Indole-Diterpene Synthetic Studies: Total Synthesis of (−)-21-Isopentenylpaxilline

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Dedicated to Professor *Duilio Arigoni*, on the occasion of his 75th birthday, with admiration and respect, for his many seminal contributions to chemistry and biosynthesis.

An efficient, stereocontrolled total synthesis of the complex indole-diterpene alkaloid (−)-21-isopentenylpaxilline (**1**) has been achieved. Key elements of the synthesis include the stereocontrolled construction of the advanced eastern hemisphere (−)-**68**, involving a highly efficient union of the eastern and western fragments (−)-**68** and **5** exploiting our 2-substituted indole synthesis, application of the *Negishi* π cycloalkylation tactic as a new, potentially general protocol for the construction of ring C, and the fragmentation of a β,γ-epoxy ketone to introduce the tertiary OH group at C(13) in the indole diterpene skeleton.

Introduction. – The indole-diterpene alkaloids comprise a diverse group of architecturally complex, naturally occurring fungal metabolites, belonging to a class of environmental neurotoxins called tremorgens, which, upon ingestion by vertebrate animals, result in tremors, limb weakness, ataxia, convulsions, and eventual death. Fortunately, the symptoms are reversible if the animal is removed from the infected area [1]. Many tremorgens also display insecticidal and/or antifeedant activity at the levels produced by the fungi [2][3]. Evolutionary considerations indicate that fungi have evolved the capacity to produce these defensive compounds to protect the sclerotium bodies against fungivorous insects [2].

In addition to the similar biological profiles, members of this class share common structural features, including a core comprised of an indole arising from tryptophan and a diterpene framework derived from mevalonate-produced isoprene units (*Fig. 1*). The diterpene framework is often fused to the indole ring in the form of a *trans-anti-trans* 5,6,6-fused ring system, with the signature structural element being vicinal quaternary Me groups disposed *anti* with an adjacent tertiary OH group.

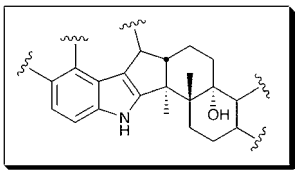


Fig. 1. *Common core structural unit of the indole-diterpene alkaloids*

Paspaline and paspalicine, structurally the simplest members of the indole-diterpene class, were first reported by the *Arigoni* group in 1966 [4–7]. Subsequently, *Arigoni* and co-workers, in elegant fashion, deduced the biosynthetic pathway, and then demonstrated that both paspalicine and paspalinine arise from paspaline [8]. Interestingly, paspaline and paspalicine, the parent congeners lacking the tertiary OH group, were neither tremorgenic nor toxic, suggesting that the tertiary OH group is critical for tremorgenic activity [9][10].

The indole tremorgens can be grouped into two rapidly growing subclasses; the structurally simpler congeners include paspaline [4][5], paspalicine [5], paxilline [11], dehydroxypaxilline [10], paspalinine [12–14], aflatrem [15], and paspalitrems A–C [1]; the architecturally more complex include the penitrems A–F [16], janthitrems E–G [17–20], and lolitrems B and C [21]. A considerable expansion of both subclasses occurred in the early 1990's, with the most recently discovered members being pennigritrem [22], the sulpinines A and B [23], secopenitrem B [23], sherinines A and B [2], terpendole C and M [24][25], paxinorol [26], nodulisporic acid A [27][28], pepenitremones A–C [29], and the thiersinines A and B [30]. The long-standing interest of our laboratory in the indole-diterpene alkaloids has led to the total syntheses of (−)-paspaline [31–33], (+)-paspalicine [34][35], (+)-paspalinine [34][35], and, most recently, (−)-penitrem D [36].

In 1995, a new congener, (−)-21-isopentenylpaxilline (**1**; *Fig. 2*), was reported by *Gloer* and *Belofsky*, along with seven other indole alkaloids isolated from the org. extracts of the sclerotioid ascostromata of *Eupenicillium shearii* (NRRL 3324) [2]. The molecular formula $C_{32}H_{41}NO_4$ was deduced from ^{13}C-NMR, DEPT, and LR-FAB-MS data. Careful analysis of the NMR data indicated that the new metabolite is quite similar in structure to the known tremorgens paxilline and paspalinine, differing only by an isopentenyl group. Key HMBC-NMR correlations permitted unambiguous placement of the isopentenyl unit on the aromatic ring at C(21). The absolute configuration of (−)-21-isopentenylpaxilline (**1**), however, was not established. Herein, we record a full account of the first total synthesis of (−)-21-isopentenylpaxilline (**1**), which both confirms the *Gloer* structure and permits assignment of the absolute configuration.

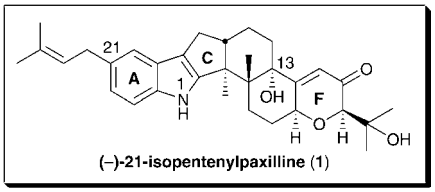


Fig. 2. *Structure of (−)-21-isopentenylpaxilline* (**1**)

Synthetic Analysis. – The core element of (−)-21-isopentenylpaxilline (**1**), the common diterpene *CDE* tricyclic skeleton, suggested that we employ our unified indole-diterpene strategy, which proved highly successful in our earlier syntheses. The cornerstone of this unified approach entails elaboration of the *Nolan–Sprengeler* lactone (−)-**2** to the requisite tricyclic skeleton (*Fig. 3*) [37].

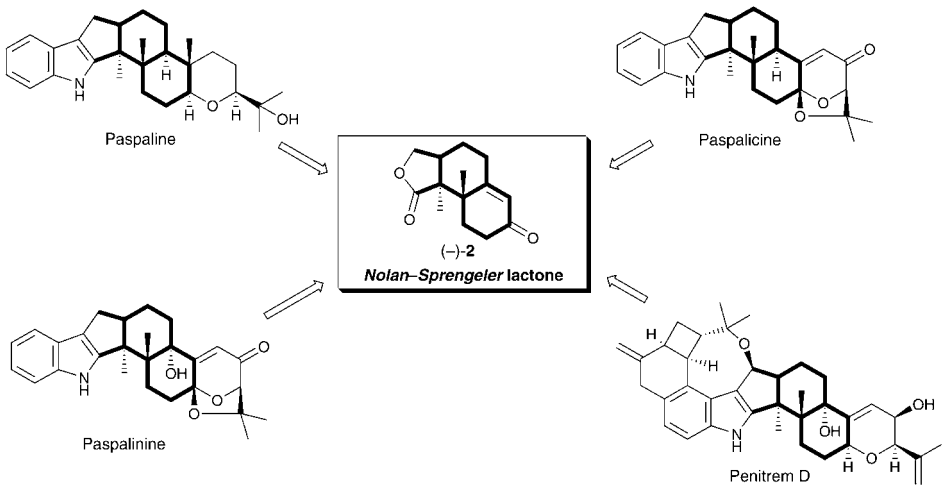
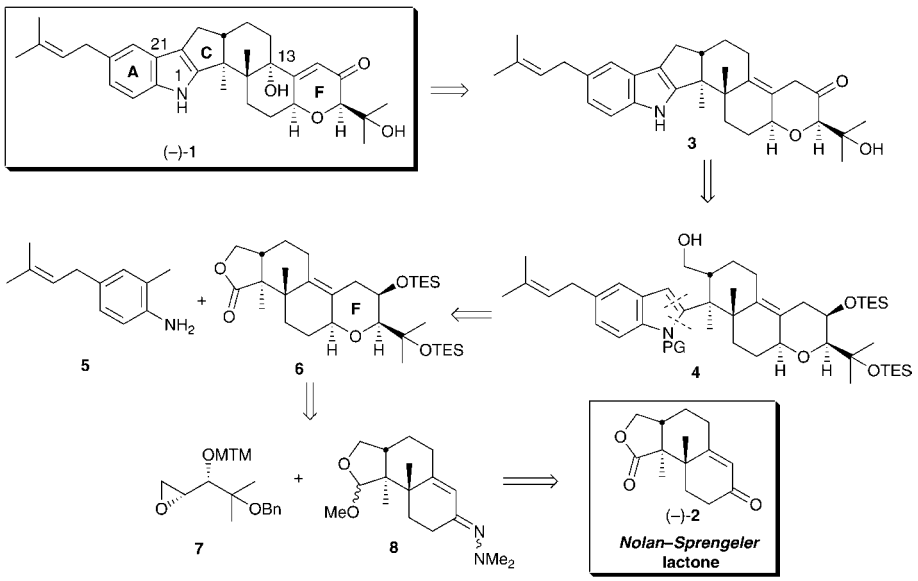


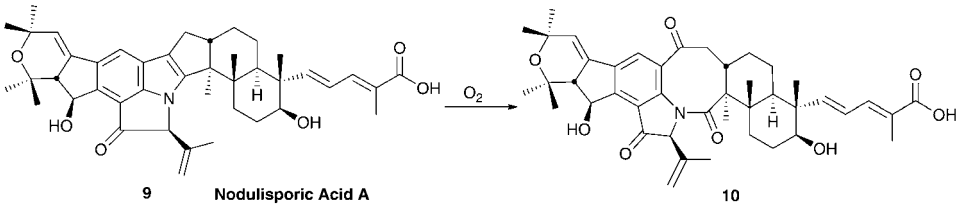
Fig. 3. Nolan–Sprengeler *lactone (–)*-**2**

To implement this plan (*Scheme 1*), we envisioned introduction of the tertiary OH group at C(13) *via* a late-stage autooxidation of α,β-unsaturated ketone **3**, which, in turn, would derive from the corresponding protected homoallylic alcohol. We were, of course, well aware of the known oxidative sensitivity of the indole nucleus. For example, paxilline and nodulisporic acid A (**9**), upon standing in air, undergo oxidative cleavage of the indole ring to furnish eight-membered-ring lactams (*Scheme 2*) [2][27].

Scheme 1



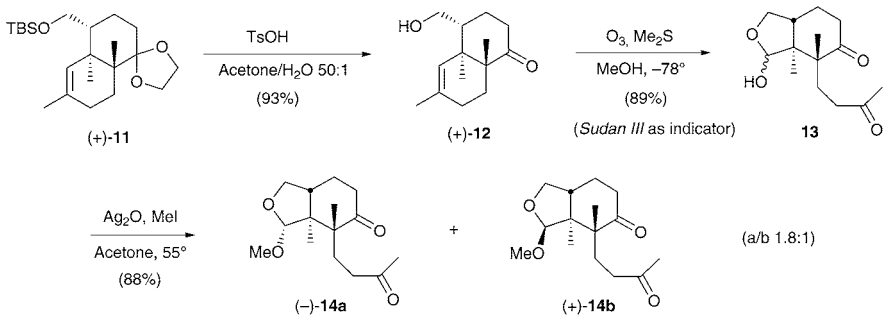
Scheme 2



Continuing with our analysis, disconnection of ring *C* would furnish hydroxy-indole **4**. To construct the latter, we planned to take advantage of our 2-substituted-indole synthetic protocol [38][39], employing the western hemisphere toluidine **5** and the highly functionalized eastern hemisphere lactone **6**. Disconnection of **6**, in turn, led to epoxide **7** and hydrazone **8**, readily available in four steps from *Nolan–Sprengeler* lactone (–)-**2**. In the forward direction, we would exploit the *Stork* metallo-enamine union of **7** and **8**, followed by a reductive cyclization, as employed in our indole synthesis [36] to access the *F*-ring tetrahydropyran in **6**. Thus, (–)-21-isopentenylpaxilline (**1**) would be constructed from three fragments: (–)-**2**, **5**, and **7**. Hydrazone **8**, derived from (–)-**2**, was selected as our initial target.

Hydrazone (+)-8 Optimization. – Experience gained during our campaign to construct (–)-penitrem D [36] demonstrated that the lactone C=O group in the *Nolan–Sprengeler* lactone (–)-**2** must be masked during the *Stork* metallo-enamine alkylation required to construct the tetrahydropyran ring. Although hydrazone (+)-**8** could be readily prepared in an efficient manner from (–)-**2** [36], a more-direct route not involving (–)-**2** appeared promising (*Scheme 3*). Toward this end, removal of the TBS group and hydrolysis of the acetal in (+)-**11**, an advanced intermediate on the way to (–)-**2**, was easily achieved to furnish keto alcohol (+)-**12**. Efficient ozonolysis of the olefin, however, initially proved elusive, affording over-oxidation products due to the difficulty in monitoring the reaction progress. Use of *Sudan III* as an indicator, which undergoes a sharp color change upon olefin cleavage (*e.g.*, red-orange to pale yellow) solved this problem [40], providing hemiacetal **13** in 89% yield on large scale. Efficient methylation of the resultant hemiacetal was then achieved in the presence of the ketone

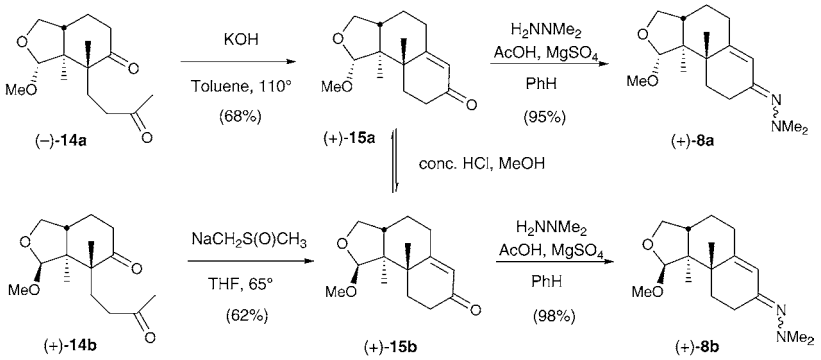
Scheme 3



by treatment with MeI and Ag_2O in acetone at reflux; a mixture (*ca.* 1.8:1) of the α- and β-methyl acetals (**14a** and **14b**, resp.) resulted in a combined yield of 88%.

Surprisingly, different conditions were required to achieve the *Robinson* aldol/dehydration sequence for the structurally similar acetals. Treatment of (−)-**14a** with KOH in toluene at reflux readily furnished the α-enone (+)-**15a** in 68% yield, while (+)-**14b** required treatment with sodium dimsylate in THF at reflux to afford the β-enone (+)-**15b** (62%). Both (+)-**15a** and (+)-**15b** were identical in all respects to intermediates prepared during our penitrem D synthesis [36]. Acetals (+)-**15a** and (+)-**15b** were then converted to the corresponding hydrazones (*Scheme 4*). The overall sequence was significantly enhanced (*ca.* 45%) compared to the previous route, requiring only five steps from (+)-**11**, *vs.* seven steps, which proceeded in 22% yield [36][37]. During this work, we also discovered the feasibility of acid equilibration of (+)-**15a** and (+)-**15b** (*ca.* 2:1), an observation that would prove important later in the synthesis (*vide infra*).

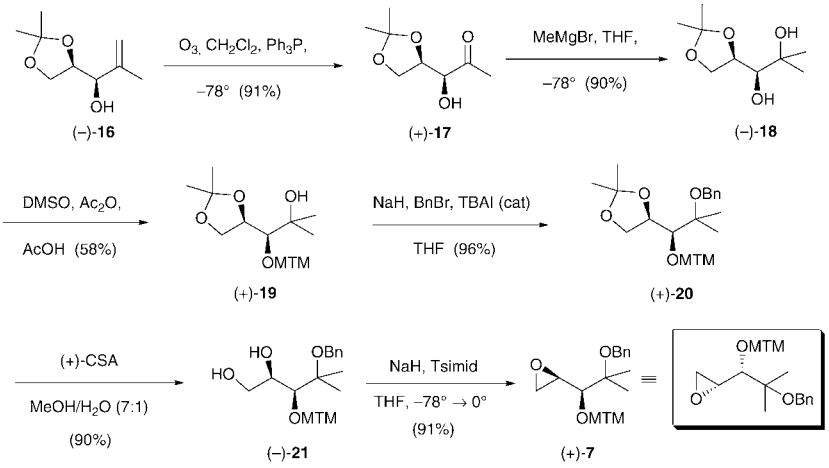
Scheme 4



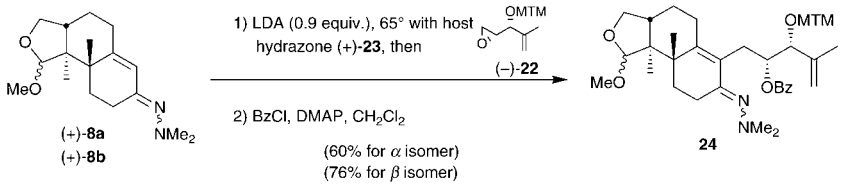
Construction of Epoxide (+)-7. – Synthesis of (+)-**7** began with known allylic alcohol (−)-**16** (*Scheme 5*) [41]; ozonolysis furnished methyl ketone (+)-**17** in 91% yield. Efforts to protect the secondary OH group as the MTM ether in (+)-**17**, however, proceeded in low yield. As an alternative, (+)-**17** was converted to diol (−)-**18** by treatment with MeMgBr; selective protection of the secondary OH group furnished (+)-**19** in 52% yield for the two steps. The tertiary alcohol was next converted to the benzyl ether to provide (+)-**20** (96%); hydrolysis of the acetal, followed by *Fraser-Reid* [42] epoxide construction (NaH, tosylimidazole (Tsimid), −78 to 0°), completed the preparation of (+)-**7** (91%).

Union of Hydrazones (+)-8a and (+)-8b with Epoxide (+)-7: A Difficult Transformation. – In our penitrem D synthesis [36], the *Stork* metallo-enamine union of hydrazones (+)-**8a** and (+)-**8b** with epoxide (−)-**22** proved quite successful (*Scheme 6*). We, thus, anticipated that union of the same hydrazone with epoxide (+)-**7** would be straightforward [43][44]. Surprisingly, the conditions employed in the penitrem D venture [36] furnished none of the coupled product. This result was

Scheme 5



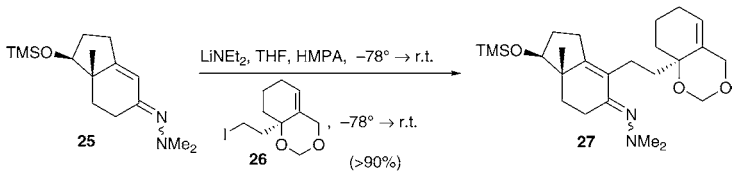
Scheme 6



remarkable, given only the minor modification of the epoxide structure. To develop viable conditions for this union, we turned to the literature.

In 1998, *Overman* and *Rucker* [45] reported that high concentrations of hydrazone **25** and electrophile **26** (*Scheme 7*), in conjunction with the use of hexamethylphosphoric triamide (HMPA), permitted efficient construction of **27** (> 90%). $LiNEt_2$ was the base of choice for deprotonation and metalloenamine equilibration. Unfortunately, these conditions did not improve the required alkylation of **8a** or **8b** with (+)-**7**, due presumably to our inability to effect equilibration of the kinetic anion of the 5,6,6-tricyclic hydrazone. An associated problem was also the difficulty in recovering the starting hydrazones.

Scheme 7



To conserve valuable material, we decided to screen a series of the coupling protocols with model hydrazone (+)-**23** [43][44]. In addition to epoxide (+)-**7**, we would also explore iodide (+)-**28** as an alternate electrophile; the latter was prepared in two steps from (+)-**7** (*Scheme 8*). Results from this study are summarized in *Table 1*. Unfortunately, under the best conditions, the yield of (+)-**30** was only modest.

Scheme 8

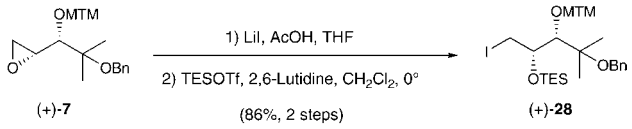
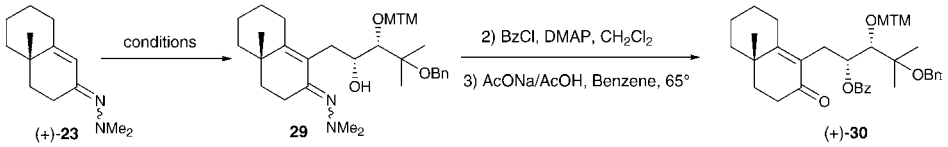


Table 1. *Optimization of Hydrazone (+)-***23** *Coupling.*



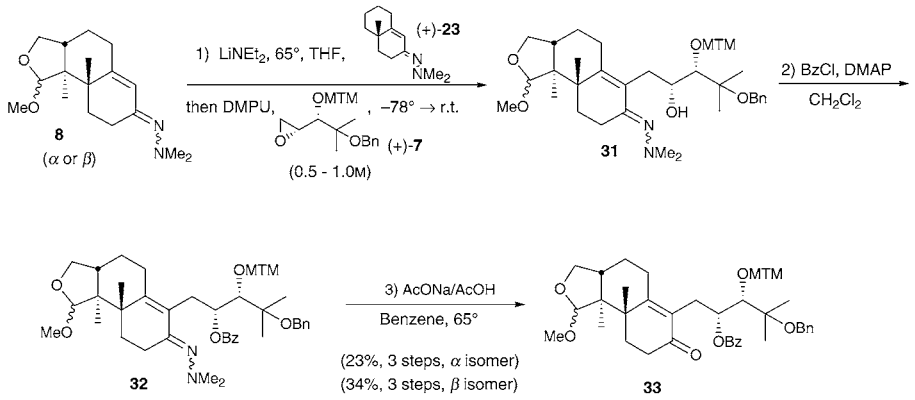
Entry	Base	*T* [°]	Cosolvent (10%)	Conc. [M]	Electrophile	Yield [%], (3 steps)
1	LDA	65	HMPA	0.1	(+)-**7**	< 5
2	$LiNEt_2$	r.t.	HMPA	0.1	(+)-**7**	0
3	$LiNEt_2$	65	HMPA	0.1	(+)-**7**	8
4	$LiNEt_2$	65	HMPA	1.0	(+)-**7**	36
5	$LiNEt_2$	65	HMPA	1.0	(+)-**28**	24
6	*$LiNEt_2$*	*65*	*DMPU*	*1.0*	*(+)-***7**	*34*[a])
7	$LiNEt_2$	65	None	1.0	(+)-**28**	< 5

[a]) Optimal conditions: $LiNEt_2$, THF, 1.0M of (+)-**23** at reflux overnight, *N*,*N*′-dimethylpropylenurea (DMPU; 10%), then epoxide (+)-**7**, −78° – r.t.

Notwithstanding the modest efficiencies observed in the model study, we explored the alkylation of hydrazones **8a** and **8b** individually with (+)-**7**, employing host hydrazone (+)-**23**, the latter to facilitate equilibration of the metallo-enolates, as required in the penitrem D synthesis (*Scheme 9*) [36]. Benzoylation of the desired alkylation products, followed by hydrolysis of the hydrazone, afforded (+)-**33a** and (+)-**33b**, respectively, in 23 and 34% yield for the three steps.

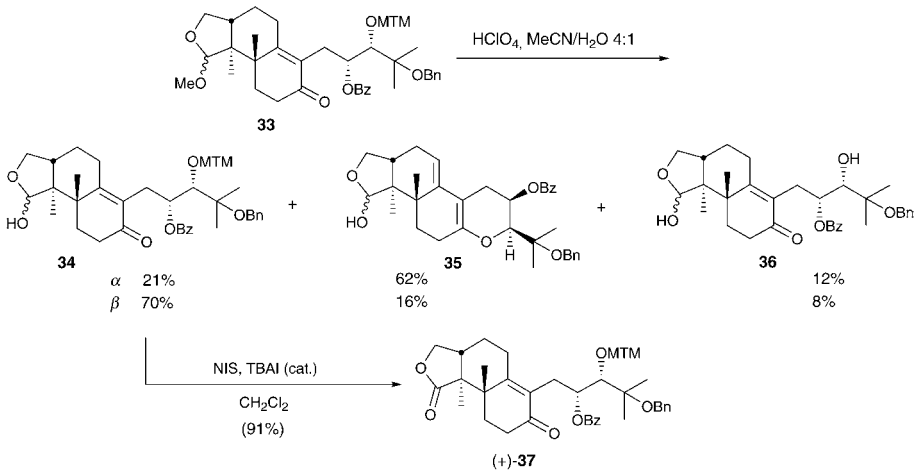
Construction of *cis*-Pyran (−)-39. – After accumulating sufficient **33a** and **33b**, we proceeded with the synthesis. The next task entailed installation of the lactone C=O group prior to *cis*-pyran formation. Hydrolysis of the β-acetal (+)-**33b** proceeded to give an epimeric mixture of lactols **34** (70%), in conjunction with minor amounts of **35** and **36**; however, these by-products could be recycled into (−)-**39**. On the other hand, hydrolysis of the α congener (+)-**33a** furnished predominately dienyl ether **35** (62%). Indeed, no more than 30% of the desired **34** could be obtained under a variety of conditions. Fortunately, this problem could be circumvented by isomerization of (+)-**15a** to (+)-**15b** as described earlier (*Scheme 4*), thereby significantly enhancing throughput of the α-isomer. Treatment of **34** with *N*-iodosuccinimide (NIS) and a

Scheme 9



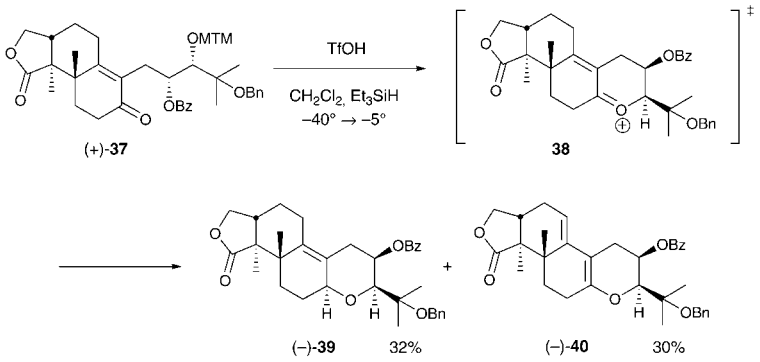
catalytic amount of tetrabutylammoniun iodide (TBAI) led to lactone (+)-**37** in 91% yield (*Scheme 10*) [46][47].

Scheme 10



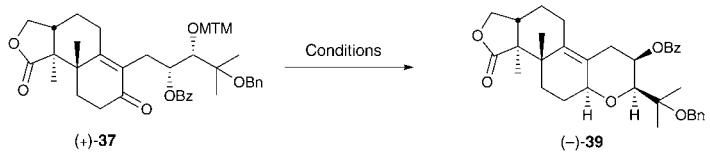
Generation of the tetrahydropyran *F* ring now called for a cascade of reactions, involving removal of the $MeSCH_2$ (MTM) group, cyclization to an intermediate hemiacetal and capture of the derived carbocation **38** with a silyl hydride. A similar tactic, initially developed by *Nicolaou* and co-workers for the construction of oxepanes [48], had been exploited with great success in our penitrem D venture [36]. Toward this end, treatment of (+)-**37** with TfOH in Et_3SiH, employing CH_2Cl_2 as solvent with careful temperature control ($-40° \rightarrow -5°$), provided the desired *cis*-pyran (−)-**39** initially in 32% yield, along with 30% of an intermediate identified as (−)-**40** (*Scheme 11*).

Scheme 11



Although (–)-**40** could be resubmitted to the same reaction conditions, this procedure both was tedious and resulted in low yields. To improve the yield of (–)-**39**, we screened a series of conditions (*Table 2*), identifying the problem to be the reduction step. Switching the silane from Et_3SiH to the less sterically demanding $EtMe_2SiH$ proved rewarding; lactone (–)-**39** was obtained in 81% yield.

Table 2. *Optimization of* cis-*Pyran (–)-***39** *Formation*

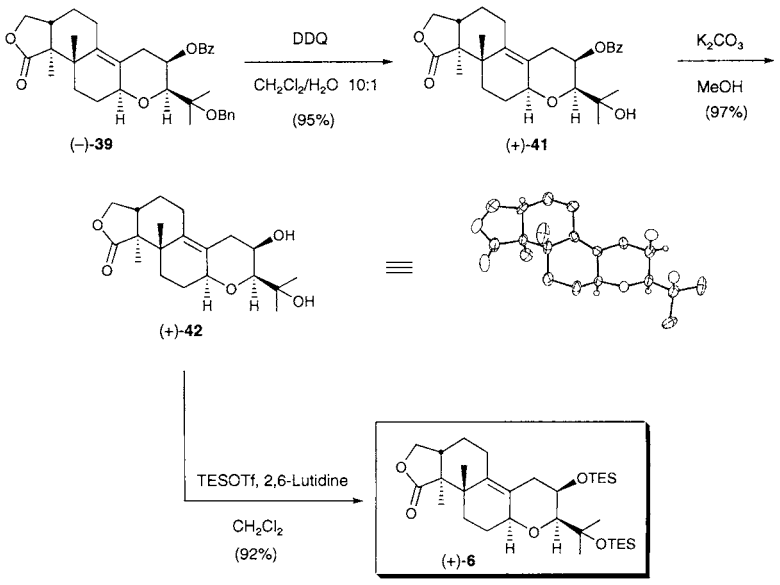


Entry	Acid	Solvent (1 : 1)	*T* [°]	Yield [%]
1	$HClO_4$	Toluene/Et_3SiH	– 78 → r.t.	No reaction
2	TfOH	Toluene/Et_3SiH	– 40 → 0	25
3	TfOH	CH_2Cl_2/Et_3SiH	– 40 → 0	22
4	TfOH/MeCN	Toluene/Et_3SiH	– 60 → – 5	35
5	*TfOH/MeCN*	*CH_2Cl_2/$EtMe_2SiH$*	*– 50 → – 20*	*81*

Completion of Eastern Hemisphere (+)-6. – All that remained to complete **6** was protecting-group adjustment. To this end, removal of the Bn group in (–)-**39** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), followed by hydrolysis of the ester with K_2CO_3 in MeOH, furnished diol (+)-**42** as a crystalline solid (92% yield, two steps; *Scheme 12*); single-crystal X-ray-analysis confirmed the structure and relative configuration. Protection of the diol as the bis-TES (Et_3Si) ether then completed construction of eastern hemisphere (+)-**6**.

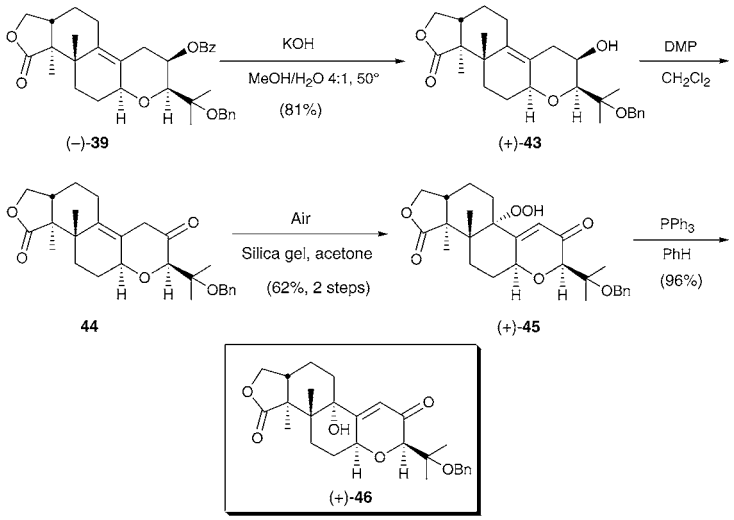
Autooxidation: A Strategic Decision. – From the outset, introduction of the tertiary allylic OH group at C(13) of (–)-21-isopentenylpaxilline (**1**) was envisioned to be achieved late in the overall synthetic sequence *via* autooxidation of an appropriate *β*,*γ*-

Scheme 12



unsaturated ketone [49][50]. However, given the ease with which highly substituted indoles are oxidized, we thought it prudent to examine at this juncture the feasibility of performing the autooxidation before introduction of the indole. We therefore removed the Bz moiety of (–)-**39** (*Scheme 13*) and subjected the derived alcohol to *Dess–Martin* oxidation to afford ketone **44**, which, without purification, was exposed

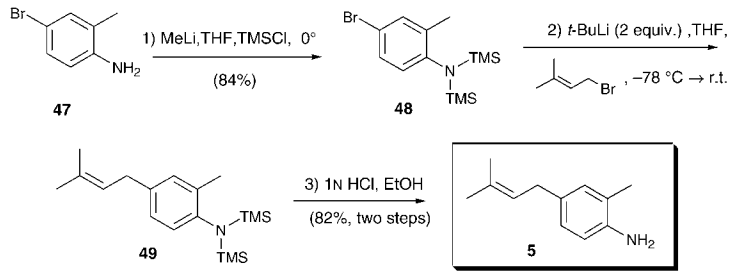
Scheme 13



for 18 h to aeration in acetone over silica gel; autooxidation furnished (+)-**45** as a stable, fully characterizable hydroperoxide in 62% yield for the two steps. Reduction with PPh_3 provided hydroxy enone (+)-**46** (96%). The relative configuration at the stereogenic center carrying the newly introduced OH group, however, was not confirmed at this stage (*vide infra*).

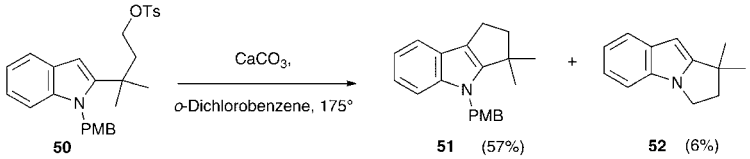
Construction of the Western Hemisphere Toluidine 5. – We began with commercially available 4-bromo-2-methylaniline (**47**; *Scheme 14*); *N*-protection as the bis-TMS (Me_3Si) ether (**48**), followed by Li/Br exchange and alkylation with prenyl bromide readily installed the isopentenyl group *para* to the amino group to provide **49**. Removal of the silyl groups (1N HCl, EtOH) then afforded toluidine **5**; the overall yield for the three-step sequence was 69%.

Scheme 14



***C*-Ring Construction: Two Model Studies.** – Construction of ring C in (−)-21-isopentenylpaxilline (**1**) was viewed as a significant challenge. Previous model work by *Haseltine* in our laboratory entailed blocking the indole N-atom in **50** as a *p*-methoxybenzyl (PMB) ether, followed by heating to 175° to effect ring closure (*Scheme 15*) [51]. Such a scenario, however, was not expected to be feasible here. First, the fully elaborated system would not in all likelihood tolerate high temperature; second, oxidative removal of the PMB group would raise the specter of indole oxidation. A milder protocol for *C*-ring construction was, therefore, sought.

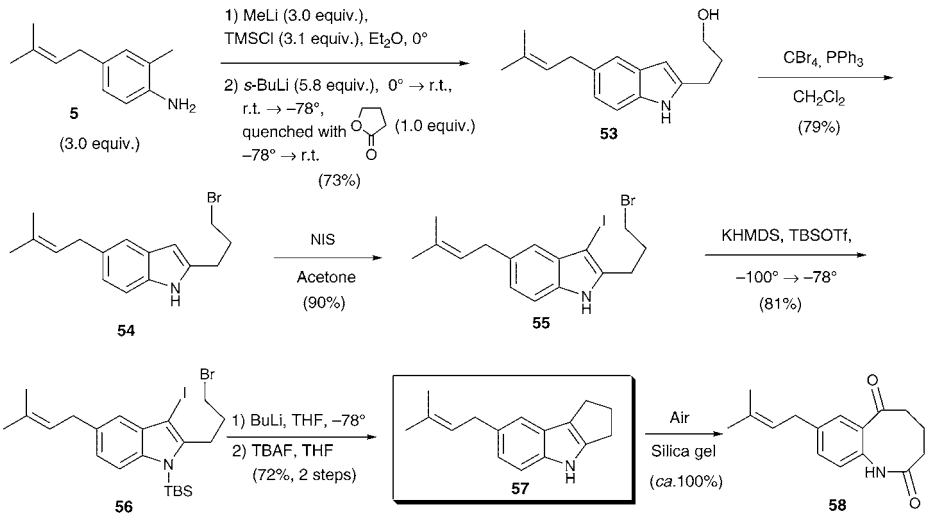
Scheme 15



In 1998, *Negishi et al.* introduced a σ-cycloalkylation tactic [52] employing alkenylmetals to construct three- to seven-membered rings in high yield. Based on this precedent, incorporation of a halogen at C(3) of the indole, followed by Li/halogen exchange would lead to an alkenyl-lithium, which we anticipated would rapidly lead to *C*-ring construction, assuming the availability of an appropriate side-chain electrophile. Two model studies were undertaken. The first called for iodo bromide **55**, readily

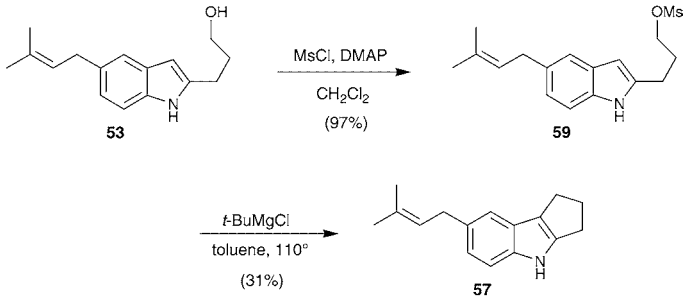
prepared *via* our indole synthesis with butyrolactone [38][39]. Conversion of the OH group to the corresponding Br derivative, followed by treatment with NIS, generated **55**. Protection of the indole N-atom with a TBS ((*t*-Bu)Me_2Si) group, followed by Li/I exchange (BuLi; −78°) led, as expected, to *C*(3)-alkylation; removal of the silyl group (TBAF (Bu_4NF)) generated **57** in 72% yield for the two steps. Not surprisingly, indole **57** proved unstable in air to silica-gel chromatography; lactam **58** was obtained in nearly quantitative yield (*Scheme 16*).

Scheme 16



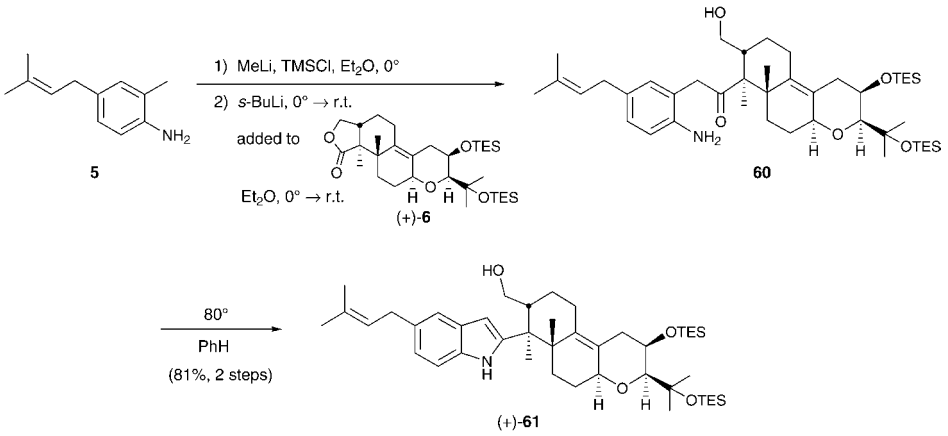
Intrigued by the possibility of a more direct route to **57**, methanesulfonate **59**, readily available from **53**, was treated with various *Grignard* reagents (*i.e.*, a π-cycloalkylation). Best results, albeit modest, were obtained with *t*-BuMgCl (1.5 equiv.) in toluene at reflux; these conditions furnished indole **57** in an unoptimized yield of 30% for the two steps (*Scheme 17*).

Scheme 17



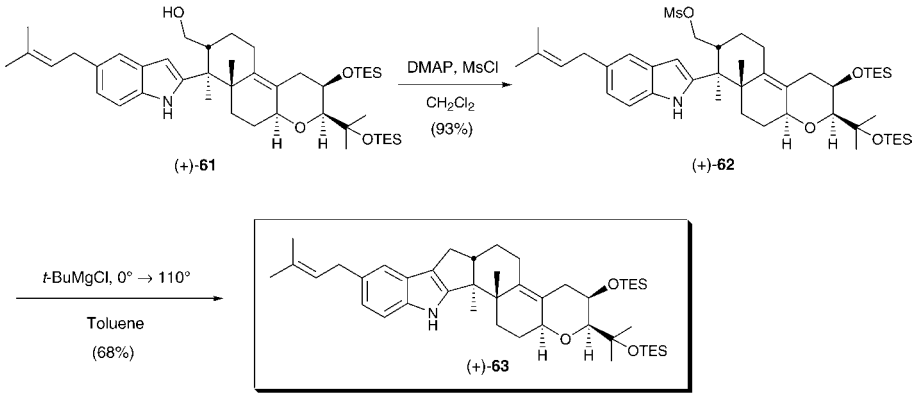
Union of the Eastern and Western Hemispheres. – Having devised two potentially viable approaches for *C*-ring construction, we turned to the union of toluidine **5** with advanced lactone (+)-**6**, exploiting our 2-substituted-indole construction (*Scheme 18*) [38][39]. Best conditions involved use of MeLi instead of BuLi to install the TMS, followed by treatment with *s*-BuLi and addition of (+)-**6** at 0°; amino ketone **60**, not the expected indole **61**, resulted. We have noticed that, in structurally complex cases (*e.g.*, the penitrem synthesis), our indole protocol does not proceed to completion, but instead furnishes a mixture of the corresponding amino ketone and indole, or only the amino ketone. In general, heating the resultant mixture completes the indole-ring construction. In the case at hand, heating **60** in benzene at reflux over a 2-day period furnished (+)-**61** in 81% yield for the two-step sequence.

Scheme 18



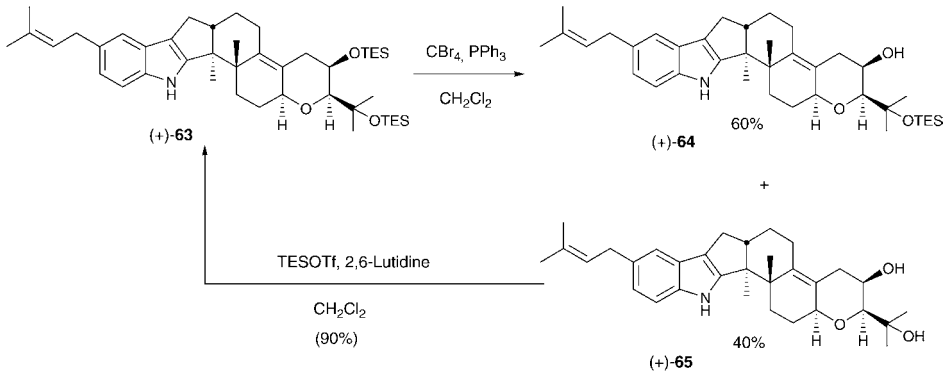
***C*-Ring Construction.** – Having achieved the union of the eastern and western hemispheres, we turned our attention to construct ring *C*, exploiting the *Negishi* σ-cycloalkylation. All attempts to convert the primary OH group in indole (+)-**61** to the corresponding Br substituent, as readily achieved in our model study, however, proved unrewarding, presumably due to the steric encumbrance of the OH group. We were, however, able to prepare methanesulfonate (+)-**62** in 93% yield. The next step in the *Negishi* σ-cycloalkylation protocol calls for introduction of the I-substituent at C(3). This reaction also was not straightforward. We, therefore, turned to the second tactic, involving the treatment of (+)-**62** with *Grignard* reagents (*i.e.*, π-cycloalkylation). Due to interference of the indole N-atom, we anticipated at best modest efficiency. Not surprisingly, with MeMgBr, no reaction took place at room temperature. However, upon heating in toluene at reflux, two products were observed; the desired hexacycle (+)-**63** was isolated in 25% yield, accompanied by the product resulting from the ring closure on the indole N-atom. Pleasingly, further investigation revealed that *t*-BuMgCl, possessing a higher pK_b value and a smaller counterion, improved the yield of carbon alkylation to the level of 68%. (*Scheme 19*).

Scheme 19



At this juncture, autooxidation to introduce the tertiary OH group at C(13) was the remaining key transformation to complete the synthesis of (−)-21-isopentenylpaxilline (**1**). This transformation required conversion of (+)-**63** to the corresponding α,β-unsaturated ketone. To our surprise, we were not able to effect this simple oxidation. Although we could obtain the monoprotected secondary alcohol (+)-**64** (*Scheme 20*), oxidation employing a variety of conditions, including *Dess–Martin* [53], *Moffatt* [54], TPAP/NMO, IBX [55][56] *etc.*, led either to recovery of starting material or to complete decomposition. We reasoned that the steric bulk of the TES (Et_3Si) group played a significant role, preventing the desired oxidation.

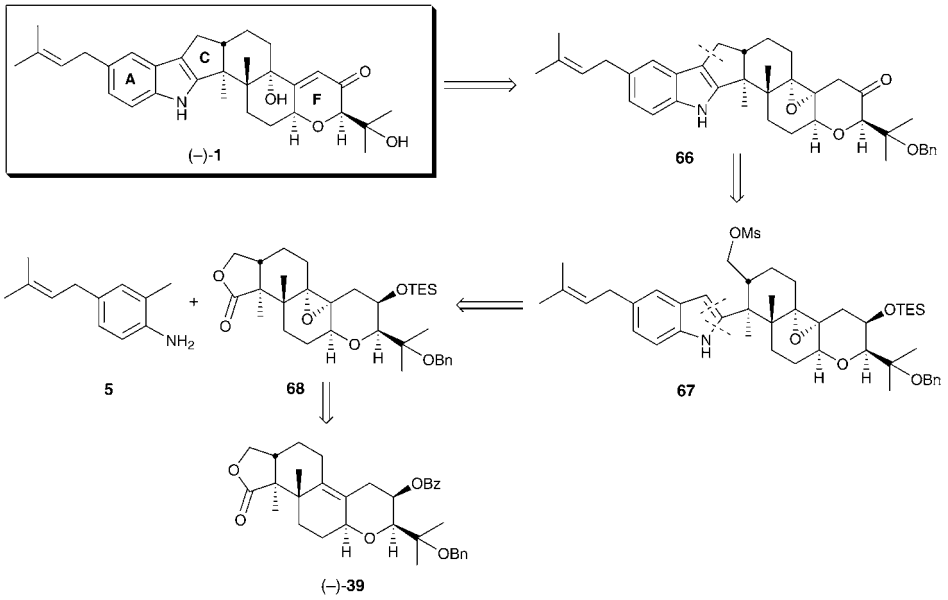
Scheme 20



A Second-Generation End-Game Strategy. – Given our inability to achieve the late-stage oxidation, we devised an alternate end-game (*Scheme 21*). We reasoned that the γ-hydroxy-α,β-enone functionality in (−)-**1** could instead be installed *via* fragmentation of β,γ-epoxy ketone **66**, available from **67** *via* *t*-BuMgCl-mediated ring-*C* closure, followed by removal of the TES group and oxidation of the derived alcohol to ketone **66**. The risk of proposing another late-stage oxidation, given the

difficulty experienced with (+)-**64**, however, did not go unnoticed! Notwithstanding this concern, indole **67** was envisioned to derive from a new eastern hemisphere (*i.e.*, **68**), again exploiting our 2-subsititued-indole protocol with toluidine **5**. The requisite configuration of the tetrasubstituted epoxide in **68**, required for α-installation of the tertiary allylic OH group in (−)-**1**, would arise from the expected facial selectivity upon epoxidation of (−)-**39** prepared earlier (*Table 2*).

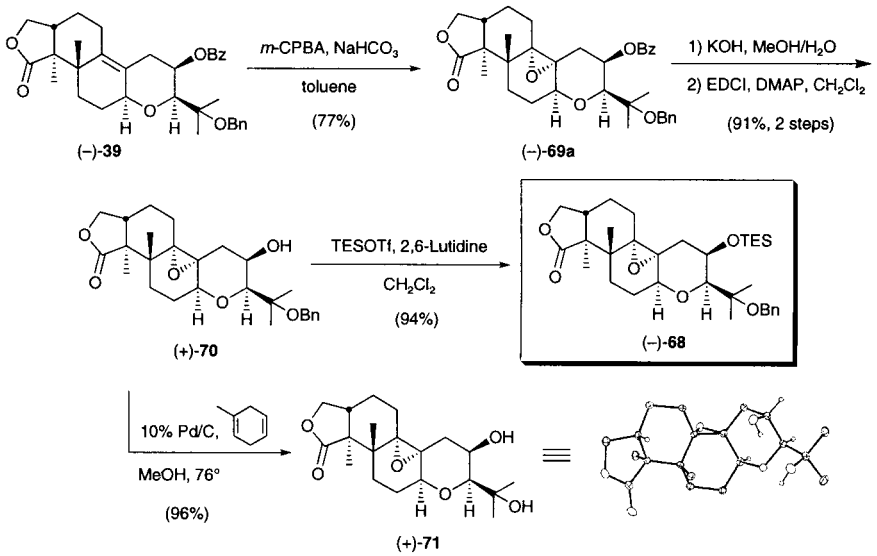
Scheme 21



With this goal in mind, attempted epoxidation of (−)-**39** (*Scheme 22*) with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2/H_2O initially proceeded with low diastereoselectivity. Other epoxidation conditions led either to decomposition or to no reaction. After considerable experimentation, we discovered that the solvent played a critical role. Best results were obtained with toluene, which afforded the desired α-epoxide (−)-**69a** in 77% yield, in conjunction with 13% of the β-diastereoisomer (**69b**). Removal of the Bz group was next achieved (*e.g.*, KOH/MeOH/H_2O), albeit with partial lactone hydrolysis; reinstallation of the lactone with 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and 4-(dimethylamino)pyridine (DMAP) furnished alcohol (+)-**70** in 91% yield for the two steps. To confirm the epoxide configuration in (−)-**69a**, transfer hydrogenation of (+)-**70** removed the Bn group to furnish (+)-**71** as a crystalline solid; single-crystal X-ray analysis confirmed the relative configuration. Silylation of (+)-**70** then completed construction of (−)-**68,** the new eastern hemisphere.

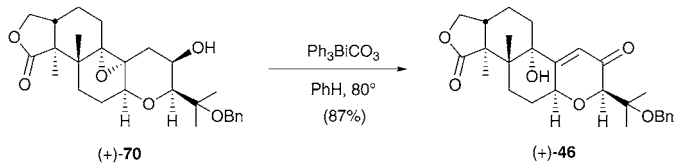
Again cognizant of the potential difficulty with the proposed late-stage oxidation of the OH group at C(13), alcohol (+)-**70** appeared to be an excellent model system to explore this oxidation. Extensive experimentation eventually revealed the oxidant Ph_3BiCO_3. Developed by *Barton* and co-workers, this hypervalent reagent permits

Scheme 22



oxidation under nearly neutral conditions, and, importantly, it is known to tolerate the indole nucleus [57]. Fortuitously, in the case at hand, treatment of (+)-**70** in benzene at reflux led not only to OH oxidation, but also to the desired epoxide fragmentation to furnish (+)-**46** (*Scheme 23*), the latter identical in all respects to that prepared previously *via* autooxidation of **44** (*Scheme 13*). The relative configuration of (+)-**46** was thus established, given the X-ray structure of (+)-**71**.

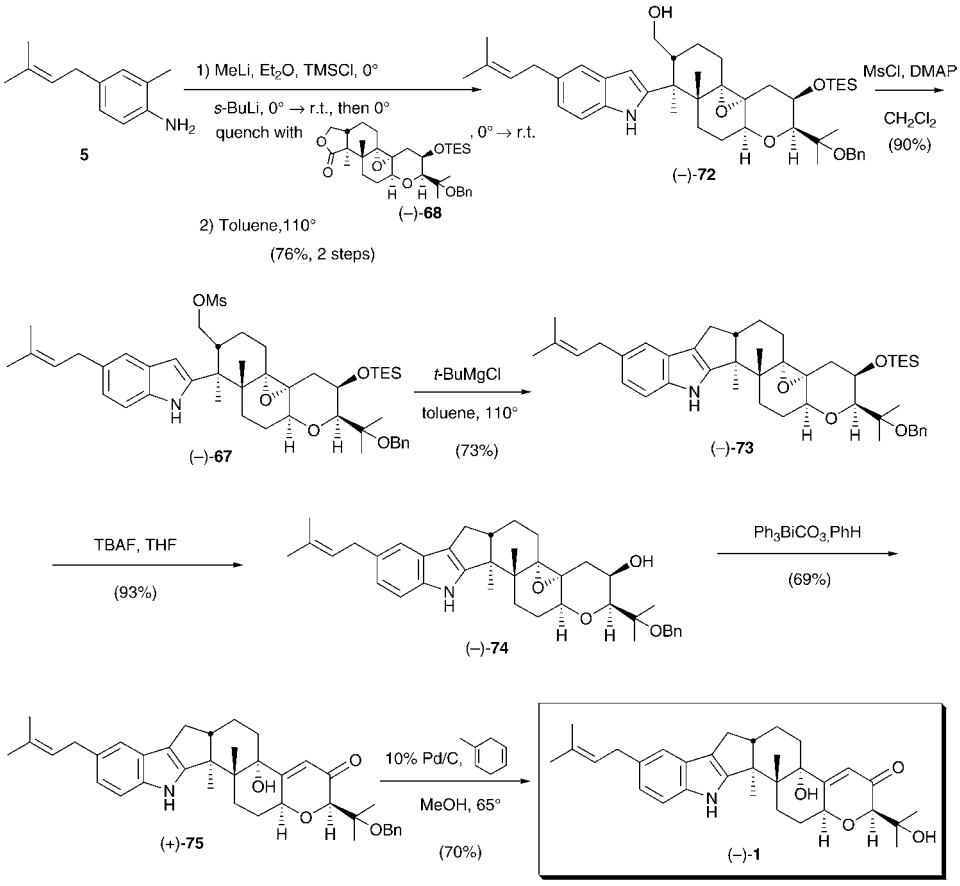
Scheme 23



Total Synthesis of (–)-21-Isopentenylpaxilline (1). – With (–)-**68**, the new eastern hemisphere in hand, we turned again to our 2-substituted indole protocol (*Scheme 24*) [38][39]. Treatment of the derived TMS derivative of **5** with *s*-BuLi, followed by the addition of (–)-**68**, as with (+)-**6** (*Scheme 18*), resulted only in acylation at the highly hindered lactone C=O group, to afford the corresponding amino ketone. As before, completion of the indole-ring construction was readily achieved by heating in toluene at reflux to furnish (–)-**72** in 76% yield for the two steps. Mesylation of the derived primary alcohol then afforded (–)-**67** (90%), substrate for the ring-*C* closure. In the event, treatment with *t*-BuMgCl smoothly furnished (–)-**73** in 73% yield. Removal of the TES group (TBAF, 93%) then set the stage for the critical Ph_3BiCO_3 oxidation/fragmentation reaction sequence. Pleasantly, γ-hydroxy-α,β-enone (+)-**75** was obtained in 69% yield.

The final challenge to complete the total synthesis of (−)-**1** entailed removal of the Bn group in (+)-**75**. The difficulty here was possible concomitant reduction of the *C*(21)-isopentenyl moiety. After considerable experimentation, transfer hydrogenation furnished 21-isopentenylpaxilline ((−)-**1**), along with a minor amount of the over-reduced product. Normal-phase high-pressure liquid chromatography afforded synthetic (−)-**1** in 70% yield, identical in all respects (*i.e.*, 500-MHz ^{1}H-NMR, 125-MHz ^{13}C-NMR, HR-MS data, and chiroptical properties) to a sample of the natural product kindly provided by Prof. *Gloer*.

Scheme 24



In summary, the first total synthesis and assignment of absolute configuration of (−)-21-isopentenylpaxilline (**1**) have been achieved. Key elements of the synthesis include the stereocontrolled construction of advanced eastern hemisphere (−)-**68**, involving a highly efficient union of eastern and western fragments (−)-**68** and **5**, exploiting our 2-substituted-indole synthesis, application of the *Negishi* π-cycloalkylation tactic as a new, potentially general protocol for the construction of ring *C*, and the

fragmentation of an β,γ-epoxy ketone to introduce the tertiary OH group at C(13) in the indole diterpene skeleton.

Experimental Part

General. All non-aq. reactions were carried out in oven- or flame-dried glassware under Ar, unless otherwise noted. All solvents were reagent-grade. Et_2O and THF were freshly distilled from Na/benzophenone ketyl under Ar. The Ar was deoxygenated by passing it through an *OXICLEAR*™ tube from *Aldrich*. CH_2Cl_2, benzene, toluene, $(i\text{-}Pr)_2NH$, and Et_2NH were freshly distilled from CaH_2. Et_3N and *N,N′*-dimethylpropylenurea (DMPU) were distilled from CaH_2 and stored over activated 4-Å molecular sieves. Anh. pyridine and DMSO were purchased from *Aldrich* and used without purification. MeLi, BuLi, *s*-BuLi and *t*-BuLi were purchased from *Aldrich*, and standardized by titration with $Ph_2CHCOOH$ or *N*-pivaloyl-*o*-toluidine. All other commercially available reagents were used as received. Except as indicated otherwise, reaction mixtures were magnetically stirred and monitored by TLC with 0.25-mm *E. Merck* pre-coated silica-gel plates. Flash chromatography (FC) was performed with silica gel *60* (particle size 230–400 mesh) supplied by *E. Merck*. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. High-performance liquid chromatography (HPLC) was performed with a *Waters* component anal. system. Optical rotations were obtained with a *Perkin-Elmer* model *241* polarimeter with a Na lamp, and are reported as follows: $[\alpha]_D^{25}$ (*c* (g/100 ml), solvent). IR Spectra were recorded with a *Perkin-Elmer* model *283B* spectrometer with polystyrene as external standard or a *Perkin-Elmer 1600* series *FTIR* spectrometer or *JascoFT/IR-480 plus* spectrometer, and are reported in cm^{-1} (abs.). ^1H- and ^{13}C-NMR spectra were recorded on a *Bruker AM-500* spectrometer. Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard relative to $CHCl_3$ (δ 7.26), benzene (δ 7.15), or CH_2Cl_2 (δ 2.05) for ^1H, and $CHCl_3$ (δ 77.0), benzene (δ 128.0), or CH_2Cl_2 (δ 2.05) for ^{13}C. High-resolution mass spectra (HR-MS) were measured at the University of Pennsylvania Mass Spectrometry Service Center on either a *VG Micromass 70/70H* or *VG ZAB-E* spectrometer. Microanalyses were performed at the University of Pennsylvania.

*Preparations. (+)-(4*R*,4a*S*,8a*R*)-3,4,4a,7,8,8a-Hexahydro-4-(hydroxymethyl)-4a,6,8a-trimethylnaphthalen-1(2*H*)-one* ((+)-**12**). A soln. of (+)-**11** (1.50 g, 3.94 mmol) in acetone (40 ml) and H_2O (0.8 ml) was treated with TsOH (76 mg, 0.4 mmol); this mixture was then stirred at r.t. for 16 h. The reaction was quenched with Et_3N (50 µl), and then the mixture was concentrated *in vacuo*. FC (hexanes/AcOEt, 2:1) provided (+)-**12** (815 mg, 93%). Colorless crystals. M.p. 58–60°. $[\alpha]_D^{25} = +149$ (*c* = 1.14, $CHCl_3$). IR (neat): 3446*s* (br.), 2959*s*, 2833*m*, 1699*s*, 1447*m*, 1373*m*, 1061*m*, 997*m*, 817*w*. ^1H-NMR (500 MHz, $CDCl_3$) 5.55 (*s*, 1 H); 4.01 (*dd*, *J* = 10.4, 3.2, 1 H); 3.43 (*dd*, *J* = 10.2, 8.0, 1 H); 2.73–2.78 (m, 1 H); 2.21–2.26 (*m*, 3 H); 1.90–1.98 (*m*, 3 H); 1.59–1.63 (*m*, 4 H); 1.47–1.51 (*m*, 1 H); 1.40 (br. *s*, 1 H); 1.16 (*s*, 3 H); 0.78 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 216.3; 132.5; 125.9; 64.2; 50.0; 42.2; 39.4; 35.6; 26.5; 25.8; 24.0; 23.4; 19.9; 19.6. HR-ESI-MS: 222.1616 (M^+, $C_{14}H_{22}O_2^+$; calc. 222.1620).

*(−)-(3*R*,3a*S*,4*R*)-3,3a,4,5,6,7-Hexahydro-3-methoxy-3a,4-dimethyl-4-(3-oxobutyl)[2]benzofuran-5(1*H*)-one* ((−)-**14a**) *and (+)-(3*S*,3a*S*,4*R*)-3,3a,4,5,6,7-Hexahydro-3-methoxy-3a,4-dimethyl-4-(3-oxobutyl)[2]benzofuran-5(1*H*)-one* ((+)-**14b**). A soln. of (+)-**12** (2.26 g, 10.2 mmol) in MeOH (120 ml) was added *Sudan III* (5 mg), the resulting orange soln. was cooled to −78° and then bubbled in O_3/O_2 for 25 min; Ar was then bubbled in for 5 min, and Me_2S (1.5 ml) was added. 10 min later, this mixture was warmed to r.t. and stirred for 3 h. The mixture was concentrated *in vacuo*. FC (hexanes/AcOEt, 1:1) provided a mixture of lactols (2.29 g, 89%).

Under Ar, a soln. of the above lactols (35.0 mg, 137 µmol) in acetone (2 ml) was treated with Ag_2O (100 mg) and MeI (300 µl), this suspension was then heated to reflux for 3.5 h. After cooling to r.t., this mixture was diluted with acetone (5 ml) and then filtered. The filtrate was concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 2:1 → hexanes/AcOEt 1:1) provided (−)-**14a** (20.8 mg, 57%) as colorless crystals and (+)-**14b** (11.5 mg, 31%) as a colorless oil.

*Data of (−)-*__14a__: colorless crystals. M.p. 98–100°. $[\alpha]_D^{25} = -11$ (*c* = 1.15, $CHCl_3$); IR (neat): 2949*s*, 1726*s*, 1703*s*, 1379*w*, 1090*w*, 1007*m*. ^1H-NMR (500 MHz, $CDCl_3$): 4.89 (*s*, 1 H); 3.87 (*t*, *J* = 7.5, 1 H); 3.64 (*dd*, *J* = 11.0, 7.7, 1 H); 3.45 (*s*, 3 H); 2.87–2.92 (*m*, 1 H); 2.62–2.68 (*m*, 1 H); 2.47–2.54 (*m*, 1 H); 2.38–2.43 (*m*, 1 H); 2.26 (*ddd*, *J* = 15.6, 5.3, 1.3, 1 H); 2.13 (*s*, 3 H); 2.01–2.07 (*m*, 1 H); 1.77–1.82 (*m*, 1 H); 1.59–1.71 (*m*, 2 H); 1.20 (*s*, 3 H); 0.85 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 214.6; 209.0; 106.0; 67.8; 57.0; 53.0; 50.8; 40.0; 39.7; 36.8; 29.8; 26.0; 20.9; 16.8; 10.0. HR-ESI-MS: 291.1578 ($[M + Na]^+$, $C_{15}H_{24}NaO_6^+$; calc. 291.1572).

*Data of (+)-***14b**: colorless oil. $[\alpha]_D^{25} = +88$ ($c = 1.50$, $CHCl_3$); IR (neat): 2952*s*, 1725*s*, 1705*s*, 1375*w*, 1091*m*, 1008*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.55 (*s*, 1 H); 4.05 (*t*, $J = 8.2$, 1 H); 3.48 (*dd*, $J = 10.2$, 8.0, 1 H); 3.30 (*s*, 3 H); 3.12–3.20 (*m*, 1 H); 2.69–2.74 (*m*, 1 H); 2.57–2.63 (*m*, 1 H); 2.29–2.36 (*m*, 1 H); 2.21 (*ddd*, $J = 15.2$, 5.4, 1.5, 1 H); 2.15 (*s*, 3 H); 2.04–2.11 (*m*, 1 H); 1.87–1.92 (*m*, 1 H); 1.56–1.64 (*m*, 2 H); 1.29 (*s*, 3 H); 0.79 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 214.9; 209.1; 110.5; 68.8; 54.4; 54.1; 52.2; 39.3; 36.6; 36.4; 29.9; 26.9; 21.3; 19.4; 15.5. HR-ESI-MS: 291.1570 ($[M + Na]^+$, $C_{15}H_{24}NaO_6^+$; calc. 291.1572).

*(+)-(1*R*,9a*S*,9b*S*)-3,3a,4,5,8,9,9a,9b-Octahydro-1-methoxy-9a,9b-dimethylnaphtho[1,2-*c*]furan-7(1*H*)-one* ((+)-**15a**). Under Ar, a soln. of (−)-**14a** (52.8 mg, 197 μmol) in toluene (8 ml) was treated with an aq. KOH soln. (8.8 mg of KOH in 300 μl H_2O, 157 mmol). This mixture was then heated to reflux by using a *Dean-Stark* trap for 2 h. After cooling to r.t., this mixture was diluted with AcOEt (20 ml), washed with H_2O (5 ml), and brine (5 ml). The org. layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. FC (Et_2O) provided (+)-**15a** (33.7 mg, 68%). White solid. M.p. 114–117°. $[\alpha]_D^{25} = +147$ ($c = 1.04$, $CHCl_3$). IR ($CHCl_3$): 2930*s*, 1660*s*, 1230*m*, 1100*m*, 1080*m*, 990*s*, 970*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.85 (*d*, $J = 2.0$, 1 H); 4.94 (*s*, 1 H); 3.89 (*t*, $J = 7.6$, 1 H); 3.68 (*dd*, $J = 7.7$, 10.9, 1 H); 3.48 (*s*, 3 H); 2.65 (*m*, 1 H); 2.52–2.42 (*m*, 2 H); 2.14–2.34 (*m*, 2 H); 2.29 (*dt*, $J = 4.7$, 14.4, 1 H); 1.70–1.64 (*m*, 2 H); 1.58 (*dq*, $J = 5.2$, 12.5, 1 H); 1.38 (*s*, 3 H): 0.89 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 198.4; 168.2; 126.8; 106.7; 68.2; 57.2; 48.0; 41.7; 40.9; 33.8; 32.0; 30.4; 21.1; 18.0; 10.4. HR-CI-MS (CH_4): 251.1638 ($[M + H]^+$, $C_{15}H_{23}O_3^+$; calc. 251.1647).

*(+)-(1*S*,9a*S*,9b*S*)-3,3a,4,5,8,9,9a,9b-Octahydro-1-methoxy-9a,9b-dimethylnaphtho[1,2-*c*]furan-7(1*H*)-one* ((+)-**15b**). Under Ar, DMSO (2.7 ml) was treated with NaH (92.3 mg), this suspension was then heated to 65° for 1.5 h. A clear soln. was formed, which was cooled to r.t. A soln. of (+)-**14b** (253 mg, 0.942 mmol) in THF (5 ml) under Ar was treated with the above base (1.4 ml). After heating to reflux for 5 h, this mixture was cooled to r.t., and the reaction was quenched with sat. aq. NH_4Cl soln. (3 ml). This mixture was then extracted with Et_2O (3 × 10 ml), and all the org. layers were combined and washed with brine (5 ml). The org. layer was then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 5:1 → hexanes/AcOEt 2:1) provided (+)-**15b** (146 mg, 62%). Colorless crystals. M.p. 111–113°. $[\alpha]_D^{25} = +273$ ($c = 1.32$, $CHCl_3$). IR ($CHCl_3$): 2940*s*, 1660*s*, 1235*m*, 1090*s*, 990*s*, 970*m* 930*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.80 (*d*, $J = 2.1$, 1 H); 4.58 (*s*, 1 H); 4.06 (*t*, $J = 8.2$, 1 H); 3.52 (*dd*, $J = 8.1$, 10.0, 1 H); 3.33 (*s*, 3 H); 2.92 (*m*, 1 H); 2.59–2.49 (*m*, 2 H); 2.39–2.30 (*m*, 3 H); 1.75–1.75 (*m*, 2 H); 1.53 (*dq*, $J = 5.3$, 12.8, 1 H); 1.49 (*s*, 3 H); 0.85 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 198.7; 170.3; 125.5; 110.7; 69.4; 54.6; 50.3; 43.0; 36.9; 33.9; 31.8; 30.2; 22.0; 20.3; 17.2. HR-CI-MS (CH_4): 273.1460 ($[M + Na]^+$, $C_{15}H_{22}NaO_3^+$; calc. 273.1467).

*(+)-(1*S*)-1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-hydroxypropan-2-one* ((+)-**17**). To a soln. of (−)-**16** (4.92 g, 28.6 mmol) in CH_2Cl_2 (300 ml) at −78° was bubbled O_2/O_3 for 1 h. After quenching with PPh_3 (8.26 g, 31.5 mmol) at −78° and stirring for 30 min, the mixture was warmed to r.t. under Ar and then concentrated. Gradient FC (hexanes/AcOEt 2:1 → hexanes/AcOEt 1:1) provided (+)-**17** (4.54 g, 91%). Colorless oil. $[\alpha]_D^{25} = +43.8$ ($c = 0.95$, $CHCl_3$). IR ($CHCl_3$): 3460*s* (br.), 2975*s*, 2880*m*, 1735*s*, 1370*m*, 1250*m*, 1230*m*, 1120*m*, 1070*m*, 845*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.44 (*ddd*, $J = 6.9$, 6.1, 2.8, 1 H); 4.06–4.09 (*m*, 2 H); 3.98 (*dd*, $J = 8.3$, 6.9, 1 H); 3.44 (*d*, $J = 6.1$, 1 H); 2.23 (*s*, 3 H); 1.36 (*s*, 3 H); 1.31 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 207.0; 109.8; 76.3; 75.5; 65.5; 26.0; 25.2. HR-CI-MS (CH_4): 159.0693 ($[M - Me]^+$, $C_7H_{11}O_4^+$; calc. 159.0657).

*(−)-(1*S*)-1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-methylpropane-1,2-diol* ((−)-**18**). Under Ar, a soln. of (+)-**17** (182.4 mg, 1.05 mmol) in THF (10 ml) at −78° was treated with MeMgBr (3.0M in Et_2O, 1.05 ml, 3.15 mmol), this mixture was then warmed to r.t. over 1 h. After quenching with sat. aq. NH_4Cl soln. (5 ml), the mixture was extracted with Et_2O (3 × 30 ml), and the org. layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Gradient FC (hexanes/AcOEt 2:1 → hexanes/AcOEt 1:1) provided (−)-**18** (179.7 mg, 90%). Colorless oil. $[\alpha]_D^{25} = -7.8$ ($c = 1.14$, $CHCl_3$). IR ($CHCl_3$): 3510*s* (br.), 2970*s*, 2920*m*, 1380*m*, 1365*m*, 1250*m*, 1140*m*, 1055*m*, 865*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.28 (*ddd*, $J = 8.1$, 7.7, 3.1, 1 H); 4.02 (*dd*, $J = 8.1$, 6.5, 1 H); 3.92 (*dd*, $J = 7.7$, 6.5, 1 H); 3.21 (*dd*, $J = 8.3$, 3.1, 1 H); 2.68 (*d*, $J = 8.3$, 1 H); 2.55 (*s*, 1 H); 1.40 (*s*, 3 H); 1.35 (*s*, 3 H); 1.24 (*s*, 3 H); 1.22 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 109.3; 75.3; 74.9; 72.5; 66.7; 26.3; 26.2; 26.1; 25.4. HR-CI-MS (CH_4): 191.1291 ($[M + H]^+$, $C_9H_{19}O_4^+$; calc. 191.1283).

*(+)-(1*S*)-1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-methyl-1-[(methylsulfanyl)methoxy]propan-2-ol* ((+)-**19**). Diol (−)-**18** (10.9 g, 57.3 mmol) was treated with DMSO (203 ml), glacial AcOH (332 ml), and Ac_2O (135 ml) at r.t. After 38 h, the resulting soln. was poured into cold sat. aq. $NaHCO_3$ soln. and stirred for 2 h. The mixture was extracted with Et_2O (3 × 500 ml), and the combined org. layers were washed with brine, dried ($MgSO_4$), and concentrated. Gradient FC (hexanes/AcOEt 20:1 → hexanes/AcOEt 5:1) provided (+)-**19** (8.3 g, 58%). Colorless oil. $[\alpha]_D^{25} = +114$ ($c = 0.95$, $CHCl_3$). IR ($CHCl_3$): 3480*s* (br.), 2970*s*, 2910*s*, 1375*m*, 1355*m*, 1235*m*, 1150*m*, 1060*m*, 1040*m*, 900*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.88 (*dd*, $J = 17.2$, 11.6, 2 H); 4.24 (app. *ddd*, $J = 8.4$, 8.2, 6.8, 1 H); 4.02 (*dd*, $J = 8.4$, 6.2, 1 H); 3.77 (*dd*, $J = 8.2$, 6.2, 1 H); 3.34 (*d*, $J = 6.8$, 1 H); 2.51

(br. *s*, 1 H); 2.18 (*s*, 3 H); 1.37 (*s*, 3 H); 1.32 (*s*, 3 H); 1.22 (*s*, 3 H); 1.18 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 108.3; 84.2; 77.3; 76.7; 72.1; 67.2; 27.1; 26.3; 25.8; 25.5;14.8. HR-CI-MS (CH_4): 251.1306 ($[M+H]^+$, $C_{11}H_{23}O_4S^+$; calc. 251.1317).

*(+)-(4*R*)-4-[(1*S*)-2-(Benzyloxy)-2-methyl-1-[(methylsulfanyl)methoxy]propyl]-2,2-dimethyl-1,3-dioxolane* ((+)-**20**). Under Ar, to a suspension of NaH (60% suspension in mineral oil, 39 mg, 0.955 mmol) in THF (1.2 ml) at 0° was added dropwise a soln. of (+)-**19** (47.8 mg, 0.191 mmol) in THF (1 ml), and this mixture was warmed to r.t. and stirred for 1 h. A soln. of BnBr (0.5M in THF, 770 µl, 0.382 mmol) and Bu_4NI (TBAI; 4 mg, 0.01 mmol) was then added, and the mixture was stirred overnight. Sat. aq. NH_4Cl soln. (3 ml) was added to quench the reaction, the entire mixture was extracted with Et_2O (3 × 5 ml), and the combined org. layers were washed with brine, dried ($MgSO_4$) filtered, and concentrated. Gradient FC (hexanes/AcOEt 20:1 → hexanes/AcOEt 5:1) provided (+)-**20** (62.2 mg, 96%). Pale yellow oil. $[\alpha]_D^{25} = +107$ ($c = 0.85$, $CHCl_3$). IR ($CHCl_3$): 2970*s*, 2920*m*, 1450*w*, 1375*m*, 1365*m*, 1230*m*, 1155*m*, 1060*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.23–7.33 (*m*, 5 H); 4.94 (*dd*, *J* = 15.3, 11.4, 2 H); 4.42 (*dd*, *J* = 12.0, 11.6, 2 H); 4.21–4.25 (*m*, 1 H); 3.95 (*dd*, *J* = 9.0, 6.0, 1 H); 3.68 (*t*, *J* = 8.7, 1 H); 3.53 (*d*, *J* = 7.9, 1 H); 2.19 (*s*, 3 H); 1.37 (*s*, 3 H); 1.35 (*s*, 3 H); 1.33 (*s*, 3 H); 1.26 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.9; 128.3; 127.5; 127.3; 107.8; 83.0; 77.6; 76.9; 68.1; 63.9; 26.6; 25.9; 23.6; 20.3; 14.9. HR-CI-MS (CH_4): 341.1778 ($[M+H]^+$, $C_{18}H_{29}O_4S^+$; calc. 341.1787).

*(−)-(2*R*,3*S*)-4-(Benzyloxy)-4-methyl-3-[(methylsulfanyl)methoxy]pentane-1,2-diol* ((−)-**21**). To a soln. of (+)-**20** (4.80 g, 14.1 mmol) in MeOH (105 ml) and H_2O (15 ml) was added (+)-camphorsulfonic acid (160 mg, 0.71 mmol) at r.t. and the resultant mixture was stirred for 2.5 h at 65°. The mixture was cooled to r.t., poured into sat. aq. $NaHCO_3$ soln. (5 ml) and AcOEt (40 ml), extracted with AcOEt (3 × 100 ml), washed with brine (70 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 2:1 → hexanes/AcOEt 1:1) provided (−)-**21** (3.77 g, 90%). Colorless oil. $[\alpha]_D^{25} = -68.3$ ($c = 1.22$, $CHCl_3$). IR (neat): 3433*s* (br.), 2922*s*, 1388*m*, 1154*m*, 1057*s*, 735*m*, 697*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.26–7.33 (*m*, 5 H); 4.88 (*dd*, *J* = 21.1, 11.6, 2 H); 4.49 (*s*, 2 H); 3.92–3.98 (*m*, 1 H); 3.64–3.70 (*m*, 2 H); 3.53 (*d*, *J* = 2.8, 1 H); 3.00 (*d*, *J* = 6.1, 1 H); 2.46 (*t*, J = 5.3, 1 H); 2.23 (*s*, 3 H); 1.41 (*s*, 3 H); 1.35 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.8; 128.4; 127.4; 127.3; 82.1; 79.3; 77.6; 70.7; 64.9; 63.9; 22.9; 21.4; 15.0. HR-CI-MS (NH_3): 323. 1289 ($[M+Na]^+$, $C_{15}H_{24}NaO_4S^+$; calc. 323.1293).

*(+)-(2*R*)-2-[(1*S*)-2-(Benzyloxy)-2-methyl-1-[(methylsulfanyl)methoxy]propyl]oxirane* ((+)-**7**). Under Ar, a soln. of (−)-**21** (772 mg, 2.57 mmol) in THF (50 ml) was treated with NaH (308 mg, 12.9 mmol) at 0°. After 1 h, the resulting mixture was cooled to −78°, and then a 1-tosyl-1*H*-imidazole soln. (629 mg, 2.83 mmol) in THF (5 ml) was added *via* a cannula. After 10 min, the mixture was allowed to warm to 0° and stirred for 1.5 h. Sat. aq. NH_4Cl soln. (15 ml) was added, the aq. layer was extracted with Et_2O (3 × 30 ml), and all org. layers were combined, washed with brine (50 ml), dried with $MgSO_4$, filtered, and concentrated. FC (hexanes/AcOEt 5:1) afforded (+)-**7** (658 mg, 91%). Pale yellow oil. $[\alpha]_D^{25} = +136$ ($c = 1.06$, $CHCl_3$). IR ($CHCl_3$): 2980*s*, 2920*s*, 1385*m*, 1350*m*, 1230*m*, 1160*m*, 1050*s*, 965*w*, 840*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.24–7.35 (*m*, 5 H); 4.94 (*dd*, *J* = 16.9, 11.5, 2 H); 4.55 (*dd*, *J* = 23.6, 11.6, 2 H); 3.31 (*d*, *J* = 7.5, 1 H); 3.18 (*ddd*, *J* = 7.5, 4.3, 2.8, 1 H); 2.80 (*dd*, *J* = 4.8, 4.3, 1 H); 2.64 (*dd*, *J* = 4.9, 2.8, 1 H); 2.18 (*s*, 3 H); 1.37 (*s*, 3 H); 1.36 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 139.5; 128.2; 127.1; 126.9; 82.8; 77.4; 75.0; 64.0; 52.4; 44.3; 23.6; 21.6; 14.4. HR-CI-MS (NH_3): 283.1363 ($[M+H]^+$, $C_{15}H_{23}O_3S^+$; calc. 283.1368).

*(+)-Benzyl (2*S*,3*S*)-4-Iodo-1,1-dimethyl-2-[(methylsulfanyl)methoxy]-3-[(triethylsilyl)oxy]butyl Ether* ((+)-**28**). Under Ar, a soln. of (+)-**7** (22.8 mg, 0.089 mmol) in THF (5 ml) was treated with LiI (30 mg, 0.226 mmol) and AcOH (14 µl, 0.244 mmol) at 0°. After 15 min, the resulting mixture was warmed to r.t. and stirred for 3 h. This mixture was then charged with Et_2O (10 ml), washed with sat. aq. Na_2SO_3 soln. (5 ml) and brine (5 ml), dried ($MgSO_4$), filtered, and concentrated. This material was used without purification in the next step.

Under Ar, the soln. of iodohydrin (30.2 mg, 73.6 µmol) in CH_2Cl_2 (2 ml) was treated with 2,6-lutidine (31 µl, 0.265 mmol) and TESOTf (47 µl, 0.206 mmol) at 0°. After 15 min, this mixture was charged with Et_2O (10 ml), washed with sat. aq. NH_4Cl soln. (5 ml) and brine (5 ml), dried ($MgSO_4$), filtered, and concentrated. FC (hexanes/AcOEt 20:1) afforded (+)-**28** (36.5 mg, 86% yield for 2 steps). Pale yellow oil. $[\alpha]_D^{25} = +14$ ($c = 1.14$, CH_2Cl_2). IR (neat): 2954*s*, 2876*s*, 1456*w*, 1180*w*, 1092*s*, 1006*w*, 732*s*. ^{1}H-NMR (500 MHz, C_6D_6): 7.29 (*d*, *J* = 7.5, 2 H); 7.20 (*t*, *J* = 7.7, 2 H); 7.10 (*t*, *J* = 7.4, 1 H); 4.89 (*dd*, *J* = 45.1, 11.6, 2 H); 4.29 (*dd*, *J* = 18.5, 11.4, 2 H); 3.90 (app. *dd*, *J* = 10.0, 4.4, 1 H); 3.76 (*d*, *J* = 5.8, 1 H); 3.44 (*ddd*, *J* = 19.3, 10.1, 4.5, 2 H); 1.93 (*s*, 3 H); 1.32 (*s*, 3 H); 1.19 (*s*, 3 H); 0.99 (*t*, *J* = 8.8, 9 H); 0.62 (*q*, *J* = 7.9, 6 H). ^{13}C-NMR (125 MHz, C_6D_6): 139.7; 128.6; 127.5; 127.4; 82.3; 78.3; 72.0; 64.0; 24.0; 21.1; 16.3; 14.7; 7.2; 5.6. HR-ESI-MS: 547.1173 ($[M+Na]^+$, $C_{21}H_{37}INaO_3Si^+$; calc. 547.1175).

*(+)-(1*R,2S*)-3-(Benzyloxy)-1-{[(4a*S*)-2,3,4,4a,5,6,7,8-octahydro-4a-methyl-2-oxo-naphthalen-1-yl]methyl}-3-methyl-2-[(methylsulfanyl)methoxy]butyl Benzenecarboxylate* ((+)-**30**). Under Ar, a 1.5M soln. of $LiNEt_2$ in THF and hexanes (0.6 ml) was added to (+)-**23** (140 mg, 0.68 mmol) in THF (300 µl) at $-40°$ and gradually heated to 65° over a 2 h period. The resulting mixture was stirred for 12 h at 65°, cooled to $-78°$, and then DMPU (150 µl) and (+)-**7** (271 mg, 0.97 mmol) were added. The mixture was warmed to r.t., stirred for 3 h, the reaction was quenched with H_2O (6 ml), and the mixture was extracted with AcOEt (3 × 10 ml). The combined org. layers were washed with brine (5 ml), dried ($MgSO_4$), filtered, and concentrated. This material was used without purification in the next step.

The above alcohol mixture in CH_2Cl_2 (5 ml) was treated with 4-(dimethylamino)pyridine (56 mg, 0.44 mmol) and BzCl (40 µl, 0.33 mmol) at r.t. The mixture was stirred for 18 h, diluted with AcOEt (10 ml), washed sequentially with H_2O (5 ml) and brine (5 ml), dried ($MgSO_4$), filtered, and concentrated. Gradient FC (95% hexanes/AcOEt → 80% hexanes/AcOEt → 65% hexanes/AcOEt) provided a mixture of benzoates.

A soln. of the crude benzoate (211 mg) in benzene (3 ml) was treated with AcONa/AcOH buffer (3 ml) at 65°. After 15 h, the mixture was cooled to r.t., the reaction was quenched with sat. aq. $NaHCO_3$ (1 ml), and the mixture was extracted with AcOEt (3 × 10 ml). The combined org. layers were washed with brine (5 ml), dried ($MgSO_4$), filtered, and concentrated. Gradient FC (95% hexanes/AcOEt → 80% hexanes/AcOEt) provided (+)-**30** (127 mg, 34% yield for 3 steps). Pale yellow oil. $[\alpha]_D^{25} = +134$ ($c = 0.89$, $CHCl_3$). IR (neat): 2927*s*, 1716*s*, 1664*s*, 1602*s*, 1451*m*, 1274*s*, 1026*m*, 711*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.96–7.98 (*m*, 2 H); 7.49–7.52 (*m*, 1 H); 7.39 (app. *t*, *J* = 7.1, 2 H); 7.20–7.31 (*m*, 5 H); 5.57 (*dt*, *J* = 10.7, 3.5, 1 H); 4.95 (*dd*, *J* = 19.2, 11.3, 2 H); 4.47 (*s*, 2 H); 3.80 (*d*, *J* = 3.3, 1 H); 3.07 (*dd*, *J* = 13.8, 10.7, 1 H); 2.67–2.72 (*m*, 2 H); 2.22–2.33 (*m*, 2 H); 2.18 (*s*, 3 H); 1.99–2.06 (*m*, 1 H); 1.69 (*dt*, *J* = 13.7, 4.9, 1 H); 1.57–1.61 (*m*, 1 H); 1.46–1.54 (*m*, 2 H); 1.37–1.40 (*m*, 1 H); 1.33 (*s*, 3 H); 1.28 (*s*, 3 H); 1.22–1.25 (*m*, 1 H); 1.04 (*s*, 3 H); 0.94–1.00 (*dt*, *J* = 13.4, 3.8, 1 H); 0.77–0.86 (*m*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 198.5; 165.7; 165.0; 139.3; 132.8; 130.4; 129.8; 129.2; 128.4; 128.2; 127.4; 127.1; 82.7; 78.8; 76.9; 72.4; 63.6; 41.7; 37.4; 36.2; 33.8; 30.3; 29.7; 29.5; 27.5; 26.5; 22.9; 22.3; 21.2; 21.1; 14.8. HR-ESI-MS: 551.2819 ($[M+H]^+$, $C_{33}H_{43}O_5S^+$; calc. 551.2831).

*(+)-(1*R,2S*)-3-(Benzyloxy)-1-{[(1*S*,9a*S*,9b*S*)-1,3,3a,4,5,7,8,9,9a,9b-decahydro-1-methoxy-9a,9b-dimethyl-7-oxonaphtho[1,2-c]furan-6-yl]methyl}-3-methyl-2-[(methylsulfanyl)methoxy]butyl Benzenecarboxylate* ((+)-**33b**). Under Ar, a 1.5M soln. of $LiNEt_2$ in THF and hexanes (6.5 ml) was added to a mixture of **8b** (832 mg, 2.85 mmol) and the (+)-**23** (924 mg, 4.48 mmol) in THF (2 ml) at $-40°$ and gradually heated to 65° over a 2 h period. The resulting mixture was stirred for 12 h at 65°, cooled to $-78°$, and then DMPU (1.5 ml) and epoxide (+)-**7** (1.95 g, 6.94 mmol) were added. The mixture was warmed to r.t., stirred for 3 h, the reaction was quenched with H_2O (60 ml), and the mixture was extracted with AcOEt (3 × 60 ml). The combined org. layers were washed with brine (60 ml), dried ($MgSO_4$), filtered, and concentrated. This material was used without purification in the next step.

The alcohol mixture in CH_2Cl_2 (80 ml) was treated with DMAP (2.7 g, 20.5 mmol) and BzCl (1.87 ml, 16.2 mmol) at r.t. The mixture was stirred for 18 h, diluted with AcOEt (100 ml), washed with H_2O (50 ml) and brine (50 ml), dried ($MgSO_4$), filtered, and concentrated. Gradient FC (95% hexanes/AcOEt → 80% hexanes/AcOEt → 50% hexanes/AcOEt) provided a mixture of benzoates.

A soln. of the crude benzoates (1.12 g) in benzene (35 ml) was treated with AcONa/AcOH buffer[1]) (25 ml) at 65°. After 45 h, the mixture was cooled to r.t., the reaction was quenched with sat. aq. $NaHCO_3$ soln. (10 ml), and the mixture was extracted with AcOEt (3 × 100 ml). The combined org. layers were washed with brine (50 ml), dried ($MgSO_4$), filtered, and concentrated. Gradient FC (95% hexanes/AcOEt → 80% hexanes/AcOEt → 65% hexanes/AcOEt) provided (+)-**33b** (615 mg, 34% yield for 3 steps). Colorless oil. $[\alpha]_D^{25} = +203$ ($c = 1.15$, $CHCl_3$). IR (neat): 2945*s*, 2879*s*, 1717*s*, 1662*s*, 1451*m*, 1272*s*, 1094*m*, 713*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.95 (*d*, *J* = 7.1, 2 H); 7.51 (*t*, *J* = 7.4, 1 H); 7.38 (*t*, *J* = 7.8, 2 H); 7.22–7.32 (*m*, 5 H); 5.16 (*dt*, *J* = 10.8, 3.6, 1 H); 4.93 (*dd*, *J* = 17.5, 11.4, 2 H); 4.48 (*s*, 2 H); 4.42 (*s*, 1 H); 3.92 (*t*, *J* = 8.1, 1 H); 3.76 (*d*, *J* = 3.8, 1 H); 3.21–3.25 (*m*, 4 H); 3.17 (*dd*, *J* = 14.0, 10.9, 1 H); 2.72–2.79 (*m*, 2 H); 2.66 (*dd*, *J* = 10.7, 3.3, 1 H); 2.18–2.31 (*m*, 7 H); 1.51–1.61 (*m*, 2 H); 1.33 (*s*, 3 H); 1.31 (*s*, 3 H); 1.30 (*s*, 3 H); 0.99 (*ddd*, *J* = 25.2, 12.9, 5.4, 1 H); 0.48 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 197.8; 165.6; 165.0; 139.3; 132.9; 130.4; 130.3; 129.7; 128.4; 128.2; 127.4; 127.1; 110.8; 82.9; 78.6; 76.9; 72.1; 69.6; 63.7; 54.5; 50.4; 43.4; 35.9; 33.7; 30.1; 29.7; 26.7; 23.2; 21.7; 20.9; 20.5; 17.0; 14.8. HR-ESI-MS: 659.3039 ($[M+Na]^+$, $C_{37}H_{48}NaO_7S^+$; calc. 659.3018).

*(+)-(1*R,2S*)-3-(Benzyloxy)-1-{[(1*R*,9a*S*,9b*S*)-1,3,3a,4,5,7,8,9,9a,9b-decahydro-1-methoxy-9a,9b-dimethyl-7-oxonaphtho[1,2-c]furan-6-yl]methyl}-3-methyl-2-[(methylsulfanyl)methoxy]butyl Benzenecarboxylate* ((+)-

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[1]) Use of toluene, instead of benzene, as with **60** (*Scheme 18*), accelerated the reaction.

33a). Under Ar, a 1.5M soln. of $LiNEt_2$ in THF and hexanes (1.5 ml) was added to a mixture of **8a** (186 mg, 0.637 mmol) and the (+)-**23** (160 mg, 0.776 mmol) in THF (0.5 ml) at $-40°$ and gradually heated to 65° over a 2 h period. The resulting mixture was stirred for 12 h at 65°, cooled to $-78°$, and then DMPU (1.5 ml) and epoxide (+)-**7** (398 mg, 1.41 mmol) were added. The mixture was warmed to r.t., stirred for 3 h, the reaction was quenched with H_2O (10 ml), and the mixture was extracted with AcOEt (3×20 ml). The combined org. layers were washed with brine (10 ml), dried ($MgSO_4$), filtered, and concentrated. This material was used without purification in the next step.

The alcohol mixture in CH_2Cl_2 (20 ml) was treated with DMAP (530 mg, 4.23 mmol) and BzCl (0.33 ml, 2.82 mmol) at r.t. The mixture was stirred for 18 h, diluted with AcOEt (30 ml), washed with H_2O (10 ml) and brine (10 ml), dried ($MgSO_4$), filtered, and concentrated. Gradient FC (90% hexanes/$Et_2O \rightarrow$ 75% hexanes/$Et_2O \rightarrow$ 50% hexanes/Et_2O) provided a mixture of benzoates.

A soln. of the crude benzoates (214 mg) in benzene (5 ml) was treated with AcONa/AcOH buffer[1]) (5 ml) at 65°. After 25 h, the mixture was cooled to r.t., the reaction was quenched with sat. aq. $NaHCO_3$ soln. (5 ml), and the mixture was extracted with AcOEt (3×20 ml). The combined org. layers were washed with brine (10 ml), dried ($MgSO_4$), filtered, and concentrated. Gradient FC (85% hexanes/AcOEt $\rightarrow$ 65% hexanes/AcOEt) provided (+)-**33a** (91.4 mg, 23% yield for 3 steps). Colorless oil. $[\alpha]_D^{25} = +144$ ($c = 0.24$, $CHCl_3$). IR (neat): 2937*s*, 1715*s*, 1664*s*, 1451*w*, 1273*s*, 1114*w*, 713*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.97 (*d*, *J* = 8.3, 2 H); 7.53 (*t*, *J* = 7.4, 1 H); 7.40 (*t*, *J* = 7.7, 2 H); 7.24–7.34 (*m*, 5 H); 5.63 (*dt*, *J* = 10.9, 3.4, 1 H); 4.95 (*dd*, *J* = 14.8, 11.4, 2 H); 4.80 (*s*, 1 H); 4.50 (*s*, 2 H); 3.79 (*d*, *J* = 3.4, 1 H); 3.76 (*t*, *J* = 7.5, 1 H); 3.43 (*dd*, *J* = 10.8, 7.7, 1 H); 3.40 (*s*, 3 H); 3.22 (*dd*, *J* = 13.9, 11.1, 1 H); 2.79 (*dd*, *J* = 16.5, 4.5, 1 H); 2.67 (*dd*, *J* = 14.0, 3.3, 1 H); 2.47–2.54 (*m*, 1 H); 2.13–2.33 (*m*, 7 H); 1.47–1.50 (*m*, 1 H); 1.38–1.43 (*m*, 1 H); 1.36 (*s*, 3 H); 1.32 (*s*, 3 H); 1.19 (*s*, 3 H); 1.04 (*ddd*, *J* = 25.6, 12.8, 5.1, 1 H); 0.55 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 197.6; 165.6; 163.2; 139.3; 133.0; 132.0; 130.2; 129.8; 128.4; 128.3; 127.5; 127.2; 107.0; 82.9; 78.7; 76.9; 71.9; 68.5; 63.7; 57.1; 48.3; 42.2; 39.4; 33.7; 30.2; 30.0; 27.0; 23.1; 21.0; 20.9; 18.5; 14.8; 10.4. HR-ESI-MS: 659.3034 ($[M + Na]^+$, $C_{37}H_{48}NaO_7S^+$; calc. 659.3018).

*(+)-(1*R*,2*S*)-3-(Benzyloxy)-1-{[(9a*S*,9b*S*)-1,3,3a,4,5,7,8,9,9a,9b-decahydro-9a,9b-dimethyl-1,7-dioxonaphtho[1,2-*c*]furan-6-yl]methyl}-3-methyl-2-[(methylsulfanyl)methoxy]butyl Benzenecarboxylate* ((+)-**37**). Under Ar, a soln. of (+)-**33b** (502 mg, 0.788 mmol) in MeCN (36 ml) and H_2O (9 ml) was treated with $HClO_4$ (70% in H_2O, 240 µl) at 55°. After 75 min, the mixture was cooled to r.t., the reaction was quenched with sat. aq. $NaHCO_3$ (5 ml), and the mixture was extracted with AcOEt (3×30 ml). The combined org. layers were washed with brine (20 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. FC afforded a mixture of aldehyde and hemiacetals **34** (343 mg, 70%) as a colorless oil, pyran **35** (94 mg, 16%) as a colorless oil, and alcohol **36** (26 mg, 8%) as a colorless oil. The alcohol **36** was further treated with HCl (1N, 0.3 ml) in THF (5 ml) and afforded additional **35** (23 mg, 90%).

Under Ar, to a soln. of NIS (233 mg, 1.04 mmol) and TBAI (76 mg, 0.207 mmol) in CH_2Cl_2 (5 ml) at 0° was added a mixture of aldehyde and hemiacetals **34b** (129 mg, 0.207 mmol) in CH_2Cl_2 (3 ml). This mixture was then warmed to r.t. for 1 h. The mixture was diluted with Et_2O (20 ml), washed with sat. aq. $Na_2S_2O_3$ soln. (10 ml), brine (5 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. FC (hexanes/AcOEt 5:1) afforded (+)-**37** (113 mg, 91% yield). Colorless crystals. M.p. 107–109°. $[\alpha]_D^{25} = +135$ ($c = 1.51$, $CHCl_3$). IR (neat): 2978*m*, 1772*s*, 1714*s*, 1665*s*, 1451*w*, 1273*s*, 1069*w*, 1026*w*, 713*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.97–7.99 (*m*, 2 H); 7.53–7.56 (*m*, 1 H); 7.41 (*t*, *J* = 7.9, 2 H); 7.22–7.33 (*m*, 5 H); 5.61 (*dt*, *J* = 10.7, 3.5, 1 H); 4.96 (*dd*, *J* = 18.9, 11.4, 2 H); 4.49 (*s*, 2 H); 4.17 (*dd*, *J* = 8.6, 7.3, 1 H); 3.79 (*d*, *J* = 3.4, 1 H); 3.74 (*dd*, *J* = 11.2, 8.7, 1 H); 2.83–2.87 (*m*, 1 H); 2.71–2.80 (*m*, 2 H); 2.06–2.40 (*m*, 7 H); 1.42–1.51 (*m*, 1 H); 1.35 (*s*, 3 H); 1.30 (*s*, 3 H); 1.19 (*s*, 3 H); 1.05 (*ddd*, *J* = 25.7, 12.9, 5.0, 1 H); 0.72 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 197.3; 178.3; 165.6; 160.3; 139.3; 133.7; 133.1; 130.1; 129.7; 128.5; 128.2; 127.5; 127.2; 83.0; 78.7; 77.0; 71.9; 68.7; 63.7; 47.2; 42.1; 38.6; 33.4; 30.3; 27.9; 26.8; 23.1; 20.9; 20.2; 19.1; 14.8; 13.2. HR-ESI-MS: 643.2727 ($[M + Na]^+$, $C_{36}H_{44}NaO_7S^+$; 643.2705).

*(−)-(2*S*,3*R*,9a*S*,9b* S*,11a*S*)-2-[1-(Benzyloxy)-1-methylethyl]-3,4,5,6,6a,7,9,9a,9b,10,11,11a-dodecahydro-9a,9b-dimethyl-9-oxo-2*H*-[2]benzofuro[5,4-f][1]benzopyran-3-yl Benzenecarboxylate* ((−)-**39**). To a soln. of (+)-**37** (220 mg, 0.354 mmol) in CH_2Cl_2 (7 ml) and Et_3SiH (7 ml) was added CF_3SO_3H (TfOH; 73 µl, 1.06 mmol) in MeCN (0.8 ml) at $-50°$, and the resultant mixture was allowed to warm to $-20°$. After 1 h, the reaction was cooled to $-40°$, quenched with sat. aq. $NaHCO_3$ soln. (3 ml), and slowly warmed to r.t. This mixture was then extracted with Et_2O (2×20 ml); the combined org. layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. FC (hexanes/AcOEt 5:1) provided (−)-**39** (156 mg, 81% yield). Colorless oil. $[\alpha]_D^{25} = -7.5$ ($c = 1.47$, $CHCl_3$). IR (neat): 2978*m*, 1772*s*, 1713*s*, 1451*w*, 1272*s*, 1070*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.99–8.01 (*m*, 2 H); 7.53–7.57 (*m*, 1 H); 7.42 (*t*, *J* = 7.7, 2 H); 7.22–7.31 (*m*, 5 H); 5.54 (app. *dd*, *J* = 3.1, 2.8, 1 H); 4.54 (*s*, 2 H); 4.17 (*dd*, *J* = 8.5, 7.5, 1 H); 4.06 (*t*, *J* = 7.8, 1 H); 3.89 (*dd*, *J* = 11.3, 8.6, 1 H); 3.60 (*s*, 1 H); 3.28 (*dd*,

J = 15.1, 3.8, 1 H); 2.72–2.79 (*m*, 1 H); 2.52–2.55 (*m*, 1 H); 2.10–2.17 (*m*, 3 H); 1.78–1.92 (*m*, 2 H); 1.52–1.59 (*m*, 2 H); 1.38 (*s*, 3 H); 1.29–1.37 (*m*, 1 H); 1.27 (*s*, 3 H); 1.25 (*s*, 3 H); 1.01 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 179.4; 165.8; 139.8; 136.0; 132.9; 130.7; 129.6; 128.6; 128.4; 128.2; 127.1; 127.0; 82.8; 76.1; 69.6; 69.0; 64.2; 47.6; 41.7; 39.4; 32.6; 26.8; 25.4; 24.0; 23.7; 22.0; 21.2; 20.5; 13.2. HR-ESI-MS: 567.2736 ($[M+Na]^+$, $C_{34}H_{40}NaO_6^+$; calc. 567.2723).

*(+)-(2*S*,3*R*,9a*S*,9b*S*,11a*S*)-3,4,5,6,6a,7,9,9a,9b,10,11,11a-Dodecahydro-2-(1-hydroxy-1-methylethyl)-9a,9b-dimethyl-9-oxo-2*H*-[2]benzofuro[5,4-*f*][1]benzopyran-3-yl Benzenecarboxylate* ((+)-**41**). Under Ar, a suspension of (−)-**39** (58.0 mg, 107 μmol) in CH_2Cl_2 (5 ml) and H_2O (0.5 ml) was treated with DDQ (43.5 mg, 192 μmol) at r.t. for 3.5 h. This mixture was then diluted with Et_2O (10 ml), washed sequentially with sat. aq. $NaHCO_3$ soln. (3 ml), and brine (3 ml). The org. layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 2:1 → hexanes/AcOEt 1:1) provided (+)-**41** (45.8 mg, 95%). Colorless oil. $[\alpha]_D^{25} = +33$ (*c* = 0.74, $CHCl_3$). IR (neat): 3512*s* (br.), 2977*s*, 1771*s*, 1713*s*, 1450*w*, 1345*w*, 1280*s*, 1118*w*, 1071*m*, 1048*m*, 714*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.96–7.98 (*m*, 2 H); 7.54–7.57 (*m*, 1 H); 7.41–7.44 (*m*, 2 H); 5.41 (*dd*, *J* = 2.7, 1.8, 1 H); 4.18 (*dd*, *J* = 8.6, 7.3, 1 H); 4.09–4.14 (*m*, 1 H); 3.89 (*dd*, *J* = 11.3, 8.6, 1 H); 3.45 (*s*, 1 H); 3.26 (*dd*, *J* = 15.1, 3.8, 1 H); 2.74–2.81 (*m*, 1 H); 2.60 (*s*, 1 H); 2.51–2.57 (*m*, 1 H); 2.09–2.20 (*m*, 3 H); 1.76–1.91 (*m*, 2 H); 1.52–1.66 (*m*, 2 H); 1.35 (*ddd*, *J* = 25.8, 12.9, 4.6, 1 H); 1.27 (*s*, 3 H); 1.23 (*s*, 3 H); 1.22 (*s*, 3 H); 1.01 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 179.3; 165.9; 136.6; 133.1; 130.3; 129.6; 128.5; 127.9; 83.1; 76.2; 71.7; 69.2; 69.0; 47.6; 41.7; 39.4; 32.6; 26.7; 26.3; 25.8; 25.3; 23.8; 21.2; 20.5; 13.2. HR-ESI-MS: 477.2251 ($[M+Na]^+$, $C_{27}H_{34}NaO_6^+$; calc. 477.2253).

*(+)-(2*S*,3*R*,9a*S*,9b*S*,11a*S*)-3,4,5,6,6a,7,9,9a,9b,10,11,11a-Dodecahydro-3-hydroxy-2-(1-hydroxy-1-methylethyl)-9a,9b-dimethyl-2*H*-[2]benzofuro[5,4-*f*][1]benzopyran-9-one* ((+)-**42**). A soln. of (+)-**41** (45.2 mg, 99.4 μmol) in MeOH (2.7 ml) and H_2O (0.3 ml) was treated with K_2CO_3 (21 mg, 149 μmol) at r.t. for 15 h. This reaction was quenched with sat. aq. NH_4Cl soln. (1 ml), and then the mixture was concentrated. The residue was extracted with AcOEt (2 × 10 ml), the combined org. layers were washed with brine (3 ml) and dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 1:2 → AcOEt) provided (+)-**42** (33.8 mg, 97%). Colorless crystals. M.p. 201–203°. $[\alpha]_D^{25} = +52$ (*c* = 0.53, $CHCl_3$). IR (neat): 3253*s* (br.), 2969*m*, 1761*s*, 1447*w*, 1231*w*, 1082*m*, 984*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.24 (*dd*, *J* = 8.3, 7.4, 1 H); 4.16 (app. *d*, *J* = 3.4, 1 H); 3.98–4.02 (*m*, 1 H); 3.93 (*dd*, *J* = 11.3, 8.6, 1 H); 3.39 (*d*, *J* = 4.5, 1 H); 3.11 (*s*, 1 H); 2.99 (*dd*, *J* = 14.9, 3.3, 1 H); 2.87–2.93 (*m*, 1 H); 2.77 (*ddd*, *J* = 15.3, 4.7, 2.0, 1 H); 2.64 (*s*, 1 H); 2.13 (app. *dd*, *J* = 11.0, 3.8, 1 H); 1.97–2.07 (*m*, 3 H); 1.68–1.82 (*m*, 3 H); 1.41 (*ddd*, *J* = 25.8, 12.9, 4.6, 1 H); 1.30 (*s*, 9 H); 1.01 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 179.4; 136.3; 128.6; 81.3; 76.7; 73.0; 69.1; 66.9; 47.9; 42.0; 39.5; 34.8; 27.6; 27.0; 25.3; 25.0; 24.0; 21.4; 21.0; 13.2. HR-ESI-MS: 373.1996 ($[M+Na]^+$, $C_{20}H_{30}NaO_5^+$; calc. 373.1991).

*(+)-(2*S*,3*R*,9a*S*,9b*S*,11a*S*)-3,4,5,6,6a,7,9,9a,9b,10,11,11a-Dodecahydro-9a,9b-dimethyl-2-{1-methyl-1-[(triethylsilyl)oxy]ethyl}-3-[(tri-ethylsilyl)oxy]-2*H*-[2]benzofuro[5,4-*f*][1]benzopyran-9-one* ((+)-**6**). Under Ar, a soln. of (+)-**42** (2.7 mg, 7.7 μmol) in CH_2Cl_2 (1 ml) was treated with 2,6-lutidine (10 μl) and TESOTf (10 μl), the resultant soln. was stirred at r.t. for 15 min. After diluting with Et_2O (10 ml), the mixture was washed sequentially with sat. aq. NH_4Cl soln. (2 ml) and brine (2 ml). The org. layer was then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. FC (hexanes/AcOEt 20:1) provided (+)-**6** (4.1 mg, 92%). Colorless oil. $[\alpha]_D^{25} = +16$ (*c* = 0.93, $CHCl_3$). IR (neat): 2954*s*, 2875*s*, 1776*s*, 1458*w*, 1375*w*, 1231*m*, 1045*m*, 1006*m*, 740*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.21–4.26 (*m*, 2 H); 3.92 (*dd*, *J* = 11.3, 8.5, 1 H); 3.89 (*t*, *J* = 7.9, 1 H); 3.01 (*s*, 1 H); 2.80–2.92 (*m*, 2 H); 2.67 (*ddd*, *J* = 14.9, 4.5, 1.8, 1 H); 2.07–2.13 (*m*, 2 H); 1.91–1.99 (*m*, 2 H); 1.68–1.86 (*m*, 3 H); 1.40 (*ddd*, *J* = 25.8, 12.9, 4.6, 1 H); 1.28 (*s*, 3 H); 1.26 (*s*, 3 H); 1.20 (*s*, 3 H); 1.02 (*s*, 3 H); 0.92–0.98 (*m*, 18 H); 0.56–0.61 (*m*, 12 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 179.5; 133.0; 130.5; 85.6; 76.7; 75.3; 69.1; 66.7; 47.9; 42.1; 39.5; 36.3; 28.2; 27.4; 26.3; 25.4; 24.1; 21.6; 21.1; 13.3; 7.1; 6.9; 6.8; 5.3. HR-ESI-MS: 601.3733 ($[M+Na]^+$, $C_{32}H_{58}NaO_5Si_2^+$; calc. 601.3721).

*(+)-(2*S*,3*R*,9a*S*,9b*S*,11a*S*)-2-[1-(Benzyloxy)-1-methylethyl]-3,4,5,6,6a,7,9,9a,9b,10,11,11a-dodecahydro-3-hydroxy-9a,9b-dimethyl-2*H*-[2]benzofuro[5,4-*f*][1]benzopyran-9-one* ((+)-**43**). Under Ar, a soln. of (−)-**39** (24.4 mg, 44.8 μmol) in MeOH (2 ml) and H_2O (0.5 ml) was treated with KOH (12.5 mg, 244 μmol), the resultant mixture was then heated to reflux for 6 h. After cooling to r.t., sat. aq. NH_4Cl soln. (5 ml) was added. This mixture was then extracted with CH_2Cl_2 (3 × 20 ml), the combined org. layers were washed with brine (10 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 5:1 → hexanes/AcOEt 2:1 → hexanes/AcOEt 1:1) provided (+)-**43** (15.9 mg, 81%, 2 steps). Colorless oil. $[\alpha]_D^{25} = +26$ (*c* = 1.11, $CHCl_3$). IR (neat): 3465*s* (br.), 2977*s*, 1771*s*, 1452*w*, 1377*w*, 1230*w*, 1047*m*, 738*w*, 697*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.22–7.32 (*m*, 5 H); 4.60 (*dd*, *J* = 56.0, 11.5, 2 H); 4.22–4.26 (*m*, 2 H); 3.91–3.95 (*m*, 2 H); 3.61 (*d*, *J* = 4.2, 1 H); 3.20 (*s*, 1 H); 2.97 (*dd*, *J* = 14.8, 3.4, 1 H); 2.87–2.93 (*m*, 1 H); 2.74–2.79 (*m*, 1 H); 1.99–2.16 (*m*, 4 H); 1.67–1.81 (*m*, 3 H); 1.43 (*s*, 3 H); 1.38 (*s*, 3 H); 1.31 (*s*, 3 H); 1.02 (*s*, 3 H). ^{13}C-NMR (125 MHz,

$CDCl_3$): 179.5; 139.3; 135.5; 129.2; 128.3; 127.4; 127.2; 83.2; 78.2; 77.1; 69.1; 66.4; 65.2; 47.9; 42.0; 39.5; 35.1; 27.1; 25.4; 24.2; 24.0; 22.4; 21.4; 21.1; 13.2. HR-ESI-MS: 441.2657 ($[M+H]^+$, $C_{27}H_{37}O_5^+$; calc. 441.2641).

*(+)-(2*R*,4b*S*,9a*S*,9b*R*,11a*S*)-2-[1-(Benzyloxy)-1-methylethyl]-5,6,6a,7,9,9a,9b,10,11,11a-decahydro-4b-(hydroperoxy)-9a,9b-dimethyl-2*H*-[2]benzofuro[5,4-*f*][1]benzopyran-3,9(4*b*H)-dione* ((+)-**45**). Under Ar, a soln. of (+)-**43** (3.9 mg, 8.9 μmol) in CH_2Cl_2 (1 ml) was treated with DMP (15% soln. in CH_2Cl_2, 60 μl), the resultant cloudy soln. was then stirred at r.t. for 1 h. This mixture was then diluted with Et_2O (10 ml), washed sequentially with sat. aq. Na_2SO_3 soln. (3 ml) and brine (3 ml). The org. layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. This crude material was used without further purification.

Under air, a soln. of the above ketone in acetone (2 ml) was treated with silica gel (200 mg). After 16 h stirring at r.t., this mixture was diluted with Et_2O (10 ml), filtered through a *Celite* pad, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 2:1 → hexanes/AcOEt 1:1) provided (+)-**45** (2.5 mg, 62%, 2 steps). Colorless oil. $[\alpha]_D^{25} = +24$ ($c = 0.28$, $CHCl_3$). IR (neat): 3329*s* (br.), 2975*s*, 1772*s*, 1684*s*, 1454*w*, 1382*w*, 1131*w*, 1068*w*, 985*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.63 (*s*, 1 H); 7.22–7.37 (*m*, 5 H); 5.85 (*d*, $J = 2.0$, 1 H); 4.54–4.59 (*m*, 3 H); 4.23 (*dd*, $J = 8.1$, 7.3, 1 H); 4.05 (*dd*, $J = 11.4$, 8.4, 1 H); 3.93 (*d*, $J = 1.6$, 1 H); 2.67–2.74 (*m*, 1 H); 2.22–2.31 (*m*, 3 H); 1.86–1.97 (*m*, 2 H); 1.66–1.73 (*m*, 2 H); 1.59 (app. *dt*, $J = 8.6$, 5.4, 1 H); 1.48 (*s*, 3 H); 1.39 (*s*, 3 H); 1.34 (*s*, 3 H); 1.07 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 194.8; 178.5; 160.8; 139.7; 128.2; 127.4; 127.2; 124.6; 89.3; 82.9; 77.2; 73.0; 68.9; 64.6; 47.7; 44.4; 40.7; 28.7; 25.3; 23.9; 23.1; 22.4; 18.7; 17.5; 12.9. HR-ESI-MS: 493.2167 ($[M+Na]^+$, $C_{27}H_{34}NaO_7^+$; calc. 493.2202).

*(+)-(2*R*,4b*S*,9a*S*,9b*R*,11a*S*)-2-[1-(Benzyloxy)-1-methylethyl]-5,6,6a,7,9,9a,9b,10,11,11a-decahydro-4b-hydroxy-9a,9b-dimethyl-2*H*-[2]benzofuro[5,4-*f*][1]benzopyran-3,9(4*b*H)-dione* ((+)-**46**). Under Ar, a soln. of (+)-**45** (2.7 mg, 5.7 μmol) in benzene (1.5 ml) was treated with PPh_3 (3 mg, 12 μmol) at r.t. for 3 h. This mixture was diluted with Et_2O (10 ml), washed sequentially with sat. aq. $NaHCO_3$ soln. (3 ml) and brine (3 ml). The org. layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 2:1 → hexanes/AcOEt 1:1) provided (+)-**46** (2.5 mg, 96%). White solid. M.p. 176–178°. $[\alpha]_D^{25} = +25$ ($c = 0.21$, $CHCl_3$). IR (neat): 3465*s* (br.), 2942*s*, 1749*s*, 1683*s*, 1453*w*, 1380*w*, 1068*w*, 737*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.36 (*d*, $J = 7.3$, 2 H); 7.32 (*t*, $J = 7.5$, 2 H); 7.23 (*d*, $J = 7.3$, 1 H); 5.83 (*d*, $J = 2.1$, 1 H); 4.69 (*dd*, $J = 10.1$, 8.2, 1 H); 4.55 (*dd*, $J = 17.7$, 11.4, 2 H); 4.23 (*dd*, $J = 8.2$, 7.0, 1 H); 4.07 (*dd*, $J = 11.6$, 8.3, 1 H); 3.91 (*d*, $J = 1.7$, 1 H); 2.68–2.74 (*m*, 1 H); 2.42 (*ddd*, $J = 22.5$, 13.6, 4.8, 1 H); 2.20–2.26 (*m*, 1 H); 1.83–2.03 (*m*, 4 H); 1.61–1.72 (*m*, 2 H); 1.49 (*s*, 3 H); 1.48 (*s*, 3 H); 1.38 (*s*, 3 H); 1.16 (*s*, 1 H); 1.02 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 195.4; 178.7; 164.5; 139.7; 128.2; 127.4; 127.1; 123.0; 83.2; 77.9; 77.2; 72.6; 68.8; 64.6; 47.7; 42.1; 40.6; 32.8; 28.2; 24.0; 23.2; 22.6; 17.8; 17.6; 12.5. HR-ESI-MS: 477.2274 ($[M+Na]^+$, $C_{27}H_{34}NaO_6^+$; calc. 477.2253).

4-Bromo-2-methyl-N,N-*bis(trimethylsilyl)benzenamine* (**48**). Under Ar, a soln. of 4-bromo-2-methylaniline (1.52 g, 8.2 mmol) in THF (35 ml) at 0° was treated with MeLi (1.4M soln. in Et_2O, 12.2 ml, 17.2 mmol), dropwise over 5 min. The resultant opaque mixture was stirred at 0° for 3 h, and TMSCl (2.2 ml, 17.2 mmol) was introduced *via* cannula, dropwise over 5 min. The resultant white suspension was then warmed to r.t. and stirred overnight. Et_2O (100 ml) was then added, followed by brine (20 ml). After separation, the org. layer was dried ($MgSO_4$). Evaporation of solvent afforded a yellow oil. Bulb-to-bulb distillation provided **48** (2.2 g, 84% yield), Pale yellow oil. IR (neat): 2954*s*, 2899*w*, 1473*s*, 1391*m*, 1263*s*, 1252*s*, 1225*s*, 1184*m*, 1119*m*, 962*s*, 930*s*, 839*s*. ^{1}H-NMR (500 MHz, C_6D_6): 7.21 (*d*, $J = 2.3$, 1 H); 7.09 (*dd*, $J = 8.3$, 2.4, 1 H); 6.52 (*d*, $J = 8.3$, 1 H); 1.94 (*s*, 3 H); 0.00 (*s*, 18 H). ^{13}C-NMR (125 MHz, C_6D_6): 145.9; 139.5; 133.6; 132.3; 129.5; 117.6; 18.9; 1.9. HR-ESI-MS: 330.0709 ($[M+H]^+$, $C_{13}H_{25}BrNSi_2^+$; calc. 330.0695).

2-Methyl-4-(3-methylbut-2-enyl)benzenamine (**5**). Under Ar, a soln. of **48** (183 mg, 0.555 mmol) in THF (11 ml) at −78° was treated with *t*-BuLi (1.7M soln. in pentane; 650 μl, 1.11 mmol). The resultant yellow soln. was stirred at −78° for 10 min, and prenyl bromide (140 μl, 1.11 mmol) was introduced dropwise *via* syringe over 5 min. The resultant orange suspension was then warmed to r.t. and stirred for 2 h. Et_2O (50 ml), then brine (10 ml) was added. After separation, the org. layer was dried ($MgSO_4$). Evaporation of solvent afforded a yellow oil, which was dissolved in MeOH (2 ml), to this soln., 1N aq. HCl soln. (3 ml) was added. After stirring at r.t. for 1 h, 10% aq. NaOH soln. was added until pH 11. The mixture was extracted with Et_2O (3 × 20 ml). Combined extracts were washed with brine (10 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Bulb-to-bulb distillation provided **5** (79.8 mg, 82% yield). Yellow oil. IR (neat): 3370*m* (br.), 2913*s* (br.), 1623*s*, 1506*s*, 1447*m*, 1277*m*, 814*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.85–6.87 (*m*, 2 H); 6.61 (*d*, $J = 7.8$, 1 H); 5.29–5.33 (*m*, 1 H); 3.49 (br. *s*, 2 H); 3.23 (*d*, $J = 7.3$, 2 H); 2.16 (*s*, 3 H); 1.73 (*d*, $J = 10.2$, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 142.3; 131.9; 131.6; 130.3; 126.6; 124.1; 122.5; 115.1; 33.5; 25.7; 17.7; 17.4. HR-CI-MS (CH_4): 175.1359 (M^+, $C_{12}H_{17}N^+$; calc. 175.1361).

*3-[5-(3-Methylbut-2-enyl)-1*H*-indol-2-yl]propan-1-ol* (**53**). Under Ar, a soln. of **5** (275 mg, 1.57 mmol) in Et_2O (6 ml) was treated with MeLi (1.4M soln. in Et_2O; 1.32 ml, 1.85 mmol) at 0°. After 30 min, the mixture was

treated with TMSCl (220 µl, 1.72 mmol) for 1 h at 0°. The mixture was then treated with *s*-BuLi (2.58 ml, 2.84 mmol) at r.t. for 70 min and cooled to −78°; neat γ-butyrolactone (50 µl, 0.66 mmol) was added, and the mixture was warmed to r.t. The reaction was quenched with sat. aq. NH_4Cl (3 ml), and the mixture was extracted with AcOEt (3 × 30 ml). The combined org. layers were washed with brine (10 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 5:1 → hexanes/AcOEt 2:1) provided **53** (116.6 mg, 73%). Yellow crystals. M.p. 66–68°. IR (neat): 3397*s* (br.), 2924*s* (br.), 1586*m*, 1479*s*, 1452*s*, 1050*s*, 800*s*. ^{1}H-NMR (500 MHz, C_6D_6): 7.57 (*s*, 1 H); 7.41 (br. *s*, 1 H); 7.14–7.20 (*m*, 2 H); 6.23 (*s*, 1 H); 5.60–5.63 (*m*, 1 H); 3.59 (*d*, *J* = 7.3, 2 H); 3.32 (*t*, *J* = 6.0, 2 H); 2.51 (*t*, *J* = 7.4, 2 H); 1.72 (*s*, 3 H); 1.70 (*s*, 3 H); 1.58–1.63 (*m*, 2 H); 1.32 (br. *s*, 1 H). ^{13}C-NMR (125 MHz, C_6D_6): 138.9; 134.9; 132.8; 130.8; 129.6; 125.2; 121.9; 119.2; 110.3; 99.4; 61.5; 34.8; 31.8; 25.5; 24.4; 17.5. HR-ESI-MS: 266.1517 ([*M* + Na]$^+$, $C_{16}H_{21}NNaO^+$; calc. 266.1521).

*2-(3-Bromopropyl)-5-(3-methylbut-2-enyl)-1*H*-indole* (**54**). Under Ar, a soln. of **53** (70.1 mg, 0.288 mmol) in CH_2Cl_2 (5 ml) was treated with PPh_3 (92 mg, 0.345 mmol) and CBr_4 (114 mg, 0.345 mmol). After 20 min, the mixture was concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 20:1 → hexanes/AcOEt 10:1) provided **54** (69.9 mg, 79%). Yellow oil. IR (neat): 3400*s* (br.), 2912*m* (br.), 1476*m*, 1452*m*, 1293*m*, 800*m*. ^{1}H-NMR (500 MHz, C_6D_6): 7.50 (*s*, 1 H); 7.15–7.17 (*m*, 1 H); 7.03 (*d*, *J* = 8.2, 1 H); 6.53 (br. *s*, 1 H); 6.09 (*d*, *J* = 1.1, 1 H); 5.56–5.60 (*m*, 1 H); 3.55 (*d*, *J* = 7.3, 2 H); 2.90 (*t*, *J* = 6.5, 2 H); 2.24 (*t*, *J* = 7.2, 2 H); 1.70 (*s*, 3 H); 1.67 (*s*, 3 H); 1.62–1.68 (*m*, 2 H). ^{13}C-NMR (125 MHz, C_6D_6): 137.3; 135.1; 133.2; 131.2; 129.8; 125.5; 122.5; 119.6; 110.6; 100.1; 35.0; 33.0; 32.2; 26.5; 25.9; 17.8. HR-CI-MS (CH_4): 305.0772 (M^+, $C_{16}H_{20}BrN^+$; calc. 305.0779).

*2-(3-Bromopropyl)-3-iodo-5-(3-methylbut-2-enyl)-1*H*-indole* (**55**). Under Ar, a soln. of **54** (56.0 mg, 0.183 mmol) in acetone (3 ml) was treated with NIS (44.4 mg, 0.197 mmol). After 20 min, the mixture was concentrated *in vacuo*, redissolved in Et_2O (15 ml), washed sequentially with sat. aq. $Na_2S_2O_3$ (5 ml) and brine (5 ml), dried ($MgSO_4$), filtered, and concentrated. Gradient FC (hexanes/AcOEt 20:1 → hexanes/AcOEt 10:1) provided **55** (70.7 mg, 90%). Yellow oil. IR (neat): 3397*s* (br.), 2911*m*, 1477*m*, 1450*s*, 1246*m*, 1230*m*, 802*m*. ^{1}H-NMR (500 MHz, C_6D_6): 7.46 (*s*, 1 H); 7.13 (*dd*, *J* = 8.2, 1.4, 1 H); 6.90 (*d*, *J* = 8.2, 1 H); 6.82 (br. *s*, 1 H); 5.47–5.51 (*m*, 1 H); 3.47 (*d*, *J* = 7.3, 2 H); 2.82 (*t*, *J* = 6.5, 2 H); 2.46 (*t*, *J* = 7.4, 2 H); 1.65 (*s*, 3 H); 1.63 (*s*, 3 H); 1.61–1.66 (*m*, 2 H). ^{13}C-NMR (125 MHz, C_6D_6): 138.2; 134.9; 134.7; 131.6; 131.5; 125.0; 123.9; 120.1; 111.1; 59.2; 34.9; 32.8; 32.1; 27.0; 25.8; 17.8. HR-CI-MS (CH_4): 430.9726 (M^+, $C_{16}H_{19}BrIN^+$; calc. 430.9746).

*1,2,3,4-Tetrahydro-7-(3-methylbut-2-enyl)cyclopenta[*b*]indole* (**57**). Under Ar, a soln. of **55** (63.2 mg, 0.146 mmol) in THF (2 ml) at −100° was treated with KHMDS (potassium 1,1,1,3,3,3-hexamethyldisilazide; 0.5M soln. in toluene, 580 µl, 0.292 mmol). After 10 min, TBSOTf (100 µl, 0.438 mmol) was added dropwise at −100°, and the soln. was warmed slowly to −78° over 10 min. Et_2O (10 ml, with 200 µl Et_3N) was then added, and the mixture was warmed to r.t. and stirred under air for 30 min. This mixture was then extracted with AcOEt (3 × 10 ml), the combined org. layers were dried ($MgSO_4$), filtered, and concentrated. FC (1% Et_2O/hexanes) provided **56** (64.3 mg, 81%) as a yellow oil. Under Ar, a soln. of **56** (30.8 mg, 56.3 µmol) in THF (2 ml) at −78° was treated with BuLi (2.5M in hexanes, 26 µl, 67 µl) for 5 min, then slowly warmed to r.t. over 45 min. This mixture was then treated with TBAF (1.0M in THF; 110 µl, 110 µmol) for 10 min. The reaction was then quenched with brine (5 ml), and the mixture was extracted with Et_2O (3 × 10 ml). The combined org. layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Gradient FC (hexanes/AcOEt 20:1 → hexanes/AcOEt 10:1) provided **57** (9.1 mg, 72%). Yellow oil. IR (neat): 3402*s* (br.), 2911*s*, 2851*s*, 1453*m*, 799*m*. ^{1}H-NMR (500 MHz, C_6D_6): 7.47 (*s*, 1 H); 7.13 (*dd*, *J* = 8.3, 1.6, 1 H); 7.03 (*d*, *J* = 8.2, 1 H); 6.43 (br. *s*, 1 H); 5.58–5.62 (*m*, 1 H); 3.57 (*d*, *J* = 7.1, 2 H); 2.75 (app. *t*, *J* = 6.9, 2 H); 2.42 (*dd*, *J* = 7.0, 6.3, 2 H); 2.22–2.28 (*m*, 2 H): 1.68 (*s*, 3 H); 1.66 (*s*, 3 H). ^{13}C-NMR (125 MHz, C_6D_6): 143.4; 140.3; 132.9; 131.0; 125.8; 125.7; 121.6; 119.4; 118.3; 111.4; 35.2; 28.9; 25.8; 24.8; 17.8. HR-CI-MS (CH_4): 226.1596 (M^+, $C_{16}H_{19}N^+$; calc. 226.1596).

*4,5-Dihydro-8-(3-methylbut-2-enyl)-1-benzazocine-2,6(1*H*,3*H*)-dione* (**58**). Compound **57** (5.2 mg, 23.1 µmol) was treated with silica gel (20 mg); after 10 min, this mixture was dissolved in Et_2O (5 ml), filtered, and concentrated. FC (hexanes/AcOEt 5:1) provided **58** (6.0 mg, 100%). Colorless crystals. M.p. 125–127°. IR (neat): 3208*s*, 3106*s*, 2967*s*, 1674*s*, 1652*s*, 1492*m*, 1456*m*, 1404*m*, 1383*m*, 1238*m*, 831*m*. ^{1}H-NMR (500 MHz, C_6D_6): 9.17 (br. *s*, 1 H); 8.24 (*d*, *J* = 2.2, 1 H); 6.98 (*dd*, *J* = 8.1, 2.2, 1 H); 6.78 (*d*, *J* = 8.1, 1 H); 5.23–5.27 (*m*, 1 H); 3.14 (*d*, *J* = 7.4, 2 H); 2.72 (br. *s*, 2 H); 2.10 (*t*, *J* = 6.9, 2 H); 1.78–1.83 (*m*, 2 H); 1.59 (*s*, 3 H); 1.50 (*s*, 3 H). ^{13}C-NMR (125 MHz, C_6D_6): 198.5; 174.6; 139.2; 136.6; 133.6; 132.9; 130.6; 130.5; 125.0; 122.6; 38.7; 33.4; 30.7; 25.4; 25.1; 17.4. HR-CI-MS (CH_4): 257.1407 (M^+, $C_{16}H_{19}NO_2^+$; calc. 254.1416).

*3-[5-(3-Methylbut-2-enyl)-1*H*-indol-2-yl]propyl Methanesulfonate* (**59**). Under Ar, a soln. of **53** (20.9 mg, 85.9 µmol) in CH_2Cl_2 (2 ml) at 0° was treated with DMAP (17 mg, 0.138 mmol) and MsCl (8 µl, 0.103 mmol) for 20 min. Sat. aq. $NaHCO_3$ soln. (1 ml) was added, and the mixture was extracted with Et_2O (10 ml). The org. layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Gradient FC (hexanes/AcOEt

2:1 → hexanes/AcOEt 1:1, containing 0.2% Et_3N) provided **59** (26.4 mg, 97%). Yellow oil. IR (neat): 3398*s* (br.), 2928*m*, 1479*m*, 1452*m*, 1350*s*, 1174*s*, 971*m*, 927*m*. ^{1}H-NMR (500 MHz, C_6D_6): 7.53 (*s*, 1 H); 7.13–7.18 (*m*, 1 H); 7.03 (br. *s*, 1 H); 6.13 (*t*, *J* = 0.6, 1 H); 5.56–5.60 (*m*, 1 H); 3.75 (*t*, *J* = 6.1, 2 H); 3.56 (*d*, *J* = 7.3, 2 H); 2.37 (*t*, *J* = 7.3, 2 H); 2.14 (*s*, 3 H); 1.70 (*s*, 3 H); 1.67 (*s*, 3 H); 1.55–1.61 (*m*, 2 H). ^{13}C-NMR (125 MHz, C_6D_6): 137.5; 135.2; 133.3; 131.2; 129.7; 125.4; 122.6; 119.6; 110.7; 100.0; 68.7; 36.4; 35.0; 29.0; 25.8; 24.0; 17.8. HR-ESI-MS: 344.1285 ([*M* + Na]$^+$, $C_{17}H_{23}NNaO_3S^+$; calc. 344.1296).

*(+)-{(2*R*,3*S*,4a*S*,6a*S*,7*S*)-2,3,4a,5,6,6a,7,8,9,10-Decahydro-6a,7-dimethyl-7-[5-(3-methylbut-2-enyl)-1*H*-indol-2-yl]-3-{1-methyl-1-[(triethylsilyl)oxy]ethyl}-2-[(triethylsilyl)oxy]-1*H*-benzo[*f*][1]benzopyran-8-yl}methanol* ((+)-**61**). Under Ar, a soln. of **5** (206 mg, 1.18 mmol) in Et_2O (4 ml) was treated with MeLi (1.6M in Et_2O, 898 µl, 0.898 mmol) at 0° for 30 min, TMSCl (155 µl, 1.53 mmol) was then added, and the resulting white suspension was stirred at 0° for 60 min. *s*-BuLi (1.3M in cyclohexane; 1.72 ml, 2.23 mmol) was then added dropwise over a period of 5 min, and this suspension was warmed to r.t. for 80 min.

Under Ar, a soln. of (+)-**6** (41.9 mg, 72.3 µmol) in Et_2O (1 ml) was treated with the above base soln. (1.7 ml) at 0° for 10 min, then warmed to r.t. for 30 min. The reaction was quenched with sat. aq. NH_4Cl soln. (1 ml), and the mixture was diluted with Et_2O (10 ml) and washed with brine (5 ml). The org. layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 5:1 → hexanes/AcOEt 1:1) provided a crude alcohol (48.9 mg) as a yellow oil.

Under Ar, a soln. of the above crude alcohol in benzene (5 ml) was heated to reflux for 48 h. After cooling to r.t., the mixture was concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 5:1 → hexanes/AcOEt 2:1) provided (+)-**61** (43.1 mg, 81% for 2 steps). Colorless oil. $[\alpha]_D^{25} = +56.5$ (*c* = 0.29, $CHCl_3$). IR (neat): 3348*m* (br.), 2954*s*, 2875*s*, 1456*w*, 1170*w*, 1097*m*, 1004*w*, 741*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.09 (br. *s*, 1 H); 7.34 (*s*, 1 H); 7.24 (*d*, *J* = 8.3, 1 H); 6.97 (*dd*, *J* = 8.3, 1.6, 1 H); 6.28 (*d*, *J* = 1.7, 1 H); 5.38–5.42 (*m*, 1 H); 4.25 (*t*, *J* = 2.7, 1 H); 3.90 (app. *dd*, *J* = 10.1, 5.2, 1 H); 3.41–3.46 (*m*, 3 H); 3.24 (*dd*, *J* = 10.2, 7.8, 1 H); 3.03 (*s*, 1 H); 2.89 (*dd*, *J* = 15.3, 2.9, 1 H); 2.68–2.72 (*m*, 1 H); 2.51–2.57 (*m*, 1 H); 2.08–2.13 (*m*, 3 H); 1.75–1.83 (*m*, 7 H); 1.56–1.62 (*m*, 3 H); 1.38–1.43 (*m*, 1 H); 1.27 (*s*, 3 H); 1.25 (*s*, 3 H); 1.20 (*s*, 3 H); 1.14 (*s*, 3 H); 0.93–0.98 (*m*, 18 H); 0.57–0.62 (*m*, 12 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 142.2; 134.9; 134.0; 133.0; 131.5; 128.1; 127.3; 124.5; 122.1; 118.8; 110.3; 102.2; 85.4; 76.6; 75.4; 66.6; 66.2; 45.7; 44.1; 42.3; 35.7; 34.4; 29.3; 28.1; 26.4; 26.3; 26.1; 25.8; 23.8; 22.5; 17.8; 15.9; 7.0; 6.9; 6.8; 5.4. HR-ESI-MS: 758.4998 ([*M* + Na]$^+$, $C_{44}H_{73}NNaO_4Si_2^+$; calc. 758.4976).

*(+)-{(2*R*,3*S*,4a*S*,6a*S*,7*S*)-2,3,4a,5,6,6a,7,8,9,10-Decahydro-6a,7-dimethyl-7-[5-(3-methylbut-2-enyl)-1*H*-indol-2-yl]-3-{1-methyl-1-[(triethylsilyl)oxy]ethyl}-2-[(triethylsilyl)oxy]-1*H*-benzo[*f*][1]benzopyran-8-yl}methyl Methanesulfonate* ((+)-**62**). Under Ar, a soln. of (+)-**61** (6.4 mg, 8.7 µmol) in CH_2Cl_2 (1 ml) was treated with DMAP (8.5 mg, 69.5 µmol) and MsCl (4 µl, 52.1 µmol) at 0°, this mixture was then warmed to r.t. for 30 min. After diluting with Et_2O (5 ml), the mixture was washed with sat. aq. $NaHCO_3$ soln. (1 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 20:1 → hexanes/AcOEt 5:1) provided (+)-**62** (6.4 mg, 93%). Yellow oil. $[\alpha]_D^{25} = +37$ (*c* = 0.30, $CHCl_3$). IR (neat): 3418*s* (br.), 2955*s*, 1457*w*, 1356*m*, 1173*s*, 1097*m*, 950*m*, 741*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.31 (br. *s*, 1 H); 7.34 (*s*, 1 H); 7.28 (*d*, *J* = 8.3, 1 H); 6.99 (*dd*, *J* = 8.3, 1.4, 1 H); 6.28 (*s*, 1 H); 5.38–5.42 (*m*, 1 H); 4.26 (*t*, *J* = 2.5, 1 H); 4.04 (br. *s*, 1 H); 3.90 (app. *dd*, *J* = 9.8, 5.2, 1 H); 3.82 (*t*, *J* = 9.6, 1 H); 3.42 (*d*, *J* = 7.3, 2 H); 3.03 (*s*, 1 H); 2.87–2.91 (*m*, 2 H); 2.85 (*s*, 3 H); 2.73 (app. *dd*, *J* = 14.8, 3.3, 1 H); 2.08–2.21 (*m*, 3 H); 1.75–1.84 (*m*, 8 H); 1.43–1.62 (*m*, 3 H); 1.27 (*s*, 3 H); 1.22 (*s*, 3 H); 1.20 (*s*, 3 H); 1.17 (*s*, 3 H); 0.93–0.99 (*m*, 18 H); 0.56–0.62 (*m*, 12 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 140.6; 134.0; 133.2; 131.6; 128.0; 124.4; 122.5; 118.8; 110.5; 102.6; 85.5; 76.4; 75.4; 74.4; 66.6; 45.5; 44.2; 39.5; 37.1; 35.8; 34.4; 29.1; 28.0; 26.4; 26.2; 25.8; 25.3; 23.4; 22.3; 17.8; 7.2; 7.0; 6.8; 5.3. HR-ESI-MS: 836.4731 ([*M* + Na]$^+$, $C_{45}H_{75}NNaO_5SSi_2^+$; calc. 836.4719).

*(+)-(2*S*,3*R*,12b*S*,12c*S*,14a*S*)-3,4,5,6,6a,7,12,12b,12c,13,14,14a-Dodecahydro-12b,12c-dimethyl-9-(3-methylbut-2-enyl)-2-{1-methyl-1-[(triethylsilyl)oxy]ethyl}-2*H*-[1]benzopyrano[5′,6′:6,7]indeno[1,2-b]indol-3-ol* ((+)-**64**), *and (+)-(2*S*,3*R*,12b*S*,12c*S*,14a*S*)-3,4,5,6,6a,7,12,12 b,12c,13,14,14a-Dodecahydro-2-(1-hydroxy-1-methylethyl)-12b,12c-dimethyl-9-(3-methylbut-2-enyl)-2*H*-[1]benzopyrano[5′,6′:6,7]indeno[1,2-b]indol-3-ol* ((+)-**65**). Under Ar, a soln. of (+)-**63** (4.7 mg, 6.5 µmol) in CH_2Cl_2 (1 ml) was treated with CBr_4 (1.9 mg, 5.8 µmol) and PPh_3 (1.7 mg, 6.5 µmol) at 0° for 30 min. The mixture was then diluted with Et_2O (5 ml), washed sequentially with sat. aq. $NaHCO_3$ soln. (1 ml) and brine (1 ml). The org. layer was then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 20:1 → hexanes/AcOEt 5:1 → hexanes/AcOEt 2:1, containing 0.5% Et_3N) afforded (+)-**64** (2.3 mg, 60%) as a colorless oil and (+)-**65** (1.3 mg, 40%) as a colorless oil.

*Data of (+)-***64**: $[\alpha]_D^{25} = +17$ (*c* = 0.10, $CHCl_3$). IR (neat): 3433*m* (br.), 3264*s* (br.), 2963*s*, 1456*m*, 1096*m*, 1079*m*, 953*w*, 745*m*. ^{1}H-NMR (500 MHz, C_6D_6): 7.63 (*s*, 1 H); 7.29–7.33 (*m*, 2 H); 7.09 (br. *s*, 1 H); 5.73

(*t*, *J* = 7.3, 1 H); 4.27 (*t*, *J* = 2.9, 1 H); 3.92 (app. *t*, *J* = 7.9, 1 H); 3.70 (*d*, *J* = 7.3, 1 H); 3.54 (*s*, 1 H); 3.07 (*s*, 1 H); 3.00–3.05 (*m*, 1 H); 2.89 (*dd*, *J* = 15.1, 3.2, 1 H); 2.82 (*dd*, *J* = 13.2, 6.5, 1 H); 2.68–2.71 (*m*, 1 H); 2.46 (*dd*, *J* = 13.1, 10.4, 1 H); 2.04–2.11 (*m*, 3 H); 1.83–1.93 (*m*, 2 H); 1.80 (*s*, 3 H); 1.79 (*s*, 3 H); 1.63–1.68 (*m*, 5 H); 1.49 (*s*, 3 H); 1.23 (*s*, 3 H); 1.10 (*t*, *J* = 8.0, 9 H); 0.89 (*s*, 3 H); 0.71 (*q*, *J* = 8.0, 6 H); 0.50 (br. *s*, 1 H). ^{13}C-NMR (125 MHz, C_6D_6): 149.4; 139.5; 136.1; 133.3; 131.1; 127.5; 126.2; 125.7; 122.0; 118.6; 118.5; 111.8; 83.3; 76.9; 72.0; 68.4; 51.2; 48.2; 43.0; 35.5; 35.2; 30.4; 27.8; 27.5; 27.4; 26.3; 25.9; 25.7; 25.5; 22.3; 16.4; 7.1; 5.6. HR-ESI-MS: 626.4001 ($[M+Na]^+$, $C_{38}H_{57}NNaO_3Si^+$; calc. 626.4005).

*Data of (+)-***65**: $[\alpha]_D^{25} = +39$ (*c* = 0.16, $CHCl_3$). IR (neat): 3435*s* (br.), 3335*s* (br.), 2968*s*, 2923*s*, 1453*m*, 1092*m*, 1076*m*, 755*w*. ^{1}H-NMR (500 MHz, C_6D_6): 7.52 (*s*, 1 H); 7.18–7.23 (*m*, 2 H); 7.01 (br. *s*, 1 H); 5.61–5.64 (*m*, 1 H); 4.03 (app. *t*, *J* = 2.7, 1 H); 3.82 (app. *t*, *J* = 7.9, 1 H); 3.59 (*d*, *J* = 7.2, 2 H); 3.47 (br. *s*, 1 H); 2.99 (*dd*, *J* = 14.7, 3.5, 1 H); 2.88–2.92 (*m*, 1 H) 2.85 (*d*, *J* = 0.8, 1 H); 2.65–2.69 (*m*, 2 H); 2.32 (*dd*, *J* = 13.3, 10.4, 1 H); 1.89–2.02 (*m*, 3 H); 1.69–1.81 (*m*, 8 H); 1.49–1.53 (*m*, 2 H); 1.30 (*s*, 3 H); 1.23 (*s*, 3 H); 1.13 (*s*, 3 H); 1.02–1.07 (*m*, 1 H); 0.77 (*s*, 3 H). ^{13}C-NMR (125 MHz, C_6D_6): 149.4; 139.5; 138.5; 133.3; 131.1; 126.8; 126.3; 125.7; 122.0; 118.8; 118.5; 111.7; 82.0; 76.9; 72.9; 67.0; 51.2; 48.3; 42.9; 35.2; 34.9; 30.3; 27.8; 27.7; 26.3; 25.9; 25.6; 25.5; 25.3; 22.1; 17.8; 16.3. HR-ESI-MS: 512.3120 ($[M+Na]^+$, $C_{32}H_{43}NNaO_3^+$; calc. 512.3141).

*(−)-(2*S*,3*R*,4a*R*,5a*S*,10a*S*,10b*R*,12a*S*)-2-[1-(Benzyloxy)-1-methylethyl]-3,4,6,7,7a,8,10,10a,10b,11,12,12a-dodecahydro-10a,10b-dimethyl-10-oxo-2*H*-[2]benzofuro[5,4-f]oxireno[2,3-e][1]benzopyran-3-yl Benzenecarboxylate* ((−)-**69a**). A soln. of (−)-**39** (68 mg, 0.125 mmol) in toluene (6 ml) was treated with $NaHCO_3$ (84 mg, 1.00 mmol) and a soln. of *m*-CPBA in toluene (1.5 ml) at r.t. for 48 h. This mixture was then diluted with AcOEt (20 ml), washed with sat. aq. Na_2CO_3 soln. (5 ml) and brine (5 ml), the org. layer was then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/Et_2O/CH_2Cl_2 3:1:1 → hexanes/AcOEt 2:1) provided (−)-**69a** (53.7 mg, 77%). Colorless oil. $[\alpha]_D^{25} = -19.2$ (*c* = 1.10, $CHCl_3$). IR (neat): 2980*m*, 1771*s*, 1715*s*, 1451*w*, 1272*s*, 1112*w*, 1072*w*, 1053*m*, 713*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.08 (app. *d*, *J* = 8.0, 2 H); 7.60 (*t*, *J* = 7.4, 1 H); 7.47 (*t*, *J* = 7.8, 2 H); 7.21–7.31 (*m*, 5 H); 5.61 (*d*, *J* = 2.8, 1 H); 4.51 (*s*, 2 H); 4.13 (*dd*, *J* = 8.4, 7.5, 1 H); 3.88–3.96 (*m*, 2 H); 3.55 (*s*, 1 H); 2.54–2.59 (*m*, 1 H); 2.28 (*dd*, *J* = 15.0, 3.7, 1 H); 2.17–2.21 (*m*, 1 H); 1.94–2.01 (*m*, 2 H); 1.78–1.85 (*m*, 2 H); 1.43–1.64 (*m*, 3 H); 1.42 (*s*, 3 H); 1.36 (*s*, 3 H); 1.35–1.38 (*m*, 1 H); 1.33 (*s*, 3 H); 1.21 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 178.5; 165.3; 139.5; 133.3; 130.0; 129.7; 128.6; 128.2; 127.0; 126.9; 83.2; 77.2; 76.4; 73.6; 69.0; 68.7; 68.6; 64.1; 58.1; 47.1; 39.7; 39.5; 33.1; 26.6; 24.7; 24.3; 22.0; 21.6; 19.1; 17.4; 11.6. HR-ESI-MS: 583.2654 ($[M+Na]^+$, $C_{34}H_{40}NaO_7^+$; calc. 583.2672).

*(+)-(2*S*,3*R*,4a*R*,5a*S*,10a*S*,10b*R*,12a*S*)-2-[1-(Benzyloxy)-1-methylethyl]-3,4,6,7,7a,8,10,10a,10b,11,12,12a-dodecahydro-3-hydroxy-10a,10b-dimethyl-2*H*-[2]benzofuro[5,4-f]oxireno[2,3-e][1]benzopyran-10-one* ((+)-**70**). Under Ar, a soln. of (−)-**69a** (21.8 mg, 38.9 μmol) in MeOH (4 ml) and H_2O (0.5 ml) was treated with KOH (17.5 mg, 311 μmol), the resultant mixture was then heated to reflux for 42 h. After cooling to r.t., sat. aq. NH_4Cl soln. (5 ml) was added. This mixture was then extracted with CH_2Cl_2 (3 × 20 ml), and the combined org. layers were washed with brine (10 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. This crude material was used without further purification.

Under Ar, a soln. of the above alcohols in CH_2Cl_2 (5 ml) was treated with DMAP (5 mg) and EDCI (15 mg). After 20-min stirring at r.t., this mixture was diluted with Et_2O (20 ml), and then washed with sat. aq. Na_2CO_3 soln. (5 ml) and brine (5 ml). The org. layer was then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 5:1 → hexanes/AcOEt 1:1 → hexanes/AcOEt 1:2) provided (+)-**70** (16.1 mg, 91%, 2 steps). Colorless oil. $[\alpha]_D^{25} = +3.5$ (*c* = 0.80, $CHCl_3$). IR (neat): 3457*s* (br.), 2981*s*, 1773*s*, 1449*w*, 1252*w*, 1055*m*, 977*w*, 737*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.24–7.33 (*m*, 5 H); 4.66 (*dd*, *J* = 19.3, 7.4, 2 H); 4.42 (*s*, 1 H); 4.29 (*s*, 1 H); 4.24 (*t*, *J* = 7.8, 1 H); 4.01 (*dd*, *J* = 11.3, 8.6, 1 H); 3.78 (app. *dd*, *J* = 9.9, 4.5, 1 H); 3.12 (*s*, 1 H); 2.83–2.88 (*m*, 1 H); 2.13–2.21 (*m*, 2 H); 1.95–2.04 (*m*, 2 H); 1.72–1.85 (*m*, 5 H); 1.52–1.57 (*m*, 1 H); 1.45 (*s*, 3 H); 1.37 (*s*, 3 H); 1.36 (*s*, 3 H); 1.25 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 178.9; 139.0; 128.3; 127.3; 127.0; 83.3; 78.6; 77.2; 73.7; 68.9; 68.6; 66.4; 65.4; 58.3; 47.3; 39.7; 39.4; 35.3; 27.2; 25.0; 24.8; 22.5; 21.7; 19.3; 17.1; 11.7. HR-ESI-MS: 479.2404 ($[M+Na]^+$, $C_{27}H_{36}NaO_6^+$; calc. 479.2410).

*(+)-(2*S*,3*R*,4a*R*,5a*S*,10a*S*,10b*R*,12a*S*)-3,4,6,7,7a,8,10,10a,10b,11,12,12a-Dodecahydro-3-hydroxy-2-(1-hydroxy-1-methylethyl)-10a,10b-dimethyl-2*H*-[2]benzofuro[5,4-f]oxireno[2,3-e][1]benzopyran-10-one* ((+)-**71**). Under Ar, a soln. of (+)-**70** (14.1 mg, 30.9 μmol) in MeOH (3 ml) was treated with 1-methylcyclohexa-1,4-diene (20 μmol) and 10% Pd/C (7 mg), the resultant mixture was then heated to reflux for 30 min. After cooling to r.t., this mixture was filtered and concentrated *in vacuo*. FC (hexanes/AcOEt 1:4) provided (+)-**71** (10.8 mg, 96%). Colorless crystals. M.p. 221–223°. $[\alpha]_D^{25} = +23$ (*c* = 0.35, $CHCl_3$). IR (neat): 3489*s* (br.), 3447*s* (br.), 2973*s*, 1769*s*, 1444*w*, 1348*w*, 1253*w*, 1084*m*, 1053*m*, 821*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.26 (*dd*, *J* = 8.5, 7.2, 1 H); 4.20–4.21 (*m*, 1 H); 4.00–4.04 (*m*, 2 H); 3.88 (*dd*, *J* = 9.9, 5.0, 1 H); 3.09 (*s*, 1 H); 2.83–2.90 (*m*, 1 H); 2.35 (*s*, 1 H); 2.11–2.22 (*m*, 2 H); 1.94–2.06 (*m*, 2 H); 1.80–1.84 (*ddd*, *J* = 13.2, 6.5, 1.8, 1 H); 1.64–1.77

(*m*, 4 H); 1.55–1.59 (*m*, 1 H); 1.34 (*s*, 3 H); 1.33 (*s*, 3 H); 1.31 (*s*, 3 H); 1.25 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 178.8; 81.0; 73.6; 73.5; 68.9; 68.7; 66.6; 58.0; 47.3; 39.7; 39.5; 35.0; 28.3; 27.1; 24.8; 24.5; 21.7; 19.3; 17.3; 11.7. HR-ESI-MS: 389.1925 ($[M+Na]^+$, $C_{20}H_{30}NaO_6^+$; calc. 389.1940).

*(−)-(2*S*,3*R*,4a*R*,5a*S*,10a*S*,10b*R*,12a*S*)-2-[1-(Benzyloxy)-1-methylethyl]-3,4,6,7,7a,8,10,10a,10b,11,12,12a-dodecahydro-10a,10b-dimethyl-3-[(triethylsilyl)oxy]-*2H*-[2]benzofuro[5,4-*f*]oxireno[2,3-*e*][1]benzopyran-10-one* ((−)-**68**). Under Ar, a soln. of (+)-**70** (15.9 mg, 34.8 μmol) in CH_2Cl_2 (2 ml) was treated with 2,6-lutidine (12 μl, 104 μmol) and TESOTf (16 μl, 70 μmol), the resultant soln. was stirred at r.t. for 20 min. After diluting with Et_2O (15 ml), the mixture was washed with sat. aq. NH_4Cl soln. (5 ml) and brine (5 ml). The org. layer was then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 20:1 → hexanes/AcOEt 5:1) provided (−)-**68** (18.5 mg, 94%). Colorless oil. $[\alpha]_D^{25} = -15.1$ ($c = 0.87$, $CHCl_3$). IR (neat): 2951*s*, 2876*s*, 1776*s*, 1452*w*, 1380*w*, 1233*w*, 1090*m*, 1053*m*, 737*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.32 (app. *d*, $J = 4.5$, 4 H); 7.23–7.25 (*m*, 1 H); 4.52 (*dd*, $J = 19.2$, 11.4, 2 H); 4.33 (app. *dd*, $J = 3.0$, 2.2, 1 H); 4.26 (*dd*, $J = 8.5$, 3.2, 1 H); 4.03 (*dd*, $J = 11.4$, 8.5, 1 H); 3.72 (*dd*, $J = 9.6$, 5.9, 1 H); 3.20 (*d*, $J = 0.9$, 1 H); 2.84–2.90 (*m*, 1 H); 2.03–2.10 (*m*, 2 H); 1.92 (*ddd*, $J = 27.4$, 13.6, 5.3, 1 H); 1.84 (app. *dd*, $J = 6.2$, 3.1, 1 H); 1.67–1.81 (*m*, 4 H); 1.50–1.54 (*m*, 1 H); 1.35 (*s*, 3 H); 1.33 (*s*, 6 H); 1.25 (*s*, 3 H); 0.92 (*t*, $J = 7.9$, 9 H); 0.60 (*q*, $J = 7.8$, 6 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 178.7;139.8; 128.1; 127.4; 127.0; 84.3; 76.9; 73.8; 69.4; 68.8; 66.2; 63.8; 58.6; 47.3; 39.7; 39.7; 37.2; 27.9; 24.8; 24.6; 21.8; 20.9; 19.4; 17.3; 11.7; 7.0; 5.2. HR-ESI-MS: 593.3263 ($[M+Na]^+$, $C_{33}H_{50}O_6NaSi^+$; calc. 593.3274).

*(−)-{(2*R*,3*S*,4a*S*,6a*R*,7*S*,10a*S*,11a*R*)-3-[1-(Benzyloxy)-1-methylethyl]-2,3,4a,5,6,6a,7,8,9,10-decahydro-6a,7-dimethyl-7-[5-(3-methylbut-2-enyl)-1*H*-indol-2-yl]-2-[(triethylsilyl)oxy]-1*H*-benzo[f]oxireno[2,3-*e*][1]-benzopyran-8-yl}methanol* ((−)-**72**). Under Ar, a soln. of **5** (253.8 mg, 1.45 mmol) in Et_2O (6 ml) was treated with MeLi (1.6M in Et_2O, 1.00 ml, 1.60 mmol) at 0° for 30 min, TMSCl (197 μl, 1.53 mmol) was then added, and the resulting white suspension was stirred at 0° for 60 min. *s*-BuLi (1.3M in cyclohexane, 2.14 ml, 2.79 mmol) was then added dropwise over a period of 5 min, and the suspension was warmed to r.t. for 80 min.

Under Ar, a soln. of (−)-**68** (39.8 mg, 69.7 μmol) in Et_2O (2 ml) was treated with the above base soln. (1.8 ml) at 0° for 10 min, then warmed to r.t. for 15 min. The reaction was quenched with sat. aq. NH_4Cl soln. (1 ml), and the mixture was diluted with Et_2O (15 ml) and washed with brine (5 ml). The org. layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 5:1 → hexanes/AcOEt 1:1) provided a crude alcohol (52.1 mg) as a yellow oil.

Under Ar, a soln. of the above crude alcohol in toluene (3 ml) was heated to reflux for 40 h. After cooling to r.t., the mixture was concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 5:1 → hexanes/AcOEt 1:1) provided (−)-**72** (38.9 mg, 76% for 2 steps). Yellow oil. $[\alpha]_D^{25} = -38.7$ ($c = 0.52$, $CHCl_3$). IR (neat): 3363*s* (br.), 2935*s*, 2875*s*, 1453*m*, 1377*m*, 1166*w*, 1094*s*, 1004*m*, 736*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.03 (br. *s*, 1 H); 7.34 (*s*, 1 H); 7.23–7.31 (*m*, 6 H); 6.98 (*dd*, $J = 8.3$, 1.4, 1 H); 6.30 (*d*, $J = 1.5$, 1 H); 5.38–5.42 (*m*, 1 H); 4.50 (*dd*, $J = 23.3$, 11.4, 2 H); 4.33 (*t*, $J = 2.6$, 1 H); 3.70 (*dd*, $J = 8.8$, 7.2, 1 H); 3.41–3.45 (*m*, 3 H); 3.32 (*t*, $J = 8.5$, 1 H); 3.20 (*s*, 1 H); 2.52–2.55 (*m*, 1 H); 2.15–2.20 (*m*, 2 H); 1.80–1.97 (*m*, 4 H); 1.76 (*s*, 3 H); 1.74 (*s*, 3 H); 1.68–1.72 (*m*, 1 H); 1.55–1.60 (*m*, 1 H); 1.38–1.47 (*m*, 1 H); 1.36 (*s*, 3 H); 1.32 (*s*, 3 H); 1.30 (*s*, 3 H); 1.22 (*s*, 3 H); 0.94 (*t*, $J = 7.9$, 9 H); 0.81–0.84 (*m*, 1 H); 0.62 (*q*, $J = 7.9$, 6 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 142.3; 139.9; 133.8; 133.0; 131.6; 128.1; 127.4; 127.0; 124.4; 122.2; 118.8; 110.3; 102.2; 83.8; 76.9; 73.7; 70.9; 66.1; 65.8; 63.8; 59.2; 45.3; 42.5; 41.4; 36.8; 34.4; 26.2; 25.8; 24.8; 24.5; 23.2; 23.1; 21.0; 20.6; 17.8; 15.0; 7.1; 5.3. HR-ESI-MS: 750.4505 ($[M+Na]^+$, $C_{45}H_{65}NNaO_5Si^+$; calc. 750.4530).

*(−)-{(2*R*,3*S*,4a*S*,6a*R*,7*S*,10a*S*,11a*R*)-3-[1-(Benzyloxy)-1-methylethyl]-2,3,4a,5,6,6a,7,8,9,10-decahydro-6a,7-dimethyl-7-[5-(3-methylbut-2-enyl)-1*H*-indol-2-yl]-2-[(triethylsilyl)oxy]-1*H*-benzo[f]oxireno[2,3-*e*][1]benzo-pyran-8-yl}methyl Methanesulfonate* ((−)-**67**). Under Ar, a soln. of (−)-**72** (10.3 mg, 14.1 μmol) in CH_2Cl_2 (2 ml) was treated with DMAP (6.1 mg, 49.4 μmol) and MsCl (2.7 μl, 35.3 μmol) at 0°; this mixture was then warmed to r.t. for 20 min. After diluting with Et_2O (5 ml), the mixture was washed with sat. aq. $NaHCO_3$ soln. (1 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 5:1 → hexanes/AcOEt 2:1) provided (−)-**67** (11.1 mg, 90%). Yellow oil. $[\alpha]_D^{25} = -48.7$ ($c = 0.55$, $CHCl_3$). IR (neat): 3415*m*, 2936*s*, 2876*s*, 1456*m*, 1356*s*, 1177*s*, 1094*m*, 952*m*, 734*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.29 (br. *s*, 1 H); 7.35 (*s*, 1 H); 7.23–7.35 (*m*, 6 H); 7.00 (*dd*, $J = 8.3$, 1.5, 1 H); 6.30 (*d*, $J = 1.2$, 1 H); 5.38–5.42 (*m*, 1 H); 4.50 (*dd*, $J = 23.3$, 11.4, 2 H); 4.33 (*t*, $J = 2.7$, 1 H); 4.02 (br. *s*, 1 H); 3.90 (*t*, $J = 9.5$, 1 H); 3.70 (app. *dd*, $J = 8.5$, 7.4, 1 H); 3.43 (*d*, $J = 7.4$, 2 H); 3.20 (*s*, 1 H); 2.84–2.86 (*m*, 4 H); 2.12–2.23 (*m*, 2 H); 1.71–1.97 (*m*, 11 H); 1.57–1.61 (*m*, 1 H); 1.38–1.44 (*m*, 4 H); 1.32 (*s*, 3 H); 1.30 (*s*, 3 H); 1.18 (*s*, 3 H); 0.94 (*t*, $J = 7.9$, 9 H); 0.62 (*q*, $J = 7.9$, 6 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 139.9; 133.3; 131.7; 128.1; 127.4; 127.0; 124.3; 122.6; 118.9; 110.5; 83.8; 76.9; 74.2; 73.6; 70.5; 66.0; 63.8; 59.3; 45.2; 41.6; 39.8; 37.0; 36.8; 34.4; 25.8; 24.8; 24.5; 22.6; 21.0; 20.4; 17.8; 7.1; 5.3. HR-ESI-MS: 828.4313 ($[M+Na]^+$, $C_{46}H_{67}NNaO_7SS_i^+$; calc. 828.4305).

*(−)-(2S,3R,4aR,5aS,13bS,13cR,15aS)-2-[1-(Benzyloxy)-1-methylethyl]-3,4,6,7,7a,8,13,13b,13c,14,15,15a-dodecahydro-13b,13c-dimethyl-10-(3-methylbut-2-enyl)-3-[(triethylsilyl)oxy]-2*H*-oxireno[2″,3″:4a′,5′][1]benzopyrano[5′,6′:6,7]indeno[1,2-*b*]indole* ((−)-**73**). Under Ar, a soln. of (−)-**67** (4.4 mg, 5.5 μmol) in toluene (1.5 ml) was treated with *t*-BuMgCl (2.0M in Et_2O, 10 μl, 20 μmol) at r.t. After 5 min, this mixture was heated to reflux for 5 min. The mixture was then cooled to r.t., the reaction was quenched with sat. aq. NH_4Cl soln. (1 ml), and the mixture was diluted with AcOEt (8 ml) and washed with brine (3 ml). The org. layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt 30:1 → hexanes/AcOEt 20:1, containing 0.5% Et_3N) provided (−)-**73** (2.8 mg, 73%). Yellow oil. $[\alpha]_D^{25} = -21.4$ ($c = 0.56$, $CHCl_3$). IR (neat): 3424*m* (br.), 3366*m* (br.), 2932*s*, 2875*s*, 1454*s*, 1375*m*, 1304*w*, 1238*w*, 1165*m*, 1091*s*, 1002*w*, 734*s*. ^{1}H-NMR (500 MHz, C_6D_6): 7.51 (*s*, 1 H); 7.39 (*d*, $J = 7.4$, 2 H); 7.25 (*t*, $J = 7.6$, 2 H); 7.14–7.19 (*m*, 3 H); 6.93 (*s*, 1 H); 5.61–5.65 (*m*, 1 H); 4.41 (*dd*, $J = 19.0, 11.4$, 2 H); 4.33 (*t*, $J = 2.7$, 1 H); 3.84 (*dd*, $J = 9.5, 6.1$, 1 H); 3.59 (*d*, $J = 7.3$, 2 H); 3.17 (*s*, 1 H); 2.95–3.01 (*m*, 1 H); 2.65 (*dd*, $J = 13.2, 6.5$, 1 H); 2.39 (*dd*, $J = 13.2, 10.5$, 1 H); 2.30 (*ddd*, $J = 19.1, 13.7, 5.2$, 1 H); 2.10–2.20 (*m*, 2 H); 1.89–1.96 (*m*, 3 H); 1.69–1.74 (*m*, 7 H); 1.54–1.60 (*m*, 2 H); 1.46 (*s*, 3 H); 1.42 (*s*, 3 H); 1.35 (*s*, 3 H); 1.20 (*s*, 3 H); 0.97 (*t*, $J = 7.9$, 9 H); 0.68–0.72 (*m*, 1 H); 0.63 (*q*, $J = 7.9$, 6 H). ^{13}C-NMR (125 MHz, C_6D_6): 150.1; 140.4; 139.2; 133.3; 129.7; 127.4; 126.2; 125.7; 121.9; 118.5; 118.2; 111.9; 84.8; 77.0; 74.9; 69.8; 66.5; 64.0; 58.4; 50.7; 49.0; 40.7; 37.2; 35.2; 30.0; 27.5; 26.6; 25.9; 25.7; 25.3; 23.2; 20.9; 19.1; 17.8; 15.5; 7.3; 5.6. HR-ESI-MS: 732.4449 ($[M + Na]^+$, $C_{45}H_{63}NNaO_4Si^+$; calc. 732.4424).

*(−)-(2S,3R,4aR,5aS,13bS,13cR,15aS)-2-[1-(Benzyloxy)-1-methylethyl]-3,4,6,7,7a,8,13,13b,13c,14,15,15a-dodecahydro-13b,13c-dimethyl-10-(3-methylbut-2-enyl)-2*H*-oxireno[2″,3″:4a′,5′][1]benzopyrano[5′,6′:6,7]indeno[1,2-*b*]indol-3-ol* ((−)-**74**). Under Ar, a soln. of (−)-**73** (16.2 mg, 22.8 μmol) in THF (3 ml) was treated with TBAF (1.0M in THF; 110 μl, 110 μmol) at r.t. for 1 h. The mixture was then diluted with Et_2O (20 ml) and washed with brine (5 ml). The org. layer was then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. FC (hexanes/AcOEt 3:1, containing 0.5% Et_3N) provided (−)-**74** (12.7 mg, 93%). Colorless oil. $[\alpha]_D^{25} = -43.5$ ($c = 0.20$, CH_2Cl_2). IR (neat): 3440*m* (br.), 3366*m* (br.), 2930*s*, 1453*s*, 1374*m*, 1305*m*, 1163*w*, 1081*m*, 801*m*, 737*m*. ^{1}H-NMR (500 MHz, CD_2Cl_2): 7.76 (br. *s*, 1 H); 7.26–7.31 (*m*, 4 H); 7.19–7.23 (*m*, 3 H); 6.88 (*dd*, $J = 8.4$, 1.4, 1 H); 5.34–5.38 (*m*, 1 H); 5.32 (*d*, $J = 1.1$, 1 H); 4.66 (*dd*, $J = 83.1, 11.3$, 2 H); 4.27–4.28 (*m*, 1 H); 4.11 (*t*, $J = 1.4$, 1 H); 3.39 (*d*, $J = 7.4$, 2 H); 3.17 (*s*, 1 H); 2.98–3.04 (*m*, 1 H); 2.71 (*dd*, $J = 13.4, 6.5$, 1 H); 2.38 (*dd*, $J = 13.4, 10.5$, 1 H); 2.30–2.37 (*m*, 1 H); 2.20–2.27 (*m*, 2 H); 2.06 (*dd*, $J = 14.1, 2.8$, 1 H); 1.82–1.92 (*m*, 2 H); 1.72–1.79 (*m*, 8 H); 1.51–1.54 (*m*, 1 H); 1.45 (*s*, 3 H); 1.37 (*s*, 3 H); 1.36 (*s*, 3 H); 1.16–1.20 (*m*, 1 H); 1.06 (*s*, 3 H). ^{13}C-NMR (125 MHz, CD_2Cl_2): 150.7; 139.7; 138.9; 133.4; 131.6; 128.7; 127.7; 127.6; 125.7; 125.1; 121.6; 118.2; 117.8; 111.5; 83.9; 78.9; 74.5; 69.3; 66.7; 65.8; 58.6; 50.7; 48.7; 40.9; 35.6; 34.8; 29.0; 27.6; 26.7; 25.8; 25.7; 25.0; 23.2; 22.6; 18.9; 17.9; 15.3. HR-ESI-MS: 618.3586 ($[M + Na]^+$, $C_{39}H_{49}NNaO_4^+$; calc. 618.3559).

*(+)-(2R,4bS,12bS,12cR,14aS)-2-[1-(Benzyloxy)-1-methylethyl]-5,6,6a,7,12,12b,12c,13,14,14a-decahydro-4b-hydroxy-12b,12c-dimethyl-9-(3-methylbut-2-enyl)-2*H*-[1]benzopyrano[5′,6′:6,7]indeno[1,2-*b*]indol-3(4b*H*)-one* ((+)-**75**). Under Ar, a soln. of (−)-**74** (4.8 mg, 8.1 μmol) in benzene (2 ml) was treated with Ph_3BiCO_3 (32 mg, 64.5 μmol), this mixture was then heated to reflux for 3.5 h. The mixture was then cooled to r.t., diluted with Et_2O (10 ml), filtered, and concentrated *in vacuo*. Gradient FC (hexanes/AcOEt, 5:1 → hexanes/AcOEt 3:1, containing 0.5% Et_3N) provided (+)-**75** (3.3 mg, 69%). Yellow oil. $[\alpha]_D^{25} = +21.3$ ($c = 0.15$, CH_2Cl_2). IR (neat): 3401*s* (br.), 2928*s*, 1675*s*, 1452*s*, 1374*w*, 1305*w*, 1126*m*, 697*w*. ^{1}H-NMR (500 MHz, C_6D_6): 7.52–7.54 (*m*, 2 H); 7.24–7.27 (*m*, 1 H); 7.13–7.19 (*m*, 5 H); 6.86 (*s*, 1 H); 5.67 (*d*, $J = 2.1$, 1 H); 5.61–5.64 (*m*, 1 H); 4.59 (*s*, 2 H); 4.52 (*dd*, $J = 10.0, 8.2$, 1 H); 3.88 (*d*, $J = 1.7$, 1 H); 3.59 (*d*, $J = 7.2$, 2 H); 2.62 (*dd*, $J = 12.7, 6.0$, 1 H); 2.36–2.54 (*m*, 3 H); 2.11–2.16 (*m*, 1 H); 1.85–1.93 (*m*, 1 H); 1.71 (*s*, 3 H); 1.69 (*s*, 3 H); 1.67 (*s*, 3 H); 1.61 (*s*, 3 H); 1.22–1.35 (*m*, 7 H); 0.77–0.97 (*m*, 2 H); 0.74 (*s*, 3 H). ^{13}C-NMR (125 MHz, C_6D_6): 194.9; 164.8; 151.9; 140.7; 139.0; 133.4; 131.1; 127.3; 126.2; 125.7; 121.9; 120.7; 118.4; 117.3; 111.8; 83.9; 77.2; 76.8; 73.1; 64.6; 50.9; 49.4; 42.9; 35.2; 33.7; 28.9; 27.9; 27.4; 25.9; 23.5; 22.6; 21.0; 19.5; 17.8; 16.4. HR-ESI-MS: 616.3385 ($[M + Na]^+$, $C_{39}H_{47}NNaO_4^+$; calc. 616.3403).

*(−)-(2R,4bS,12bS,12cR,14aS)-5,6,6a,7,12,12b,12c,13,14,14a-Decahydro-4b-hydroxy-2-(1-hydroxy-1-methylethyl)-12b,12c-dimethyl-9-(3-methylbut-2-enyl)-2*H*-[1]benzopyrano[5′,6′:6,7]indeno[1,2-*b*]indol-3(4b*H*)-one* (*=(−)-21-Isopentenylpaxilline*; (−)-**1**; *synthetic*). Under Ar, a soln. of (+)-**75** (0.7 mg, 1.2 μmol) in MeOH (1 ml) was treated with 1-methylcyclohexa-1,4-diene (10 μmol) and 10% Pd/C (7 mg), the resultant mixture was then heated to reflux for 1.5 h. After cooling to r.t., the mixture was filtered and concentrated *in vacuo*. Gradient normal-phase HPLC separation (hexanes/AcOEt 3:1 → hexanes/AcOEt 3:2 → hexanes/AcOEt 1:1, containing 0.1% Et_2NH) provided (−)-**1** (0.4 mg, 70%). Colorless oil: $[\alpha]_D^{25} = -17$ ($c = 0.03$, C_6D_6). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.51 (*s*, 1 H); 7.23 (*s*, 1 H); 6.81 (br. *s*, 1 H); 5.60–5.63 (*m*, 2 H); 4.42–4.47 (*m*, 2 H); 3.74 (*d*, $J = 1.9$, 1 H); 3.58 (*d*, $J = 7.4$, 1 H); 2.62 (*dd*, $J = 12.7, 6.0$, 1 H); 2.34–2.50 (*m*, 3 H); 2.04–2.09 (*m*, 1 H); 1.71–1.79 (*m*, 1 H); 1.69 (*s*, 3 H); 1.68 (*s*, 3 H); 1.64–1.67 (*m*, 1 H); 1.59 (*s*, 3 H); 1.55 (*s*, 3 H); 1.24–1.29

(*m*, 5 H); 0.87–0.93 (*m*, 1 H); 0.74–0.79 (*m*, 2 H); 0.70 (*s*, 3 H). ^{13}C-NMR (125 MHz, C_6D_6, resolved peaks): 198.8; 167.0; 138.8; 125.4; 121.7; 119.6; 118.2; 111.5; 84.0; 72.7; 49.1; 34.9; 33.4; 28.5; 27.6; 27.1; 27.0; 25.6; 24.4; 20.6; 19.1; 16.1. HR-ESI-MS: 526.2928 ($[M+Na]^+$, $C_{32}H_{41}NNaO_4^+$; calc. 526.2933).

(−)-21-Isopentenylpaxilline ((−)-**1**; *natural*). Yellow oil. $[\alpha]_D^{25} = -12$ ($c = 0.30$, $CHCl_3$). ^{1}H-NMR (500 MHz, C_6D_6): 7.51 (*s*, 1 H); 7.23 (*s*, 1 H); 6.81 (br. *s*, 1 H); 5.60–5.63 (*m*, 2 H); 4.51 (*s*, 1 H); 4.44 (*dd*, $J =$ 10.8, 8.1, 1 H); 3.74 (*d*, $J = 1.9$, 1 H); 3.58 (*d*, $J = 7.4$, 1 H); 2.62 (*dd*, $J = 12.7$, 6.0, 1 H); 2.34–2.50 (*m*, 3 H); 2.04–2.09 (*m*, 1 H); 1.71–1.79 (*m*, 1 H); 1.69 (*s*, 3 H); 1.68 (*s*, 3 H); 1.64–1.67 (*m*, 1 H); 1.59 (*s*, 3 H); 1.55 (*s*, 3 H); 1.24–1.29 (*m*, 5 H); 0.87–0.93 (*m*, 1 H); 0.74–0.79 (*m*, 2 H); 0.70 (*s*, 3 H). ^{13}C-NMR (125 MHz, C_6D_6, resolved peaks): 198.8; 167.0; 138.8; 125.3; 121.7; 119.6; 118.2; 111.5; 84.0; 72.7; 49.1; 34.9; 33.4; 28.5; 27.6; 27.1; 27.0; 25.6; 24.4; 20.6; 19.1; 16.1. HR-ESI-MS: 526.2926 ($[M+Na]^+$, $C_{32}H_{41}NNaO_4^+$; calc. 526.2933).

Financial support was provided by the *National Institutes of Health* (*Institute of General Medical Science*) through grant GM-29028. We thank Prof. *J. B. Gloer* (University of Iowa) for providing a generous sample of natural (−)-21-isopentenylpaxilline. We also wish to thank Dr. *G. Furst*, Dr. *R. K. Kohli* and Dr. *P. J. Caroll*, Directors of the University of Pennsylvania Spectroscopic Facilities, for assistance in obtaining NMR spectra, high-resolution mass spectra, and X-ray crystallographic analyses, respectively.

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Received August 11, 2003