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A NEW SYNTHETIC APPROACH TO THE BICYCLO[5.3.1]UNDECANE RING SYSTEM IN TAXANES

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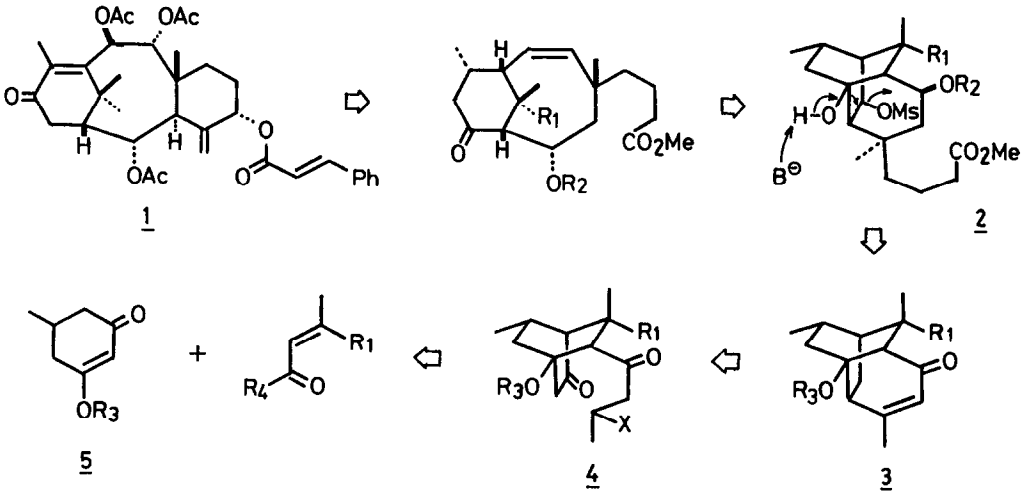
Summary: The bicyclo[5.3.1]undecane derivative 19, which was referred to the A,B ring system of taxane diterpenes, was synthesized by a base-induced fragmentation reaction of the tricyclic diol monomesylate 18 derived highly stereoselectively from 5-methyl-1,3-cyclohexadione.

The taxane diterpenes,[1] such as taxinine (1), isolated from various species of Taxus have a novel tricyclic carbon skeleton. The synthesis[2] of taxanes is one of current intrest for organic chemist not only because of the unique structural feature but also thier potent anticancer activity.[3] In this paper we wish to report a highly stereocontrolled synthesis of bicyclo[5.3.1]undecane ring system which is an important structural element of the taxane diterpenes.

Our retrosynthetic analysis for taxinine (1) is outlined in Scheme I. The key step in this route is a Grob fragmentation reaction of tricyclo[5.3.1.$0^{3,8}$]-undecane derivative 2, which can be synthesized from enone 5 through sequential Michael reaction, intramoleculer cyclization of 4, and stereoselective introduction of requeisite carbon units into α,β-unsaturated ketone 3.

Scheme I

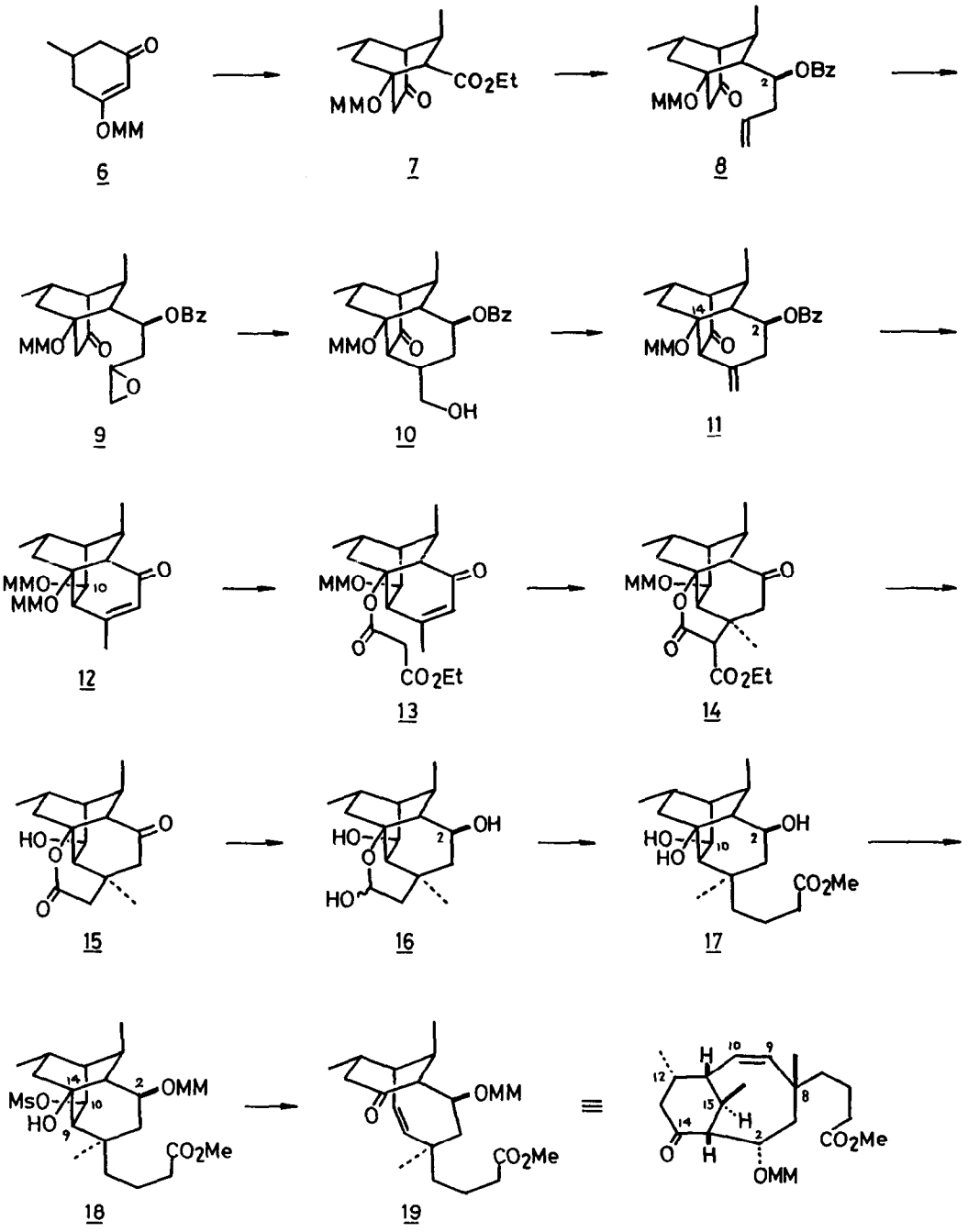


Sequential Michael reaction of the lithium enolate of 6, easily prepared from 5-methyl-1,3-cyclohexadione ($MeOCH_2Cl$, $i\text{-}Pr_2NEt$, CH_2Cl_2, rt), with ethyl crotonate at -20°C in THF gave bicyclo[2.2.2]octanone 7[4,5] as a single isomer in 94% yield. Transformation of 7 into the keto olefin 8 was carried out by means of a four-step sequence. Reduction and oxidation of the ester group in 7 (i. $LiAlH_4$, Et_2O, rt; ii. PCC, 4Å molecular sieves, CH_2Cl_2, 81% yield over two steps) followed by regio- and stereoselective introduction of an allyl group into the resulted keto aldehyde (CH_2=$CHCH_2MgBr$, $ZnBr_2$, Et_2O, -78°C, 95%) produced the homoallylic alcohol,[6] whose hydroxyl group was protected as benzyl ether to give 8 ($PhCH_2Br$, KH, THF, rt, 93%). The keto olefin 8 was subjected to epoxidation ($m\text{-}Cl\text{-}PhCO_3H$, Na_2HPO_4, CH_2Cl_2, 88%) to give a diastereomeric mixture (1:1) of the keto epoxide 9. Cyclization was cleanly effected by treatment of 9 with t-BuOK to furnish the tricyclic alcohol 10 as a mixture of diastereomeric isomers(92%). After dehydration of 10 into the exocyclic olefin 11 (i. N-(phenylthio)-succinimide, $n\text{-}Bu_3P$, C_6H_6, rt;[7] ii. $m\text{-}Cl\text{-}PhCO_3H$, CH_2Cl_2, -78°C; iii. $i\text{-}Pr_2NEt$, o-dichlorobenzene, 180°C, 74% overall yield), 11 was converted into the enone 12 by means of a five-step sequence. Stereoselective reduction of the ketone group in 11 ($i\text{-}Bu_2AlH$, PhMe, -78°C)[8] followed by protection of the hydroxyl group[9] ($MeOCH_2Cl$, $i\text{-}Pr_2NEt$, CH_2Cl_2, rt) produced the bis(methoxymethyl) ether, which was then transformed into 12 by deprotection of the benzyl group (Li, liq.NH_3, THF, -34°C), Jones oxidation, and subsequent isomerization (Al_2O_3, Et_2O, rt) in 91% overall yield from 11.

Stereoselective introduction of the requisite carbon units into the β-position of the unsaturated ketone 12 for construction of the C ring system of the natural product was accomplished by means of intramolecular Michael reaction as follows. Regioselective deprotection of the methoxymethyl group of the tertiary alcohol in 12 (4:1 AcOH-H_2O, 60°C, 88%), followed by treatment with ethyl malonyl chloride (pyridine, rt, 98%) yielded 13. Base-induced cyclization (NaH-K_2CO_3, THF, rt) of 13 afforded the lactone 14 in nearly quantitative yield. Decarboethoxylation of 14 under an acidic condition (1N HCl, dioxane, 100°C) gave 15, which was reduced with $i\text{-}Bu_2AlH$ (Et_2O, -78°C) to afford the hemiacetal 16[10] in 73% yield from 14. After Wittig reaction of 16 with Ph_3P=$CHCO_2Me$ (CH_2ClCH_2Cl, 50°C), the resulted α,β-unsaturated ester was hydrogenated (H_2, 10% Pd-C, MeOH, rt) to give the triol ester 17 in 84% yield from 16. The key intermediate 18 was obtained from 17 by a three-step sequence. Methoxymethylation of the triol 17 ($MeOCH_2Br$, $i\text{-}Pr_2NEt$, CH_2Cl_2, rt, 91%) giving its bis(methoxymethyl) ether [C(2) and C(10)], removal of one of the methoxymethyl group at C(10) under acidic condition (4:1 AcOH-H_2O, 50°C, 69%), and selective mesylation of the hydroxyl group at C(10) (MsCl, pyridine, CH_2Cl_2, 0°C, 89%) gave the mesylate 18.

Having the key intermediate tricyclic diol monomesylate 18 in hand, the fragmentation of the C(9)-C(14) bond to generate the bicyclo[5.3.1]undecane

Scheme II


OMM
6
MMO
CO2Et
7
OBz
8
9
10
OH
11
12
13
14
15
16
17
MsO
18
19
CO2Me
MM = CH2OMe

system referred to the A,B ring in the natural product was examined. Treatment of 18 with potassium hydride in toluene at 100°C for 10 min followed by methylation (CH_2N_2, Et_2O, 0°C) produced the expected bicyclic keto olefin 19,[11] [^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.05 (3H, s, CH_3 at C.8), 1.06 (3H, d, J=6.6Hz, CH_3 at C.12 or C.15), 1.21 (3H, d, J=7.3Hz, CH_3 at C.12 or C.15), 3.39 (3H, s, $-OCH_2O\underline{Me}$), 3.66 (3H, s, CO_2Me), 3.68 (1H, m, H-2), 4.54 and 4.72 (1H each, d, J=6.8Hz, $-OC\underline{H}_2OMe$), 5.33 (1H, dd, J=9.7, 1.0Hz, H-9), 5.79 (1H, dd, J=9.7, 5.6Hz, H-10); IR ($CHCl_3$) 1735, 1715 cm^{-1}; High resolution MS (m/z) Calcd. for $C_{21}H_{34}O_5$ (M^+): 366.2404, Found: 366.2414], in 94% overall yield from 18.

Studies on the application of this synthetic strategy to the total synthesis of taxinine will be reported in due course.

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Refernces and Notes

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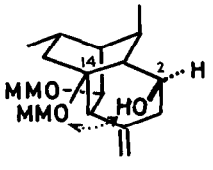
4. All new compounds have been satisfactorily charactrized by IR, ^{1}H-NMR (200MHz or 400MHz), high resolution mass spectroscopy and/or combustion analysis.
5. A similar tandem conjugate addition reaction has been reported by M.R.Roberts and R.H.Schlessinger, J.Am.Chem.Soc., 103, 724 (1981).
6. Stereochemistry of the hydroxyl group at C(2) was determined by measurement of intramolecular hydrogen bonding between the hydroxyl group at C(2) and the methoxymethyl ether at C(14) in the high dilution IR spectrum of i, which was derived from the compound 11.



i

7. K.A.M.Walker, Tetrahedron Lett., 4475 (1977).
8. The stereoselectivity was found to be rather sensitive to the reaction temperature and the solvent used.
9. Stereochemistry of the hydroxyl group at C(10) was determined by the analysis of ^{1}H-NMR (400MHz).
10. Stereoselective reduction of the ketone group at C(2) in 15 was explained by the less hindered side hydride attack.
11. The corresponding bicyclic compound with E olefin was not detected in the reaction product.

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