Pergamon

Tetrahedron Letters, Vol. 37, No. 19, pp. 3313-3316, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00538-2

Diastereoselective Synthesis of a Taxane Precursor

Benoît Muller, Francette Delaloge, Marc den Hartog, Jean-Pierre Férézou*
Ange Pancrazi*, Joëlle Prunet, Jean-Yves Lallemand

Laboratoire de Synthèse Organique associé au C.N.R.S., DCSO, Ecole Polytechnique, F-91128, Palaiseau, France.

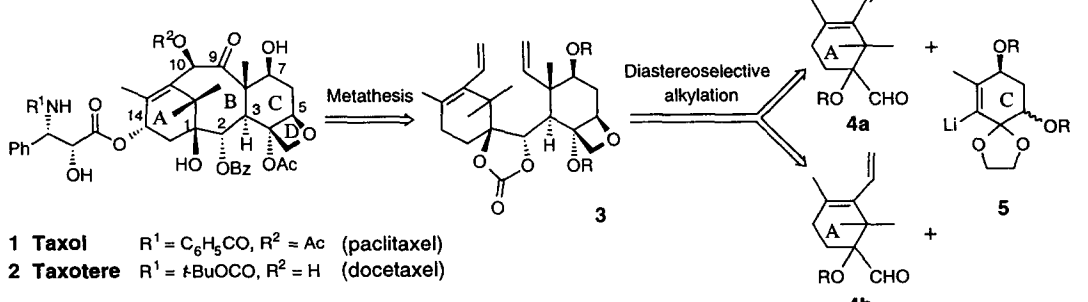
Alain Neuman, Thierry Prangé

Laboratoire de Chimie Structurale Biomoléculaire, Université Paris Nord, 74 rue Marcel Cachin, F-93017 Bobigny France.

Abstract : A highly diastereoselective synthesis of the taxane potential precursor **16** is achieved. An unexpected diastereoselectivity was observed upon condensation of the α-trimethylsilyloxyaldehydes **9a** or **9b** with the cyclohexenyllithium **10**. The single diol isomers **13A** and **14A** exhibiting the required 1β,2α relative configuration are obtained in good yields.

Taxol® **1** [1] and taxotere® **2**,[2] two potent antitumor agents, have been approved for clinical use in several countries. In addition to their novel mode of action, their unusual and interesting structure as well as their low natural availability stimulated tremendous synthetic efforts from organic chemists. To date three total syntheses of taxol have been reported [3] and the huge amount of work done in this area is summarized in several reviews.[4]

Our program towards the total synthesis of taxol relies on convergent approaches with the late assembly of properly suited A and C rings where all the taxol functionalities are potentially present. One of these approaches involves a ring closure olefin metathesis [5] reaction as a key step for the construction of the C9-C10 8-membered B ring bond (**Scheme 1**).[6] For the construction of the B-seco taxane **3**, we envisaged coupling the A and C rings **4** and **5** *via* a diastereoselective formation of the C2-C3 bond followed by subsequent vinyl cuprate addition on the enone obtained after ketal deprotection.[7]

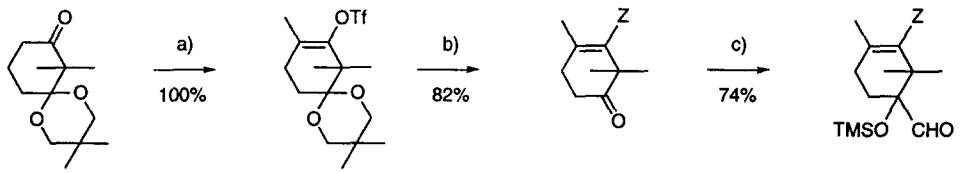


1 Taxol $R^1 = C_6H_5CO$, R^2 = Ac (paclitaxel)
2 Taxotere R^1 = *t*-BuOCO, R^2 = H (docetaxel)

Scheme 1

To our knowledge, the only examples of such coupling reactions involve additions of aryl-metal analogues of C ring to C-2 aldehydes precursors of A ring.[8] As further functionalization of an aromatic C ring precursor seems to be difficult to achieve, we decided to study the addition of cyclohexenyllithium nucleophiles such as **5** on A ring precursors bearing either an enyne (**4a**) or a diene (**4b**) moiety.[9]

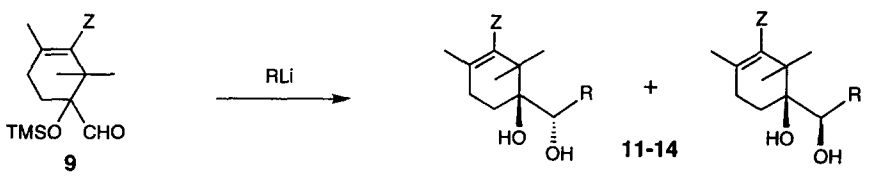
The synthesis of the A rings encompassing the required α-oxygenated aldehyde function started from the already reported cyclohexan-1,3-dione monoketal **6** (**Scheme 2**).[10] For the construction of the enyne or diene system, the Stille triflate coupling reaction under Pd (0) catalysis was adressed. C-Methylation of the lithium enolate of **6** and treatment of the methylated ketone with LDA/$PhNTf_2$ led to the corresponding vinyltriflate **7** in excellent yield. Condensation of **7** with tributylstannyltrimethylsilylacetylene or tributylstannylethylene under $Pd(PPh_3)_4$/LiCl conditions followed by hydrolysis of the cyclic ketal afforded the enynone **8a** or the dienone **8b** in 92% and 82% yields respectively for the last two steps.[11] The corresponding α-trimethylsilyloxyaldehydes **9a** and **9b** were then prepared in 67% and 74% yields respectively by zinc iodide catalyzed addition of TMSCN followed by reduction of the resulting nitriles with DIBAL-H.[12]

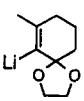
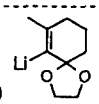


a) i- LDA, THF, MeI (1.5 eq); ii- LDA, THF, $PhNTf_2$ (1.6 eq). **b)** i- $Bu_3SnC{=}CH_2$ or $Bu_3SnCCTMS$ (1.5 eq), LiCl (3 eq), cat. $Pd(PPh_3)_4$, THF, reflux; ii- cat. TsOH, Acetone, H_2O. **c)** i- TMSCN (1.5 eq), cat. ZnI_2, CH_2Cl_2; ii- DIBAL-H (1.5 eq), Hexane

Scheme 2

Having secured the preparation of the α-oxygenated aldehydes **9a** and **9b**, we next turned to their condensation reaction with vinyllithium nucleophiles and some results are summarized on **Scheme 3**.[13]

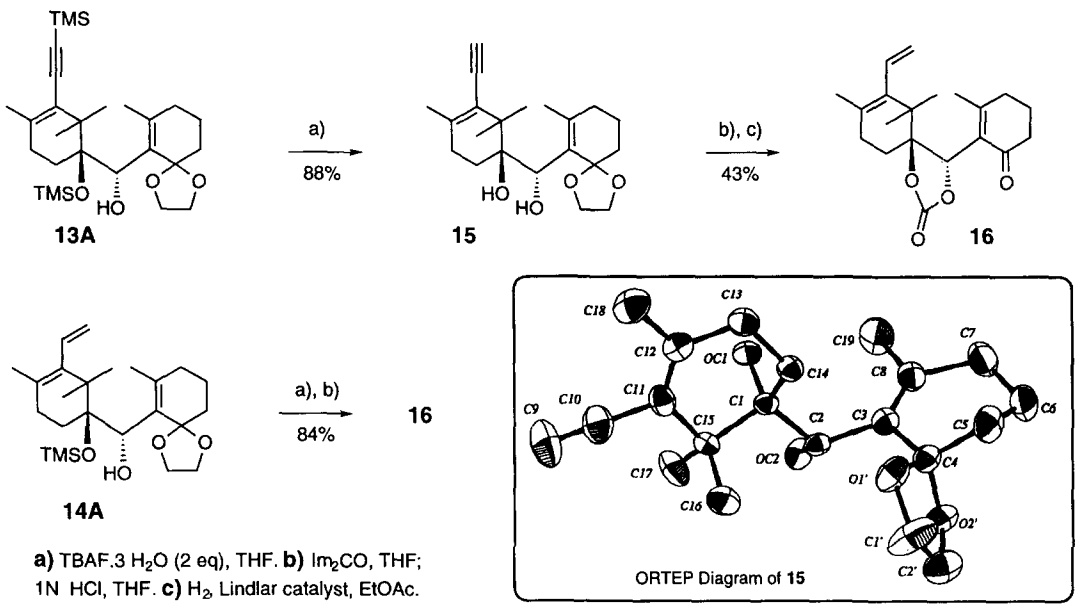


	RLi		Yield (%)	A		B
9a Z = C≡C—TMS	MeLi	**11**	100	60	:	40
		**12**	66	33	:	67
	 **10**	**13**	72	100	:	0
9b Z = CH=CH2	 **10**	**14**	52	100	:	0

Scheme 3

In a preliminary experiment, when methyllithium or *o*-lithiated styrene were added to the acetylenic aldehyde **9a**, mixtures of diol diastereomers **11A/11B** and **12A/12B** were obtained.[14] To our surprise, when

10 was added to the aldehyde **9a**, only one isomer **13A** was isolated,[15] whose structure was unambiguously established by X-ray crystallography of a later intermediate, the diol **15** (**Scheme 4**).[16] The relative configuration of the C-1 and the C-2 hydroxyl groups is that required for Taxol. Increasing the number of equivalents of nucleophile from 1.5 to 5 improved the yield in **13A** from 30% to 72%. No trace of the other diastereomer was detected by 400MHz ^{1}H NMR analysis of the crude reaction mixture. When the nucleophile **10** was condensed with the α-trimethylsilyloxyaldehyde **9b**, the diene **14A** was obtained in 52% yield with no trace of the epimeric **14B**. The same outstanding selectivity was reported when *o*-lithiated aryl derivatives were added to the α-metalloxyaldehyde precursor of the A ring of taxol, through chelation control.[8b)c)] The reason why the bulkier nucleophile **10** behaves differently from an aromatic one is still unclear. The alcohols **13A** and **14B** were transformed into the carbonate **16** *via* standard functional group manipulations (**Scheme 4**).



Scheme 4

At this stage, preparation of the B-seco taxane **3** would require a conjugate addition of a vinyl copper reagent onto **16**. In the case of the definitive synthesis of taxol, the correct stereochemistry of this addition is assumed to be dictated by the vicinal 7-OH group of **5**.[7] However, preliminary attempts to add vinylcopper nucleophiles onto **16** failed and studies are still in progress to develop this convergent new route towards taxanes.

Acknowledgments : The CNRS and the Ecole Polytechnique are thanked for financial support. We wish to thank Rhône-Poulenc S.A. Industry for a fellowship for B. M. and F. D.

References and Notes :

1. a) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325-2327. b) ACS Symposium Series 583, *Taxane Anticancer Agents : Basic Science and Current Status*; Georg, G.I.; Chen, T.T.; Ojima, I.; Vyas, D.M., Eds.; American Chemical Society, Washington D.C., 1995.

2. Lavelle F.; Guéritte-Voegelein, F.; Guénard, D. *Bull. Cancer*, **1993**, *80*, 326-338. Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160-167 and references cited therein.
3. a) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630-634. Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624-633. Nicolaou, K. C.; Liu, J. J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C. K.; Nakada, M.; Nantermet, P. G. *ibid.* **1995**, *117*, 634-644. Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *ibid.* **1995**, *117*, 645-652. Nicolaou, K. C.; Ueno, H.; Liu, J. J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *ibid.* **1995**, *117*, 653-659. b) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang., P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597-1598. Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang., P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *ibid.* **1994**, *116*, 1599-1600. c) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723-1726.
4. See Ref. 1b); Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15-44. Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemp. Org. Synth.* **1994**, *1*, 47-75. Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1-206. Swindell, C. S. *Stud. Nat. Prod. Chem.* **1993**, *12*, 179-231. Paquette, L. A. *Stud. Nat. Prod. Chem.* **1992**, *11*, 3-69. Kingston, D. G. I. *Pharmac. Ther.* **1991**, *52* , 1-34. Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465-543.
5. Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446-452.
6. Taxol numbering is used throughout the paper.
7. Polla, M.; Frejd, T. *Tetrahedron* **1993**, *49*, 2701-2710. Furukawa, T.; Seto, M.; Horiguchi, Y.; Kuwajima, I. *Chem. Lett.* **1993**, 1279-1282.
8. a) Masters, J. J.; Jung, D. K.; Bornmann, W. G.; Danishefsky, S. J.; De Gala, S. *Tetrahedron Lett.* **1993**, *34*, 7253-7256. b) Nakamura, T.; Waizumi, N.; Tsuruta, K.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1994**, 584-586. c) Young, W.B.; Masters, J. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5228-5234.
9. The chemistry of such enynes is parallely developed for other synthetic approaches of taxol (to be published).
10. Jacobson, B. M.; Soteropoulos, P.; Bahadori, S. *J. Org. Chem.* **1988**, *53*, 3247-3255. Kress, M. H.; Ruel, R.; Miller, W. H.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 5999-6002.
11. Stille, J. K.; Scott, W. J . *J. Am. Chem. Soc.* **1986**, *108*, 3033-3040. Ritter, K. *Synthesis* **1993**, 735-762. Queneau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 4043-4047.
12. Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55-56. Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, 4929-4932.
13. **10** was obtained from the corresponding bromide, which was synthesised in 2 steps from 3-methyl-2-cyclohexen-1-one according to Smith, III, A. B.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855-1869: a) Br_2, CCl_4, Et_3N, 70%. b) Ethylene glycol, TsOH, benzene, Dean-Stark apparatus, 57%.
14. This result is in agreement with Danishefsky's findings for the addition of *o*-lithiated styrene to the aldehyde **9**, Z = I; see ref. 8a,c.
15. All new compounds have been fully characterized by ^1H NMR, ^{13}C NMR, IR, mass spectrometry and combustion analysis. Stereochemical assignments have been thoroughly established through careful 400 MHz 2D ^1H NMR NOESY experiments.
13A: white crystalline solid, **mp** 104-105 °C; **IR** (KBr) ν 3491, 2955, 2892, 2130, 1661, 1630, 1441, 1379, 1301, 1252, 1099, 1068, 1031, 871, 856, 758 cm^{-1}; **^1H NMR** (400 MHz, $CDCl_3$) δ 4.62 (br s, 1H, 2-H), 3.98-3.88 (m, 4H, OCH_2CH_2O), 3.86 (br s, 1H, 2-OH), 2.38-2.28 (m, 1H), 2.10-2.02 (m, 1H), 1.95-1.83 (m, 2H), 1.88 (s, 3H, 12-CH_3), 1.83 (s, 3H, 8-CH_3), 1.83-1.71 (m, 2H), 1.64-1.41 (m, 4H), 1.17, 1.10 (2s, 6H, $C(CH_3)_2$), 0.15, 0.10 (2s, 18H, 2 $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.5 (11-C), 142.3 (3-C), 130.3 (8-C), 123.8 (12-C), 108.8 (4-C), 105.3, 96.6 (9-C, 10-C), 74.5 (1-C), 69.8 (2-C), 63.7, 63.5 (OCH_2CH_2O), 43.3 (15-C), 35.5, 33.8 (5-C, 7-C), 29.4, 26.9 (13-C, 14-C), 20.0 (6-C), 26.7, 22.6, 22.4, 22.0 (4 CH_3), 0.4, 0.1 (2 $Si(CH_3)_3$); **MS** (DI, CI, NH_3) m/z 491 (MH^+), 473 ($MH^+ - H_2O$), 429, 401, 339, 255, 90; **Anal.** Calcd for $C_{27}H_{46}O_4Si_2$: C, 66.07; H, 9.45. Found: C, 65.82; H, 9.33.
15: white crystalline solid; **mp** 159-160 °C; **IR** (KBr) ν 3475, 3382, 3288, 2955, 2901, 2079, 1655, 1633, 1417, 1374, 1296, 1198, 1080, 1055, 912, 780, 602 cm^{-1}; **^1H NMR** (400 MHz, $CDCl_3$) δ 4.95 (d, 1H, *J* = 7.6 Hz, 2-H), 4.14-4.11 (m, 2H, OCH_2CH_2O), 4.02 (d, 1H, *J* = 7.6 Hz, 2-OH), 4.00-3.96 (m, 2H, OCH_2CH_2O), 3.90 (br s, 1H, 1-OH), 3.02 (s, 1H, 9-H), 2.35-2.26 (m, 1H), 2.11-2.09 (m, 1H), 1.90 (s, 3H, 12-CH_3), 1.79-1.65 (m, 3H), 1.71 (s, 3H, 8-CH_3), 1.56-1.48 (m, 3H), 1.44, 1.26 (2s, 6H, $C(CH_3)_2$); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 142.5 (11-C), 141.3 (3-C), 128.6 (8-C), 123.9 (2-C), 110.2 (4-C), 83.0 (10-C), 80.4 (9-C), 75.2 (1-C), 75.0 (2-C), 63.6, 63.1 (OCH_2CH_2O), 42.3 (15-C), 33.0, 32.7 (5-C, 7-C), 28.5, 27.8 (13-C, 14-C), 19.3 (6-C), 25.9, 23.2, 22.5, 21.1 (4 CH_3); **MS** (DI, CI, NH_3) m/z 329 ($MH^+ - H_2O$), 285, 267, 183; **Anal.** Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found : C, 72.62; H, 8.62.
16. Compound **15** crystallized from CH_2Cl_2/Et_2O as small white needles Space group $P2_12_12_1$ with parameters a = 16.852, b = 11.338, c = 9.932 Å. Final R Factor = 4.6% for 2632 structure factors.

(*Received in France* 24 *January* 1996; *accepted* 17 *March* 1996)