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TAXOL AND DERIVATIVES: A BIOGENETIC HYPOTHESIS[1]

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ABSTRACT.—Based on the structural differences of compounds isolated from various species of *Taxus*, this brief review suggests a biogenetic approach to taxol [1]. This hypothesis could be of some help in the synthesis of this complex molecule exhibiting significant antitumor properties.

Among the antimitotic agents, taxol [1] (1), which possesses an original diterpene carbon skeleton 2 (2), exhibits a unique mode of action on microtubule proteins responsible for the formation of the spindle during cell division. In contrast with other "spindle poisons" such as vinblastine or colchicine, which both prevent the assembly of tubulin (3,4), taxol is the only plant product known to inhibit the depolymerization process of tubulin (5). Because of this biological feature and its unusual chemical structure, taxol may well represent the prototype of a new class of chemotherapeutic agents, and it is currently in clinical trials both in France and in the USA. Taxol was originally isolated from the stem bark of the yew *Taxus brevifolia* Nutt. (1) and has also been found in other *Taxus* species (6,7) although in relatively low yield. Several attempts to synthesize taxane diterpenes have been reported (8-29). The main difficulty with this synthesis lies less in the construction of the tricyclic carbon framework $[9.3.1.0.^{3,8}]$ pentadecene 2 than in the introduction of the suitable functional groups with their correct configurations. The activity of natural and semisynthetic congeners of taxol have been studied both in vitro and in vivo. Slight structural modifications may lead to important changes in the biological activity (30-33).

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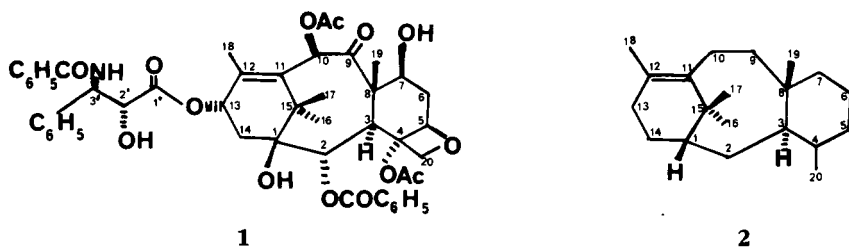
Biogenetic-type synthesis has often been used to elaborate complex natural compounds and has been proven to be a very fruitful approach to achieve synthesis of vinblastine (34), ervatamine (35), and colchicine (36). Biosynthetic studies of taxol [1] are quite difficult to undertake, but some biogenetic hypotheses may be tested by a synthetic approach. Indeed, the observation of the structural differences between taxane derivatives combined with the chemical reactivities of some analogs led us to suggest a biogenetic approach to taxol [1].

I. ORIGIN OF THE TRICYCLIC TAXANE RING SYSTEM 2.—So far, about 40 different taxane derivatives have been isolated from various species of *Taxus* (*T. baccata, T. brevifolia, T. cuspidata, T. floridana, T. mainni, T. wallichiana*). In a recent review (37), Miller described most of the compounds isolated since their first discovery by Lucas in

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[1]This article commemorates the 50th year of publication of the *Journal of Natural Products* (formerly *Lloydia*).

[2]Member of the Editorial Advisory Board of the *Journal of Natural Products* (*Lloydia*) since 1980.

1856 (38). Looking at the structural differences among these compounds and those which have been isolated more recently, four structural groups can be distinguished: (a) Compounds having an exocyclic methylene group at C-4 [**A**]; (b) Compounds with a 4(20)-oxirane ring [**B**]; (c) Compounds with an oxetane ring [**C**]; and (d) One compound having a C_4-C_{20} endo double bond [**D**].
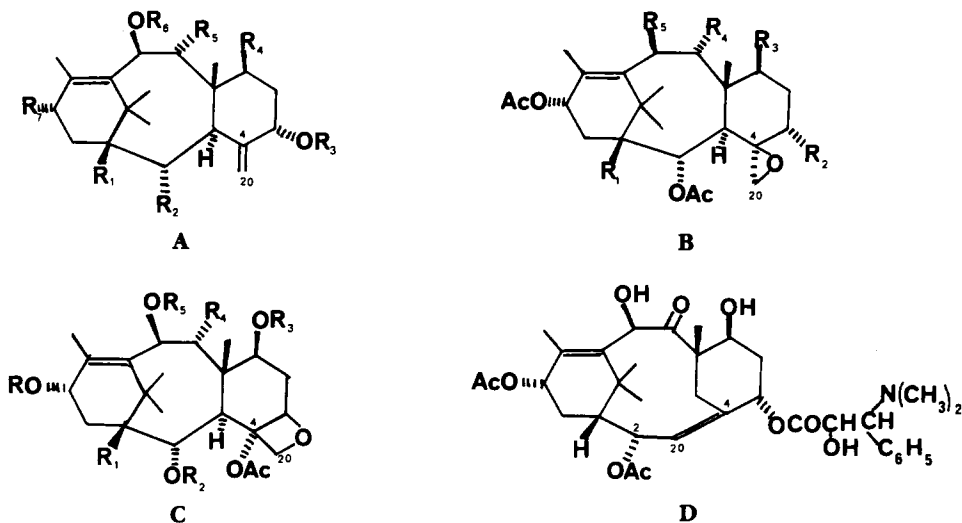

The only known compound of the last group (taxine A) was found in *T. baccata*, and its structure was determined by X-ray analysis (39). Taxine A differs from the other structural groups by the presence of an endocyclic double bond between C_4 and C_{20}. From a biogenetic point of view, this compound may derive from geranylgeraniol pyrophosphate but through a cyclization reaction different from the one leading to group **A**, **B**, and **C** (Scheme 1). In 1966, Lythgoe and collaborators suggested that the
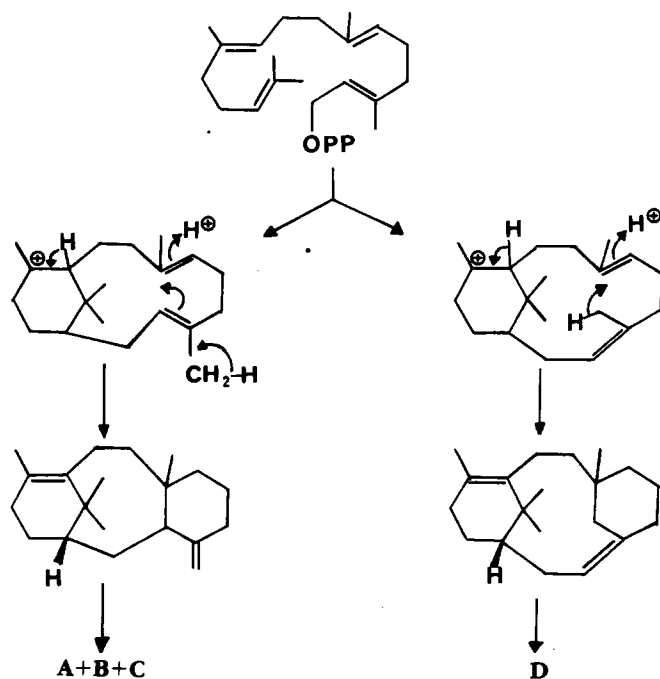
SCHEME 1

taxane carbon framework may arise biogenetically from geranylgeraniol by cyclization reactions (40). A similar biogenesis has been suggested for the monocyclic diterpenes cembrene A [3] (41,42) and casbene [4] (43), and for the bicyclic diterpene verticillol [5] isolated from the coniferous *Sciadopitys verticillata* (Taxodiaceae) (42). Verticillene [6] is considered to be the most likely intermediate between geranylgeraniol pyrophosphate and the taxane type of diterpenes. The recent total synthesis of verticillene [6] (44) allowed Pattenden to investigate transannular cyclization of both this compound and verticillol [5] in order to vindicate the biogenesis hypothesis mentioned above (45). Unfortunately, verticillene [6] has failed so far to undergo in vitro cyclization to the corresponding tricyclic ring system.

3 cembrene A

4 casbene

5 verticillol

6 verticillene
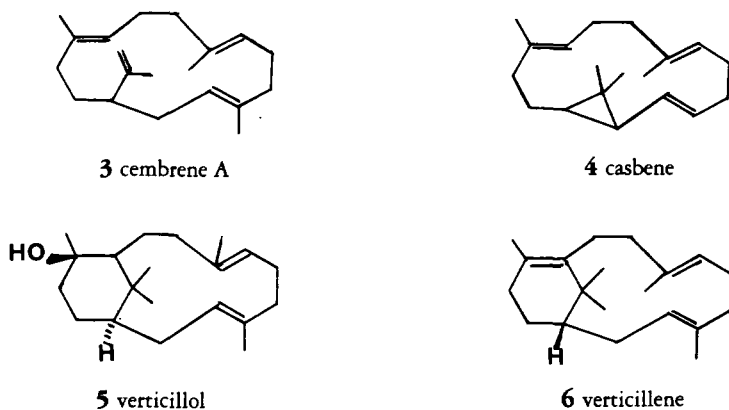
II. BIOGENETIC RELATIONS BETWEEN THE THREE STRUCTURAL GROUPS **A**, **B**, AND **C**.—Considering the structures of the products isolated from various species of yew tree, we can assert the following facts: (a) Compounds of group **A** (exocyclic methylene group at C_4) contain different functionalities at C_{13}: ketone [7, 8, 9], hydroxyl [10a, 10b], acetate [11a through 11j].

Three other compounds [12a-12c] from this group without any functionality at C_{13} have been isolated by Della Casa de Marcano and his colleagues (53).

Among the derivatives described above, some obviously come from the decomposition of the alkaloidal mixture called taxine (38) which is responsible for the poisonous nature of the yew. The basic character of this mixture is due to the 3-dimethylamino-3-phenylpropionic acid (Winterstein's acid) residue which esterifies various nitrogen-free polyhydroxylic taxane compounds (56-58). Because of the difficulties in isolating such esters, most of them have never been obtained as such except in the form of their desdimethylamino derivatives. For example, taxine II [13] decomposes with elimination of dimethylamine to give the corresponding taxinine cinnamate [7a] (59). However, three new taxane derivatives with a nitrogen side chain (Winterstein's type esters) at C_5 have been isolated recently in our Institute from the stem bark of *Austrotaxus spicata* Compton collected in New Caledonia: **11h, 11i,** and **11j** (55).[3]

(b) Compounds of group **B** [14 and 15] have been shown to contain a C-4 (20) oxirane ring. From a biogenetic point of view, baccatin I [14a], 5-deacetyl baccatin I [14b], and 1β- hydroxybaccatin I [14c] (60) could well derive from the corresponding exocyclic methylene compounds (Group **A**) by epoxidation of the double bond.
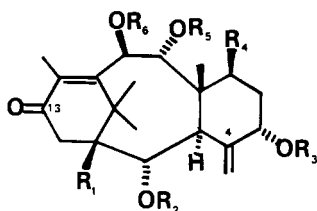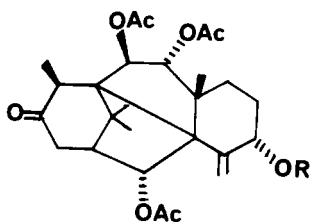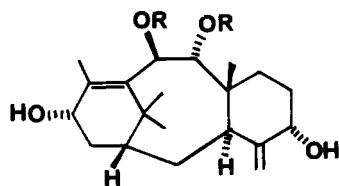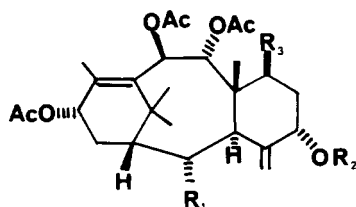

	R_1	R_2	R_3	R_4	R_5	R_6	Ref.
7a	H	Ac	COCH=CHC$_6$H$_5$	H	Ac	Ac	(37,46)
7b	H	Ac	H	H	Ac	Ac	(37,47)
7c	H	Ac	COCH=CHC$_6$H$_5$	OAc	Ac	Ac	(37,48)
7d	H	Ac	Ac	H	Ac	Ac	(37,47)
7e	OH	H	H	H	H	H	(37,49)
7f	OH	Ac	COCH=CHC$_6$H$_5$	H	Ac	Ac	(50)
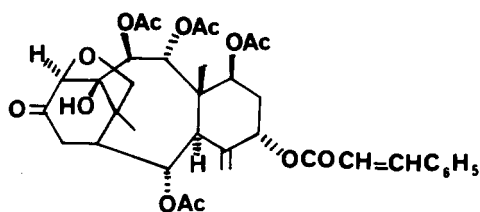
8 (51)

9a R=H (37,47)
9b R=Ac (37,47)

10a R=H (37,52)
10b R=Ac (37,53)

	R_1	R_2	R_3	Ref.
11a	H	Ac	H	(37,53)
11b	H	Ac	OAc	(37,53)
11c	OAc	COCH=CHC$_6$H$_5$	H	(37,48)
11d	OAc	COCH=CHC$_6$H$_5$	OAc	(37,48)
11e	OAc	Ac	H	(37,53)
11f	OAc	Ac	OAc	(37,53)
11g	OAc	H	OAc	(54)
11h	OAc	COCHCHC$_6$H$_5$ HO N(CH$_3$)$_2$	H	(55)
11i	OAc	COCHCHC$_6$H$_5$ AcO N(CH$_3$)$_2$	H	(55)
11j	OAc	COCH$_2$CHC$_6$H$_5$ N(CH$_3$)$_2$	H	(55)

Compound **15** (7) contains a hydroxyl group attached to C_7 with an opposite configuration (7α) to that found in all other taxane derivatives (7β). This epimerization of the secondary hydroxyl group at C_7 also occurs in the oxetane derivatives (Group **C**) via a retro-aldol reaction. Though no compound of group **B** bearing a ketone group at C_9 has been ye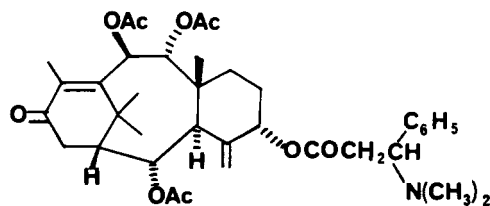t isolated from the yew tree, taxane derivative **15** could well be produced from a compound such as **14d** through an oxidation at C_9, retro aldol process, and then reduction. Other explanations can also be put forward. Recently new compounds from this group bearing cinnamic ester or 3-dimethylamino-3-phenylpropionic ester (Winterstein's ester) at C_5 have been isolated in our Institute from the stem bark of *Austrotaxus spicata* Compton: **14e**, **14f**, and **14g** (55).[3]
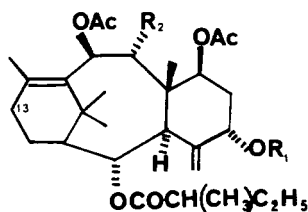
12a R_1=Ac, R_2=H (53)
12b R_1=H, R_2=OAc (53)
12c R_1=Ac, R_2=OAc (53)

13
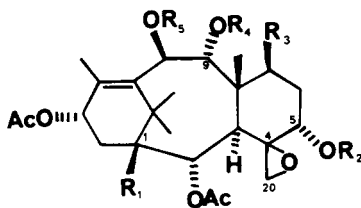
	R_1	R_2		R_3	R_4	R_5	Ref.
14a	H	Ac		OAc	Ac	Ac	(60)
14b	H	H		OAc	Ac	Ac	(60)
14c	OH	Ac		OAc	Ac	Ac	(60)
14d	OH	Ac		OH	Ac	Ac	
14e	H	COCH=CHC$_6$H$_5$		H	H	Ac	(55)
14f	H	COCH$_2$CHC$_6$H$_5$		H	H	Ac	(55)
		N(CH$_3$)$_2$					
14g	H	COCH$_2$CHC$_6$H$_5$		H	Ac	H	(55)
		N(CH$_3$)$_2$					
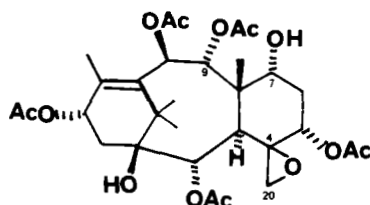
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(c) Compounds of group **C** (oxetane ring) contain a hydroxyl group at C_{13} [**16**] or an ester group [**1**, **17**, and **18**].

The C_{13} hydroxylated compounds **16b** and **16c** could be considered as precursors of the more elaborated derivatives **1** and **18**. Examination of both molecular models and the structure obtained by molecular mechanics calculations shows a complete folding of the molecule in which the α-hydroxyl group at C_{13} is very close to the 4α-acetyl group (interatomic distances: C_{13}-OH. . .O=C-O-C_4=2.50 Å)(32). That particular conformation hinders easy intermolecular esterification at C_{13}. Indeed, under usual esterification conditions, the hydroxyl group attached to C_{13} does not react as well as the two other secondary hydroxyl groups (30,32). On the contrary, acyl transfer from a C_4 ester to C_{13} could well operate with this kind of derivative. However, no compound of group **C** bearing a more complicated ester than acetyl at C_4 has yet been isolated.

Recently, we have been able to show that a structural modification of the oxetane type compounds allows an easy esterification at C_{13}. Treatment of compound **19** (32) with zinc chloride in toluene yielded the new derivative **20**.[4] Careful examination of
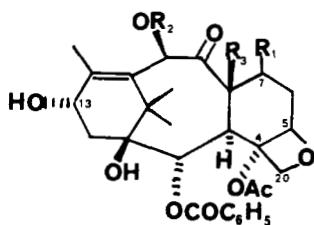
	R_1	R_2	R_3	Ref.
16a	OH(7α)	Ac	CH_3	(37,61)
16b	OH(7β)	Ac	CH_3	(37,62)
16c	OH(7β)	H	CH_3	(37,62)
16d	OH(7β)	H	CH_2OH	(62)
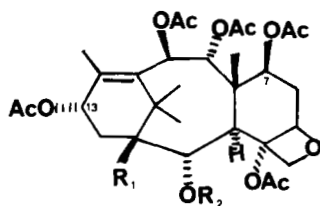
17a	R_1=OH, R_2=Ac (63)
17b	R_1=H, R_2=Ac (63)
17c	R_1=OH, R_2=COC$_6$H$_5$ (63)
17d	R_1=OH, R_2=COC$_5$H$_{11}$ (63)

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[4]This new compound and its mechanism of formation will be described and discussed in a forthcoming paper.
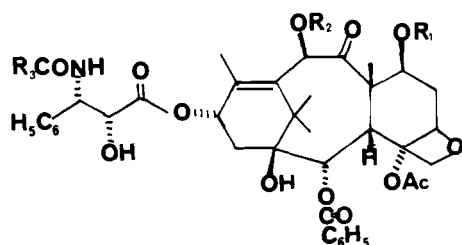
	R_1	R_2	R_3	Ref.
1	H	Ac	C_6H_5	(1,6,7)
18a	H	Ac	$CH_3CH=C(CH_3)$	(6,7)
18b	β-xylose	H	C_6H_5	(7)
18c	β-xylose	H	$CH_3CH=C(CH_3)$	(7)
18d	β-xylose	H	C_5H_{11}	(7)
18e	β-xylose	Ac	C_6H_5	(7)
18f	β-xylose	Ac	$CH_3CH=C(CH_3)$	(7)
18g	β-xylose	Ac	C_5H_{11}	(7)
18h	H	H	C_6H_5	(7,62)
18i	H	H	$CH_3CH=C(CH_3)$	(7,62)
18j	H	$\overset{\text{OH}}{\underset{|}{COCH_2CHCH_3}}$	C_6H_5	(7)
18k	H	$COCH_2\overset{|}{C}HCH_3$ with $\underset{OH}{}$	$CH_3CH=C(CH_3)$	(7)
18l	β-xylose(OAc)	Ac	$CH_3CH=C(CH_3)$	(7)

the ^{1}H-nmr spectrum of **20** showed changes in the geminal coupling constant for the C_{20} protons ($J=12$ Hz) as compared with a value of 9 Hz in compounds of group **C** (with an intact oxetane ring) and in the resonance of the C_5 proton. The disappearance of the signal corresponding to one of the methyl groups at C_{15} as well as the presence of two singlets at 4.72 and 4.83 ppm support structure **20** for this new derivative. The structural modification in rings A and D favors the intermolecular acylation of the C_{13} hydroxyl group in contrast to baccatin III [**16b**] and 10-deacetylbaccatin III [**16c**]. Similar derivatives in which the oxetane ring is opened have also been obtained from taxol {**1**} by Kingston.[5] It will be interesting to know whether the opening of the oxetane ring without further structural modifications in ring A will still favor the esterification at C_{13}.

These different observations suggest that natural compounds of group **C** (taxol, **1**, cephalomannine, **18a**, etc) could be derived from exocyclic methylene type compounds (group **A**) through intramolecular esterification (Scheme 2). Indeed, one of the conformations[6] which can be assigned to compound **I**, taken as an example, leads to the possibility of orthoester formation (**II**). This intermediate of an intramolecular transesterifi-
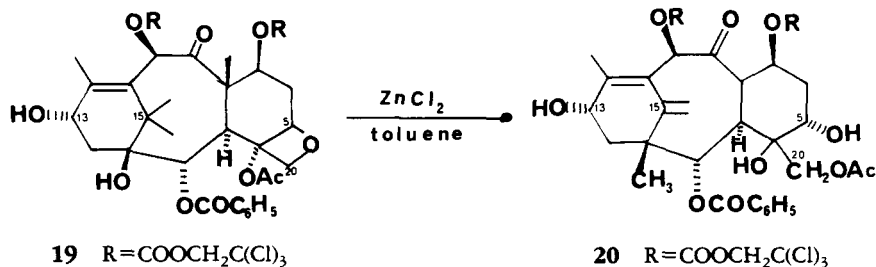

19 R=COOCH₂C(Cl)₃   **20** R=COOCH₂C(Cl)₃

cation process between C_{13} and C_5 could lead to **III** (group **A**). Through epoxidation and acetylation, **III** could be converted into **IV** (group **B**) and **V** after opening of the oxide ring. Finally, the β attack of the resulting hydroxylated intermediate **V** and acetyl transfer from C_5 to the C_4 carbonium ion would give derivative **VI** (group **C**).[7]

As new oxirane-type compounds bearing nitrogen side chains at C_5 have been recently isolated, an alternative hypothesis would be that an equally feasible acyl transfer took place at this stage from the C_5 to the C_{13} hydroxyl group.

Baccatin V [**16a**] (61) contains a hydroxyl group at C_7 with an α configuration. This compound is probably an artifact formed from baccatin III [**16b**]: indeed, the 7β-hydroxyl group of baccatin III [**16b**] and 10-deacetyl baccatin III [**16c**] can easily epimerize in vitro into the 7α isomer via a retro aldol mechanism (62).

SCHEME 2

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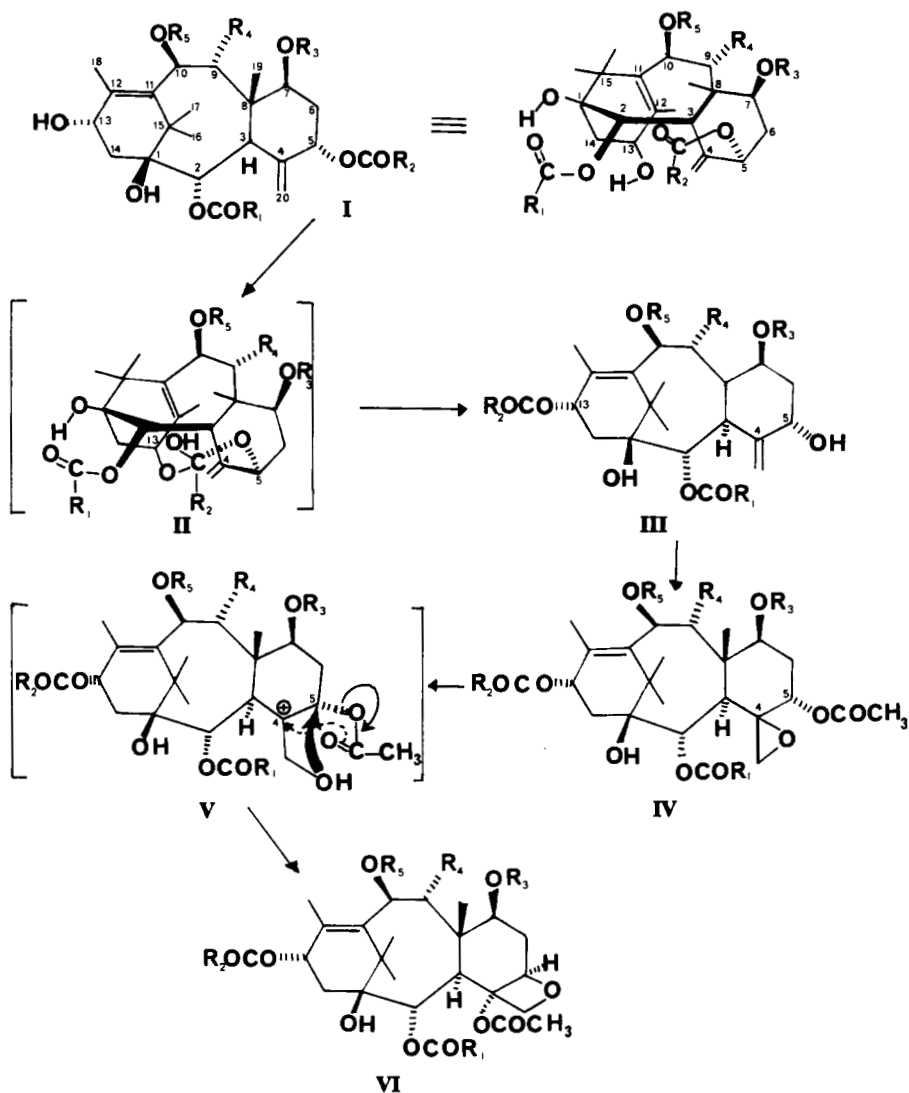
[7]For other suggestions regarding the formation of the oxetane ring, see Della Casa de Marcano *et al.* (61), Swindell and Britcher (66), and Berkowitz and Amarasekara (67).

III. BIOGENESIS OF THE TAXANES—SIDE CHAIN.—Acid hydrolysis of taxine gives (3R)-3-dimethylamino-3-phenylpropionic acid (Winterstein's acid) (56,57,68). Biosynthetic studies on this acid have been reported first by Leete (69) and more recently by Haslam (70). It has been demonstrated that in *T. baccata*, biosynthesis of Winterstein's acid proceeds through a stereospecific process from (2S)-phenylalanine and that cinnamic acid was a poor precursor (70). No biosynthetic studies have been reported on the taxol *threo* side chain [(2R,3S)-N-benzoyl-3-phenylisoserine]. The recent discovery of new exocyclic methylene compounds (group **A**) bearing a 2-hydroxy-3-dimethylamino-3-phenylpropionic ester at C_5 suggests but does not prove that hydroxylation might occur on the simpler side chain (3R)-3-dimethylamino-3-phenylpropionic acid found in taxine. In a similar way the C_{13} side chain in taxol could be derived from (2S)-phenylalanine via an exocyclic methylene or oxirane type derivative with the appropriate side chain at C_5.

CONCLUSION

Several observations reported in this article show that, to prepare taxol derivatives synthetically, it may be more advisable to perform intramolecular esterification of the C_{13}-hydroxyl group on the C-4 (20) exocyclic methylene or oxirane derivatives bearing an appropriate side chain at C_5. Modification of the exocyclic methylene or oxirane group could then take place to give the oxetane ring which seems to be necessary for biological activity in the taxol series. Another alternative would be to carry out intermolecular esterification at C_{13} on a D-seco-taxol (oxetane ring opened) such as **20**. The conformational change observed in this kind of derivative must effectively improve esterification at C_{13} in contrast with the oxetane-bearing type of compounds where external access to position 13 is severely hindered.

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