Pergamon

Tetrahedron Letters, Vol. 37, No. 51, pp. 9139-9142, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02159-4

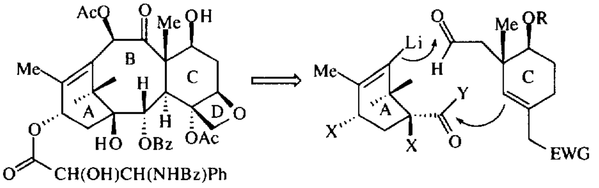
Concise Synthesis of Taxol A-Ring Components: Remote Diastereoselective Additions of Alkenyl Lithiums to Aldehydes

Christopher Frost, Patrick Linnane, Philip Magnus* and Mark Spyvee

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712.

Abstract: The acid chloride **6** provides access to **7** (R,S and S,S) which upon bromine-lithium exchange undergoes remarkably highly diastereoselective additions to aldehydes; **7** is also readily elaborated into the acetal **10**.
Copyright © 1996 Elsevier Science Ltd

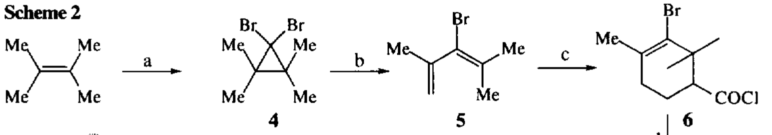
Scheme 1



1, Taxol **2** **3**

One of the most direct and convergent approaches to the synthesis of the highly functionalized taxol core structure[1] is depicted in **Scheme 1**.[2] Construction of the A-ring component and the C-ring unit allows for a multitude of ways to subsequently link them together, one of which is the union of **2** and **3**.[3] To explore this, and other options, we required a short route to the A-ring **2** (or equivalent) in an enantiomerically enriched form. While there have been many reports describing the synthesis of the taxol A-ring in various oxidation levels,[4] the chemistry described here uncovered some new observations which are useful for the specific case of taxol, but also should be valuable in the broader arena of synthesis.

Scheme 2



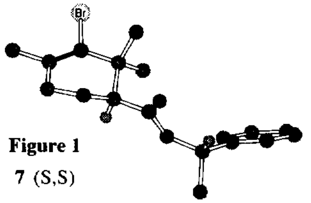
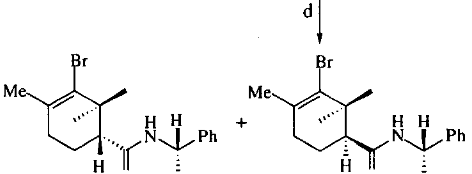


Figure 1
7 (S,S)



7 (R,S) **7** (S,S)

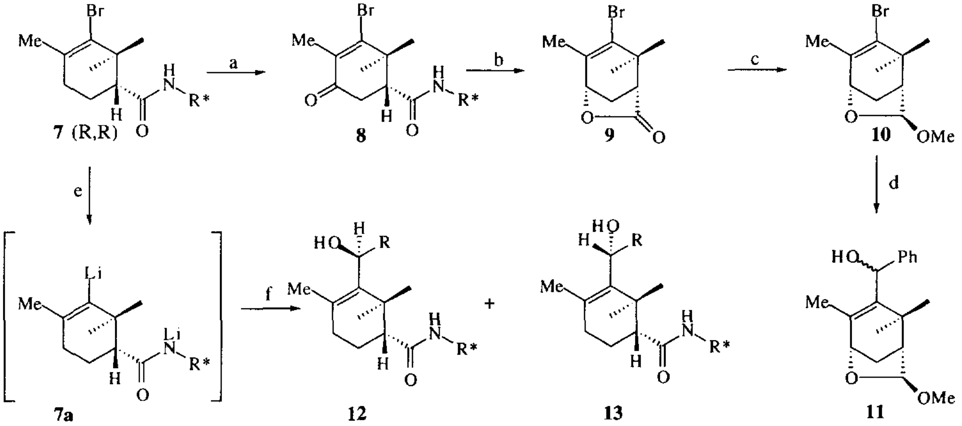
Conditions:-a) $CHBr_3$/*t*-BuOK/pentane, **4** (95%). b) $PhNMe_2$/148°C, **5** (>95%). c) $CH_2CHCOCl$/110°C, **6** (95%). d) S-(-)-PhCHMeNH$_2$, **7** (100%).

Tetramethylethylene was converted into the *gem*-dibromocyclopropane **4**, which on treatment with $PhNMe_2$ at 148°C gave the bromodiene **5**, **Scheme 2**.[5] This modification of the literature procedure more than doubles the yield of **5** and is amenable to large scale (100 g). The diene **5** reacted cleanly with acryloyl chloride in a thermal (110°C) Diels-Alder process to give **6** (95%), with no more than traces of the other regioisomer

(<5%). All attempts to catalyze this reaction with chiral Lewis acids, or chiral derivatives of acryloyl chloride were unsuccessful.[6] Consequently, **6** was treated with S-(-)-$PhCHMeNH_2$ to give a 1:1 mixture of **7** (R,S) and **7** (S,S) which were readily separable, and the absolute stereochemistry of one of the diastereomers determined by X-ray crystallography. **Figure 1** show a Chem 3D representation from the x-ray coordinates of the **7** (S,S) diastereomer, and therefore the other diastereomer **7** (R,S) corresponds to the correct absolute configuration needed for the synthesis of taxol.

Since the *sec*-amide formation to give **7** had accomplished the resolution of the A-ring we decided to examine halogen-metal exchange on this derivative rather than the traditional esters, **Scheme 3**.

Scheme 3 [R* = R-(+) PhCHMe or S-(-) PhCHMe]



Conditions:-a) CrO_3/3,5-DMP/CH_2Cl_2/-15°C **8** (76%). b) i. $N_2O_4/CCl_4/CHCl_3$/-40 to 0°C (96%). ii. 0.1 M NaOH/80°C (66%). iii. MeI/acetone/K_2CO_3 (89%). iv. $NaBH_4$/MeOH/-15°C (91%). v. K_2CO_3/PhCl/135°C **9** (76%). c) DIBAL-H/CH_2Cl_2/-78°C, followed by $(MeO)_3CH$/MeOH/CSA **10** (68%). d) *t*-BuLi/Et_2O/-78°C, followed by PhCHO **11** (80%, 3:2). e) *t*-BuLi (6 eq.)/Et_2O/-78°C/3 h. f) RCHO (10 eq.)/-78°C/Et_2O, **12/13**.

Treatment of **7** (**TABLE 1**) with *t*-BuLi (6 equiv. in hexane) gave the dianion **7a** which was quenched with an aldehyde to give two diastereomers **12** and **13** (R = Me, Et, Ph and *t*-$BuCH_2$). Remarkably, even though the newly created stereogenic center is 7 atoms removed from the chiral benzylic position and 4 atoms from C-1, the observed diastereoselectivity is extraordinarily high. In the case of acetaldehyde (R = Me) the ratio was 20:1, and the structure of the major product was determined by X-ray crystallography, **Figure 2**.

TABLE 1

Substrate	Solvent	Base	Aldehyde	Prodts	Yield %	By-prodt
7 (R,R)	Et_2O	*t*-BuLi (hex)	MeCHO	20 : 1	60	Alkene
7 (R,R)	THF	*t*-BuLi (hex)	MeCHO	20 : 1	30	Alkene
7 (R,R)	Et_2O	*t*-BuLi (hex)	EtCHO	15 : 1	65	Alkene
7 (R,R)	Et_2O	*t*-BuLi (hex)	PhCHO	7 : 1	50	Alkene
7 (S,R)	Et_2O	*t*-BuLi (hex)	PhCHO	6 : 1	80	Alkene
7 (R,R)	Et_2O	*t*-BuLi (hex)	*t*-$BuCH_2CHO$	10 : 1	50	Alkene
7 (S,R)	Et_2O	*t*-BuLi (hex)	*t*-$BuCH_2CHO$	10 : 1	50	Alkene

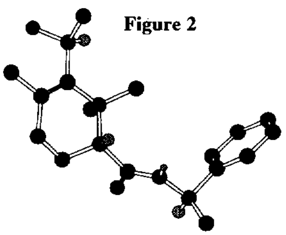


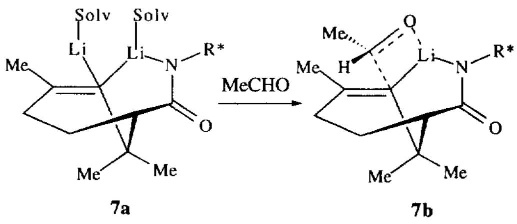
Figure 2

The only significant by-products were the alkene **7** (Br replaced by H), and small amounts of compounds that were derived from *o*-metallation of the phenyl ring followed by quenching with the aldehyde. Also, in order to establish that **12** and **13** are diastereomers only at *sec*-OH position and no epimerization at C-1 has taken place, we subjected the mixture of **12** and **13** to the Dess-Martin oxidation conditions to give a single enone.

By way of attempted comparison, the C-1 derivatives -CONMeR*, -CO_2Bu^t and -CO-oxazolidinone of **6** did not undergo clean halogen metal exchange, and from the complex mixtures obtained the only discernible product(s) were attack of the *t*-BuLi on the C-1 carbonyl group. The *sec*-amide in **7** thus provides a protecting facility for C-1 through the amide anion **7a**.

While it is possible to introduce the C-13 oxygen functionality into very advanced taxol intermediates[7] we were intrigued with the possibility of subjecting **7** to allylic oxidation reactions. A priori, an electron-deficient vinyl bromide might be rather resistant towards this type of transformation, and indeed perusal of the literature did not reveal any pertinent examples other than the oxidation of a vinyl iodide to a β-iodoenone during the course of Kishi's approach to taxol.[8] In the event, treatment of **7** with CrO_3.3,5-dimethylpyrazole[9] gave the required β-bromoenone **8** (76%).[10] *N*-Nitrosation of **8**, followed by hydrolysis, esterification, reduction and lactonization gave the known lactone **9**.[11] The lactone was reduced with DIBAL-H and the crude lactol treated with $CH(OMe)_3/MeOH/H^+$ to give **10**. Bromine-lithium exchange (*t*-BuLi) of **10** and quenching with PhCHO gave **11** (80%) as a 3:2 mixture of diastereomers. Wender has reported that the lactone **9** gave a 3.1:1 ratio of diastereomers (Li, followed by PhCHO).[10] Therefore it appears that the *sec*-amide is the source of the enhanced diastereoselectivity, presumably through a possible lithium-bridged chelate.[12] It is probable that the dilithio species **7a** is in fact a bridged compound, and the more sophisticated representation in **Scheme 4**, as either a solvated monomer or aggregated species, is a more plausible picture. Reaction of **7a** with acetaldehyde would favor **7b**, which leads to the major diastereomer **12**. It would seem unlikely that the cause of the diastereoselectivity is confined only to substrate **7**, and we are exploring the notion of long-range lithium chelation (supramolecular) as a more general phenomena to control stereochemistry.[13]

Scheme 4



Acknowledgments. The National Institutes of Health, National Science Foundation and the Welch Foundation are thanked for their support of this research.

References and Footnotes.

1. Bauta, W.; Booth, J.; Bos, M. E.; DeLuca, M.; Diorazio, L.; Donohoe, T.; Magnus, N.; Magnus, P.; Mendoza, J.; Pye, P.; Tarrant, J.; Thom, S.; Ujjainwalla, F. *Tetrahedron Lett.* **1995**, *36*, 5327. Magnus, P.; Booth, J.; Magnus, N.; Tarrant, J.; Thom, S.; Ujjainwalla, F. *Tetrahedron Lett.* **1995**, *36*, 5331. Magnus, P.; Pye, P. *J. Chem Soc. Chem. Commun.* **1995**, 1933.

2. Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15. Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. "*Recent Progress in the Synthesis of Taxanes*", *Contemporary Organic*

Synthesis, **1994**, *1*, 47. "*Taxane Diterpene Synthesis Strategies. A Review*", Swindell, C. S; *Organic Preparations and Procedures Int.*, **1991**, *23(4)*, 465.

3. Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Clairborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature*, **1994**, *367*, 630. Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624. Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1723. Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843.

4. For recent syntheses of A-ring units see: 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. *J. Am. Chem. Soc.* **1995**, *117*, 634. Nicolaou, K. C.; Hwang, C.-K.; Sorensen, E. J.; Clairborne, C. F. *J. Chem. Soc. Chem. Commun.* **1992**, 1117. Arseniyadis, S.; Yashunsky, D. V.; Pereira de Freitas, R.; Dorado, M. M.; Toromanoff, E.; Potier, P. Tetrahedron Lett. 1993, 34, 1137. Masters, J. J.; Jung, D. K.; Danishefsky, S. J.; Snyder, L. B.; Park, T. K.; Isaacs, R. C. A.; Alaimo, C. A.; Young, W. B. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 452. Golinski, M.; Vasudevan, S.; Floresca, R.; Brock, C. P.; Watt, D. S. *Tetrahedron Lett.* **1993**, *34*, 55. Doi, T.; Robertson, J.; Stork, G.; Yamashita, A. *Tetrahedron Lett.* **1994**, *35*, 1481. Tjepkema, M. W.; Wilson, P. D.; Wong, T.; Romero, M. A.; Audrain, H.; Fallis, A. G. *Tetrahedron Lett.* **1995**, *36*, 6039. Lu, Y-F.; Fallis, A. G. *Tetrahedron Lett.* **1993**, *34*, 3367.

5. Skell, P.S.; Garner, A. *J. Am. Chem. Soc.* **1956**, *78*, 5430.

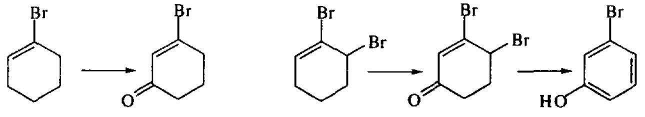
6. Under Lewis acid reaction conditions the bromodiene **5** was rapidly polymerized.

7. Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513.

8. Kress, M. H.; Ruel, R.; Miller, W.H.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 5999.

9. Corey, E. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1973**, *14*, 4499. Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.

10. We have also oxidized **I** and **III** with CrO_3.3,5-DMP to give **II** and **IV** respectively. It is noteworthy that **IV** can be isolated and only slowly (at RT) loses HBr to give **V**.



I **II** (64%) **III** **IV** (50%) **V**

II is normally made from cyclohex-1,3-dione/Br_2/PPh_3, "*Comprehensive Organic Functional Group Transformations*", Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W. **1995**, *Vol. 3*, p. 239. Pergamon.

11. Wender, P. A.; Wessjohann, L. A.; Peschke, B.; Rawlins, D. B. *Tetrahedron Lett.* **1995**, *36*, 7181.

12. Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624.

13. Aston, P. R.; Hörner, B.; Kocian, O.; Menzer, S.; White, A. J. P.; Stoddart, J. J.; Williams, D. J. *Synthesis*, **1996**, 930, and references therein.

(*Received in USA* 26 *September* 1996; *accepted* 29 *October* 1996)