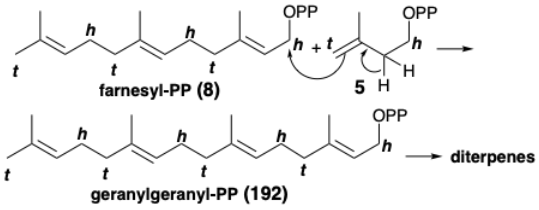
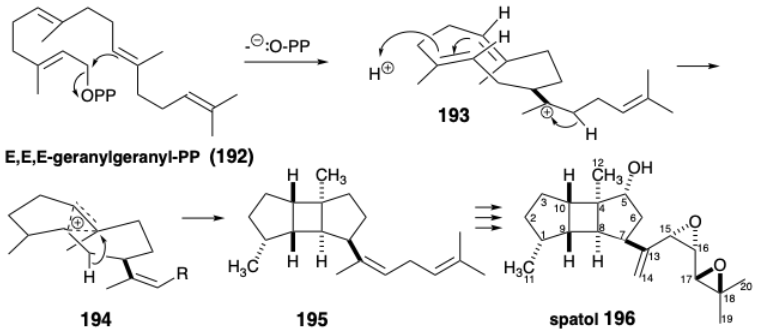
4.6: Biosynthesis and Total Syntheses of Diterpenes - Spatol

Biosynthesis

As for all natural products, a successful synthetic strategy for spatol existed before any human endeavor. It is always interesting to examine Nature's strategy because an analogous approach, a **biomimetic strategy** (mimicing Nature), may be effective in the laboratory. Thus, the diterpenes are C_{20} compounds derived biogenetically from E,E,E-geranylgeranyl-PP (**192**) or its geometrical isomers.

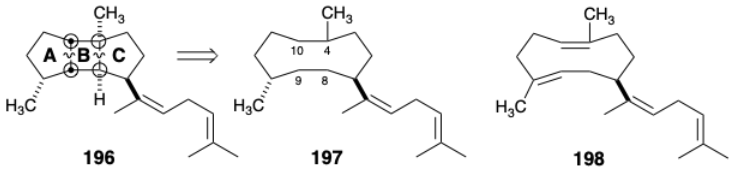


These acyclic tetramers of Δ^3-isopentenyl-PP (**5**) arise from reaction of **5** with a trimer such as E,E-farnesyl-PP (**8**). Subsequent intramolecular electrophilic addition of the allylic pyrophosphate to the trisubstituted C=C bonds can lead to various mono and multicyclic carbocations such as **193**. Another general route to carbocationic electrophiles involves protonation of C=C bonds. A hypothetical pathway for the biosynthe- sis of spatol (**196**) involves protonation of a C=C bond and intramolecualr electrophilic addition of the resulting carbocation to produce a cyclobutane (**195**) by proton loss from **194**. This hypothesis derives support from the natural occurrence of **195**.[14] The oxygen functionality in **196** is presumed to arise from oxidative metabolism of **195** by the marine organisms that produce this tricyclic diene and a wide variety of oxygenated metabolites with the spatane carbon skeleton.



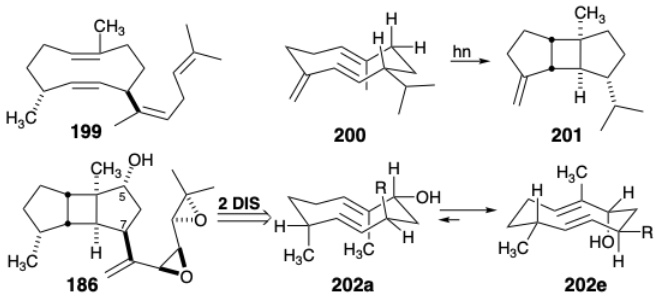
Topological Analysis of Spatol

Ex post facto topological retrosynthetic analysis of the biosynthetic strategy reveals an important feature. The tricyclo[5.3.0.$0^{2,6}$]decane nucleus of the spatane diterpenes incorporates 4 common atoms (circled in **196**), the four atoms of the B-ring. The biosynthetic strategy benefits from the powerful topological simplification that accrues from removing bonds between two sets of common atoms, 4-8 and 9-10. This suggests a monocyclic topological synthon **197**. For this synthon, one synthetic equivalent, **198**, is suggested by our biogenetic hypothesis.



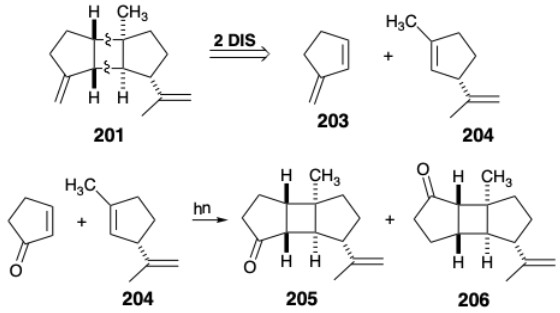
Another synthetic equivalent, **199**, is suggested by the possibility of an intramolecular 2π + 2π cycloaddition. An expeditious synthesis[15a] of the sesquiterpene b-bourbonene (**2 0 1**) exploits intramolecular photocycloaddition of germacrene D (**200**) an intermediate analogous to **199**. UV evidence (λ_{max} = 259 mm, ε = 4500 in n-hexane) indicates a significant transannular interaction between the two endocyclic C=C bonds in the sesquiterpene **200**. Thus, **200** probably prefers a conformation in which the two endocyclic C=C bonds are situated parallel and face to face with each other, and the isopropyl substituent occupies the less sterically hindered equatorial configuration. Thermodynamic control of the conformation of **200** assures the proper configuration at the isopropyl bearing carbon while stereoelectronic control (syn periplanar = suprafacial addition) assures the correct *cis,anti,cis*

configurations at the cyclobutane stereocenters. An analogous photocyclization to generate a precursor **202** for spatol is not favorable since a substituent R which is to become the side chain must occupy a more sterically encumbered axial position as in **202a** rather than the more thermodynamicaly favorable conformation **202e**.

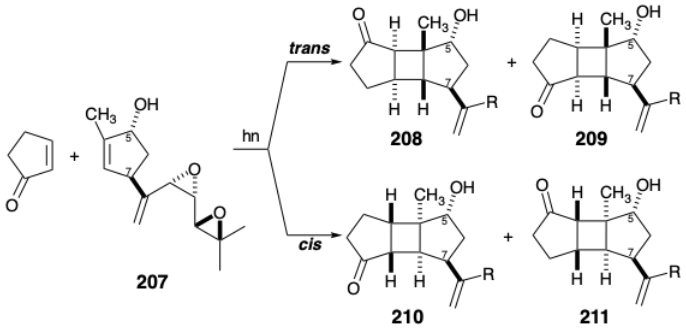


A Topological and Stereochemical Strategy

A different topological disection of the *cis-anti-cis*-tricyclo[5.3.0.0^{2,6}]decane nucleus of β-bourbonene (**201**) has also been exploited for its synthesis. Thus, removing two bonds between pairs of common atoms can generate two cyclopentene precursors, **203** and **204**, that could be united by a 2πs + 2πs photocycloaddition (see section 3.3). In fact, UV irradiation of 2-cyclopenten-1-one with **204** results in a photocycloaddition that is orientationally nonselective, producing a 1:1 mixture of structural isomers **205** and **206**.[15b] However, the cycloaddition is favorably stereoselective owing to a steric approach controlled preference for cycloadddition to the face of the cyclopentene ring opposite the isopropyl substituent. This stereoselectivity detracts from the utility of a similar synthesis for spatol because the allylic diepoxide side chain in spatol (**196**) is *cis* to the cyclobutane rather than *trans* as is the isopropyl group in **201** or **205**.

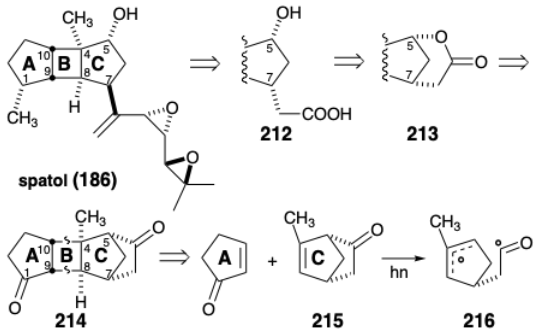


Thus, the allylic diepoxide side chain or its precursor in a cyclopentene intermediate **207** can be expected to favor the wrong stereoselectivity in a photocycloaddition with 2-cyclopenten-1-one, i.e., favoring **208** or **209** rather than the desired adduct **210** or its structural isomer **211**.

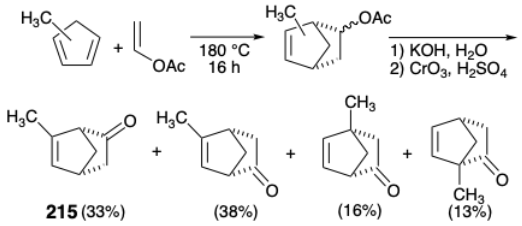


One strategy to surmount this shortcoming of cyclopentene photocycloadditions for the total synthesis of spatol uses a temporary bridge to shield one face of a cyclopentene ring to preclude addition to that face.[16] Thus, such a bridge can be provided by linking the hydroxyl group at the 5-position with a carboxymethyl group that also serves as a progenitor of the sidechain at position 7 as in lactone **213**. Furthermore, the lactone can be derived from a latent precursor, ketone **214**, by a Baeyer-Villiger oxidation. Double disconnection of **214** by a cycloelimination suggests photocycloaddition of a norbornenone **215** with cyclopent-2-en-1-one. Thus,

in **214** a temporary oxoethano bridge shields the α-face of the incipient C-ring enforcing stereoselective cycloaddition of the A-ring precursor cyclopent-2-en-1-one *trans* to the incipient 5-hydroxyl group.

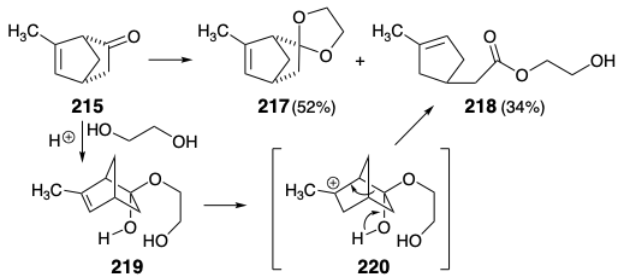


This strategy has one obvious flaw. The strained bicyclic homoallylic ketone **215** was expected to readily undergo photoinduced cleavage to diradical **216**. However, masking of the carbonyl in **215** would circumvent this problem and facilitate differentiation between the two carbonyl groups in the photocycloadduct **214**. Also, the configuration at the 7-position in **212** would have to be inverted to provide the requisite configuration at this stereocenter in spatol. A synthesis of 6-methylbicyclo[2.2.1]hept-5-ene-2-one (**215**) from vinyl acetate and methyl-1,5-cyclopentadiene is possible through a Diels-Alder reaction of these starting materials. Although the reaction produces a mixture of structural isomers, saponification followed by oxidation gives a mixture of isomeric ketones from which **215** can be isolated by distillation.



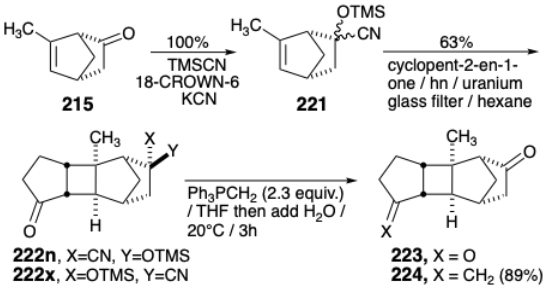
Masking a Sensitive Ketone

Masking of the carbonyl group in **215** proved unexpectedly difficult. Only a moderate yield of the ethylene ketal **217** was available by acid-catalyzed ketalization of **215** under conditions which give an excellent yield of ketal from the 6-unsubstituted analogue, bicyclo-[2.2.1]hept-5-en-2-one, owing to a competing fragmentation to **218**. The proclivity of **215** toward this fragmentation undoubtedly arises from the relative stability of the tertiary carbocation **220** and the relief of ring strain attending conversion of **219** to **220**.



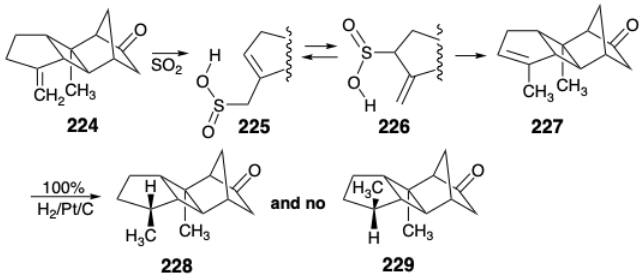
An unusual choice for the masking group was developed during a search for a group that could be introduced under nonacidic conditions. Thus, ketone **215** is converted quantitatively into an epimeric mixture of cyanohydrin silyl ethers **221** by reaction with trimethylsilyl cyanide. While the use of an unsymmetrical masking group might seem unwise since this leads to epimeric mixtures of several intermediates, this is a small price to pay for the otherwise ideal characteristics of the cyanohydrin silyl ether masking group. Thus, photocycloaddition with cyclopent-2-en-1-one delivered two epimeric adducts **222x** and **222n** with high stereo (cis,anti,cis ring fusions and exo addition to the bicyclohept[2.1.1]ene) and orientational (cyclopentane carbonyl remote from the bridgehead methyl group) selectivity. Serendipitously, the major adduct **222x** crystallized from the photoreaction mixture together with the dimer of cyclopentenone from which it was readily separated by trituration with hot hexane leaving behind pure dimer. Pure **222x** was then obtained in 51% yield, based on **2 2 1** , by elution of the partially purified product through a column of silica

gel with ethyl acetate- hexane. Column chromatography of the hexane soluble photoproduct afforded a fraction from which nearly pure minor cycloadduct **222n** crystallized together with a little **222x**. This mixture is suitable for Wittig olefination to produce methylidene ketone **224**, *vide infra*. The combined isolated yield of **222x** plus **222n** exceeds 60%. A sample of pure **222n** was obtained by HPLC. The epimeric relationship between **222x** and **222n** was demonstrated by production of the same diketone **223** upon hydrolysis of the cyanohydrin silyl ether masking group and also by production of the same methylidene ketone **224** upon reaction with methylenetriphenylphosphorane followed by hydrolysis of the cyanohydrin silyl ether. The conversion of **222** into **224** was performed as a one-pot procedure affording pure **224** in 89% overall yield. The utility of the cyanohydrin silyl ether masking group in the above transformations is noteworthy. It is introduced under mild neutral reaction conditions. It is sufficiently robust to survive UV irradiation, chromatography on silica gel, and Wittig olefination; but it is readily converted to a carbonyl group by the aqueous base generated upon addition of water to the Wittig reaction mixture.



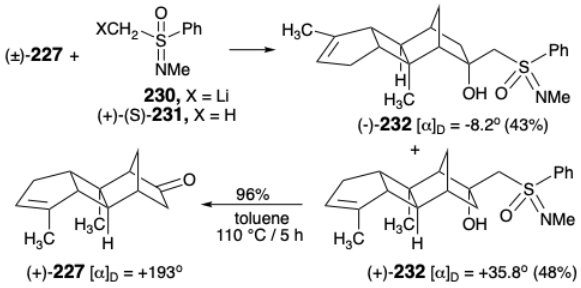
Amplifying SAC

Catalytic hydrogenation of **224** favored the required epimer **228** over the useless byproduct **229** by 10:1 owing to steric approach control by the methyl group in **224** that shields the α-face of the A-ring. However, separation of **228** from the mixture could not be achieved by any method except fractional crystallization, and this only allowed isolation of the desired epimer in only fair yield. To circumvent this separation problem, **224** was isomerized to the endocyclic alkene **227** by SO_2. This clean, quantitative isomerization presumably involves ene addition of SO_2 to **224** producing **225**. Subsequent [1.3] sigmatropic rearrangement of sulfur affords **226** that undergoes retro ene fragmentation delivering **227**. Catalytic hydrogenation of **227** delivers **228** cleanly and quantitatively. Apparently the closer proximity of the endocyclic C=C bond to the methyl group in **227** than the exocyclic C=C to the methyl group in **224** results in greater steric hindrance to α hydrogen delivery in **227** than in **224**.



Resolution

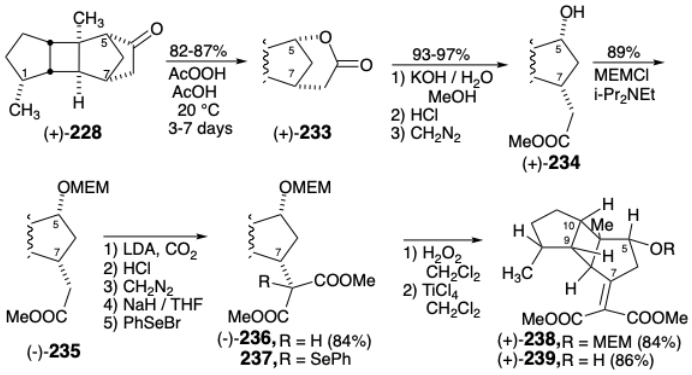
Efficient, virtually quantitative resolution of ketone **227** was readily achieved by flash chromatography and crystallization of the 1,2-adduct with chiral lithiosulfoximine **230**. Retro ene elimination of the less soluble dextrorotatory diastereomer (+)-**232** delivered ketone (+)-**227** that was correlated with (+)-spatol by conversion to a degradation product from natural spatol (*vide infra*). The sulfoximine (+)-(S)-**231** was recovered in 96% yield.



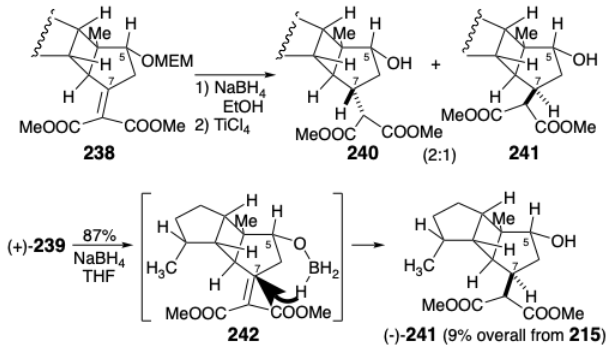
A Temporary Bridge During Hydride Delivery

Catalytic hydrogenation of (+)-**227** provided ketone (+)-**228**. Introduction of oxygen at position 5, cleavage of the temporary bridge, and inversion of configuration at the 7-position were then addressed. Thus, Baeyer-Villiger oxidation to give lactone

(+)-**233**, saponification, and methylation of the resulting acid provided alcohol (+)-**234**. Masking of the 5-hydroxyl provided (-)-**235** that was carboxylated to give malonic ester (-)-**236**. Epimerization at the 7-position was initiated by selenenylation followed by oxidative deselenenylation of the resulting **237** to deliver alkylidene malonic ester **238**. Reduction of **238** with $NaBH_4$ followed by removal of the MEM protecting group with $TiCl_4$ afforded a 2:1 mixture respectively of the *cis* hydroxy malonic ester **240** and its C-7 epimer, the desired *trans* hydroxy malonic ester **241**. This disappointing result suggested that the 2-methoxyethoxymethoxy (OMEM) substituent at the 5-position sterically hinders hydride delivery to the α- face of the C=C bond in **238**.

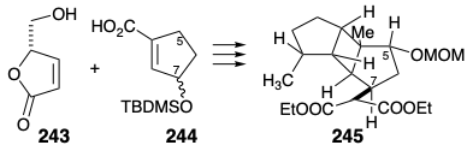


A remote hydroxyl group was found to foster pseudointramolecular *syn* hydride delivery via an alkoxyborohydride intermediate **242**. Thus, treatment of the derived hydroxy alkylidene malonate (+)-**239** with $NaBH_4$ delivered the desired *trans* hydroxy malonic ester (-)-**241** completely stereoselectively. The overall yield was 9% from C-ring precursor **215** in 21 steps including the resolution.

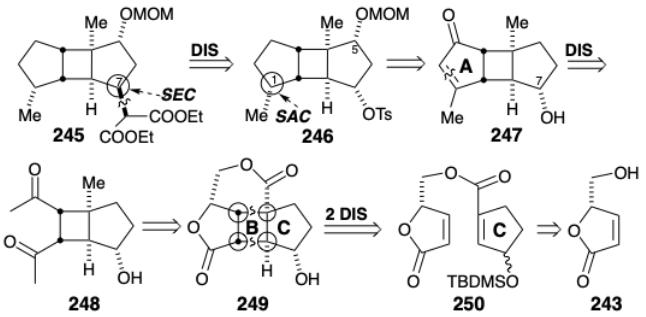


Enantiospecific Synthesis with a Chiral Auxillary

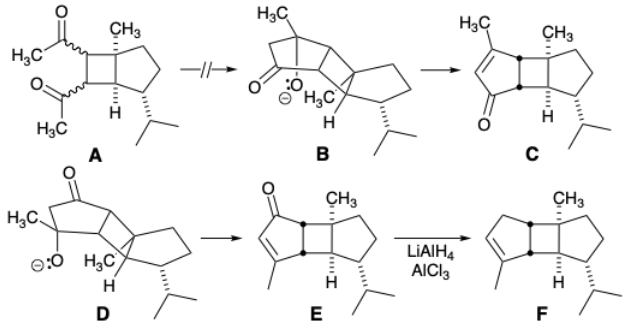
A different synthesis[18] of a homochiral tricyclodecylmalonic ester intermediate **245** (an analogue of **241**) was designed with a focus on exploiting butenolide **243** as a chiral auxiliary to establish the correct absolute configuration during generation of the B-ring by a 2π + 2π photocycloaddition with A-ring precursor **244**. Homochiral butenolide **243** is readily available from L-glutamic acid. An allylic oxygen substituent in **244** provides a point of attachment for the malonic ester side chain and activation for the introducing oxygen at the 5-position.



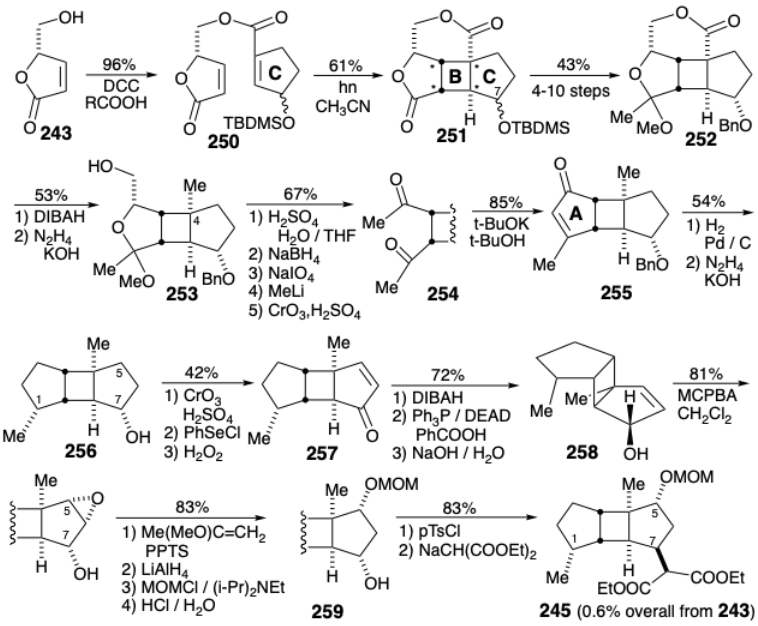
In a retrosynthetic format, the strategy envisions attachment of the malonic ester last by a stereospecific S_N2 alkylation with **246**. Since the chiral auxiliary **243** does not provide the cyclopentane ring required for the A-ring of **245**, this ring will have to be generated after the photocycloaddition of **250**.



The A-ring might be created by an intramolecular aldol condensation of a bis methylketone precursor **248**. This step is potentially flawed because an undesireable alternative aldol condensation is possible. However, an excellent precedent is provided by a similar step in a total synthesis of the sesquiterpene α- bourbonene (**F**). Thus, intramolecular aldol condensation of **A** delivers cyclopentenone **E** and none of the isomeric cyclopentenone **C**. Apparently, cyclization to the aldol condensation product **B** is disfavored by steric hinderance by the angular methyl substituent in the alternative aldol condensation product **D**. Steric approach control (*SAC*) should favor β-delivery of hydrogen during reduction of **247** to give the requisite configuration at position 1 in **246**. The proper orientation during generation of the B-ring can be assured by a temporary bridge, an ester, between **243** and the C-ring precursor **244**.



Intramolecular photocycloaddition of the ester **250** from the chiral auxiliary **243** delivered cyclobutane **251**. Addition of a methyl group, the one carbon needed to complete the A-ring required 4-10 steps depending on the configuration of the C-7 substituent in **251**. Reduction of the remaining ester in **252** then provided the methyl group at position 4 in **253** which had been functionalized solely to allow construction of the temporary bridge in **250**. Functional group manipulation then provided dione **254** which underwent completely selective aldol condensation affording **255**. Stereoselective hydrogenation of **255** created the stereocenter at position 1 and removed the benzyl protecting group. Wolff-Kishner reduction of the resulting saturated ketone delivered **256**. Introduction of the 5-hydroxyl and 7-malonic ester substituents then required oxidation to **257**, reduction and Mitsunobu inversion to give **258**, stereoselective epoxidation followed by hydride reduction, protection, and deprotection to deliver **259** and nucleophilic substitution which provided malonic ester **245** in *0.6% yield overall from **243** in 29-35 steps*.

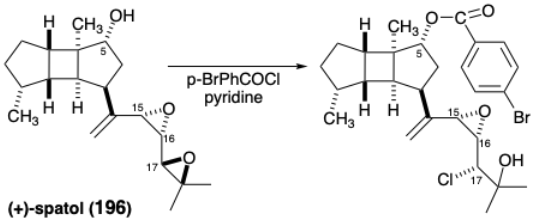


Convergent and Linear Strategies

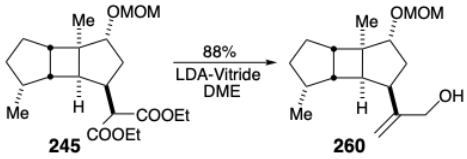
The overall yield of homochiral malonic ester (-)-**241** from racemic (±)-**215** in the first synthesis was 9%, more than an order of magnitude higher than the 0.6% overall yield of homochiral malonic ester **245** from homochiral **243** in the second synthesis. The success of the first synthesis, that relies upon resolution to introduce asymmetry, is especially noteworthy because resolution is inherently inefficient -- it provides at best as 50% yield of the correct enantiomer. Two factors diminish the penalty for using resolution. First, the resolution is performed very early in the first synthesis and, therefore, the effort wasted by discarding half of the racemic product is minimized. Second, Johnson's sulfoximine method is spectacularly effective. Furthermore, the advantages of the clever plan to exploit the readily available chiral auxiliary **243** to introduce asymmetry into the second synthesis cannot overcome the penalty arising from the absence of a methyl group at position 4 or a hydroxyl group at position 5, and the lack of an A-ring in the photocycloadduct **251** from **243**. The first synthesis is more **convergent** than the second. Thus, two large fragments are constructed that contain most or all of the skeletal atoms and functionality of the target and these fragments are then united. Such an approach has several advantages over a **linear** synthesis, that is one in which the molecule is constructed by sequentially uniting many small fragments or introducing functionality after skeletal construction is complete. A convergent synthesis is more efficient as measured by overall yield. If the average yield of an n-step synthesis is Ψ%, then the overall yield will be $100(\Psi/100)^n$%. A 21-step ***linear synthesis*** with an average 95% yield will have an overall 34% yield, or an overall 11% with an average 90% yield, or *an overall 0.9% with an average 80% yield*. In contrast for a ***convergent synthesis*** that combines two intermediates each prepared by 10-step syntheses (i.e. a total of 21 steps), the overall yield will be 56% with an average 95% yield, or an overall 31% with an average 90% yield, or *an overall 9% with an average 80% yield*. In effect the convergent synthesis is only 11 steps. The two abovementioned syntheses are a case in point. The average yield per step, 84-87%, in the second synthesis was almost as high as the 89% average per step yield in the first synthesis. The 15 fold lower overall yield for the second synthesis is almost entirely the consequence of its greater length, 29-35 steps versus 21 steps.

Stereocontrolled Sidechain Construction

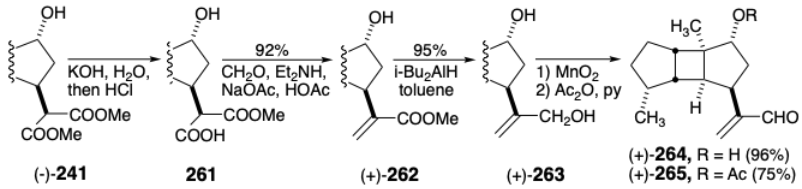
Two strategic challenges must be met for completion of a total synthesis of spatol (**196**). First, the unique allylic vicinal diepoxide in **196** was presumed to be highly electrophilic because epoxide ring opening by chloride, a weak nucleophile, accompanies esterification upon treatment of **196** with p-bromobenzoyl chloride and pyridine. Second, the three stereocenters of the flexible sidechain must be assembled with the correct configurations relative to those in the rigid tricyclic nucleus.



The malonic ester group in the intermediates (-)-**241** and **245** could provide a three-carbon allylic precursor of the spatol side chain. Koga converted **245** into allylic alcohol **260** by a modified Marshall reduction.

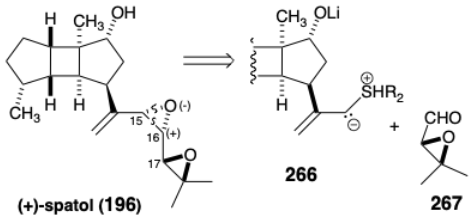


However, attempted one-step conversion of (-)-**241** into the allylic alcohol **263** by the Marshall reduction, i.e. LAH reduction of the sodium enolate, failed completely. Therefore, this transformation was accomplished by monosaponification to **261** and decarboxylative aldol condensation with formaldehyde to provide acrylic ester (+)-**262**. Hydride reduction then delivered allylic alcohol (+)-**263** that was selectively oxidized with MnO_2 to the aldehyde (+)-**264**. To correlate this synthetic intermediate with the natural product, (+)-**264** was acetylated. The totally synthetic acetate showed $[\alpha]_D^{22}$ +25.1° that compares well with the naturally derived acetate which showed $[\alpha]_D^{22}$ +26.5°.[1]

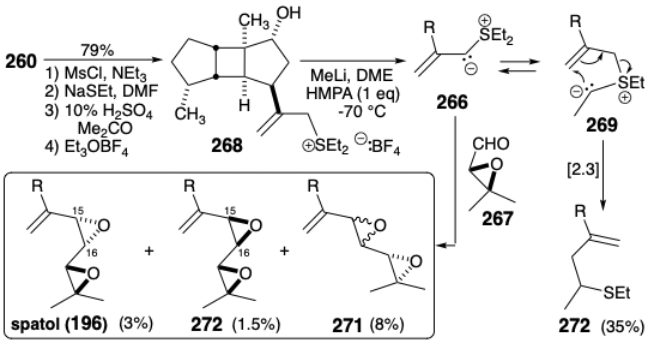


An Absolute Asymmetric Strategy

Disconnection of both a nucleophilic oxygen and an electrophilic carbon from carbon 15 of spatol suggests a precursor **266** in which the sulfonium functional group provides the requisite biphilic reactivity at carbon 15.[19] The correct relative configurations for the stereocenters in the tricyclic nucleus and at position 17 are assured in an **absolute asymmetric synthesis** by using building blocks **266** and **267** with the correct absolute configurations. Although very short, this convergent strategy provides no control over the configurations at positions 15 and 16.

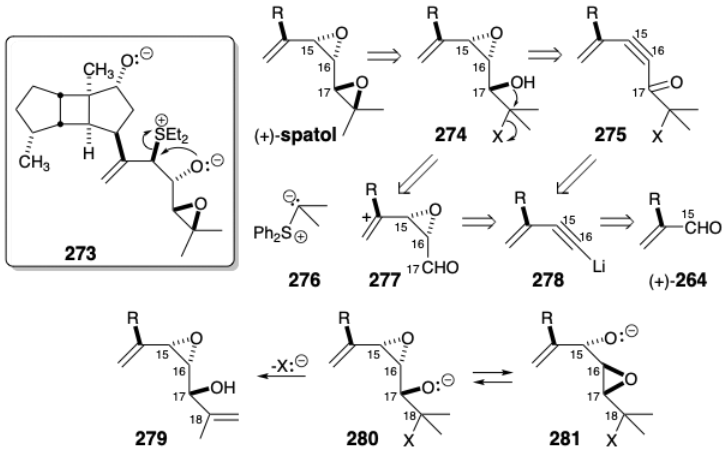


Ylide **266** was prepared from allyic alcohol **260** through sulfonium salt **268**. Reaction of ylide **266** with aldehyde **267** produced spatol in only 3% yield together with the isomeric allylic *cis* diepoxide **270** (1.5%) and a mixture of *trans* diepoxides **271** (8%). Moreover, **266** exists in equilibrium with an alternative ylide **269** that underwent [2.3] sigmatropic rearrangement producing the homoallylic sulfide **272** (35%) as the major product of the reaction.

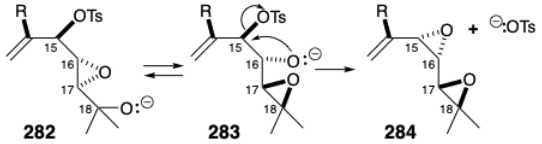


A Stereospecific Epoxydiol Rearrangement Strategy

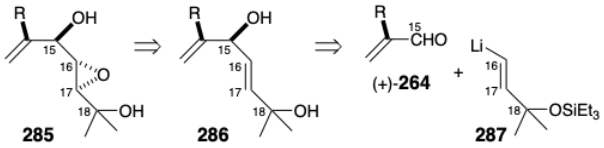
The last step in the reaction of ylide **266** with aldehyde **264** involves vicinal alkylation of an alkoxide during cyclization of **273**. The reaction of aldehyde **277** with ylide **276** is a related strategy. The epoxy aldehyde **277** might be available from aldehyde (+)-**264** by Corey-Fuchs alkynylation to give **278**, homologation with formaldehyde, Lindlar reduction of the resulting propargyl alcohol, asymmetric epoxidation of the derived allylic alcohol, and Swern oxidation of the resulting epoxy alcohol. Alternatively, **278** might be homologated to **275**. Then, after assymmetric reduction of this propargyl ketone, Lindlar reduction, and $VO(acac)_2$-catalyzed epoxidation, heterocyclization of the resulting **274** might deliver (+)-spatol. However, these strategies are too long, and ring closures of intermediates such as **274** may be derailed considering the potential, *inter alia*, for E-1 elimination and transepoxidation. Thus, intramolecular attack of the alkoxide in **280** at the 2° 16-position to give **281** rather that at the 3° 18-position to give spatol might even be favored. Such transepoxidation reactions (Payne rearrangements) are well known. However, the rearrangement to **281** is reversible while heterocyclization of **280** would be irreversible. Nevertheless, E1 elimination to give **279** seemed a reasonable concern.



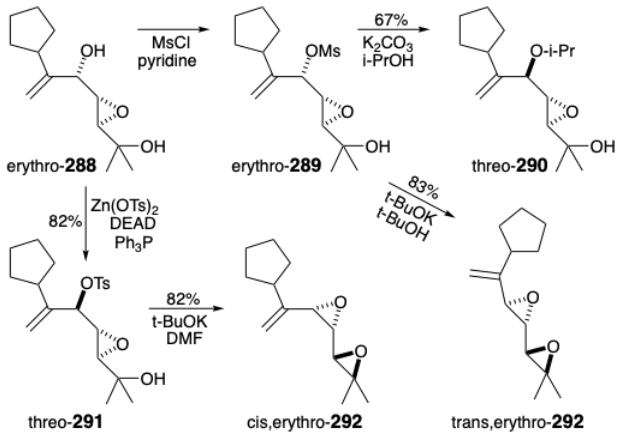
An alternative strategy is possible involving an epoxy alkoxide similar to **281** but with the positions of the nucleofuge and alkoxide exchanged. Thus, Payne rearrangement should produce **283** but the *trans* stereochemistry of the epoxide in **282** should virtually preclude direct attack of the alkoxide at the 15-position to produce a tetrahydrofuran. The allylic electrophile at position 15 in **283** should be particularly effective in alkylating the neighboring alkoxide producing an allylic diepoxide **284**.



Furthermore, an efficient strategy for assembling an epoxydiol precursor **285** for **282** seemed feasible. Thus, **285** should be available by regioselective epoxidation of **286** which should, in turn, could be prepared by the union of a C_{15} electrophile (+)-**264** with a C_5 nucleophile **287**.

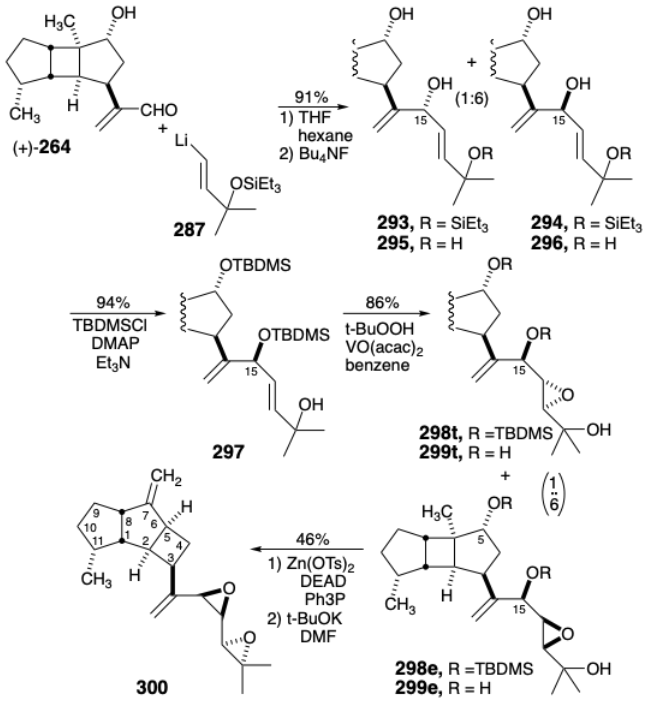


In model studies, a method was sought to produce the allylic diepoxide array of the spatol side chain from appropriately activated derivatives of epoxydiol **285**. Initial results were disappointing. Thus, activation of erythro-**288** as a mesylate, erythro-**289**, followed by treatment with solid K_2CO_3 in boiling isopropanol delivered threo-**290** by intermolecular S_N2 displacement rather than the desired vicinal diepoxide by Payne rearrangement followed by heterocyclization. Since the tertiary hydroxyl group in erythro-**289** appeared not to be sufficiently nucleophilic to displace the epoxy leaving group, conditions were sought that would generate an alkoxide from the tertiary hydroxyl. Treatment with t-BuOK in t-BuOH promoted a clean, stereospecific rearrangement and heterocyclization to deliver the diepoxide trans,erythro-**292**. A route from the erythro-**288** to an activated derivative of the *threo* epoxy alcohol requires activation with concomitant inversion of configuration. This was accomplished by the Still modification of the Mitsunobu reaction. Thus, reatment of erythro-**288** with $Zn(OTs)_2$, diethyl azodicarboxylate, and triphenylphosphine, gave tosylate threo-**291** that, upon treatment with t-BuOK in DMF, afforded the allylic diepoxide cis,erythro-**292** in 82% yield.

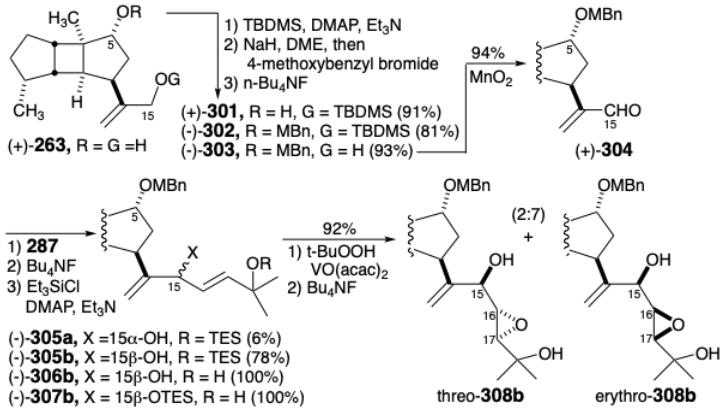


The substitution reaction of mesylate erythro-**289** with isopropanol to give threo-**290** suggested that a similar substitution with tetrabutylammonium hydroxide might provide a route to the inverted alcohol. Instead, however, a high yield of diepoxide trans,erythro-**292** was obtained. The unexpected stability of this allylic diepoxide toward hydroxide is especially interesting in view of the epoxide-cleaving substitution reaction of spatol with the less nucleophilic chloride anion that gives a chlorohydrin (*vide supra*). Apparently, the latter reaction is an *acid-catalyzed epoxide opening induced by pyridinium hydrochloride*, a byproduct of the acylation with p-bromobenzoyl chloride in the presence of pyridine.

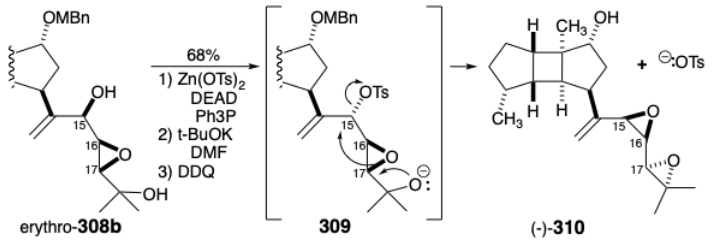
In a first attempt to implement the plan, addition of vinyllithium **287** to aldehyde (+)-**264** provided a 1:6 mixture of triols **295** and **296** respectively after desilylation of the intermediate monosilyl ethers **293** and **294**. To control the regioselectivity of epoxidation, the triol **296** was selectively disilylated. Vanadium-catalyzed epoxidation of **297** was then directed to the 15,16-C=C bond by the remaining allylic hydroxyl. Since the major epoxide product was the erythro derivative **298e**, selective activation of the less hindered 15-hydroxyl in the corresponding triol **298e** was performed with inversion of configuration. However, treatment with base produced an allylic diepoxide **300** with a *cis,anti,cis*- tricyclo[5.3,0,$0^{2,5}$]decane nucleus. Thus, Wagner-Meerwein rearrangement of the *cis,anti,cis*-tricyclo[5,3,0,$0^{2,6}$]decane nucleus of **298e** to give **300**, apparently owing to an unintended activation of the 5-hydroxyl that accompanied the desired activation of the hydroxyl at the 15-position.



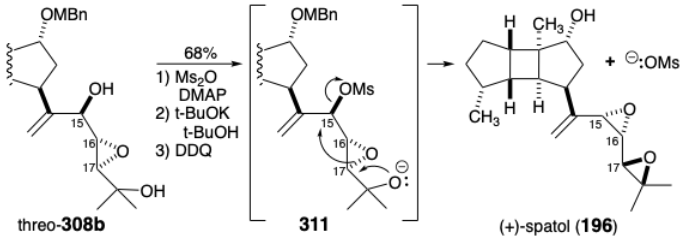
These results suggested that derivatives of epoxy triols **299e** and **299t** in which the hydroxyl at position 5 is masked were needed for generation of the spatol side chain without accompanying rearrangement of the tricyclic nucleus. The lability of the allylic diepoxide array in spatol (**196**) under acidic conditions limited the choice of derivatives to those with masking groups that would be removable under neutral or basic reaction conditions. The further requirement for stability towards a vinyllithium reactant and the presence of unsaturation in the synthetic target recommended p-methoxybenzyl (MBn) ether derivatives. The MBn masking group is removable under mild conditions by oxidative cleavage with DDQ. Therefore, the MBn derivatives *erythro*-**308b** and *threo*-**308b** of **298e** and **298t** were prepared from diol (+)-**263**.



The assignment of an S absolute configuration at the 15-position to the major epimer (-)-**305b** was based on correlation with natural (+)-spatol (*vide infra*). Epoxidation of the derived silyl ether (-)-**307** provided a 2:7 mixture of threo and erythro epoxides **308b**. The major isomer, erythro-**308b**, was converted into a cis, erythro diepoxide (-)-**310** by conversion to a threo tosylate with inverted configuration at the 15-position followed by base-induced Payne rearrangement, heterocyclization, and finally by deprotection of the 5-hydroxyl. That (-)-**310** was not spatol (**196**) was evident from its optical activity, $[\alpha]_D$ = -10.0° in contrast with $[\alpha]_D$ = +45.6° reported for the natural product. Small chemical shift differences, e.g. vinyl ^{1}H NMR resonances at δ5.14 and 5.09, confirmed that (-)-**310** is epimeric at positions 15, 16, and 17 with (+)-spatol which exhibits vinyl resonances at δ5.13 and 5.02.

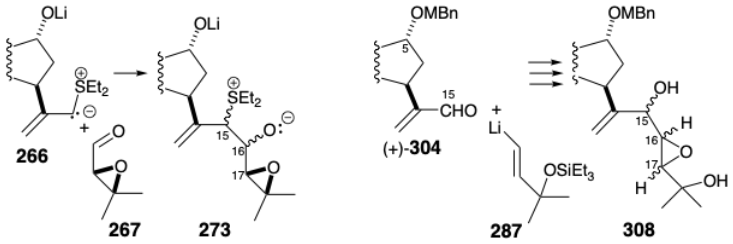


The minor isomer, threo-**308b**, was converted into (+)-spatol (**196**) by monomesylation followed by base-induced Payne rearrangement, heterocyclization, and deprotection of the 5-hydroxyl. Each resonance in the ^{1}H NMR spectrum of synthetic (+)-spatol coincided within 0.01 ppm with a spectrum of an authentic sample of natural spatol.

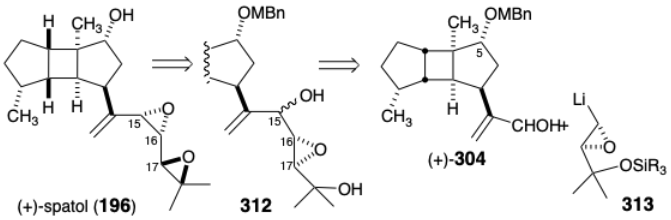


An Absolute Asymmetric Stereoconvergent Strategy

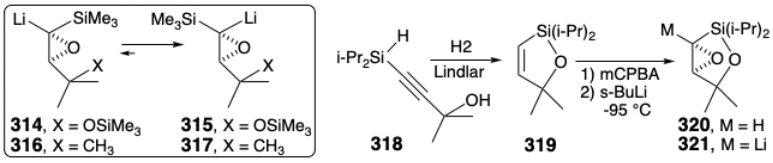
Both of the aforementioned strategies for the spatol allylic diepoxide suffer from inadequate stereocontrol. Thus, while the correct absolute configuration at position 17 in **273** is assured by using the correct enantiomer of **267**, generation of the stereocenters at positions 15 and 16 in **273** is not selective. Similarly, although either epimer at position 15 in **308** can provide an activated derivative with the correct configuration, i. e. by activation with retention or inversion of configuration, generation of the stereocenters at positions 16 and 17 in **308** is not favorably selective.



Since *either* epimer of epoxydiol **312** can be converted stereospecifically into spatol, the synthesis is **stereoconvergent**, and stereocontrol at the 15-position is unnecessary for an efficient total synthesis.. The correct stereochemistry at positions 16 and 17 could be assured by an **absolute asymmetric strategy** that combines the homochiral C_{15} aldehyde (+)-**304** and a homochiral C_5 α-epoxy nucleophile **313**.



Because α-silyl epoxides are readily hydrodesilylated by moist fluoride with complete retention of configuration, a possible synthetic equivalent of synthon **313** is the silyl-stabilized α-lithioepoxide **314**. However, a serious flaw could sabotage this strategy. Thus, although α-lithioepoxides are generally configurationally stable, the α-lithioepoxide **316**, a close analogue of **314**, exhibits an unusual configurational instability rearranging completely to **317** owing, no doubt to steric strain that is relieved upon trans-cis isomerization. A similar isomerization of **314** to **315** would derail the synthesis. This pitfall was circumvented by a temporary bridge between the C-silyl substituent and neighboring oxygen in **321**. Thus, intramolecular O-silylation precludes isomerization of the carbanion **321** obtained by metallation of **320**. Racemic **321** was prepared through epoxidation of a vinylsilane **319** that was generated by a novel hydrogenation-dehydrogenative-heterocyclization of **318**.



In a model study, reaction of α-lithioepoxide **321** with 2-(i-propyl)acrolein delivered an epimeric mixture of adducts **322** favoring the erythro diastereomer by 7:3. Desilylation of erythro-**322** gave epoxydiol erythro-**323**. Thus, the racemic intermediate **321** provides a two-step synthesis of epoxydiol precursors of the spatol allylic diepoxide. However, only conjunction of aldehyde (+)-**304** with the correct enantiomer of **321** will provide the correct absolute configurations at positions 16 and 17 in **312** that are required to accomplish an efficient construction of natural spatol (**196**). A route to optically pure epoxide **321** must yet be found.