% h) MeOH, CSA, DMF, 74%; TESCl, imidazole, DMF, 96%; DIBAL, CH_2Cl_2, 74%; TBSCl, imidazole, 91%; CH_3CO_2H, H_2O, THF, 95% i) Swern oxid. 82%; trimethyl phosphonoacetate, NaH, THF, 90%; DIBAL, CH_2Cl_2, 93%; H_2/Pd-C, EtOAc, 86% j) Swern oxid.; MeMgBr, THF; Swern oxid.; LiN(TMS)$_2$, TMSCl, THF; NBS, THF; 1M HCl, THF; Swern oxid. **1b**; 40%, **1c**; 31%, **1d**; 35%, **1e**; 27%, (7 steps). k) Same as step j) except using EtMgBr, 44% (7 steps).

The heptanol intermediates **7b-e** obtained above were, respectively, converted to ω-(α-bromoketo) octanals **1b-e** and ω-(α-bromoketo) nonanal **1f** according to the following procedures: primary alcohols of **7b-e** were transformed to methylketone derivatives and **7c** was also converted to an ethylketone derivative using the conventional methods of Swern oxidation, alkylation with Grignard reagent, and further Swern oxidation of secondary alcohols thus formed. Then the α-position of the resulting ketones was brominated with *N*-bromosuccinimide (NBS) *via* the corresponding enol silyl ether. After removal of the terminal silyl protecting groups, the desired ω-(α-bromoketo) octanals **1b-e** and ω-(α-bromoketo) nonanal **1f** were formed by Swern oxidation.

Then cyclization of **1b-f** was tried using SmI_2 solution (0.1 M in THF) at appropriate temperatures, as shown in the Table. Cyclization of **1f**, which had one extra carbon corresponding to angular methyl on the taxane framework, proceeded in acceptable yield at -20°C while the other substrates including **1c**, the demethyl analog of **1f**, gave moderate yields at the same temperature. The yields were increased at lower temperature (-78°C) affording cyclooctanone **2b**, **2c**, and **2f** in sufficient yields. On the other hand, the

yields were insufficient in C2, C10-dideoxygenated octanal **1d**, and C10, C11-dideoxygenated octanal **1e**. The NMR spectrum of the isolated by-products suggested that an undesirable intermolecular aldol reaction took place in parallel under the above conditions. Then, the cyclization was tried by slowly adding the substrates to diluted SmI_2 solution (0.05 M in THF) and yield improved in the case of **1d** or **1e**.

Table. Sm(II)-Mediated Cyclization of **1b-f** and Dehydration of **2b-f**.

1b-f $\xrightarrow{SmI_2, THF}$ **2b-f** $\xrightarrow[2)\ DBU,\ 60°C]{1)\ Ac_2O,\ Py,\ R.T.}$ **3b-f**

	R^1	R^2	R^3	R^4	R^5		Yield (%) of **2** -20°C[a]	-78°C[a]		d.r.[b]		Yield (%) of **3**
(**1a**	BnO	PMBO	TBSO	BnO	H	**2a**	91[c]			4/1	**3a**	81[d])[e]
1b	BnO	PMBO	TBSO	H	H	**2b**	54	81		-[f]	**3b**	68
1c	H	TBSO	PMBO	BnO	H	**2c**	57	77		4/1	**3c**	62
1d	H	TBSO	PMBO	H	H	**2d**	60	66	78[g]	2/1	**3d**	62
1e	BnO	PMBO	H	H	H	**2e**	41	49	66[g]	-[f]	**3e**	63
1f	H	TBSO	PMBO	BnO	Me	**2f**	72	80		-[f]	**3f**	74

a) Reaction temperature. b) Diastereomeric ratio (polar/less polar) at -78°C. c) Performed at 0°C. d) Dehydration *via* a mesylate. e) Ref. 3. f) Single product. g) By slow addition of **1**.

Dehydration of the aldols **2b-f**, including minor diastereomers of **2c** and **2d**, gave the corresponding (*Z*)-cyclooctenons **3b-f**. The procedure is as follows: formation of their acetates and subsequent elimination using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). These cyclooctenones **3b-f** would be similarly employed as the synthetic intermediates of taxane frameworks by constructing peripheral ring structures from our previously reported methods.[3,4]

Thus, several optically active ω-(α-bromoketo) octanals **1b-e** deoxygenated at the C2 or C10 position and C2-deoxygenated ω-(α-bromoketo) nonanals **1f** were stereoselectively prepared and were subjected to Sm(II)-mediated cyclization reaction. All of the substrates afforded cyclized products **2b-f** in satisfactory yields under appropriate conditions where yields were influenced by the substituents of the linear polyoxy precursors. Synthetic studies on Taxol analogs using cyclooctenones **3b-f** thus prepared are now in progress.

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