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Patupilone

Rec INN

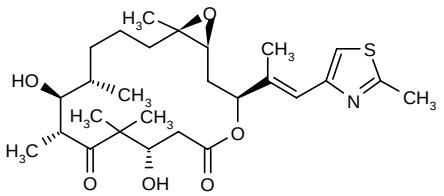
Antimitotic Drug
Microtubule-Stabilizing Agent
Oncolytic

EPO-906
Epothilone B

(4*S*,7*R*,8*S*,9*S*,13*R*,14*S*,16*S*)-13,14-Epoxy-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2(*E*)-(2-methylthiazol-4-yl)vinyl]-1-oxacyclohexadecane-2,6-dione

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(*E*)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

InChI=1/C27H41NO6S/c1-15-9-8-10-27(7)22(34-27)12-20(16(2)11-19-14-35-18(4)28-19)33-23(30)13-21(29)26(5,6)25(32)17(3)24(15)31/h11,14-15,17,20-22,24,29,31H,8-10,12-13H2,1-7H3/b16-11+/t15-,17+,20-,21-,22-,24-,27+/m0/s1



$C_{27}H_{41}NO_6S$
Mol wt: 507.6836

CAS: 152044-54-7

EN: 222557

Abstract

Patupilone (epothilone B, EPO-906) is one of six epothilones that have been evaluated in early clinical trials for the treatment of cancer. Epothilones are cytotoxic macrolides that induce microtubule stabilization, a mechanism of action similar to paclitaxel. Patupilone has demonstrated activity in taxane-resistant settings in preclinical models and phase I studies have shown that the dose-limiting toxicity is diarrhea, in contrast to other epothilones and taxanes for which neurotoxicity and neutropenia are generally dose-limiting. Several phase II studies of patupilone for the treatment of cancer have been reported, and significant activity in taxane-sensitive tumor types, such as lung, ovarian and prostate cancer, has been reported. Randomized trials are now necessary to define the role of patupilone in the treatment of cancer.

Synthesis*

Patupilone can be synthesized following several different synthetic strategies.

A number of procedures are based on the macrocyclization of the bis-TBDMS-protected linear hydroxyacid (Ia) (1-8), the TBDMS/Troc-protected hydroxyacid (Ib) (8-10) or the unprotected trihydroxyacid (Ic) (8) utilizing EDC, 2,4,6-trichlorobenzoyl chloride (TCB-Cl) or phenylsulfonyl chloride in the presence of tertiary amines as the coupling reagents. Subsequent removal of any existing trichloroethoxycarbonyl (Troc) groups by means of Zn/NH_4Cl and/or TBDMS groups with HF-pyridine, TFA or TBAF, and finally epoxidation of the endocyclic double bond with mCPBA, methyl trifluoromethyl dioxirane (MTFDO) or dimethyl dioxirane (DMDO), furnishes the title epothilone (1-10). A related macrolactonization procedure is based on the cyclization of the hydroxytrienoic acid (II) with TCB-Cl, followed by TFA-promoted desilylation, selective hydrogenation of the 9-10 double bond with *in situ*-generated diimide, and epoxidation with DMDO (11-14). Macrolactonization of the epoxy hydroxyacids (IIIa) (15) and (IIIb) (16-18) has also been reported utilizing TCB-Cl. Subsequent removal of the Troc protecting groups with Zn/NH_4Cl and/or TBDMS groups with either TFA or HF-pyridine furnishes patupilone (15-18). Two additional synthetic strategies have been reported, in which ring closure is achieved through C-C bond formation. Intramolecular aldol condensation of the linear ace-

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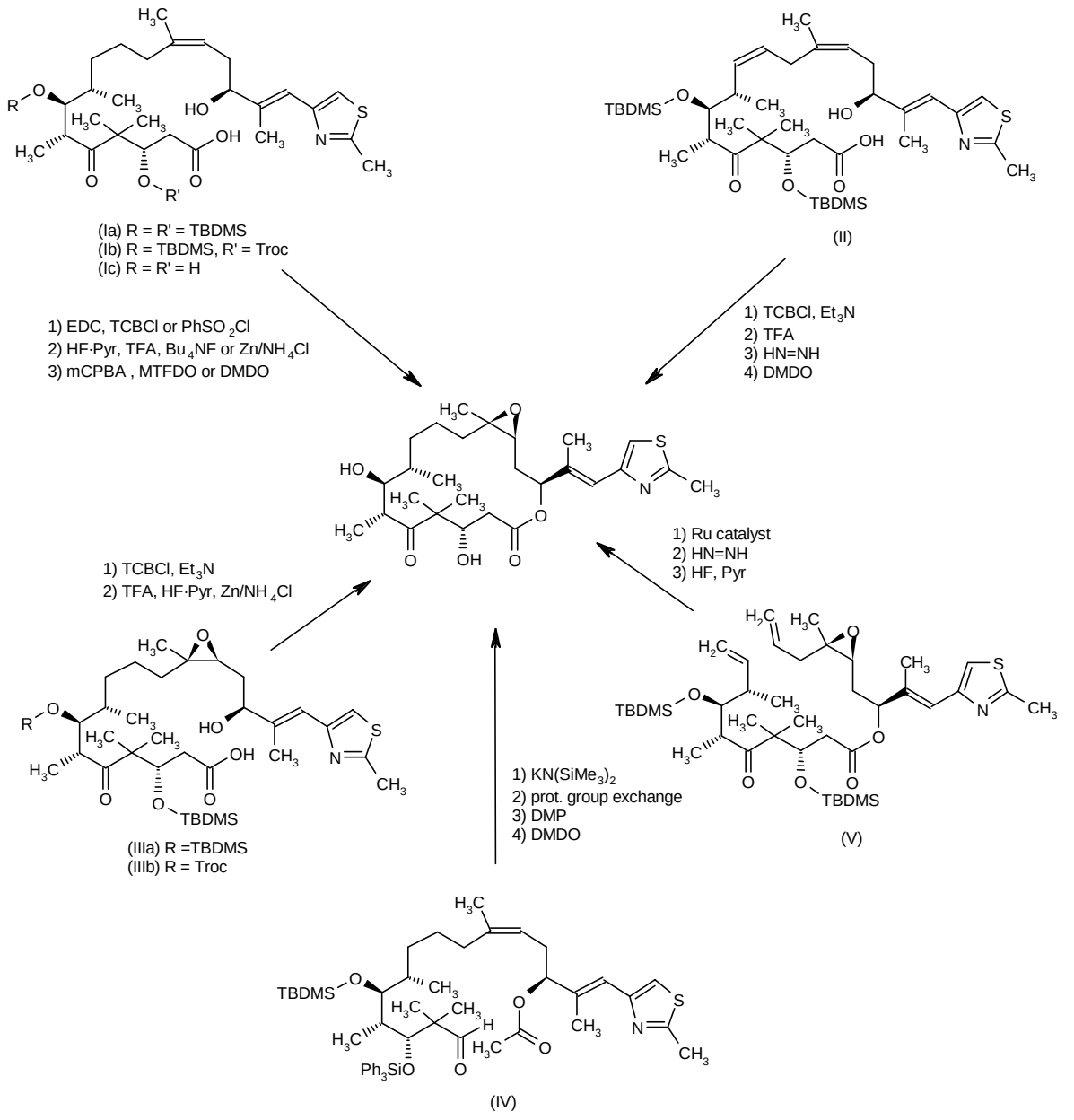
toxy aldehyde (IV) in the presence of KHMDS produces the corresponding macrolactone as an epimeric mixture at the 3-hydroxyl group. The desired isomer is then desilylated at C5 with HF-pyridine, followed by selective protection of the 3-hydroxyl with TBDMS triflate and Dess-Martin oxidation of the free 5-hydroxyl. Full desilylation with HF-pyridine and subsequent epoxidation employing DMDO gives the title compound (19, 20). A different strategy utilizes in the key synthetic step a ring-closing olefin metathesis of the linear diolefin (V) in the presence of organoruthenium catalyst, followed by saturation of the newly formed double bond with *in situ*-generated diimide, and finally desilylation with HF-pyridine (21-23). Scheme 1.

Aldehyde (XIV), a common key intermediate in several synthetic routes, is prepared by the following methods. Wittig reaction of the thiazolylmethyl phosphonium salt (VIa) with monosilylated dihydroxypentanone (VII), followed by Swern oxidation, provides aldehyde (VIIIa) (1, 5). Starting from the thiazolyl propenal (IX) (prepared from 2-methylthiazole-4-carbaldehyde and 1-formylethylidene triphenylphosphorane), aldehyde (VIIIa) is obtained by addition of cyanotrimethylsilane in the presence of

Scheme 1: Synthesis of Patupilone

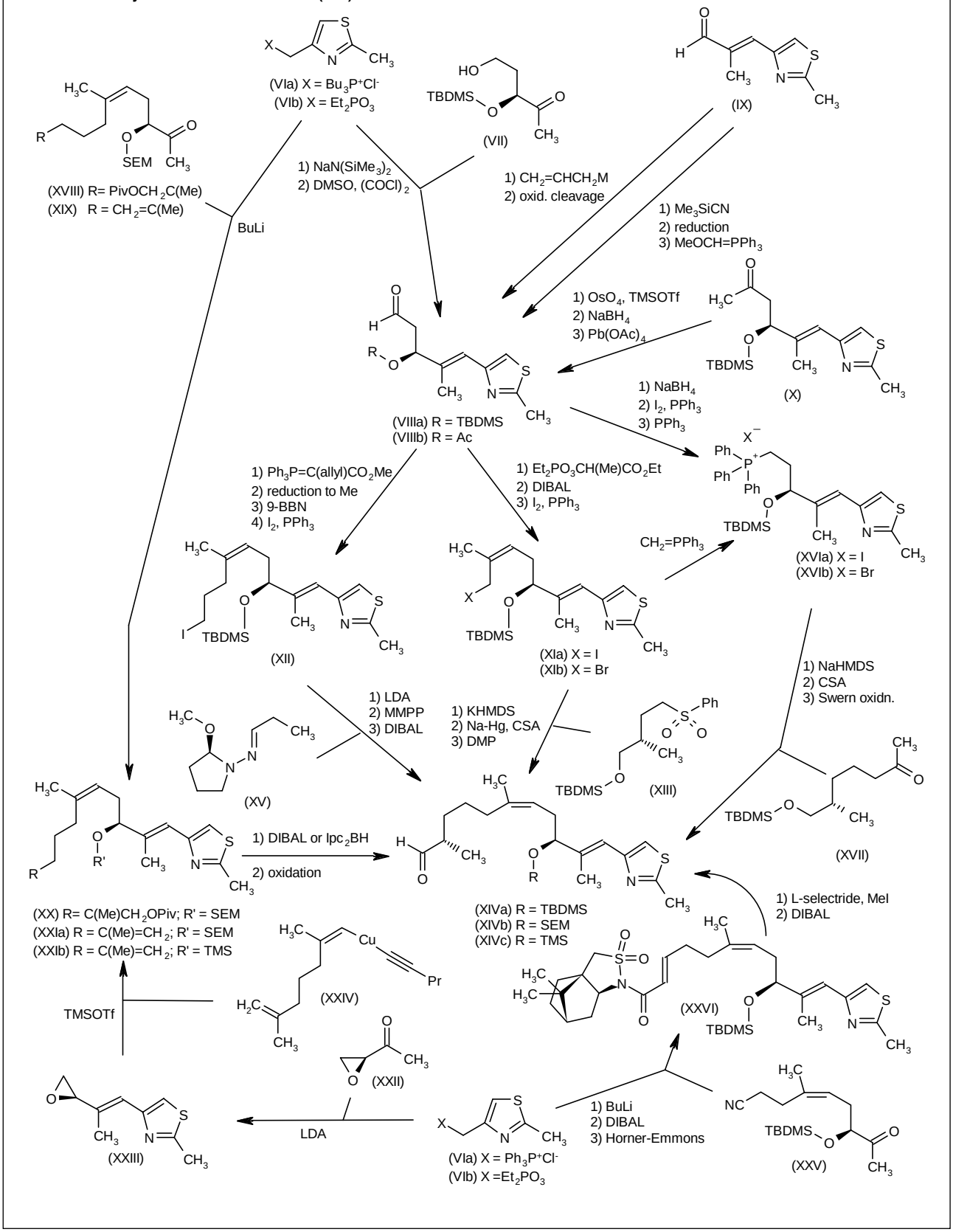


Et_2AlCl and chiral bidentate phosphine oxide, followed by alcoholysis, protection, reduction to α-silyloxy aldehyde, and then aldehyde homologation with methoxymethylene triphenylphosphorane (3). Alternatively, condensation of (IX) with either *B*-allyl-di-(+)-isopinocampheylborane (2, 7) or with allyl tributyltin and (*S*)-BINOL (20), followed by *O*-silylation or *O*-acetylation of the resulting β,γ-unsaturated alcohol and oxidative cleavage with OsO_4 and $Pb(OAc)_4$, gives the β-silyloxy (VIIIa) and β-acetoxy aldehyde (VIIIb), respectively. A further procedure is based on the oxidative cleavage of the methyl ketone (X) via hydroxylation of the corresponding silyl enol ether, followed by reduction to diol and then treatment with lead tetraacetate (21-23). Horner-Emmons condensation of aldehyde (VIIIa) with triethyl 2-phosphonopropionate and subsequent ester group reduction with DIBAL, and iodination with I_2/PPh_3, provides the allylic iodide (XIa) (1, 5). Optionally, reaction of (VIIIa) with 1-(methoxycarbonyl)-3-butenylidene triphenylphosphorane gives an α-allyl unsaturated ester, which is stepwise reduced to the methyl compound, followed by hydroboration and iodination to give (XII) (2, 21-23). After condensation of iodide (XIa) with the potassium derivative of sulfone (XIII), desulfuration with sodium amalgam and regioselective desilylation of the primary alcohol, oxidation with Dess-Martin periodinane gives the key aldehyde (XIVa) (1, 5). Alternatively, the chiral propylidene pyrrolidine (XV) is diastereoselectively alkylated with the alkyl iodide (XII) in the presence of LDA, followed by oxidation of the intermediate hydrazone with magnesium monoperoxyphthalate and then reduction of the resulting nitrile with DIBAL, to furnish the target aldehyde (XIVa) (2). A further procedure starting from aldehyde (VIIIa) consists of conversion to the phosponium salt (XVIa) via reduction to alcohol, followed by iodination with I_2/PPh_3, and iodide displacement with PPh_3 at 100 °C (2). Wittig reaction of (XVI) with 7-silyloxy-6(*S*)-methyl-2-heptanone (XVII), followed by selective desilylation of the primary hydroxyl and Swern oxidation, provides the target aldehyde (XIVa) (2, 4). Alternatively, the phosphonium salt (XVIb) can be obtained by condensation of bromide (XIb) with methylene triphenylphosphorane (13, 14). Other strategies to (XIV) are based on the Horner-Emmons condensation of phosphonate (VIb) with either the diprotected 3(*S*),11-dihydroxy-6,10(*S*)-dimethyl-5-undecen-2-one (XVIII) (6) or the SEM-protected 3(*S*)-hydroxy-6,10-dimethyl-5,10-undecadien-2-one (XIX) (8-10) to furnish adducts (XX) and (XXIa), respectively. Either the terminal olefin of (XX) or the pivaloyloxy group of (XXI) is converted to alcohol via reductive cleavage of the pivalate ester (6) or asymmetric double bond hydroboration (8-10), and then subjected to Swern oxidation to produce aldehyde (XIVb) (6, 8-10). An alternative route to (XXIb) consists of condensation of phosphonate (VIb) with 2(*S*)-acetyloxirane (XXII) to produce the thiazolylvinyl oxirane (XXIII), which then undergoes epoxide ring opening with the organocopper reagent (XXIV) (generated from 4-methyl-4-pentenylmagnesium bromide, propylene, CuBr and pentynyllithium), followed by protection with trimethylsilyl triflate (8). Finally, aldehyde (XIVa) is obtained by condensation of the phosphonium salt (VIa) with 7(*S*)-TBDMS-oxy-4-methyl-8-oxonon-4-enenitrile (XXV) (produced from methyl lactate via a silicon-tethered ring-closing metathesis reaction), followed by reduction of the cyano group with DIBAL and Horner-Emmons condensation with Oppolzer's chiral phosphonate, to yield (XXVI). The one-pot reduction and diastereoselective methylation of (XXVI) with L-selectride and iodomethane, followed by reductive cleavage of the chiral auxiliary group, then furnishes the target aldehyde (XIVa) (24). Scheme 2.

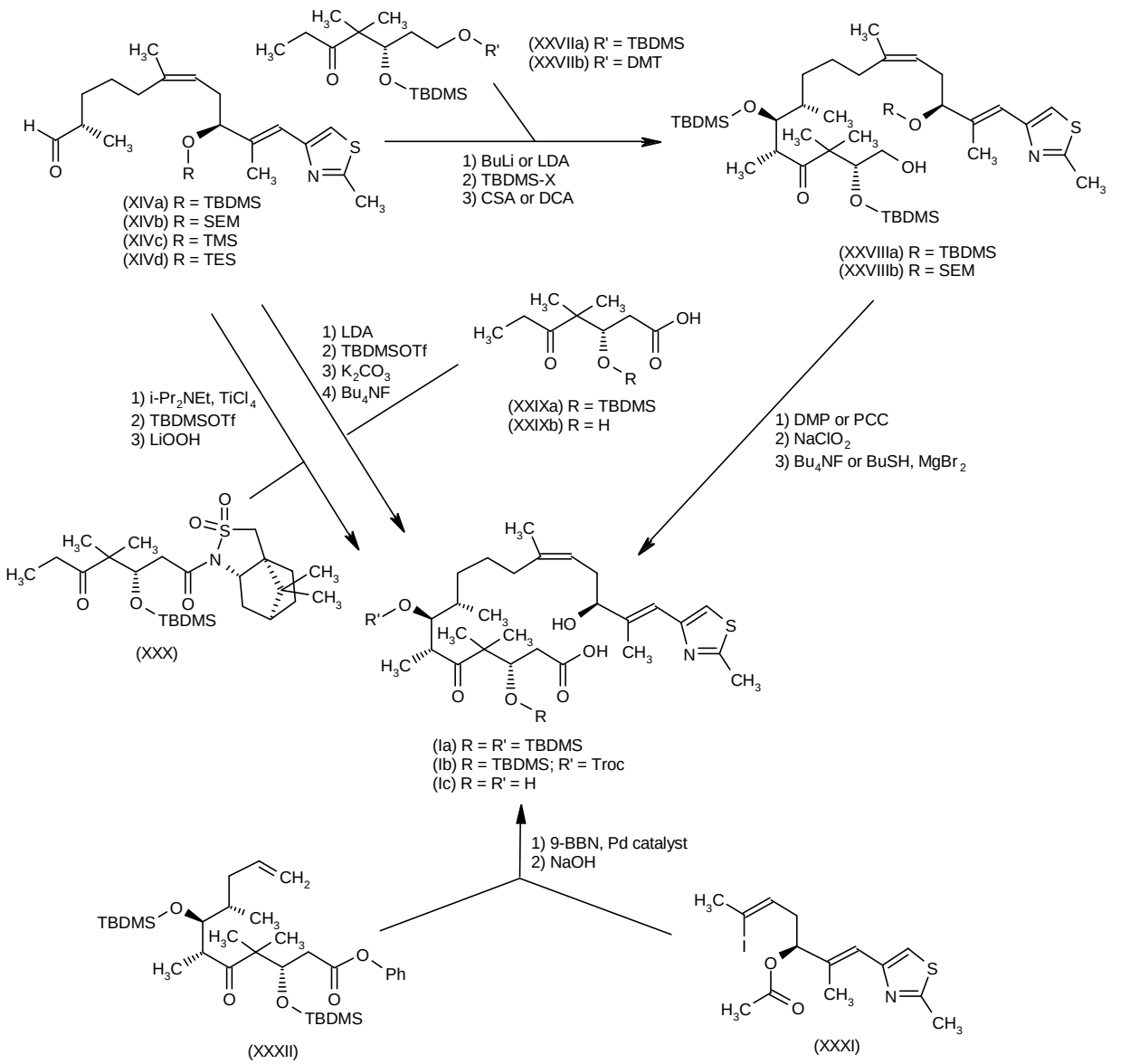
The hydroxyacid precursors (I) are prepared from aldehydes (XIV) by several related procedures. Aldol condensation of (XIVa) (1, 5, 7) or (XIVb) (6) with diprotected 5,7-dihydroxy-4,4-dimethylheptan-3-ones (XXVIIa) (1, 5, 7) or (XXVIIb) (6), followed by silylation with TBDMS triflate or chloride and regioselective deprotection of the primary hydroxyl with either camphorsulfonic acid (CSA) or dichloroacetic acid (DCA), gives the primary alcohols (XXVIIIa) or (XXVIIIb) (1, 5-7). Then, stepwise oxidation of alcohols (XXVIII) with DMP or PCC followed by $NaClO_2$, and subsequent selective deprotection of the 15-hydroxyl, furnishes the precursor hydroxyacid (Ia) (1, 5-7). In a related method, aldehyde (XIVa) (2, 4, 8) or (XIVb) (9) is condensed with either the TBDMS-protected (XXIXa) or the unsilylated 4,4-dimethyl-3(*S*)-hydroxy-5-oxoheptanoic acid (XXIXb), optionally followed by protection of the 7-OH (with TBDMS-OTf or Troc-Cl) and subsequent selective deprotection of the 15-OH, to furnish the corresponding hydroxy acids (Ia), (Ib) and (Ic) (2, 4, 8, 9). Similarly, the intermediate hydroxyacid (Ia) is obtained by condensation of aldehyde (XIVd) with the chiral *N*-heptanoyl camphorsultam derivative (XXX), followed by silylation and hydrolysis of the chiral auxiliary group (2, 25, 26). In a different strategy, (Ia) is prepared by coupling of the vinyl iodide (XXXI) with the phenyl undecenoate derivative (XXXII) utilizing 9-BBN and a $PdCl_2$ complex, followed by alkaline hydrolysis of the phenyl ester group (3). Scheme 3.

The hydroxytrienoic acid precursor (II) can be obtained by two related methods utilizing common synthetic intermediates. The allylic bromide (XIb) is prepared by Horner-Emmons condensation of diethyl (2-methyl-4-thiazolylmethyl)phosphonate (VIb) with the diprotected 3(S),7-dihydroxy-6-methylhept-5-en-2-one (XXXIII), followed by selective hydrolysis of the tetrahydropyranyl group and bromination of the deprotected alcohol (11, 13). Alternatively, bromide (XIb) can be obtained by reaction of (VIb) with 6(*S*)-acetyl-2-methoxy-3-methyl-5,6-dihydro-2*H*-pyran (XXXIV) and subsequent ketal hydrolysis, reduction, bromination and silylation (14). The aldehyde esters (XXXVIII) are in turn prepared by addition of the lithium enolate of *tert*-butyl acetate to disilylated 5,7-dihydroxy-2,2,4,6-tetramethyl-3-oxoheptanal (XXXV), followed by deprotection and oxidation (14), or by condensation of 4,4-dimethyl-5(*S*)-(TBDMS-oxy)oct-7-en-3-one (XXXVI) with 3-(*p*-methoxybenzyloxy)-2(*S*)-methylpropanal (XXXVII), followed by several oxidation and protection steps (2, 11, 13). Aldehyde (XXXVIIIb) is

Scheme 2: Synthesis of Intermediate (XIV)



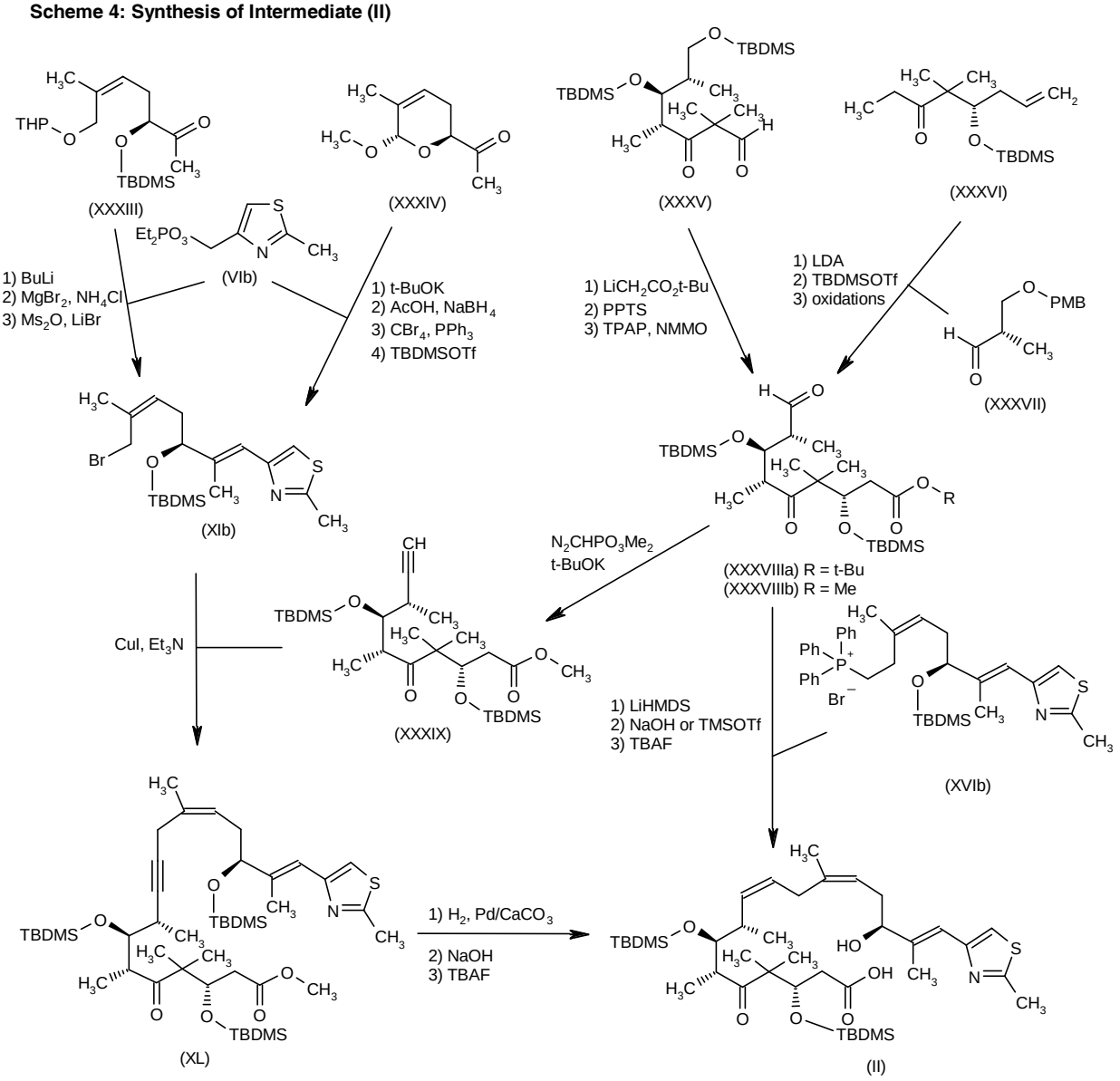
Scheme 3: Synthesis of Intermediate (I)



optionally converted to the terminal acetylene derivative (XXXIX) by condensation with dimethyl diazomethylphosphonate (11, 12). Coupling of (XXXIX) with the allylic bromide (XIb) in the presence of CuI and Et_3N furnishes the disubstituted acetylene (XL), which is then subjected to partial hydrogenation of the triple bond over Lindlar catalyst to furnish, after saponification and selective 15-*O*-desilylation, the target trienoic acid precursor (II) (11, 12). In an alternative method, Wittig reaction of aldehydes (XXXVIIIa) (14) or (XXXVIIIb) (2, 11, 13) with the phosphonium salt (XVIb) (prepared from bromide [XIb], as shown in Scheme 1), followed by methyl or *tert*-butyl ester cleavage and selective desilylation, provides the trienoic hydroxy acid (II). Scheme 4.

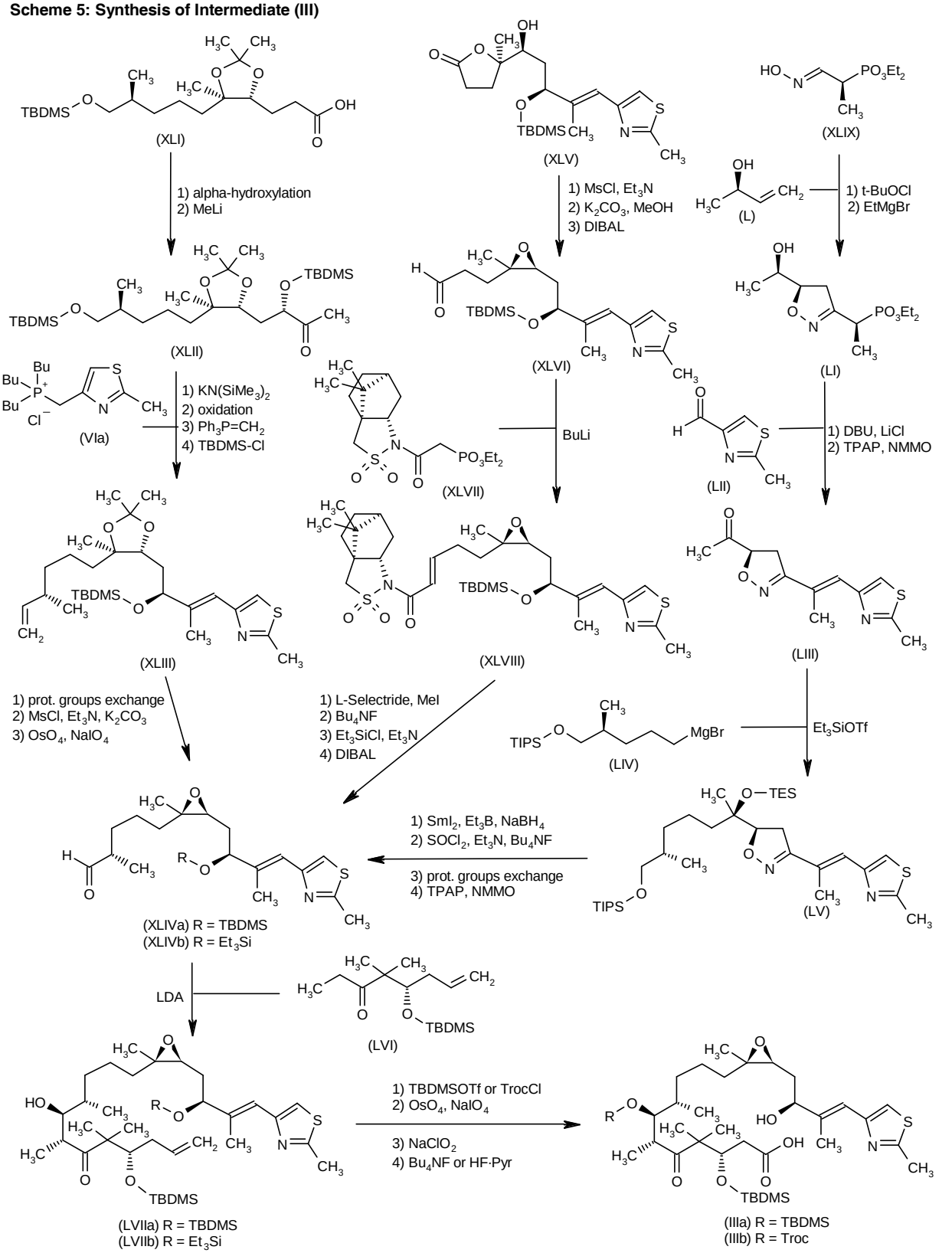
The epoxy acid precursor (III) is prepared by the following methods. The protected trihydroxydecanoic acid (XLI) is converted to the corresponding 3-acyl-4(*S*)-methyl-5(*R*)-phenyl-2-oxazolidinone, which undergoes α-hydroxylation upon treatment with Davis oxaziridine and NaHMDS. After conversion to the corresponding Weinreb amide and subsequent *O*-silylation, treatment with methyllithium affords the methyl ketone (XLII). Wittig reaction of ketone (XLII) with the phosphonium salt (VIa), followed by deprotection and oxidation of the primary

Scheme 4: Synthesis of Intermediate (II)



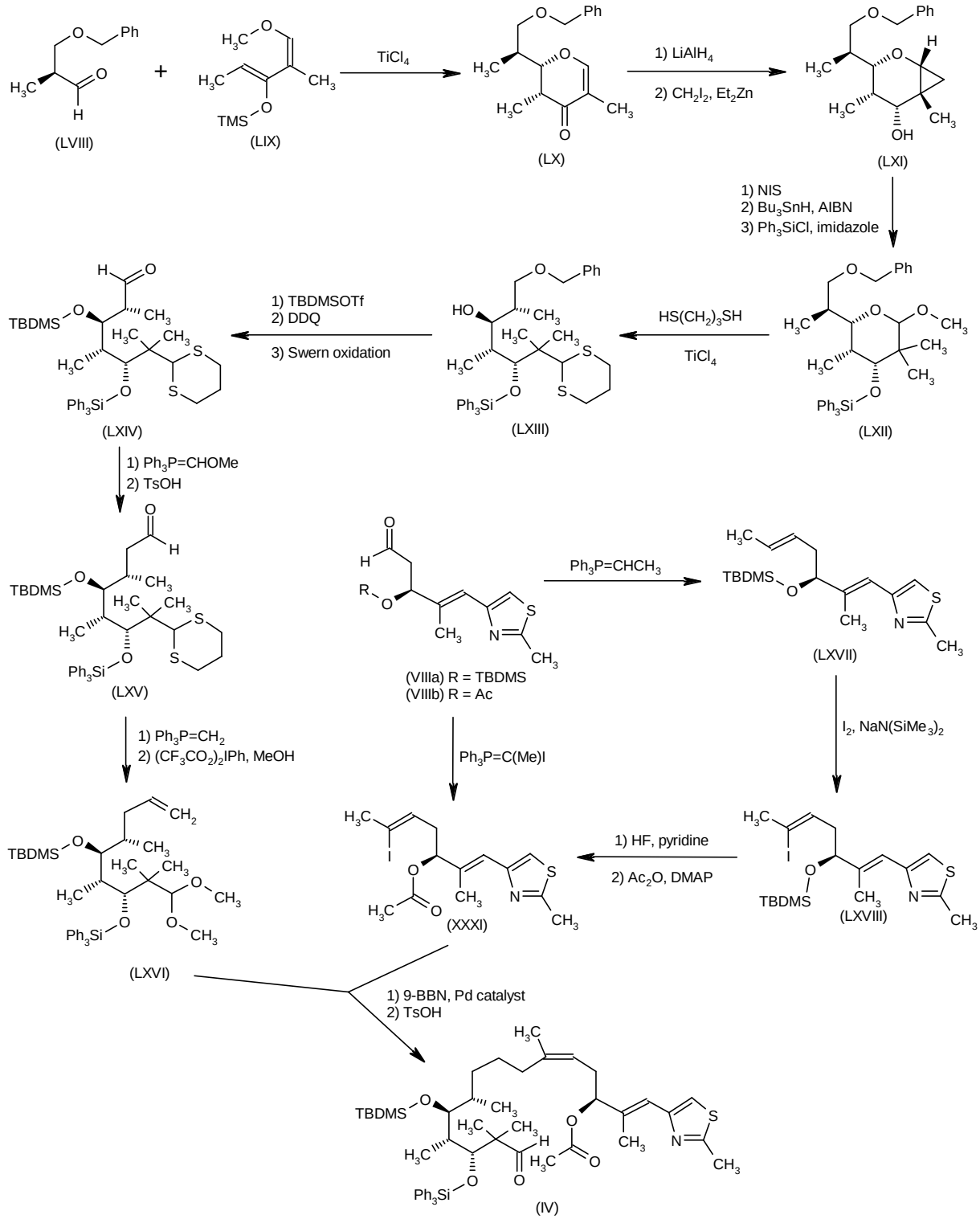
alcohol, produces the corresponding aldehyde, which is then converted to the olefin (XLIII) via condensation with methylene triphenylphosphorane. Simultaneous desilylation and hydrolysis of the acetonide (XLIII), followed by selective reprotection of the allylic alcohol, produces a vicinal diol, which is converted to the desired epoxide by mesylation and basic cyclization of the hydroxy mesylate. Subsequent oxidative cleavage of the terminal olefin furnishes aldehyde (XLIVa) (15). The analogous TES-protected aldehyde (XLVIb) is obtained from the butyrolactone derivative (XLV), which, upon mesylation, rearrangement with methanolic K_2CO_3 and subsequent reduction of the resulting epoxy ester, gives the aldehyde (XLVI). Horner-Emmons condensation of aldehyde (XLVI) with the Oppolzer's chiral phosphonate (XLVII) then produces the unsaturated acyl camphorsultam (XLVIII), which is converted to the target aldehyde (XLIVb) by one-pot reduction and methylation with L-selectride and MeI, followed by replacement of the TBDMS protecting group with a TES group, and then reductive cleavage of the chiral sultam moiety (16). In a further route to the aldehyde (XLIVb), chlorination of oxime (XLIX) with *tert*-butyl hypochlorite, followed by condensation with 1-methylallyl alcohol (L) by means of EtMgBr, gives the isoxazoline phosphonate (LI), which, after condensation with 2-methylthiazole-4-carbaldehyde (LII), is oxidized to the acetyl isoxazoline (LIII) utilizing TPAP and NMMO. Addition of the Grignard reagent (LIV)

Scheme 5: Synthesis of Intermediate (III)



to the ketone (LIII), followed by silylation of the resulting carbinol, leads to the triethylsilyl ether (LV). Then, stepwise reduction of isoxazoline (LV) with SmI_2, followed by $Et_3B/NaBH_4$, gives an open-chain 1,3-diol, which is further elaborated to the epoxy aldehyde (XLIVb) by treatment with $SOCl_2$, followed by desilylation/cyclization, pro-

Scheme 6: Synthesis of Intermediate (IV)

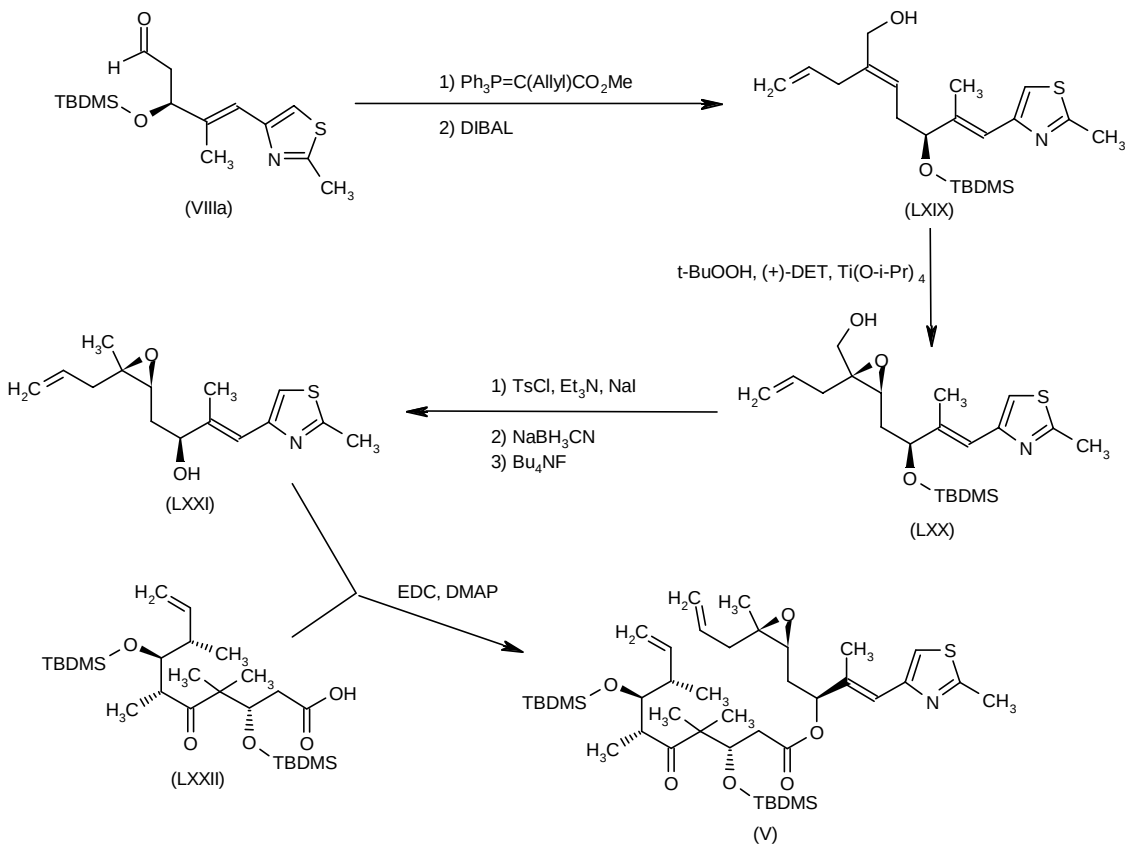


tecting group exchange and oxidation with TPAP/NMMO (18). Then, condensation of aldehydes (XLIVa/b) with 5(*S*)-TBDMS-oxy-4,4-dimethyloct-7-en-3-one (LVI) produces the respective epoxy aldol adducts (LVIa/b). These are finally converted to the target hydroxyacids (IIIa) or (IIIb) by the sequence of protection with either TBDMS-OTf or Troc-Cl, oxidative cleavage of the vinyl group and selective desilylation of the 15-hydroxyl (15-18). Scheme 5.

The acetoxy aldehyde precursor (IV) is synthesized as follows. The cyclization of 3-benzyloxy-2(*S*)-methylpropanal (LVIII) with the bis-enol ether (LIX) by means of $TiCl_4$ produces the dihydropyranone (LX), which, after reduction to alcohol with $LiAlH_4$, undergoes cyclopropanation to (LXI) upon treatment with diiodomethane and Et_2Zn. Cyclopropane ring cleavage by means of NIS, followed by reduction of the resulting iodomethyl derivative and hydroxyl group silylation, provides the gem-dimethyl tetrahydropyran (LXII). Opening of the cyclic acetal (LXII) with 1,3-propanedithiol and $TiCl_4$ yields the dithiolane derivative (LXIII), which, after silylation and debenzylation, is oxidized to aldehyde (LXIV) under Swern conditions. Subsequent condensation of aldehyde (LXIV) with methoxymethylene triphenylphosphorane produces the derivative (LXV), which is then desulfurated by treatment with phenyl iodonium bis(trifluoroacetate), providing the dimethyl acetal (LXVI) (19). Wittig reaction of aldehyde (VIIIa) with ethylidene triphenylphosphorane yields the olefin (LXVII), which is iodinated to (LXVIII) by treatment with iodine and NaHMDS. Subsequent desilylation of (LXVIII) with HF-pyridine, followed by acetylation with Ac_2O gives the vinyl iodide (XXXI) (3). Alternatively, vinyl iodide (XXXI) can be obtained by Wittig reaction of the acetoxy aldehyde (VIIIb) with 1-iodoethylidene triphenylphosphorane (19). Then, palladium-catalyzed coupling of the iodovinyl derivative (XXXI) with olefin (LXVI), followed by acidic acetal hydrolysis, furnishes the target acetoxy aldehyde (IV) (19). Scheme 6.

Finally, the preparation of the open-chain diene (V) is illustrated in Scheme 7. Wittig reaction of aldehyde (VIIIa) with 1-(methoxycarbonyl)-3-butenylidene triphenylphosphorane, followed by DIBAL reduction of the carboxylate group, provides the allyl alcohol adduct (LXIX) (2, 21-23). Sharpless asymmetric epoxidation of (LXIX) in the presence of *tert*-butyl hydroperoxide and (+)-diethyl tartrate leads to the hydroxymethyl oxirane (LXX), which is converted to the methyl analogue (LXXI) by iodination with TsCl and NaI, followed by reduction with $NaBH_3CN$ and desilylation with TBAF. Then, coupling of alcohol (LXXI) with 3,7-bis(TBDMS-oxy)-4,4,6,8-tetramethyl-5-oxo-9-

Scheme 7: Synthesis of Intermediate (V)



decenoic acid (LXXII) employing EDC and DMAP furnishes the target diene substrate for the ring-closing metathesis (V) (21-23). Scheme 7.

Background

Patupilone (epothilone B, EPO-906) is one of six epothilones under evaluation for the treatment of cancer. Patupilone is a natural product (27), while the other five epothilones are synthetic: ixabepilone (aza-epothilone B or BMS-247550), BMS-310705, KOS-862 (epothilone D or desoxyepothilone B), KOS-1584 and ZK-EPO (ZK-219477). Patupilone is a 16-membered macrolide that was first described when antifungal activity was found in the culture broth of the myxobacterium *Sorangium cellulosum* (27) and cytotoxicity mediated via microtubule stabilization was noted (28). The taxanes paclitaxel (29) and docetaxel also act via microtubule stabilization (30) and are used in the treatment of a number of tumor types, including breast, lung, ovarian and prostate cancer. Taxane resistance, however, is a common clinical problem in cancer treatment and one of the main reasons for the interest in patupilone is that cytotoxicity has been demonstrated in taxane-resistant preclinical models. Taxanes are also associated with significant side effects, including fatigue, alopecia, myelosuppression, hypersensitivity reactions and peripheral neuropathy. The clinical development of patupilone for the treatment of cancer is set against this background.

Preclinical Pharmacology

Microtubules are protein polymers that are components of the cytoskeleton of eukaryotic cells and have a critical role in a number of cellular processes, including mitosis. Microtubules are composed of α- and β-tubulin heterodimers and are targets for a number of drugs, including the antineoplastic vinca alkaloids and taxanes (31). Patupilone, like paclitaxel, causes polymerization and stabilization of microtubules *in vitro*, leading to cell cycle arrest at the G2/M boundary and subsequent apoptotic cell death. Furthermore, patupilone displaces [^{3}H]-paclitaxel from microtubules with similar or greater efficiency than unlabeled paclitaxel or docetaxel, suggesting that the drugs may share a similar binding site on the tubulin molecule (28, 32).

Drug resistance is an important problem in the treatment of cancer and there is evidence that both tubulin mutations (33) and the altered expression of tubulin isotypes (34, 35) may be implicated in this phenomenon. Patupilone became a focus of interest for development as an anticancer agent when cell culture studies showed cytotoxicity towards cell lines resistant to paclitaxel as a result of overexpression of the P-glycoprotein efflux pump (28, 32, 36). Growth inhibition was seen in a number of cell lines derived from bladder, breast, colorectal, lung and prostate carcinomas, with patupilone generally being an order of magnitude more potent than paclitaxel. Patupilone is also cytotoxic to some cell lines resistant to paclitaxel as a result of mutations in β-tubulin (37).

In animal models, patupilone caused growth retardation of a number of xenografted cell lines, some of which overexpressed the P-glycoprotein efflux pump and were insensitive to paclitaxel (36, 38). Despite the fact that the P-glycoprotein efflux pump is overexpressed in a number of human cancers, such as ovarian cancer (39, 40), the clinical relevance of this to taxane resistance in human cancers is unknown.

Clinical Studies

Three schedules of patupilone administration have been evaluated in patients with cancer. In one trial, reported in abstract form only, a three-weekly schedule was investigated in 42 patients (41). Diarrhea was the dose-limiting toxicity (DLT) at a patupilone dose of 8 mg/m^2 and the maximum tolerated dose (MTD) was 6 mg/m^2. Severe (grade 3) fatigue (n=4) and nausea or vomiting (n=2) were also reported. In a second trial, 91 patients were treated on either a 3 weeks on/1 week off or a 6 weeks on/3 weeks off schedule (42). The MTD was 2.5 mg/m^2, with diarrhea being the most common DLT for both schedules above this dose. Drug clearance was nonrenal and unrelated to body surface area; systemic drug exposure was approximately dose-proportional and C_{max} values were in excess of IC_{50} values reported for patupilone in cell lines. There was no evidence of significant alopecia, mucositis or myelosuppression in either study. Patupilone therefore has a markedly different side effect profile from taxanes and ixabepilone, the other epothilone furthest advanced in clinical trials for cancer. The DLTs of taxanes and ixabepilone (43-45) are neutropenia and neuropathy; patupilone is structurally similar to ixabepilone and the reason for the difference in side effect profile is unknown.

Patupilone has also been combined with gemcitabine, capecitabine, estramustine and carboplatin in studies reported to date in abstract form only. Patupilone and gemcitabine were both administered weekly for 3 of 4 weeks (46); gemcitabine was given at a dose of 800 mg/m^2. The MTD of patupilone was 2 mg/m^2, with DLT, most commonly diarrhea, at 2.5 mg/m^2. Patupilone was administered on the same schedule in combination with capecitabine (47). Capecitabine was given at a dose of 1250 mg/m^2 orally twice daily during weeks 2 and 3. The MTD for patupilone was 1.5 mg/m^2, with DLT, including diarrhea and nausea, at 2 mg/m^2. The same 3 weeks on/1 week off schedule for patupilone was also used in combination with estramustine (48). Estramustine was administered orally at a dose of 280 mg twice daily for 3 days every week for 3 of 4 weeks, starting a day before the infusion of patupilone. The MTD of patupilone was 2.5 mg/m^2, with DLT, again including diarrhea and vomiting, seen at higher doses. In a phase Ib trial in relapsed ovarian carcinoma, carboplatin (area under the time-concentration curve [AUC] 5 or 6) and patupilone were administered every 3 weeks. The MTD of patupilone was 4.8

mg/m^2 in combination with carboplatin AUC6, with fatigue the most common grade 3 or 4 toxicity. The majority (70%) of patients had potentially platinum-sensitive disease: 22 of 29 patients (76%) evaluable by CA125 had at least a 50% response and 8 of the 21 (38%) patients evaluable by RECIST (49) had an objective response to treatment.

Several phase II studies of patupilone given as a single agent (Tables I and II) in colorectal, gastric, non-small cell lung (NSCLC), neuroendocrine, ovarian, prostate and renal cancers have been presented in abstract form. The majority of studies treated patients on the 3 weeks on/1 week off schedule; there were no significant differences in toxicity between the weekly and three-weekly schedules. The most common grade 3 toxicity was diarrhea, occurring in approximately one-quarter of patients. Grade 3 fatigue, nausea and vomiting were also reported. More recently, dose escalation of the 3-weekly schedule has been evaluated in ongoing trials in NSCLC (50) and ovarian (51) cancer. Doses of patupilone up to 11.0 mg/m^2 have been administered with the use of aggressive antidiarrheal management, and interestingly, preliminary data suggest that neuropathy rather than diarrhea may be dose-limiting.

Patupilone did not show significant activity in the treatment of neuroendocrine tumors or renal cell carcinoma. Recent data have suggested modest activity in colorectal and gastric carcinoma; these data require confirmation and will not be considered further here. Clear activity was seen in NSCLC, ovarian and prostate cancers and the role of patupilone in these tumor types will be discussed further below.

A response rate to patupilone of 11% has been reported in platinum-pretreated NSCLC (50) in the dose-escalation phase of a phase I/II study. Fifty patients were treated, 28% of whom had received prior taxane therapy. Patupilone was administered at doses of 6.5-13.0 mg/m^2 every 3 weeks and the recommended phase II dose was 10 mg/m^2. The standard treatment of NSCLC in this setting is docetaxel, with response rates in the range of 8.8-14% reported (52-54). On the basis of these data, docetaxel and patupilone appear to have similar activity and further evaluation of patupilone in NSCLC is warranted.

Significant activity has been reported for patupilone in platinum- and taxane-resistant ovarian cancer in another phase I/II study (51). Patupilone was administered at doses of 6.5-11.0 mg/m^2 every 3 weeks. Forty-five patients with refractory/resistant ovarian carcinoma were treated, 94% of whom had received prior taxane therapy. The recommended phase II dose was 11.0 mg/m^2 and 8 (25%) of 32 patients evaluable for response had a complete (n=1) or partial response (n=7) to treatment with patupilone by RECIST. While this is interesting, a response rate of 22% has been reported for docetaxel in

Table I: Summary of activity of patupilone in phase II clinical trials in cancer.

Tumor type	Patient number[1]	Response rate[2]	Dose/schedule	Ref.
Colorectal	91	4%	6 mg/m^2 d1 q2 12.5 mg/m^2 d1,8,15 q28	58
Gastric	22	9%	2.5 mg/m^2 d1,8,15 q28	59
Neuroendocrine	14	Nil	2.5 mg/m^2 d1,8,15 q28	60
NSCLC	47	11%	6.5-13 mg/m^2 d1 q21	50
Ovarian	32	25%	2.5 mg/m^2 d1,8,15 q28	51
Prostate	20	20%	2.5 mg/m^2 d1,8,15 q28	56
Renal	52	4%	2.5 mg/m^2 d1,8,15 q28	61

[1]Number of patients with measurable disease evaluable for response. [2]Confirmed responses.

Table II: Summary of toxicity of patupilone in phase II clinical trials in cancer.

Tumor type	Toxicity	Dose/schedule	Ref.
Colorectal	29% grade 3/4 diarrhea 10% grade 3/4 nausea/vomiting	6 mg/m^2 d1 q21 2.5 mg/m^2 d1,8,15 q28	58
Gastric	18% grade 3 diarrhea 27% grade 3/4 nausea/vomiting	2.5 mg/m^2 d1,8,15 q28	59
Neuroendocrine	46% grade 3/4 diarrhea 8% grade 3/4 nausea/vomiting	2.5 mg/m^2 d1,8,15 q28	60
NSCLC	14% grade 3 diarrhea	6.5-13 mg/m^2 d1 q21	50
Ovarian	19% grade 3 diarrhea 9% grade 3 fatigue	6.5-11 mg/m^2 d1 q21	51
Prostate	19% grade 3/4 diarrhea 14% grade 3/4 fatigue	2.5 mg/m^2 d1,8,15 q28	56
Renal	8% grade 3 diarrhea	2.5 mg/m^2 d1,8,15 q28	61

a phase II study in which 60 patients with paclitaxel-resistant ovarian cancer were treated (55). Docetaxel was administered at a dose of 100 mg/m^2 every 21 days; this dose can be associated with significant toxicity and 75% of patients in this study had grade 4 neutropenia.

An objective tumor response rate of 20% has been reported for patupilone in hormone-refractory prostate cancer in a study in which 37 patients were treated on the 3 weeks on/1 week off schedule (56). The majority of patients (78%) had received one (unspecified) prior line of chemotherapy. These data compare with the 12% objective tumor response rate to docetaxel in combination with prednisone, the standard first-line treatment option in this disease, in the phase III TAX 327 study (57). Randomized studies are recruiting in order to further define the efficacy and safety of patupilone in comparison with standard treatment in hormone-refractory prostate cancer. It seems possible that patupilone will have a role in the management of this disease in the future, given the encouraging efficacy reported and the fact that few other agents are active.

Conclusions

Patupilone appears to have a toxicity profile distinct from both other epothilones and taxanes inasmuch as diarrhea is the DLT, rather than neutropenia and neuropathy. Patupilone does not cause alopecia, an important consideration, particularly in the treatment of women. Preliminary data have shown that patupilone can be combined safely with other cytotoxic agents because of nonoverlapping toxicity profiles. Although patupilone has shown activity in taxane-resistant settings in preclinical models, it is not clear from the phase II studies reviewed here that patupilone is more active than taxanes in the treatment of cancer. For example, in the case of taxane-resistant ovarian carcinoma, the activity of patupilone is similar to that of docetaxel in paclitaxel-resistant disease reported in a phase II study (55). All the phase II trials of patupilone reported to date have been single-arm studies and as such must be interpreted with caution; randomized trials comparing patupilone with standard treatments are necessary to further evaluate this agent for cancer treatment.

Source

Novartis AG (CH).

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