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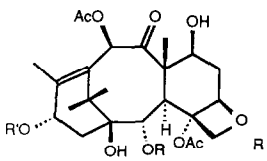
INTRAMOLECULAR NICKEL CATALYZED CYCLOADDITIONS OF BIS-DIENES:[1] 3 APPROACHES TO THE TAXANE SKELETON

Paul A. Wender* and Marc L. Snapper
Department of Chemistry, Stanford University, Stanford, California 94305 USA

Abstract: The successful application of the nickel catalyzed, intramolecular [4+4] cycloaddition of bis-dienes to the preparation of both the AB and BC ring systems of the taxane diterpenes is described. This cycloaddition methodology provides the basis for a general and efficient route to angularly alkyl-substituted bicyclo[6.4.0]dodecanes and to bicyclo[5.3.1]undecanes.

Taxol (**1**) and several other members of the taxane family represent exciting leads for the design of new cancer chemotherapeutic agents.[2] These compounds have been shown to exhibit *in vivo* activity against P-388, P-1534, and L-1210 mouse leukemias, and CX-1 colon, LX-1 lung, and MX-1 breast xenografts.[2a] While the mechanistic basis for these activities has not been delineated, it is noteworthy that taxol possesses a rather unique and potentially exploitable ability to promote the assembly and enhance the stability of microtubules.[2b] Due in part to these activities and to the unusual and complex structures of the taxanes, this family represents one of the most interesting and challenging problems in contemporary eight-



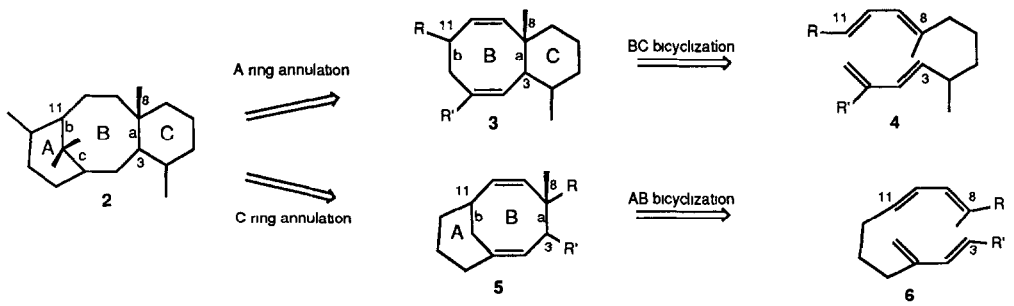
R = Bz-, R' = $C_6H_5CONHC(C_6H_5)HC(OH)HCO$-

taxol (**1**)

membered ring synthesis.[3] In connection with our interest in this area and other problems associated with the synthesis of substituted cyclooctanes, we recently reported an initial investigation of nickel catalyzed, intramolecular [4+4] cycloadditions of bis-dienes.[1] We describe herein two model studies for taxane synthesis based on this new methodology. These studies additionally serve to extend the general applicability of this new intramolecular reaction to the preparation of angularly alkyl-substituted bicyclo[6.4.0]dodecanes and of bicyclo[5.3.1]undecanes.

A central issue in the design of a taxane synthesis is the construction of its eight-membered (B) ring. Of the options available for this purpose, those involving bicyclizations, in which bonds a and b or bonds a and c (**2**) are formed, allow for the greatest increase in structural complexity in going from precursor to product (Scheme I). For example, in the conversion of **4** to **3**, an acyclic bis-diene would be transformed

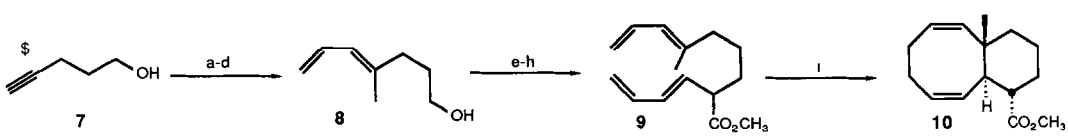
Scheme I



into a BC bicyclic system with key target stereocenters and with appendages **R** and **R'** poised for closure of the A ring. A similar complexity increase would be obtained in the conversion of **6** to **5** which delivers the bridged AB bicyclic system of the target and appendages located for elaboration of the remaining C ring. Each strategy poses new questions regarding alkyl substitution and tether attachment variations in the intramolecular nickel catalyzed cycloaddition which are addressed in Models A and B, respectively.

For Model A, which tests the BC bicyclization strategy for taxane synthesis, the cycloaddition precursor (**9**) was prepared through an eight step sequence starting from commercially available ($) 4-pentyn-1-ol (**7** : Scheme II). An important and general feature of this sequence is the use of an alkyne

Scheme II (Model A)



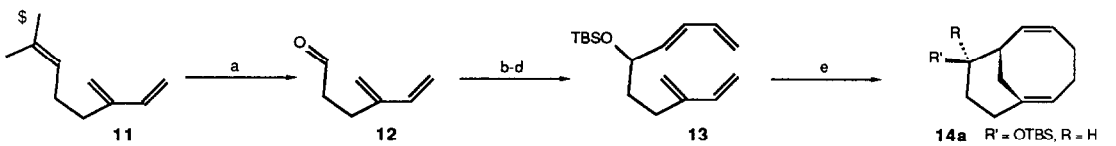
a. TBDMSCl, DMF, imid, b. $(Me)_3Al$, Cp_2ZrCl_2, CH_2Cl_2, c Dibal, $(Ph_3P)_2PdCl_2$, $ZnCl_2$,THF, vinyl bromide, d. AcOH, THF, H_2O, e. MsCl, Et_3N, CH_2Cl_2, f. NaI, acetone, g. LDA,THF, HMPA, sorbic acid; h CH_2N_2, Et_2O, i Ph_3P, $Ni(COD)_2$, toluene, [9] = 0 1M

carbometalation and $Pd(O)/ZnCl_2$ catalyzed coupling[4] to construct the diene subunit of **8,** which in this case proceeds with 94% *E* selectivity in a 43% overall yield from **7.** The cycloaddition of bis-diene **9** was found to be readily accomplished with commercially available $Ni(COD)_2$ catalyst (10 mole %) and triphenylphosphine (20 mole %) in toluene at 60°C (3 h). Gratifyingly, cycloadduct **10** was obtained with greater than 97% diastereoselectivity and in 92% yield at 94% conversion.[5] The structure and stereochemistry of **10** were unequivocally established by its oxidative conversion to a known stereoisomer

of trimethyl 1-methylcyclohexane-1,2,3-tricarboxylate.[6] It is noteworthy that the efficiency and stereoselectivity of the transformation of **9** to **10** are similarly high for the cycloaddition of the nor-methyl analog of **9**. In stark contrast, the corresponding *intermolecular* cycloaddition of dienes is markedly or completely retarded by similar alkyl substitution of the diene reactants.[7]

For the complementary bicyclization strategy (Model B) involving construction of the AB taxane rings, the key cycloaddition precursor **13** (Scheme III) was prepared in a four step sequence with 93% E selectivity and a 27% overall yield based on commercially available myrcene (**11**). Cycloaddition of bis-diene **13** was effected with 20 mole % $Ni(COD)_2$ in the presence of triphenylphosphine (40 mole %) in toluene at 110°C (2.5 h). Cycloadducts **14a** and **14b** (1.3:1, respectively) were obtained in 52% yield at

Scheme III (Model B)



a. O_3, MeOH, Me_2S; b. MeLi, vinyl acetylene, THF; c. LAH, THF; d. TBDMSCl, DMF, i mid; e. Ph_3P, $Ni(COD)_2$, toluene, [13] = 0.002 M.

68% conversion.[8] The structure and stereochemistry of these cycloadducts were unequivocally determined by their conversion to the silyl-ethers of *cis*- and *trans*-2-methylcyclohexanols.[9] The lower yield and conversion obtained with **13** relative to **9** is in part attributable to the more vigorous conditions required for the transformation of the former substrate. At the required elevated temperatures (>90°C), Diels-Alder reactions begin to compete with the desired transformation, a situation which is further complicated by deactivation of the catalyst in a process involving the formation of biphenyl.[10] While the basis for the differing reactivity of these dienes remains to be determined, molecular models suggest that the relative strain of the precursors to **10** and **14** might play a significant role.

Successful nickel catalyzed [4+4] cycloadditions in both Model A and Model B demonstrate the viability of this methodology for the synthesis of taxane ring systems. The high stereoselectivity of the cycloaddition in the case of bis-diene **9** is in accord with a recently developed model for predicting diastereoselection for this reaction class.[1b] Further studies are in progress.

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1. For previous work in this series, see: a) Wender, P.A.; and Ihle, N.C., *J. Am. Chem. Soc.* **1986**, *108*, 4678; b) Wender, P.A.; and Ihle, N.C., *Tetrahedron Lett.*, submitted for publication.
2. Miller, R.W., *J. Nat. Prod.*, **1980**, *43*(4), 425; Wani, M.C.; Taylor, H.L.; Wall, M.E.; Coggon, P. and McPhail *J. Am. Chem. Soc.*, **1971**, *93*(9), 2325; a) For related studies and lead references see: Magri, N.F. and Kingston, D.G.I., *J. Org. Chem.*, **1986**, *51*, 797; Kingston, D.G.I.; Hawkins, D R.; and Ovington, L., *J. Nat. Prod.*, **1982**, *45*(4),466; b) Parness, J.; Kingston, D.G.I.; Powell, R.G.; Harracksingh, C.; and Horwitz, S.B., *Biochem. Biophy. Res. Comm.*, **1982**, *105*(3), 1082; Schiff, P.B.; Fant, J.; and Horwitz, S.B., *Nature*, **1979**, *277*, 665.
3 Studies bearing on the syntheses of the taxanes have been reported from the laboratories of: Borkowitz, W.F.; Blechert, S ; Fetizon, M.; Gadwood, R.; Holton, R.A.; Inouye, Y.; Jenkins, P.R.; Kato, T.; Kende, A.S.; Kitagawa, I.; Martin, S.F.; Oishi, T.; Pattenden, G.; Sakan, K.; Shea, K.J.; Swindell, C.S.; Trost, B.M.; Winkler, J.D.; and Yamada, Y. Complete references to these contributions can be found in Winkler, J.D. and Hey, J.P., *J. Am. Chem. Soc.*, **1986**, *108*, 6425; Kende, A.S.; Johnson, S.; Sanfilippo, P.; Hodges, J.C.; Jungheim, L.N., *J. Am. Chem. Soc.* **1986**, *108*, 3513; and Swindell, C.S. and Britcher, S F., *J. Org. Chem.*, **1986**, *51*, 793.
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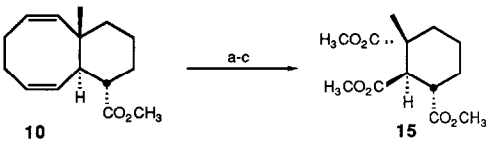
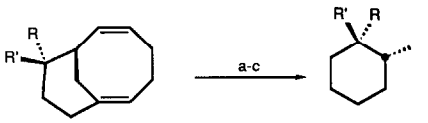
5 New compounds have been characterized by ^{1}H NMR, IR, MS and elemental analysis. The following NMR data is given for correlation purposes. **10** ^{1}H NMR (400MHz, $CDCl_3$), d 5.43(m, 2H); 5 17(br d, 2H); 3.64(s, 3H); 3.44(dd, 1H); 3.01(m, 1H); 2.47(m, 1H); 2.42(m, 1H), 1.90-2.10(2H); 1.34-1.65(6H); 0.92(s, 3H).
6. Conversion of **10**, as outlined below, produced one product **15** in 54% yield. Stereochemistry was confirmed by comparison with published NMR data. (Balasubrahmanyam, S.N., Balasubramanian, M., *J. Chem. Soc. (B)*, **1970**, 212.)



10 **15**

a O_3, EtOAc, b Jones oxidation, c. CH_2N_2, Et_2O

7. For recent reviews of *intermolecular* nickel catalyzed cycloaddition reactions see: Tenaglia, A., Brun, P. and Waegell, B , *J Organomet. Chem.*, **1985**, *285*, 343; Bartik, T.; Heimbach, P.; and Himmler, T., *J. Organomet. Chem.*, **1984**, *276*, 399; Jolly, P.W., *Comp. Organomet. Chem.*, **1982**, 671.
8 **14a** ^{1}H NMR(400MHz, $CDCl_3$), d 5.46(m, 1H); 5,24(br m, 2H); 3.82(d, 1H); 2.88(br m, 1H),2.80(br d,1H); 2.71(br s, 1H); 2.48(m, 1H); 2.39(br d, 1H); 2.33(br d, 1H); 2.08-1.90(3H); 1.67(br d, 1H); 1.55(m, 1H); 0.91(s, 9H); 0.05(s, 6H).
14b ^{1}H NMR(400MHz, $CDCl_3$);d 5.77(br d, 1H); 5.53(m, 1H); 5.27(dd, 1H); 3.76(ddd, 1H); 3.09(dt,1H); 2.89(m, 1H); 2.82(m, 1H); 2.45(br m, 1H); 2.11(m, 2H); 1.98(m, 2H); 1.87(m, 1H); 1.78(br d, 1H); 1.45(m,1H); 0.90(s, 9H); 0.06(s, 6H).
9 The stereochemistry of **14a** and **14b** was established by their individual transformation to **16a** and **16b**, respectively as outlined below.



14a R' = OTBS, R = H **16a** R' = OTBS, R = H
14b R' = H, R = OTBS **16b** R' = H, R = OTBS

a O_3, $CHCl_3$, $NaBH_4$, b $(Me_2N)_2P(O)Cl$, TMEDA, n-BuLi, THF, c. Et_2NH, Li, t-BuOH

10. For catalyst deactivation references see: Garrou, P.E., *Chem. Rev.*, **1985**, *85*(3), 171; Ortiz, J.V.; Havlas, Z. and Hoffmann, R., *Helv. Chem. Acta*, **1984**, *67*(1), 1.

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