PREPARATION OF USEFUL SYNTHETIC INTERMEDIATES OF TAXOL ANALOGS, CYCLOOCTENONE DERIVATIVES

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Stereoselective syntheses of \( \omega-(\alpha\text{-bromoketo}) \) octanal 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; \( \omega-(\alpha\text{-bromoketo}) \) 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 of an optically active acyclic \( \omega-(\alpha\text{-bromoketo}) \) octanal 1a, as shown in Chart 1. 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. Further asymmetric total synthesis of Taxol has recently been completed according to this synthetic strategy.

![Chart 1. Syntheses of Cyclooctenone Derivatives 3. (R1 R2 and reaction conditions: see Table)](image)

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 \( \omega-(\alpha\text{-bromoketo}) \) octanal 1b-e and \( \omega-(\alpha\text{-bromoketo}) \) nonanal 1f, and subsequent Sm(II)-mediated aldol-type cyclization of 1b-f. The resulting \( \beta \)-hydroxy cyclooctanones 2b-f were converted to the corresponding cyclooctenones 3b-f, respectively, via the dehydration process.

As shown in Chart 2, preparation of \( \omega-(\alpha\text{-bromoketo}) \) octanals 1b-e and \( \omega-(\alpha\text{-bromoketo}) \) 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,\(^1\) 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\(^1\) led to the desired \( \alpha \)-epoxide 6 with high diastereoselectivity (92% de) using m-chloroperoxybenzoic acid (m-CPBA).\(^7\) 2,3-Epoxide 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).\(^9\) Epoxide 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-
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-butylidimethylsilyl (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, oxaly chloride, CH₂Cl₂; Et₃N (Swern oxid.) 98%; trimethyl phosphonoacetate, NaH, THF, 96%; DIBAL, CH₂Cl₂, 92% b) m-CPBA, CH₂Cl₂, 96% c) LiBH₄, BH₃, THF, 72%; 4-MeOPhCH(O)Me₂, 10-camphorsulfonic acid (CSA), CH₂Cl₂, 83%; DIBAL, CH₂Cl₂, 80% d) PhNCO, Et₃N, CH₂Cl₂, 98%; EtAlCl₂, Et₂O; HClO₄, THF, 89% (2 steps) e) 1M NaOH, MeOH, 92%; CH₂COCl, iPr₂NEt, CH₂Cl₂, 89% f) 4-MeOPhCH(O)Me₂, CSA, C₆H₆, 89%; 1M NaOH, MeOH, THF, 93%; BnBr, NaH, DMF, 98% g) DIBAL, CH₂Cl₂, 74% h) MeOH, CSA, DMF, 74%; TESCl, imidazole, DMF, 96%; DIBAL, CH₂Cl₂, 74%; TBSCI, imidazole, 91%; CH₃CO₂H, H₂O, THF, 95) i) Swern oxid. 82%; trimethyl phosphonoacetate, NaH, THF, 90%; DIBAL, CH₂Cl₂, 93%; H₂Pd-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) octanols 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) octanols 1b-e and ω-(α-bromoketo) nonanal 1f were formed by Swern oxidation.

Then cyclization of 1b-f was tried using SmI₂ 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 dimethyl 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
yards were insufficient in C2, C10-dideoxyoctanoyl octanal 1d, and C10, C11-dideoxyoctanoyl 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 Sml2 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.

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
<th>Yield (%) of 2</th>
<th>Yield (%) of 3</th>
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<tbody>
<tr>
<td>1a</td>
<td>BnO</td>
<td>TBSO</td>
<td>BnO</td>
<td>H</td>
<td>2a 91c</td>
<td>3a 81 d</td>
</tr>
<tr>
<td>1b</td>
<td>BnO</td>
<td>PMBO</td>
<td>TBSO</td>
<td>H</td>
<td>2b 54 81</td>
<td>3b 68</td>
</tr>
<tr>
<td>1c</td>
<td>H</td>
<td>TBSO</td>
<td>PMBO</td>
<td>BnO</td>
<td>H</td>
<td>2c 57 77</td>
</tr>
<tr>
<td>1d</td>
<td>H</td>
<td>TBSO</td>
<td>PMBO</td>
<td>H</td>
<td>2d 60 66 78 e</td>
<td>3d 62</td>
</tr>
<tr>
<td>1e</td>
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<td>PMBO</td>
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<td>H</td>
<td>2e 41 49 66 e</td>
<td>3e 63</td>
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<tr>
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<td>TBSO</td>
<td>PMBO</td>
<td>BnO</td>
<td>Me</td>
<td>2f 72 80</td>
</tr>
</tbody>
</table>

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)-cyclooctenones 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.

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.

REFERENCES AND NOTES
5) Satisfactory spectroscopic data were obtained for all new compounds.
7) Diastereomeric excess of 6 ([α]D27.2-2.45 (c=2.79, CHCl3)) was determined by HPLC and NMR analysis of its benzoate. α-Epoxide 6 was also obtained by Sharpless’ asymmetric epoxidation using (-)-diethyl tartrate.
10) Conversion of 6 to 8 was performed similarly to that in the following report; Roush W. R., Brown R. J., J. Org. Chem., 47, 1371-1373 (1982).

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