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Construction of an Advanced Taxane Synthesis Intermediate with an Oxygenated B-ring and a Non-Aromatic C-Ring through Intramolecular Pinacol Coupling at C-1--C-2

Charles S. Swindell* and Weiming Fan

Department of Chemistry, Bryn Mawr College, 101 North Merion Avenue, Bryn Mawr, Pennsylvania 19010-2899

Abstract: Advanced taxane synthesis intermediate 4 is available through a thirteen-step sequence wherein the key step is a stereoselective intramolecular pinacol coupling that joins C-1-C-2 within the eight-membered B-ring. Copyright © 1996 Elsevier Science Ltd

In recent reports,¹ we described the construction of $taxol^2$ synthesis intermediate candidates with aromatic C-rings (cf. 1) through a strategy whose key step is the stereoselective connection of C-1–C-2 by way of an intramolecular pinacol coupling. Whereas we disclosed^{1c} that neither Barbier nor pinacol coupling procedures formed this bond in respective substrates 2 and 3, we now report that advanced intermediate 4 is indeed available through intramolecular pinacol coupling at C-1–C-2. The construction of 4 in this manner is noteworthy because the C-19 angular methyl group is incorporated before the efficient B-ring closure step. The direct and efficient delivery of tricyclic intermediates having sufficient complexity built into their C-rings at an appropriate stage has proved to be one of the more significant challenges in the synthesis of the taxanes.

The assembly of keto aldehyde pinacol coupling substrate 12 from 5^3 is illustrated in Scheme 1. Of stereogenic centers C-9 and C-10, C-9 previously had been identified as playing the dominant role in the in-





duction of the relative configurations at stereogenic centers C-1 and C-2 created through the intramolecular pinacol coupling process.^{1b,d} Thus, it was deemed particularly important to establish the relative configurations of C-8 and C-9 before the intramolecular pinacol coupling process so that through it the important C-1– C-2–C-8 relationship would be installed. We had hoped that an Ireland ester enolate Claisen rearrangement carried out on a glycolate ester⁴ of **6** could establish the C-8–C-9 relationship at the stage of **8**, especially since Shea⁵ had shown a very similar glycolate enolate Claisen rearrangement (of 14) to favor this diastereomeric type. However, numerous experiments carried out with 15 aimed at optimizing either E(O)-enolate formation,⁶ which would require a boat transition structure to deliver Claisen rearrangement product type **8**, or Z(O)-enolate formation,⁶ which would produce the type **8** diastereomer through a chair transition structure, failed to cause the desired product to predominate to an acceptable degree and in good yield.⁷ Thus, recourse was made to the Johnson ortho ester variant of the Claisen rearrangement to produce ester **7**, which then was subjected to the Davis enolate oxidation procedure.⁸ That **8** possessed the desired relative stereochemistry was proved through its conversion to lactone **16**: **16** exhibits an NOE involving the H-9 proton and Me-19



(taxane numbering) that is absent in lactone stereoisomer 17. It is probable that the formation of 8 is favored by the shielding of the enolate β -face by the silyloxymethyl group in conformation 18.

Protection of hydroxy ester 8 and adjustment of its oxidation state through a reduction-oxidation⁹ sequence produced aldehyde 9. Prior experience with similarly protected α -hydroxy aldehydes^{1a,b,d} indicated them to undergo predominantly Felkin-Ahn-controlled additions of the organometallic reagent 10,^{1b,d,10} which furnishes the A-ring. However, 9 interacted with 10 to give apparent chelation-controlled adduct 11 as the sole detectable stereoisomer.⁵ If 11 results from an addition to aldehyde conformation 19 stabilized by genuine chelation of lithium cation, the intervention of the chelated transition structure must benefit from the interference with the trajectory of the nucleophile by the silyloxymethyl group in the alternative Felkin-Ahn pathway (cf. 20). Further processing of 11 delivered pinacol coupling substrate 12.¹¹



Subjection of 12 to samarium iodide¹² treatment produced tricycle $4.^{13}$ The stereochemistry of 4 was confirmed after its conversion to tetraol $13,^{14}$ which exhibited NOE's involving four partly overlapping sets of spatially proximate protons:¹⁵ Me-17 and M-16; H-2, H-9, and Me-16; H-2, H-9, and Me-19; and H-10 and Me-18. These observations are consistent with the three-dimensional representation of 13 below, which must arise through the endo boat-chair transition structure (cf. 12) characteristic of the major reaction channel for these intramolecular pinacol couplings.¹



The key to the conversion of 12 into 4 in the face of our previous inability to cause the cyclization of substrates 2 and 3 is clearly the presence of the $\Delta^{3,4}$ olefinic bond. This structural feature, which should provide an entrée to the oxetane substructure of taxol, obviates the closure of the B-ring in *trans*-fused fashion relative to the C-ring, as would be the case for 2 and 3. It also is probably relevant that unsaturated and

aromatic carbonyl compounds are intrinsically more reactive in pinacol coupling and related chemistry than saturated ones.¹⁶ Whatever the reason for the successful conversion of 12 into 4, 4 represents a potentially valuable advanced intermediate for complex taxane synthesis.

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- 13. Data for 4: mp 176–179 °C; ¹H NMR (300 MHz; CDCl₃) δ 5.90 (t, J = 4, 1H), 4.78 (d, J = 9.6, 1H), 4.24 (d, J = 9.6, 1H), 4.17 (s, 1H), 2.5–1.45 (m, 10H), 1.69 (d, J = 0.8, 3H), 1.50 (s, 3H), 1.48 (s, 3H), 1.43 (s, 3H), 1.25 (s, 3H), 1.14 (s, 3H); ¹³C NMR (75 MHz; CDCl₃) δ 145.3, 142.4, 130.6, 121.7, 107.3, 82.8, 82.6, 75.6, 70.9, 40.9, 37.5, 31.9, 28.4, 28.0, 27.4, 27.0, 25.7, 25.0, 24.9, 21.8, 19.9, 17.8. Anal. Calcd. for C₂₂H₃₄O₄: C, 72.90; H, 9.45. Found: C, 73.03; H, 9.32.
- 14. Data for 13: mp 166–168 °C; ¹H NMR (300 MHz; CDCl₃) δ 5.82 (t, J = 5, 1H), 4.78 (d, J = 9.7, 1H), 4.16 (d, J = 9.7, 1H), 4.11 (s, 1H), 2.31–1.51 (m, 10H), 1.67 (s, 3H), 1.48 (s, 3H), 1.27 (s, 3H), 1.13 (s, 3H); ¹³C NMR (75 MHz; CDCl₃) δ 146.3, 139.0, 133.9, 119.3, 81.8, 79.3, 72.9, 70.9, 41.1, 40.6, 31.4, 28.6, 27.8, 26.2, 24.9, 24.8, 21.7, 20.3, 18.0. Anal. Calcd. for C₁₉H₃₀O₄: C, 70.77; H, 9.37. Found: C, 70.90; H, 9.15.
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