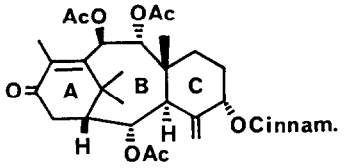
Tetrahedron Letters, Vol.27, No.2, pp 203-206, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

A SYNTHETIC APPROACH TO TAXANE DITERPENES. A SYNTHESIS OF THE BICYCLO[5.3.1]UNDECENONE RING SYSTEM

Yasuo Ohtsuka* and Takeshi Oishi*
RIKEN (The Institute of Physical and Chemical Research)
Wako-shi, Saitama 351, Japan

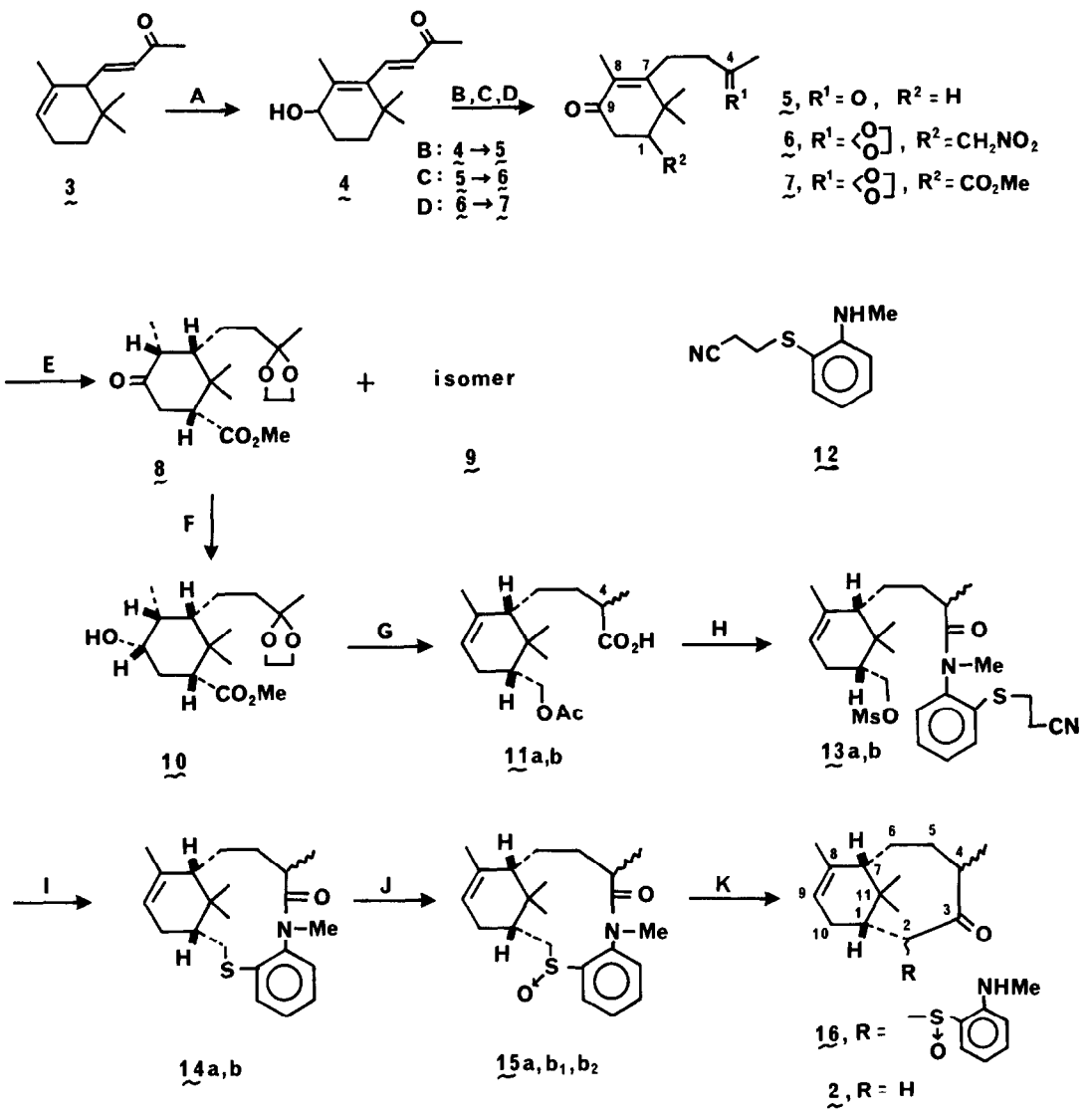
Summary: Bicyclo[5.3.1]undecenone **2** corresponding to A and B rings in taxane diterpenes was synthesized. The eight-membered ring was constructed by a base-induced intramolecular cyclization of twelve-membered lactam sulfoxides **15**.

The crucial problem in the synthesis of the taxane diterpenes[1] such as taxinine (**1**) possessing unique tricyclic carbon skeleton is obviously in the construction of the sterically congested eight-membered B ring and thus several approaches involving fragmentation[2a], rearrangement[2b] or intramolecular Diels-Alder reaction[2c] have already been reported. Independently, we focused our attention on a direct closure of the eight-membered ring from a suitable precursor, by the novel intramolecular cyclization process we developed recently for the preparation of medium-ring ketones.[3] We report here a synthesis of bicyclo[5.3.1]undec-8-en-3-one **2** corresponding to taxane A and B rings and having functionality in the B ring for the construction of C ring.



Taxinine (1)

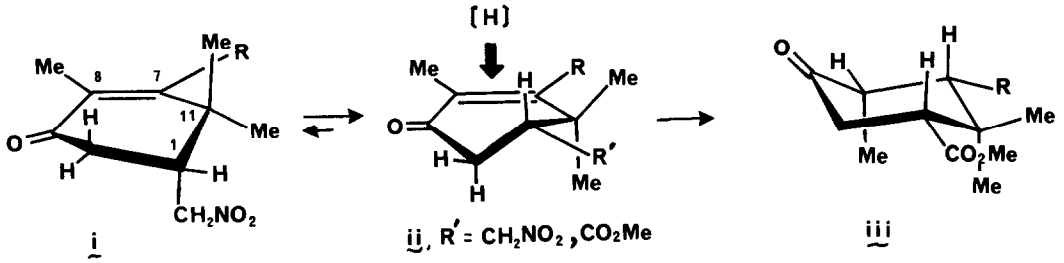
Selective epoxidation of the double bond in cyclohexane moiety of α-ionone (**3**) followed by K_2CO_3-MeOH treatment afforded dienyl ketone **4**. The double bond next to the carbonyl group was then selectively reduced with NaTeH[4] and the resulting keto allyl alcohol was oxidized with CrO_3 to give diketone **5** in 62 % yield.[5,7] Conversion of **5** into **6** having a nitromethyl group at C-1 position was accomplished in three steps: i) preferential acetalization of saturated ketone in the presence of α,β-unsaturated ketone by ethylene glycol-TsOH, ii) DDQ oxidation to give cross-conjugated dienone, iii) Michael addition of CH_3NO_2 to C-1 position. Conversion of a nitromethyl group into a methoxycarbonyl group was effected by $TiCl_3$-MeONa treatment,[8] Jones' oxidation, methylation with dimethylsulfate and reacetalization. High-pressure catalytic hydrogenation of **7** and the subsequent PCC oxidation of a C-9 hydroxyl group afforded **8** (86 %)[9] along with a small amount of isomer **9** (10 %). Keto ester **8** was found to be a desired compound having cis-diequatorial substituents at C-1 and C-7 positions. The predominant formation of **8** over **9** may be considered as follows:



3 4 8 9 10 11a,b 12 13a,b 14a,b 15a,b₁,b₂ 16

(A) mCPBA/CH_2Cl_2, K_2CO_3/MeOH (reflux), (B) NaTeH/EtOH, Jones' reagent (62 %, **3**→**5**, 4 steps), (C) ethylene glycol/TsOH/benzene, DDQ/benzene (80°C) (69.5 %, 2 steps), CH_3NO_2/i-Pr_2NH/DMSO (75°C, 97 % based on consumed material), (D) MeONa/$TiCl_3$/$AcONH_4$/aq.MeOH, Jones' reagent, Me_2SO_4/K_2CO_3, ethylene glycol/TsOH/benzene (67.5 %, 4 steps); (E) H_2(100 atm)/Pd-C/AcOEt, PCC/AcONa/CH_2Cl_2 (92 %); (F) $NaBH_4$/EtOH (-10°C, 93 %,); (G) Ph_3P/$(NCO_2Et)_2$/THF (78 %), $LiAlH_4$/Et_2O, Ac_2O/Py, TsOH/acetone (95 %, 3 steps), Ph_3P=CHOMe/THF, Ac_2O/Py, $HClO_4$ aq., Jones' reagent (70 %, 4 steps); (H) 1N KOH, MsCl/Et_3N/CH_2Cl_2, $(COCl)_2$/benzene, **12**/K_2CO_3/Et_2O (46 %, 4 steps), (I) K_2CO_3/$NaBH_4$/DMF (135°C, 70 %), (J) $NaIO_4$/aq.MeOH; (K) LDA/THF (-65°- 0°C, 60-65 % based on consumed material), Na-Hg/Na_2HPO_4/MeOH (86 %, **a**/**b** ratio, 5/3).

Initial Michael addition of CH_3NO_2 to the cross-conjugated dienone derivative of **5** may proceed from the direction perpendicular to the π-system affording **i**. However, ring inversion should take place giving the more stable conformer **ii**, in which the nitromethyl group is in quassi-equatorial position. The methoxycarbonyl derivative should hold the same conformation **ii** as the nitromethyl derivative.[10] In conformer **ii** (R'= CO_2Me), the α-side is sterically much more hindered than the β-side due to a quassi-axial methyl group at C-11 position and thus catalyst may approach from the β-side giving mainly 1,7-cis (diequatorial) **8** (**iii**).



Sodium borohydride reduction of **8** produced the C-9 α-alcohol **10** predominantly (α/β ratio, 40:1). Alcohol **10** was treated with Ph_3P and $(NCO_2Et)_2$ to give Δ^8-unsaturated ester,[11] which was converted into an epimeric mixture (1:1) of **11a,b** at C-4 by a series of reactions ($LiAlH_4$ reduction, acetylation, hydrolysis to give ketone, one-carbon elongation with Ph_3P=CHOMe, reacetylation, acidic hydrolysis to give aldehyde and Jones' oxidation). Compounds **11** were, after conversion of the acetate into the mesylate and a carboxyl group into the acid chloride, treated with amino sulfide **12**[3b] yielding a mixture (1:1) of amide **13a,b.** Removal of a S-protecting group from **13a,b** and the concomitant twelve-membered lactam sulfide formation was effected with K_2CO_3 in DMF in the presence of $NaBH_4$ at 135°C giving **14a,b** as an epimeric mixture at C-4 (70 %, **a/b** ratio, 2:3).[12] On $NaIO_4$ oxidation, **14a** afforded sulfoxide **15a** and **14b** produced a mixture of $\mathbf{15b}_1$ and $\mathbf{15b}_2$.[13] Each of the isomers was subjected to a LDA-induced intramolecular cyclization and a mixture of eight-membered keto sulfoxides **16** was obtained in 60-65 % yield (based on the consumed starting material) in every case. Mixtures of **16** obtained from different sources, $\mathbf{15a,b}_1,\mathbf{b}_2$, were combined and subjected to desulfurization with Na-Hg in MeOH in the presence of Na_2HPO_4 producing the desired bicyclic ketones **2a,b** as a separable mixture of stereoisomers at C-4 (86 %, **a/b** ratio, 5:3).[14]

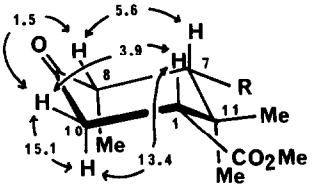
The present strategy for the formation of eight-membered B part of taxane skeleton would be applicable in general for the synthesis of more complex analogues. Synthesis of taxane ring skeleton from a derivative of **2** will be published in the forthcoming paper from this laboratory.

References and Notes

1. Several compounds belonging to Taxus species are reported to have potent antileukemic and tumor inhibitory properties: M.C. Wani, H.L. Taylor, M.E. Wall, P. Coggon and A.T.

McPhail, J. Am. Chem. Soc., **93**, 2325 (1971); R.W. Miller, R.G. Powell and C.R. Smith, Jr., J. Org. Chem., **46**, 1469 (1981); G. Chauviere, D. Guenard, C. Pascard, F. Picot, P. Potier and T. Prange, J. Chem. Soc. Chem. Commun., 495 (1982).

2. a) B.M. Trost and H. Hiemstra, J. Am. Chem. Soc., **104**, 886 (1982); R.A. Holton, ibid., **106**, 5731 (1984); H. Nagaoka, K. Ohsawa, T. Takata and Y. Yamada, Tetrahedron Lett., **25**, 5389 (1984); T. Kojima, Y. Inouye and H. Kakisawa, Chem. Lett., 323 (1985); b) S.F. Martin, J.B. White and R. Wagner, J. Org. Chem., **47**, 3190 (1982); c) K.J. Shea and P.D. Davis, Angew. Chem. Int. Ed. Engl., **22**, 419 (1983); K. Sakan and B.M. Craven, J. Am. Chem. Soc., **105**, 3732 (1983); P.A. Brown, P.R. Jenkins, J. Fawcett and D.R. Russell, J. Chem. Soc. Chem. Commun., 253 (1984); cf.) A.S. Kende, M. Benechie, D.P. Curran and P. Fludzinski, Tetrahedron Lett., 4513 (1979); Y. Inouye, C. Fukaya and H. Kakisawa, Bull. Chem. Soc. Jpn., **54**, 1117 (1981); R.Z. Andriamialisoa, M. Fetizon and I. Hanna, Tetrahedron, **40**, 4285 (1984).
3. a)Y. Ohtsuka and T. Oishi, Tetrahedron Lett., 4487 (1979); Chem. Pharm. Bull., **31**, 454 (1983); b) Synthetic application to caryophyllenes: Y. Ohtsuka, S. Niitsuma, H. Tadokoro, T. Hayashi and T. Oishi, J. Org. Chem., **49**, 2326 (1984).
4. M. Yamashita, Y. Kato and R. Suemitsu, Chem. Lett., 847 (1980).
5. Diketone **5** has already been prepared from **3** by epoxidation followed by MeONa treatment, but the yield of **5** was only 8.3 %.[6]
6. M. Rosenberger, P. McDougal and J. Bahr, J. Org. Chem., **47**, 2130 (1982).
7. All new compounds have been satisfactorily characterized by IR, ^{1}H NMR (60 or 400 MHz) and high resolution mass spectrometry (or elemental analysis).
8. J.E. McMurry and J. Melton, J. Org. Chem., **38**, 4367 (1973).
9. The stereostructure of **8** was deduced as **8-A** by ^{1}H NMR (400 MHz) analysis. This assignment was confirmed by conversion into **2** as described later. ^{1}H-NMR($CDCl_3$, 400 MHz) **8**: δ 1.09, 1.12, 1.40 and 3.70 (each s, Me), 1.14 (d, J= 7.6 Hz, 8α-Me), 2.30 (10β-H), 2.57 (8β-H), 2.61 (1β-H), 2.96 (10α-H), 3.9-4.0 (m, 4H).
By-product **9** is considered to be a stereoisomer of **8** from ^{1}H NMR data, but its stereostructure is remained unknown.



8-A

10. Even if epimerization takes place during conversion of **6** into **7**, the resulting **ii** having a quassi-ax CO_2Me group may be flipped into a more stable **i** having a quassi-eq CO_2Me group, which is an enantiomer of **ii** having a quassi-eq CO_2Me group.
11. The corresponding Δ^9-isomer was not detected in this reaction.
12. ^{1}H NMR ($CDCl_3$) **14a**(less polar gum): δ 0.89, 1.36 and 3.23 (each s, Me), 1.13 (d, J= 6.7 Hz, Me), 1.54 (d, J= 1.7 Hz, Me). **14b**(more polar gum): δ 0.79 and 0.92 (each s, Me), 1.08 (d, J= 6.5 Hz, Me), 1.65 (d, J= 1.5 Hz, Me), 3.15 (s, 2.5H), 3.42 (s, 0.5H).
13. Compounds $\mathbf{b_1}$, $\mathbf{b_2}$ are stereoisomers due to sulfoxide moiety. ^{1}H NMR($CDCl_3$) **15a**(86 %): δ 0.99, 1.23 and 3.37 (each s, Me), 1.16 (d, J= 6.7 Hz, Me), 1.55 (d, J= 1.9 Hz, Me). $\mathbf{15b_1}$(less polar, 61 %): δ 0.86, 1.02 and 3.15 (each s, Me), 1.07 (d, J= 6.5 Hz, Me), 1.62 (d, J= 1.4 Hz, Me). $\mathbf{15b_2}$(more polar, 27 %): δ 1.00, 1.51 and 3.40 (each s, Me), 1.19 (d, J= 6.7 Hz, Me), 1.68 (d, J= 1.2 Hz, Me).
14. **2a** (less polar oil, 53.5 %): ^{1}H NMR($CDCl_3$) δ 0.96 (d, J= 6.8 Hz, 4-Me), 0.98 and 1.18 (each s, 11α- and 11β-Me), 1.62 (d, J= 1.6 Hz, 8-Me), 5.25- 5.55 (m, 9-H), IR(CCl_4) 1720(sh), 1695 cm^{-1}, High resolution MS(m/z) Calcd for $C_{15}H_{24}O(M^+)$: 220.1826, Found: 220.1837. **2b** (more polar oil, 32 %): ^{1}H NMR($CDCl_3$) δ 0.97 and 1.15 (each s, 11α- and 11β-Me), 1.04 (d, J= 7 Hz, 4-Me), 1.64 (d, J= 1.7 Hz, 8-Me), 5.15- 5.45 (m, 9-H), IR(CCl_4) 1735(sh), 1685 cm^{-1}, High resolution MS(m/z) Found: 220.1820.

(Received in Japan 8 October 1985)