

Studies Towards the Total Synthesis of Taxoids Synthesis of an A-ring Building Unit

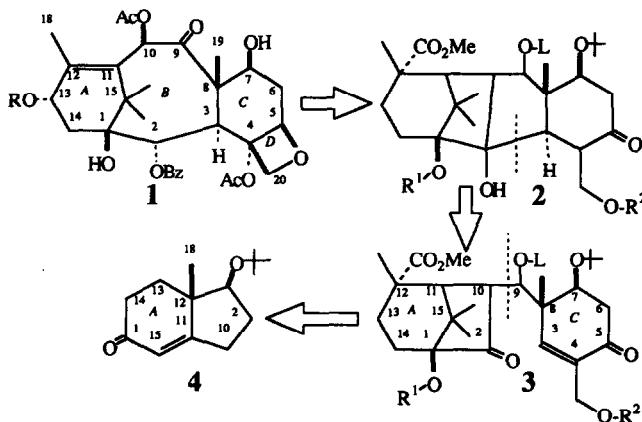
S.Arseniyadis*, D.V.Yashunsky, R.Pereira de Freitas, M.Muñoz Dorado,
E.Toromanoff and P.Potier

Institut de Chimie des Substances Naturelles, CNRS, F-91198 Gif-sur-Yvette(France)

Abstract: An efficient 11-step synthesis of the optically homogeneous bridged ring system 13, by a $S_{\text{M}}1_2$ mediated reductive pinacol coupling is presented.

The spindle poisons (colchicine, vinblastine, taxol) have been extensively studied in our Institute under their chemical and pharmacological aspects for the past two decades¹. Accordingly we developed a comprehensive synthetic program for taxol and its analogs².

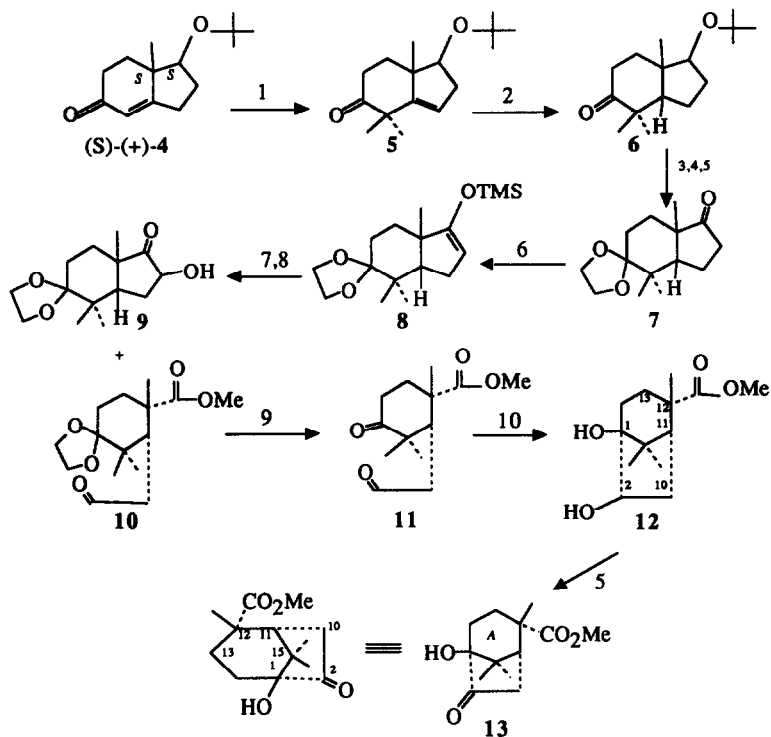
Since taxol **1** was first reported to be a promising anticancer drug several dozens of (as yet unaccomplished) synthetic approaches have been published³. As part of our ongoing studies we desire to develop an efficient synthesis of **2** that contains the ABC preformed framework of taxol (summarized in Scheme 1). Our interest in this synthesis has focused on the use of the known lower analogue **4**⁴ of Wieland-Miescher ketone as an A-ring precursor. We disclose herein a short and efficient synthesis of **13** in its optically homogeneous form .



Scheme 1

The retrosynthetic analysis for synthesizing the bicyclo[3.2.1]octane unit involves two critical steps, the elaboration of the cis-fused hydrindane **6** and the carbon-carbon bond formation leading to the bridged system **12**. The above mentioned considerations led us to develop a synthesis via the corresponding precursor **4**. The interesting biological activities found among molecules containing the relatively rigid bicyclo[3.2.1]octane ring system⁵ have made the design

of synthetic routes to this ring system a challenging problem⁶. Retrosynthetic analysis showed that **12** could be obtained by an appropriate elaboration of **4** which secures the relative (and absolute) stereochemistry and can further be brought into taxol's A-ring using literature conditions. The key step of our synthetic scheme was the construction of the suitably functionalized bicyclo[3.2.1]octane ring system **12** either by a C-1/C-2 or C-2/C-10 intramolecular carbon-carbon bond formation. Scheme 2 summarizes the successful C-1/C-2 approach.



Scheme 2: 1) *t*-BuOK, *t*-BuOH, MeI, 2) H₂-Pd/C 10%, benzene-heptane, r.t., 3) BF₃·Et₂O, DCM, r.t., 4) HO(CH₂)₂OH, *p*TosOH, benzene, Δ, 5) DMSO, (COCl)₂, Et₃N, DCM, -60°C, 6) TMSOTf, collidine, DCM, r.t., 7) O₃, DCM, Py, -78°C, then PPh₃, 8) CH₂N₂, Et₂O, 0°C, 9) 1N HCl-THF, r.t., 10) SmI₂, THF-MeOH, -25°C.

Thus, following Scheme 2, we prepared **5** bearing the C-15 geminal methyl group (by treatment with *t*-BuOK in *t*-BuOH at 0°C for 30 min followed by addition of an excess methyl iodide) the double bond being shifted to the five membered ring. Catalytic reduction in benzene-heptane (H₂-Pd/C, 50psi, 30 h) afforded a stereoisomeric mixture of *cis* and *trans* fused hydrindanones in 86% yield and a 32:1 ratio respectively⁷. The two compounds were easily separated by crystallization from pentane thus affording the optically pure **6**⁸. The *cis* ring junction was necessary to ensure the C-1 carbon center (taxane numbering) in its required absolute stereochemistry. Removal of the *t*-butyl protecting group was accomplished as described in reference 4 (BF₃·Et₂O, DCM, r.t.) in 99% yield. Ketalization of the C-1 carbonyl with ethylene glycol (benzene, *p*TosOH, Δ, Dean-Stark, 93%), followed by a Swern oxidation of the free

hydroxyl group ((COCl)₂, DMSO, Et₃N, DCM, -60°C) furnished ketone-ketal **7** (90%). Formation of its corresponding silyl enol ether **8** (TMSOTf, collidine, DCM, r.t., 93%) and subsequent ozonolysis (DCM, Py, -78°C), followed by work-up with triphenylphosphin and esterification with diazomethane afforded **9⁹** (23%) and **10** (60%). Acid catalyzed deketalization of **10** with 1N HCl in THF at r.t. gave the desired keto-aldehyde **11** (96%). The acyloin **9** was smoothly converted to **10** by treatment with NaIO₄ in THF-H₂O at r.t. for 10 min. and esterification with diazomethane, increasing considerably the yield of the required keto-aldehyde **11**. A number of reagents are known to promote pinacolic coupling reaction of ketones or aldehydes¹⁰. Substrate **11** was submitted to standard reductive cyclization conditions mediated by SmI₂ (2.8 equivalents of SmI₂¹¹, 2.2 equiv of MeOH in THF at -25°C)¹² and gave **12** in 91% yield¹³. The configurations at the newly formed asymmetric centers are assigned to be as in **12** by considering the compulsory bottom-side attack of C-1 carbonyl thus insuring the facial selectivity on C-1. Experimental evidence favouring the structure **12** came from n.o.e studies (400MHz NMR) and was in agreement with molecular mechanics calculations (Figure 1), using Still's Macromodel program, with Allinger's basic MM2 force field¹⁴. Swern oxidation of **12** (DMSO, (COCl)₂, Et₃N, DCM, -60°C to r.t.) afforded the key intermediate **13** (85%).¹⁵

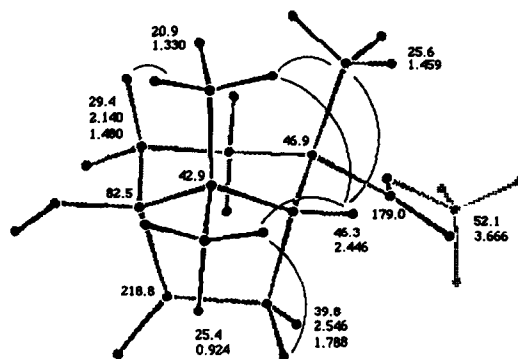


Figure 1: The Lowest Energy Conformer of **13** (the arcs indicate observed nuclear Overhauser enhancements).

In summary, a concise synthesis of **13** was achieved over 11 steps. A salient feature of this scheme is that the stereocenter at C-1 was constructed in a highly stereoselective manner and the utility of a new methodology for preparing taxol's A-ring was demonstrated. Further investigations of the conversion of **13** to a taxane framework via a B-seco taxane **3** are in progress.

Acknowledgements: The authors wish to thank Pr.G.Ourisson (Université Louis Pasteur, Strasbourg) for useful discussion, CAPES (Brazil) and Universidad de Granada (Spain) for fellowships to R.P. de Freitas and M.M. Dorado respectively.

References and Notes:

- 1- P.Potier, *Chem.Soc.Reviews* 113-119 (1992) and references cited therein.
- 2- J.N.Denis, A.E.Greene, D.Guénard, F.Guéritte-Voegelein, L.Mangatal, and P.Potier, *J.Am.Chem.Soc.*, **110**, 5917-5919(1988).

- 3- Review articles: C.S.Swindell, *Organic Preparations and Procedures Int.*, **23**, 465-543(1991); S.Blechert and D.Guenard, *The Alkaloids*, vol.**39**, 195-238(1990); R.A.Holton, *Strategies and Tactics in Organic Synthesis*, vol. **3**, 165-197(1991).
- 4- S.Arseniyadis, R.Rodriguez, E.Cabrera, A.Thompson, and G.Ourisson, *Tetrahedron*, **47**, 7045-7058(1991) and references cited therein.
- 5- Gibberellins : G.Stork, R.K.Boeckmann,Jr., D.F.Taber, W.C.Still, and J.Singh, *J.Amer.Chem.Soc.*, **101**, 7107-7109(1979); E.J.Corey and J.E.Munroe, *ibid*, **104**, 6129-6130(1982); Helminthosporanes: E.Piers and H.P.Isenring, *Can.J.Chem.*, **55**, 1039-1044(1977).
- 6- J.Baker, M.J.Begley, M.Mellor, D.A.Otieno, and G.Pattenden, *J.Chem.Soc.Perkin Trans I*, 1893-1900(1983); A.S.Kende, B.Roth, and P.J.Sanfilippo, *J.Amer.Chem.Soc.*, **104**, 1784-1785(1982).
- 7- The trans hydrindanone was obtained in an approximately 3% yield. For *cis* and *trans* identities see: G.Stork and D.Kahne, *J.Amer.Chem.Soc.*, **105**, 1072-1073(1983).
- 8- **6** (*cis*-fused): IR (nujol): 2970, 2871, 1702, 1456, 1383, 1370, 1191, 1104, 1025; ¹H-NMR (400MHz, CDCl₃): 1.003 (3H,s); 1.139 (3H,s); 1.167 (9H,s); 1.223 (3H,s); 1.48 (2H,m); 1.73 (2H,m); 1.85 (3H,m); 2.24 (1H,m); 2.54 (1H,m); 3.51 (1H,t,J=7.1); ¹³C-NMR (62.5MHz, CDCl₃): 23.5, 24.6, 26.6, 26.7, 28.7, 32.0, 32.1, 34.7, 42.2, 47.1, 54.8, 72.6, 79.4, 217.1; EIMS: 252 (M⁺, 16), 196 (100), 178 (10), 168 (22), 136 (16), 125 (18), 93 (14), 71 (24), 57 (63); m.p.: 72-73°C (pentane); [α]_D +63 (c=1.0, CHCl₃); **6** (*trans*-fused): IR (film): 2970, 2930, 2871, 1702, 1456, 1383, 1370, 1191, 1104, 1025; ¹H-NMR (400MHz, CDCl₃): 1.01 (3H,s); 1.04 (3H,s); 1.09 (3H,s); 1.13 (9H,s); 1.40-2.05 (7H,m); 2.31 (1H,ddd, J=2.4, 5.6, 16.1); 2.66 (1H,ddd, J=6.8, 13.0, 16.1); 3.37 (1H,dd J=7.8, 8.9); ¹³C-NMR (62.5MHz, CDCl₃): 12.1, 20.0, 20.9, 25.7, 28.7, 31.3, 34.7, 35.9, 42.1, 47.5, 53.3, 72.4, 80.0, 217.1; EIMS: 252 (M⁺, 14), 196 (34), 135 (26), 125 (39), 107 (20), 95 (17), 83 (20), 81 (20), 57 (100); [α]_D +11 (c=1.0,CHCl₃).
- 9- R.Clark and C.H.Heathcock, *Tetrahedron Lett.*, 2027-2030(1974); R.D.Clark and C.H.Heathcock, *J.Org.Chem.*, **41**, 1396-1402(1976).
- 10- G.A.Molander, *Chem.Rev.*, **92**, 29-68(1992); B.E.Kahn, R.D.Rieke, *ibid*, **88**, 733-745(1988); J.Nakayama, S.Yamaoka, M.Hoshino, *Tetrahedron Lett.*, **28**, 1799-1802(1987).
- 11- P.Girard, J.L.Namy, and H.Kagan, *J.Amer.Chem.Soc.*, **102**, 2693-2698(1980); H.Kagan, *N.J.Chim.*, **14**, 453-460(1990).
- 12- The Sml₂ in THF was added via a syringe pump over a period of 6 h.: G.A. Molander, C.Kenny, *J.Org.Chem.*, **53**, 2134-2136(1988).
- 13- **12**: IR (nujol): 3356, 2951, 1722; ¹H-NMR (400MHz, CDCl₃): 1.07 (3H,s); 1.16 (3H,s), 1.32 (3H,s); 1.37 (1H, ddd, J=4.0, 6.6, 12.8); 1.53 (1H,dd,J=8.1,14.9); 1.58 (1H,m); 1.97 (1H,ddd, J=3.5, 7.4, 14.9); 2.00 (1H,m); 2.07 (1H,dd, J=5.8, 13.6); 2.12 (1H,dd,J=1.4, 7.3); 2.63 (1H,br.s); 2.87 (1H,br.s); 3.645 (3H,s); 3.83 (1H,dd,J=3.6, 8.1); ¹³C-NMR (62.5MHz, CDCl₃): 21.6, 25.1, 25.6, 27.5, 30.4, 37.1, 43.9, 46.8, 49.6, 51.9, 73.4, 78.6, 178.0; EIMS: 242 (M⁺, 65), 210 (100); HREIMS: for C₁₃H₂₂O₄ calc. 242.1518, found 242.1513; m.p.: 107-8°C (pentane-ether); [α]_D -21 (c=0.9, CHCl₃).
- 14- Molecular mechanics calculations were performed on a Silicon Graphics Work Station (4D25) with MacroModel v3.1 as software using Allinger's basic MM2 force field and Monte Carlo method to generate conformers: Still, W.C., Mohamadi, F., Richards, N.G.J., Guida, W.C., Lipton, M., Liskamp, R., Chang, G., Hendrickson, T., De Gunst, F., and Hasel, W., MacroModel V 3.1, Dept of Chemistry, Columbia University, New-York, N.Y. 10027.
- 15- **13** : IR (nujol): 3436, 2977, 2937, 2904, 2851, 1742, 1722, 1456, 1377. ¹H-NMR (400MHz, CDCl₃): 0.92 (3H,s); 1.33 (3H,s); 1.46 (3H,s); 1.48 (1H,m); 1.73 (1H,m); 1.79 (1H,d,J=19.5); 2.06 (1H,dt,J=6.4, 14.6); 2.14 (1H,dt,J=6.1,12.8); 2.45 (1H,d,J=7.6); 2.55 (1H,dd,J=7.6, 19.5); 3.66 (3H,s); ¹³C-NMR (62.5MHz, CDCl₃): 20.9, 25.4, 25.6, 27.8, 29.4, 39.8, 42.9, 46.4, 46.9, 52.1, 82.6, 178.9, 218.8; EIMS: 240, (M⁺, 3), 212 (100), 180 (67); HREIMS for C₁₃H₂₀O₄, calc. 240.1361, found 240.1368.; m.p.: 71-2°C (pentane); [α]_D +43 (c=1.0, CHCl₃).