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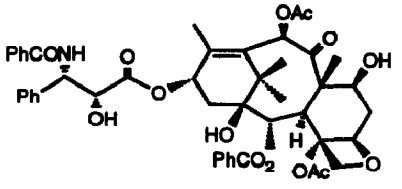
Synthesis of the Tricyclo[9.3.1.0^{3,8}]pentadecane (ABC) Ring System of Taxane Diterpenes†

Miguel A. Romero*#, Rubén Pérez Franco, Raymundo Cruz-Almanza, and Fernando Padilla

Instituto de Química, Universidad Nacional Autónoma de México,
Circuito Exterior, Ciudad Universitaria, Coyoacán 04510, México, D.F.

Abstract: The synthesis of diketone **14** possessing the tricyclo[9.3.1.0^{3,8}]pentadecane (ABC) taxane ring system is described. This concise approach employs a Wacker oxidation, intramolecular aldol condensation-dehydration, and a highly *exo*-stereoselective intermolecular Diels-Alder reaction as key steps.

There is currently considerable interest in the synthesis[1] of the potent antitumor agent Taxol® (**1**), [2] as well as related, therapeutically promising analogues[3] which contain varied arrays of functionality on the basic carbocyclic nucleus. We report here a short synthesis of the tetracyclic compound **14** in which the tricyclo[9.3.1.0^{3,8}]pentadecane ring system **2** is present. The key synthetic steps include a stereoselective intramolecular aldol condensation[4] and a highly *exo*-selective intermolecular Diels-Alder reaction.



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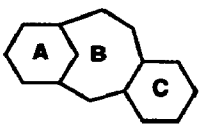

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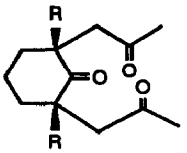

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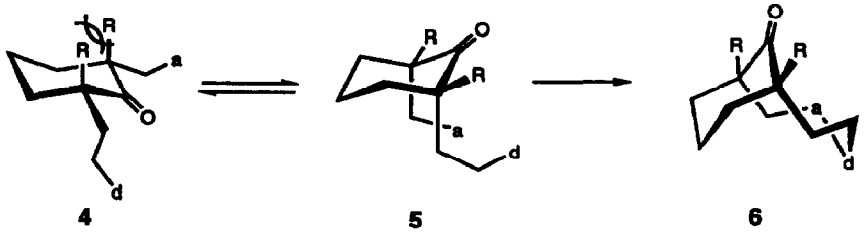
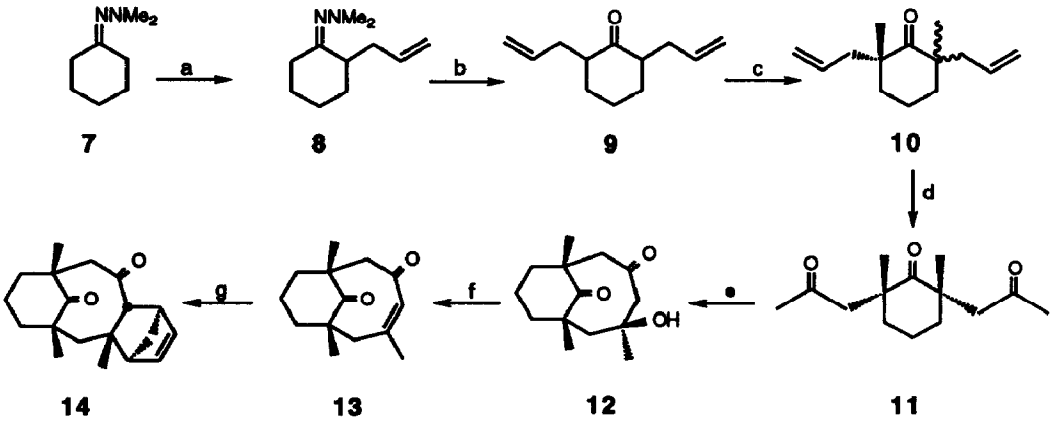
In our synthetic strategy we envisaged that an unprecedented aldol condensation of systems of type **3** (R≠H) could be used for the construction of the bicyclo[5.3.1]undecane (AB) ring system. At the outset it was appreciated that the success of the cyclization step would be strongly dependent on the presence of the appropriate α,α'-cyclohexanone substituents R (see conformational formulas **4** and **5**, Equation 1). We considered that this structural feature would shift the conformational equilibrium in the desired direction by virtue of the 1,3-diaxial interaction present in conformer **4**, so that the proximity of the donor(d)-acceptor(a) centres in the side chains would be enhanced in order to form **6**.



4 **5** **6** (1)

These ideas have been successfully put into practice by the transformation of **11** to the key intermediate **12** (Scheme I). Alkylation of the LDA-generated anion of cyclohexanone dimethylhydrazone **7**[5] with allyl bromide gives the monoallylated derivative **8** in 93% yield. A single pot alkylation-acidic hydrolysis procedure provides the 2,6-diallylcyclohexanone **9** as a mixture of epimers in 51% yield. This mixture, when subjected to exhaustive methylation (KH, excess MeI, THF) affords **10** in 67% yield as a 2.2:1 mixture of epimers. Based on the experiments described below it was concluded that the major isomer bears the two allyl substituents in a *syn* arrangement. Wacker oxidation[6] (O_2, $PdCl_2$, $CuCl_2$, DMF-H_2O, 48 h) of **10** leads to a chromatographically separable mixture of two isomeric triketones in a combined yield of 48%. Treatment of the major isomer **11** with 30% KOH in MeOH (reflux, high dilution) gives the ketol **12** in 66% yield. The corresponding α-OH epimer was not detected by either ^{1}H-NMR of the crude reaction mixture, or during the course of the reaction.

Scheme I

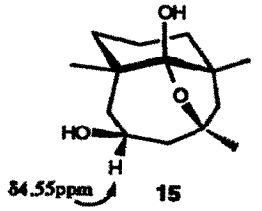


Reagents: a) LDA, THF, $BrCH_2CH{=}CH_2$, -78 to 25°C (93%); b) LDA, THF, $BrCH_2CH{=}CH_2$, -78 to 25°C; HCl 4N, 0°C (51%); c) NaH, THF; MeI, 0 to 25°C (67%, 2.2:1 *syn:anti*); d) O_2, $PdCl_2$ (0.6 eq.), $CuCl_2$, DMF-H_2O, 48h (48%); chromatography; e) 10% KOH / MeOH (0.01M **11**), reflux (66%); f) *p*-TsOH, C_6H_6, 80°C, (quant.); g) cyclopentadiene, $AlCl_3$, CH_2Cl_2-Et_2O, -78 to -10°C (77%).

The relative configuration of the tertiary alcohol moiety in **12** was established as follows. Reduction of **12** with sodium borohydride in methanol at -10°C leads to the hemiketal **15** in which the tertiary alcohol moiety has closed onto the remaining ketone carbonyl group. This was confirmed by the observation that D_2O exchange in the ^{1}H-NMR spectrum of **15** simplifies the methine hydrogen resonance at δ4.55 ppm. Simplification of this signal is not possible if the secondary alcohol participates in the cyclization to form the corresponding hemiketal. The relative configuration of the secondary alcohol in **15** was not established unambiguously, but the assignment shown is consistent with the results reported by Paquette[7] on nucleophilic additions to related systems. Thus, hydride attack likely occurrs with high chemoselectivity and π-facial diastereoselectivity from the less hindered face of the carbonyl group on the more stable ring B "boat-chair" conformer of **12** (see conformational formula **16**).

As anticipated, the presence of the α, α'-cyclohexanone methyl groups is crucial to the success and high stereoselectivity of the cyclization reaction leading to **11**.[8] Treatment of the triketone **17** under the

same reaction conditions that produced **12** from **11** gave only an intractable mixture. The rationale for the stereoselectivity of the aldol cyclization is consistent with either kinetic or thermodynamic arguments.



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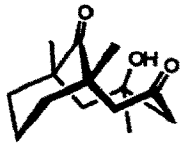

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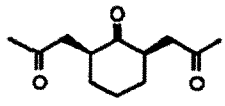

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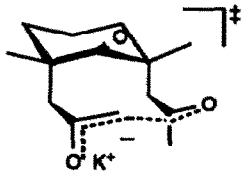

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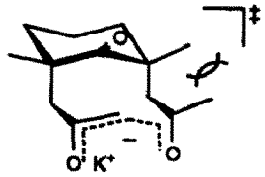

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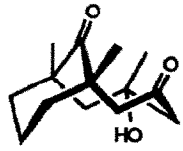
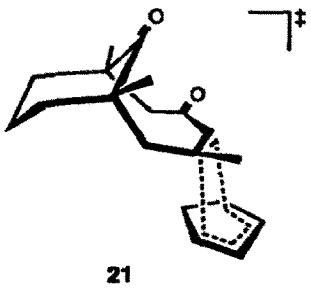


20

In a kinetically controlled reaction the preferred reaction pathway should occur *via* transition structure **18** as opposed to **19**, in which a destabilizing *gauche* steric interaction is present. Moreover, theoretical calculations predict that **20** is 3 kcal mol^{-1} less stable than the ketol **16**, the product formed under thermodinamic control.



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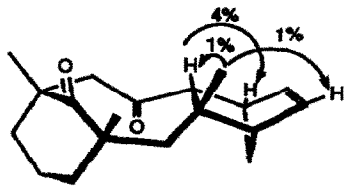

14

(2)

Upon treatment of **12** with *p*-TsOH in warm benzene, the enone **13** was obtained in quantitative yield. The $AlCl_3$-catalyzed Diels-Alder reaction of **13** with cyclopentadiene in CH_2Cl_2 at -78°C gave the desired tetracyclic compound **14** in 77% yield (no other isomeric products were detected by ^{1}H-NMR). The relative stereochemistry of the *exo*-adduct **14** was unambiguously established on the basis of ^{1}H-^{1}H nOe experiments (summarized in Equation 2). The reaction proceeds by addition to the diene from the less sterically hindered α-face of the *exo*-conformer of the dienophile (see transition structure **21**). The diene approaches the enone in the *exo*-orientation thus avoiding the non bonded interaction between the enone β–methyl group and the cyclopentadiene methylene hydrogen.[9] The assignment of relevant NMR signals in the spectra of **14** was established by COSY, DEPT, nOe, and ^{1}H-^{13}C HETCOR experiments, however, it was not possible to unambiguously establish the conformation of ring B. It is suggested that **14** exists primarily in the conformation shown in Equation 2 based on the examination of models and on theoretical calculations.[10]

In summary, a 6-step construction of an intermediate bearing the tricyclo[9.3.1.$0^{3,8}$]pentadecane (ABC) ring system present in the taxane diterpenes from the known hydrazone **8** has been accomplished. The remarkable stereo- and facialselectivity of the Diels-Alder reaction to produce **14** and the high stereoselectivity of the intramolecular aldol condensation leading to **11** are worthy of note. Further work on this general strategy for the construction of taxanes and [n.3.1]bicyclic ring systems will be pursued.

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References and Notes:

(1) For recent comprehensive reviews on synthetic approaches to taxanes see: Kingston, D.G.I; Molinero, A.A.; Rimoldi, J.M. In *Progress in the Chemistry of Organic Natural Products;* Herz, W., Kirby, G.W., Moore, R.E., Steiglich, W., Tamm, Ch., Eds.; Springer-Verlag: New York, 1993; Vol. 61, pp 1-192; Paquette, L. A. In *Studies in Natural Products Chemistry*; A. U. Rahman, Ed.; Elsevier: Amsterdam, 1992; Vol. 11; pp 3-69; Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465-543.

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(4) For recent intramolecular aldol condensation approaches to taxanes see: Chai, K.-B.; Sampson, P. *J. Org. Chem.* **1993**, *58*, 6807-6813; Morihira, K.; Seto, M.; T.Furukawa; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 345-348.

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(6) Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, *34*, 2975-2976.

(7) The proposal that the ketol **15** ring B exists preedominantly in a boat-chair conformation and that the sodium borohydride reduction is π-facial diastereoselective is supported by Paquette's elegant work on addition reactions and structural analysis of *cis*-[n.3.1]bicyclic ketones, see: Paquette, L. A.; Underiner, T. L.; Gallucci, J. C. *J. Org. Chem.* **1992**, *57*, 86-96.

(8) A Thorpe-Ingold effect exerted by the α and α' methyl groups may also play a role in bringing the acetonyl sidechains of **11** closer together, thus facilitating the ring closure reaction. For a related case see: Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Jr., D. W. S.; Schultz, G. R.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978-10980.

(9) The enhanced *exo* diastereoselectivity for the $AlCl_3$- catalyzed reactions of cyclopentadiene with a-methyl-α,β-unsaturated ketones is known and has been termed the "α-methyl effect". Wenkert's rationale of a "one-step reaction with an unsymmetrical, non-synchronous transition state in which σ-bond formation with the β-carbon of the α,β-unsaturated ketone is in advance of that at the α-carbon site..." is in accord with the high *exo* -selectivity observed in our case. Thus, a similar "β-methyl effect" might be operating such that the steric, non-bonded interactions override to a greater extent the attractive secondary orbital interaction present in the alternative *endo* transition state, see: Angell, E. C.; Fringuelli, F.; Guo, M.; Minuti, L.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1988**, *53*, 4325-4328. See also: Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380-3387.

(10) MM+ calculations (Hyperchem) show that the "ring B carbonyl down" conformer **14** (Equation 2) is 5 Kcal $mole^{-1}$ more stable than the "ring B carbonyl up" conformer.

Address for correspondence: Dr. Miguel A. Romero, Investigación Aplicada, S.A., 7 Norte #356, Tehuacán, Puebla, 75700. Mexico. Fax (238)30214

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