Pergamon

Tetrahedron Letters 40 (1999) 4943–4946

TETRAHEDRON LETTERS

Stereospecific synthesis of 7-deoxy-6-hydroxy paclitaxel

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Received 30 March 1999; accepted 26 April 1999

Abstract

The synthetic transposition of the 7-hydroxyl group of paclitaxel to the 6-position is described. The route presented prepares both the 6-α- and β-isomers stereospecifically. The key step of this transposition involves the stereoselective reduction of the 6,7-α-thiocarbonate using tributylgermanium hydride. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: taxoids; deoxygenation; germanium compounds; thiocarbonates.

The expanding clinical use of Taxol® for the treatment of a wide array of tumor types has fueled the search for second generation taxanes with improved clinical efficacy and safety. With this goal in mind, we began to examine the possibility of transposing the 7-hydroxyl of paclitaxel to the 6-position. Aware of the fact that the major human metabolite of paclitaxel is 6-α-hydroxylation,[1–3] it was felt that altering the oxidation state of the C-7 carbon could eleviate the pharmacokinetic liabilities present in paclitaxel. Such transposition should result in a more chemically stable taxane by removing the potential for base mediated retroaldol reaction.[4] Most intriguing was the possibility of improving chemical and metabolic stability with such a subtle structural change.

It has been observed that metabolic oxidation at C-6 produces 6-α-hydroxy paclitaxel which is significantly less potent than paclitaxel.[1] Kingston has reported that 7-deoxy paclitaxel is more cytotoxic than paclitaxel.[5] These two results encouraged us to pursue the synthesis of both stereoisomers of 7-deoxy-6-hydroxy paclitaxel. In this account, we describe a stereoselective synthesis of each isomer, taking advantage of the tendency of the C-ring to react via the α-face.

Starting with the previously described olefin **1**[6] all attempts (varying borane reagents and catalysts) to hydroborate this olefin failed to yield even a trace of the desired product. Since the conversion of olefin

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PII: S0040-4039(99)00864-3

1 to the α-diol 2 has been described,[7] we turned our attention to a strategy to selectively remove the 7-hydroxyl while retaining the 6-hydroxyl.

The 6-hydroxyl in 2 could be selectively acetylated, silylated, or alkylated, but we were unsuccessful in preparing thiocarbonates or xanthates of the 7-hydroxyl. Reasoning that the protecting group at the C-6 position was blocking approach to the 7-hydroxyl, we prepared the cyclic thiocarbonate 3.[8] Treatment of the diol 2 with 1,1-thiocarbonyl diimidazole and DMAP in THF provided the cyclic thiocarbonate. At this juncture we expected that radical deoxygenation of the cyclic thiocarbonate would provide a mixture of 6- and 7-deoxygenated products. To our surprise, treatment of thiocarbonate 3 with tributyltin hydride and AIBN afforded only the 6-hydroxy product 4 along with material in which both the 7-hydroxyl and the 10-acetate[9] were removed. The selectivity for removal of the 7-hydroxyl seems to be governed by a combination of steric and electronic factors (see Fig. 1). Intermediate A is inductively favored relative to B since the carbon radical is adjacent to a single C–O bond in A as compared with two in intermediate B. Sterically, intermediate A is favored over B due to the placement of the tributylstannyl thiocarbonate in the less congested 6-position.

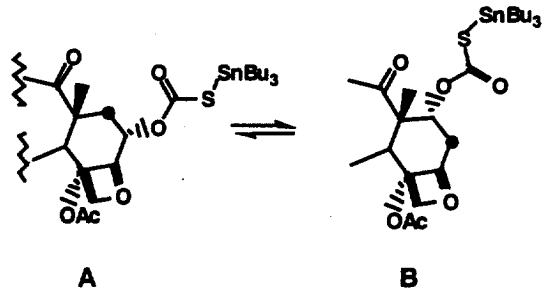
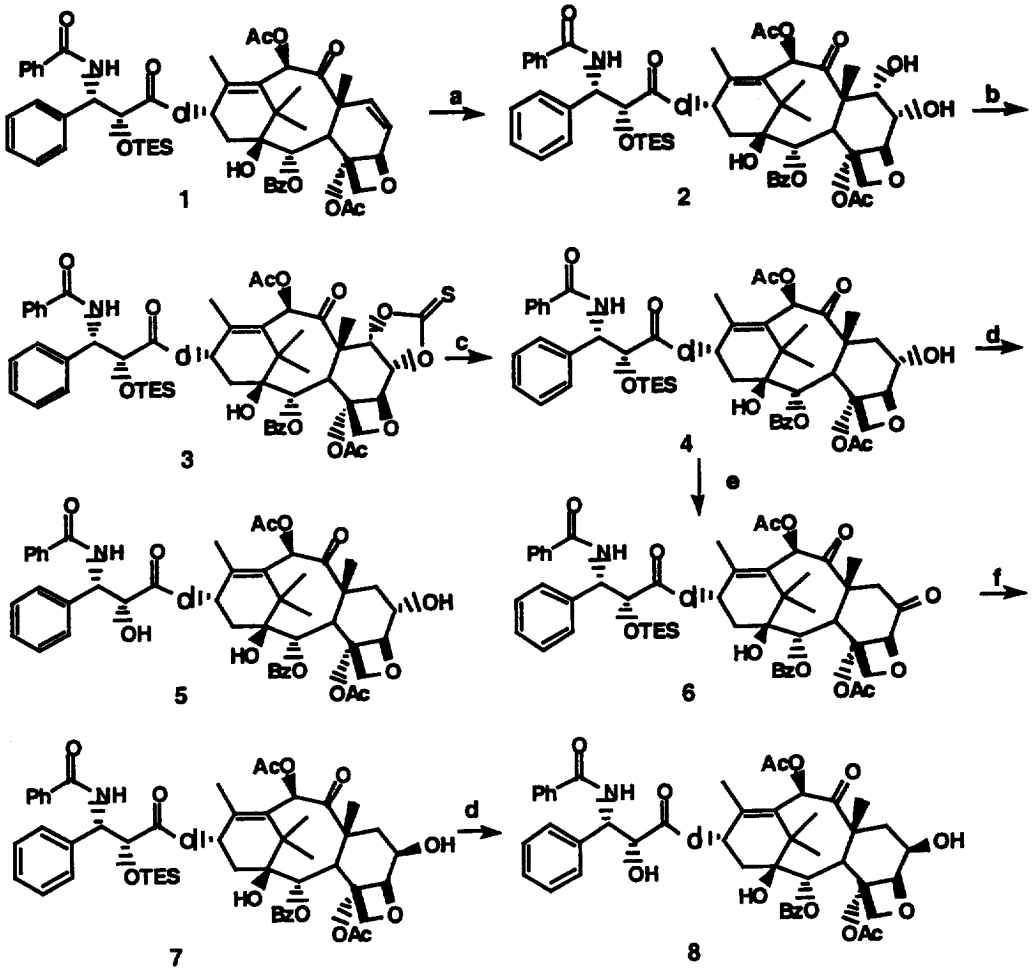


Figure 1.

While this result provided a route to one of the compounds of interest, the practical difficulty of removing the varying amounts of the 10-deacetoxylation product proved tedious. It has been suggested that the first step in the radical deoxygenation reaction is the addition of the tributyl tin radical to the thiocarbonate[8] or ester.[10] We reasoned that a less reactive hydride reagent might react more selectively with the thiocarbonate over the acetate. For this reason, we attempted the reduction in the presence of tributylgermanium hydride[11] and found that the competing 10-deacetoxylation reaction was not observed. Deprotection of 4 afforded the 6-α-hydroxy-7-deoxy paclitaxel 5. TPAP oxidation[12] of alcohol 4 provided the ketone 6 which could be stereoselectively reduced with $NaBH_4$ to afford the isomeric alcohol after deprotection. The stereoselectivity of the borohydride reduction is governed by approach of the reducing agent from the less hindered α-face as is observed in the osmylation of the 6,7-olefin 1.[4]

Compounds 5 and 8 were tested in a tubulin polymerization assay[13] and found to be equipotent to paclitaxel. Both isomers were less potent than paclitaxel in our cytotoxicity assay[14] with 5 being the more potent (Scheme 1).

In conclusion, we have demonstrated a strategy for transposing the 7-hydroxyl group of paclitaxel to the 6-position that involves a radical deoxygenation of a 6,7-cyclic thiocarbonate to remove the 7-hydroxyl group. We have described a stereoselective synthesis of both 6-hydroxy isomers that takes advantage of the α-facial selectivity of the C-ring of the paclitaxel nucleus. The in vivo biological activity of these compounds and other analogs in this series will be presented in due course.



Scheme 1. Reagents and conditions: (a) OsO_4, NMO acetone:water (8:1) (75%); (b) thiocarbonyldiimidazole, DMAP, THF (90%); (c) Bu_3GeH, AIBN, THF/toluene, 100°C (71%); (d) 1 N HCl, acetonitrile, 0°C (>95%); (e) TPAP, NMO, CH_2Cl_2 (95%); (f) $NaBH_4$, EtOH, 0°C (87%)

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