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A Photochemical Approach to the Taxanes

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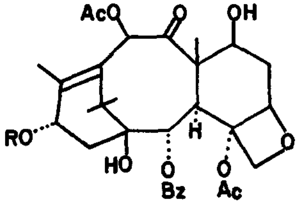
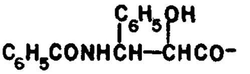
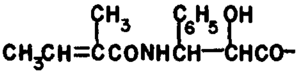
Summary: The de Mayo sequence has been applied to the inter- and intramolecular photocycloaddition of various cycloalkenes with homocamphorquinone derivatives to generate a model for the A,B, and C rings of the Taxanes.

The recent publication of two photochemical (de Mayo) approaches[1] to the Taxanes (1)[2] has prompted us to report our own progress in this area.



1a: Taxol, R=


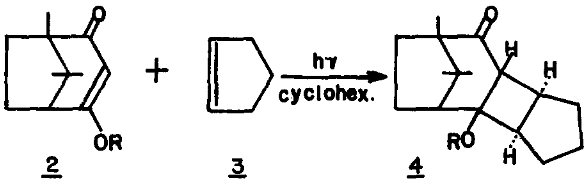
$C_6H_5CONHCH(C_6H_5)-CH(OH)CO-$

1b: Cephalomannine, R=


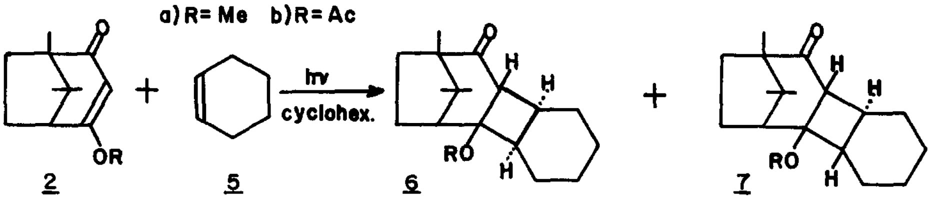
$CH_3CH=C(CH_3)CONHCH(C_6H_5)-CH(OH)CO-$

1c: Baccatin III, R=H-

Photoaddition of various cycloalkenes to homocamphorquinone derivatives 2a[3], 2b gave the following results:[4]

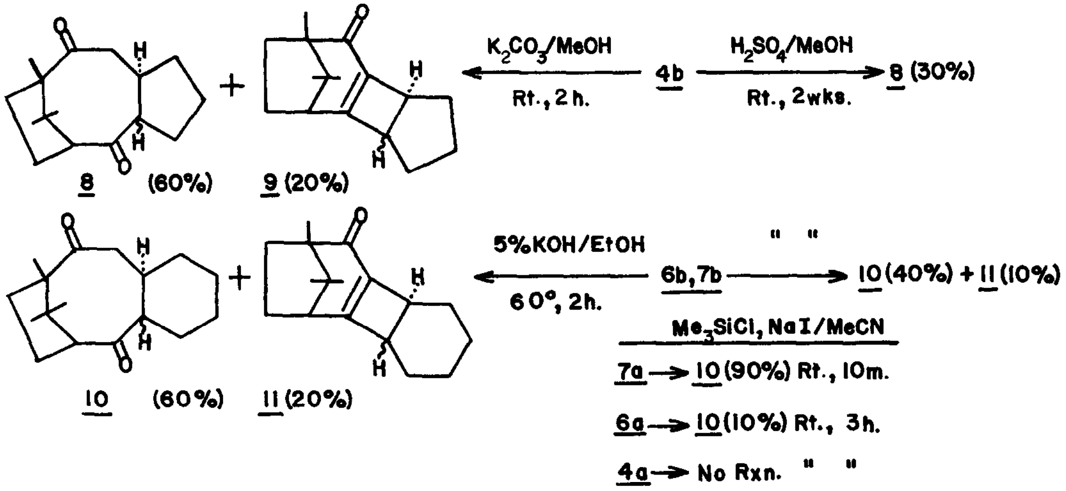


Yields. 4a,55%; 4b,50%
6a+7a,55%(~1/1)
6b+7b,50%(~1/1)



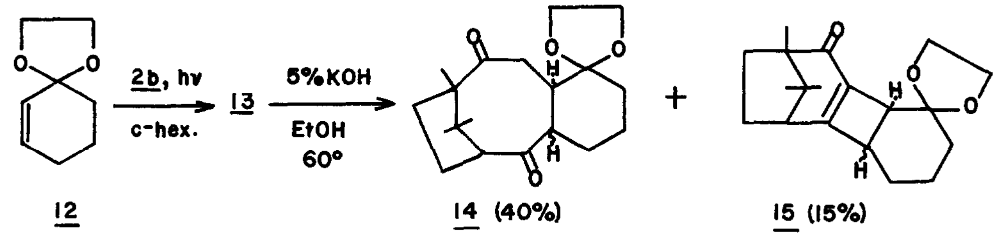
Whereas cyclopentene gave only the *cis*-*anti*-*cis* adducts 4a and 4b, cyclohexene gave a ca. 1/1 mixture of two adducts, 6 and 7 (a,b). Apparently, the *gem* dimethyl group overwhelmingly forces photoaddition from the *endo* side of the enone, but the cyclohexane residue is flexible enough to close in a *trans* fashion as well.[5] Structures 4a, 6a, and 7a have been confirmed by X-Ray analysis, most graciously performed by Dr. J.F. Blount of Hoffman La Roche (Nutley, N.J.).

Various ring opening reactions of the adducts have been investigated, with the following results:

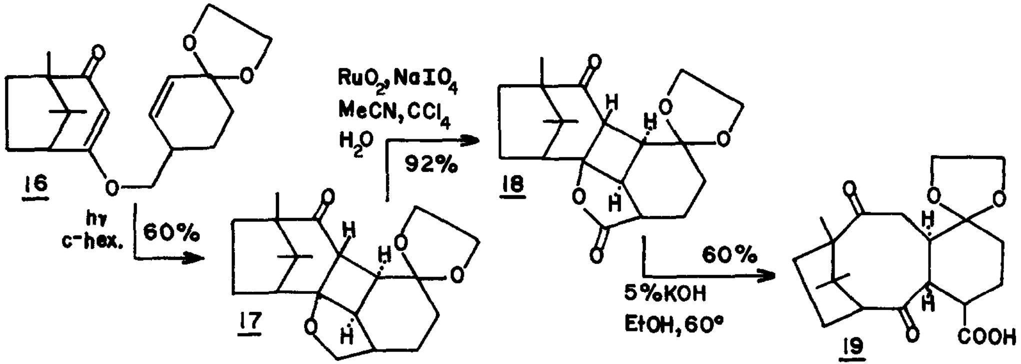


Both acidic and basic conditions served to open the cyclobutane ring in a retro-aldol fashion. The yields with base were higher, and adequate for synthetic purposes even though elimination was a competing process[1]. It is quite likely that the ring of the *trans* isomer 7b opened faster than that of the *cis* isomer 6b, whereas the latter was the major source of the elimination product. This is supported by our results with trimethylsilyl iodide: the *trans* methyl ether 7a gave a 90% yield of ring opened product 10 (identical to that produced from 6b,7b and base) in 10 minutes at room temperature, whereas *cis*- methyl ether 6a gave only 10% of 10 in 3 hours. We impute the difference to the additional strain in the *trans* fused rings of 7a, as the geometry of the methoxy (acetoxy), carbonyl and the fractile cyclobutane bond are virtually identical in the two isomers. The fact that the cyclobutane bond is in the plane of the carbonyl group rather than in the preferential pi-bond plane must mitigate the ring opening reaction and allow elimination to compete, even though the new double bond is endocyclic to a four membered ring.

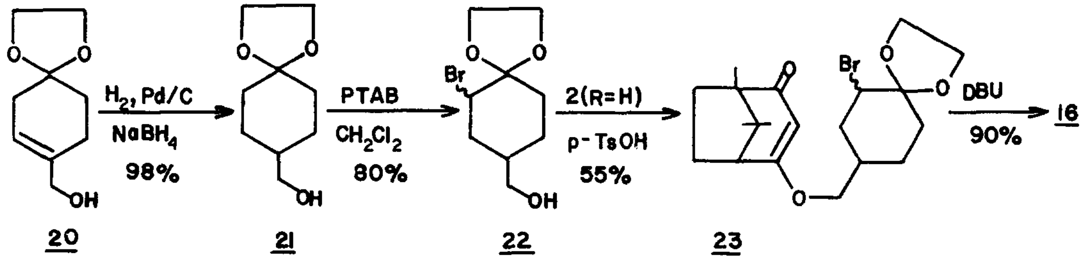
The photoadduct 13 of ketal 12 and 2b was not isolated, but was converted to 14 and 15. We assume that the stereochemistry of photoaddition parallels that of the previous examples, and that the regiochemistry (head to head addition) is consistent with de Mayo's results in a similar system[6].



We have also examined the intramolecular photoaddition and ring opening sequence of 16. Again we assume that the photoaddition occurred from the *endo* side. Only one photoadduct was formed, probably the *cis-anti-cis* isomer. Oxidation of the tetrahydrofuran ring to a lactone with the Sharpless variation[7] of the Rylander oxidation occurred in good yield, allowing convenient ring fragmentation by base.



Enol ether 16 was prepared from 20[8], as shown. Hydrogenation resulted in some isomerization to an aldehyde, which was further reduced *in situ* to 21 by borhydride. Bromination (phenyltrimethyl ammonium perbromide) gave a mixture of epimers which were dehydrohalogenated, after coupling to the diketone, with DBU[9].



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[1] a) Neh, H.; Blechert, S.; Schnick, W.; Jansen, M.; Angew. Chem. Int. Ed. Engl. (1984), 23, 905. b) Swindell, C.S.; de Solms, S.J.; Springer, J.P.; Tet. Letters (1984), 25, 3797. c) Swindell, C.S.; de Solms, S.J.; ibid. 3801.

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[4] All compounds isolated gave a correct elemental analysis, and all spectra are consistent with the structures presented. Compounds 16, 21, and 23 were not analysed.

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