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MetAP-2 Inhibitors Based on the Fumagillin Structure. Side-Chain Modification and Ring-Substituted Analogues

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The preparation of a series of new fumagillin-derived MetAP-2 inhibitors is described. The synthetic approach was designed so as to permit modification of the fumagillin backbone at sites inaccessible through semisynthesis or previously existing total syntheses. An Evans aldolization and a ring-closing metathesis allowed the preparation of a pivotal intermediate which could then be functionalized in various ways using already established or newly developed methodologies.

Introduction

Angiogenesis is believed to play an important role in tumor development as well as in certain inflammatory diseases such as rheumatoid arthritis or psoriasis. As early as 1971,[1] inhibition of angiogenesis has been suggested as a potential new therapeutic approach to the above disorders, and over the years, evidence supporting this earlier proposal has accumulated. The potential of antiangiogenic agents as new antitumor agents, alone or combined with other drugs, is currently widely accepted and several molecules structurally quite different (proteins, low molecular weight compounds) are undergoing extensive biological testing.[2] Among small molecular weight antiangiogenic agents, certain semisynthetic analogues of fumagillin have reached the stage of advanced preclinical or even clinical studies for cancer treatment.[2] Until recently, however, the mode of action of this class of molecules remained obscure.

In 1998, the identification of a biological target for fumagillin, the enzyme methionine aminopeptidase 2 (MetAP-2), and the publication of the X-ray structure of a MetAP-2-fumagillin complex[3] provided a starting point for the rational design of fumagillin analogues and triggered a renewed interest from synthetic chemists. Following the first total synthesis of fumagillin (**1**, Figure 1) by Corey et al. in 1972,[4] little (chemical) research activity in the area had been reported, but, within the past 7 years, eight total syntheses or approaches to fumagillin and analogues have been described.[5]

On the basis of inspection of the MetAP-2-fumagillin complex, Clardy et al. determined several sites of the fumagillin molecule important for binding to MetAP-2. In particular, the spiroepoxide moiety (see Figure 1) plays a crucial role by creating a covalent bond with an histidine residue (His^{231}) of the enzyme. The side chain appeared to be involved in the recognition process in two ways: in addition to establishing hydrophobic interactions with several lipophilic amino acids, it interacts with the protein via the 1′−2′ epoxide which functions as an H-bond acceptor for a defined water molecule within the enzyme's recognition site. This latter hypothesis served as a rationale for targeted modification of the fumagillin structure as recently reported by Baldwin et al.[6] The role of the side chain with respect to binding to MetAP-2 and inhibition of endothelial cell proliferation is still unclear, however: Liu et al. observed that removal of the side chain epoxide in biotinyl esters of fumagillol did not result in significant loss of activity in a MetAP-2 binding assay.[7] Additional data, from the patent literature, suggested that modification of the C1′−C8′ side chain was possible while maintaining—at least in part—biological activity.[8] Inspection of the fumagillin structure bound to MetAP-2 reveals a pocket in the vicinity of the C7−C8 (see Figure 1 for numbering) part of the molecule (see

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(2) For reviews on the clinical potential of antiangiogenic agents, see: (a) Norrby, K. *APMIS* **1997**, *105*, 417−437. (b) Liekens, S.; De Clercq, E.; Neyts, J. *Biochem. Pharmacol.* **2001**, *61*, 253−270.
(3) (a) Liu, S.; Widom, J.; Kemp, C. W.; Crews, C. M.; Clardy, J. *Science* **1998**, *282*, 1324−1327. (b) Sin, N.; Meng, L.; Wang, M. Q. W.; Wen, J. J.; Bornmann, W. G.; Crews, C. M. *Proc. Natl. Acad. Sci. U.S.A.* **1997** *94*, 6099−6103.
(4) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549−2550.
(5) (a) Kim, D.; Ahn, S. K.; Bae, H.; Choi, W. J. Kim, H. S. *Tetrahedron Lett.* **1997**, *38*, 4437−4440. (b) Taber, D. F.; Christos, T. E.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1999**, *121*, 5589−5590. (c) Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 971−974. (d) Picoul, W.; Urchegui, R.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 4797−4800. (e) Moffat, D.; Simpkins, N. S. *Synlett* **2001**, 63−64. (f) Boiteau, J.-G.; Van de Weghe, P.; Eustache, J. *Org. Lett.* **2001**, *3*, 2737−2740. (g) Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Chirality* **2003**, *15*, 156−66. (h) Picoul, W.; Bedel, O.; Haudrechy, A.; Langlois, Y. *Pure Appl. Chem.* **2003**, *75*, 235−249.
(6) Baldwin, J. E.; Bulger, P. G.; Marquez, R. *Tetrahedron* **2002**, *58*, 5441−5452.
(7) (a) Griffith, E. C.; Su, Z.; Niwayama, S.; Ramsay, C. A.; Chang, Y.-H.; Liu, J. O. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 15183−15188.
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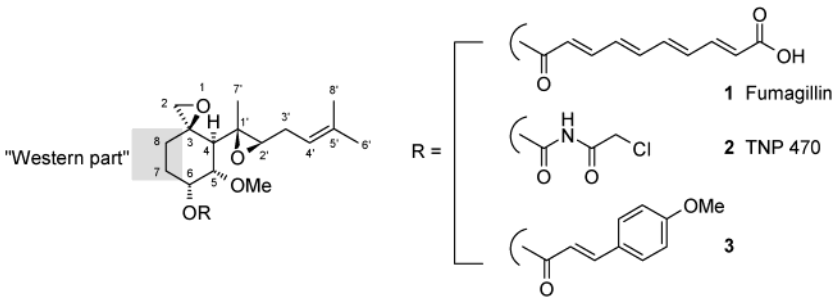


FIGURE 1. Active MetAP-2 inhibitors based on the fumagillin structure.

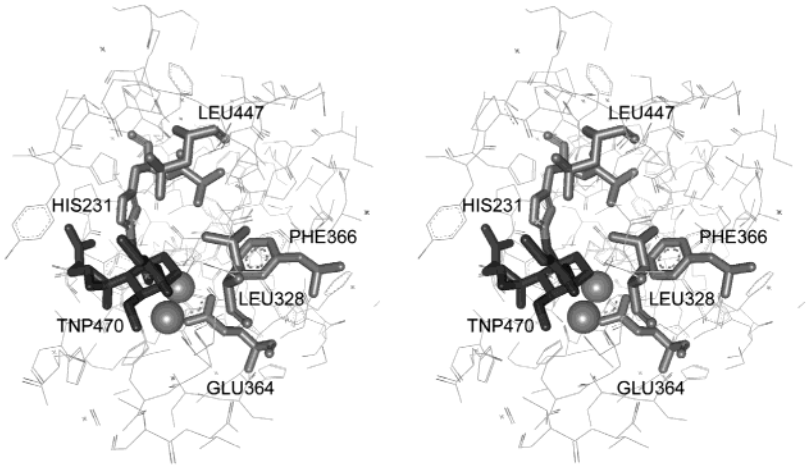


FIGURE 2. Stereoview of TNP 470 bound to Met-AP2 (only relevant amino acids are shown).

Figure 2), which we thought might be exploited for the design of improved fumagillin analogues. This information led us to target two sites of the fumagillin structure for our exploratory studies: the side chain and the C7−C8 (close to the cobalt binding site) "western" part of the fumagillin. This latter area of the molecule is not readily accessible: it bears no functionality which could serve as a starting point for derivatization, which precluded semi synthetic approaches, and the reported total syntheses were of little help for solving our problem. This led us to develop our own approach to the fumagillin skeleton, specially aimed at providing an advanced, versatile synthetic intermediate, from which a palette of analogues, modified at the C7−C8 carbons could be prepared. We recently described a synthesis of fumagillol based on this approach[5f] and we now disclose the successful application of this strategy to the preparation of novel fumagillin analogues.

Results and Discussion

Strategy for Structural Modifications. When this work was initiated, most biologically active fumagillin analogues only differed from the parent molecule (fumagillin) in the nature of the ester at position 6 (Figure 1). This is the case for TNP-470 (**2**)—the most studied fumagillin analogue—and also for a recently described series of cinnamyl esters of fumagillol which showed a strongly increased cell proliferation inhibitory activity as

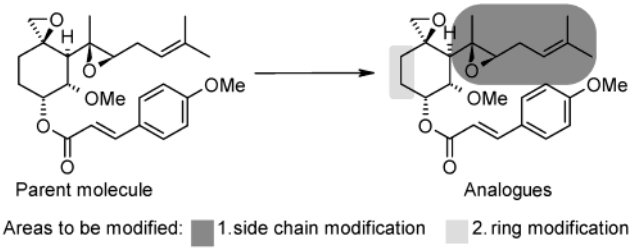


FIGURE 3. Fumagillol *p*-methoxycinnamyl ester: areas targeted for modification.

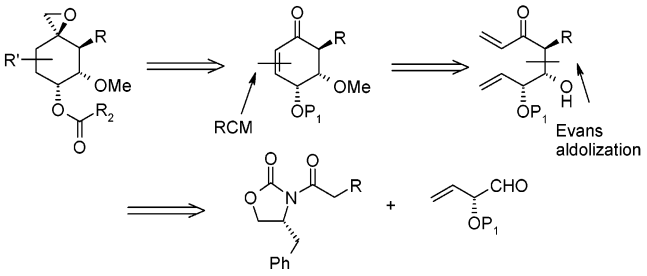
compared to fumagillin or TNP-470[9] and therefore may be considered as "the state of the art" in this research area. The *p*-methoxycinnamyl ester **3**, the most active representative of the series, was chosen as parent molecule for our studies. The planned transformations are shown in Figure 3. While the synthesis of modified side chains did not appear to constitute a major problem, the introduction of substituents at positions C7 and C8 was far from obvious and dictated our strategy depicted in Scheme 1.

An α,*β*-unsaturated ketone was chosen as advanced intermediate. α,*β*-Unsaturated ketones are highly reactive and can be easily converted to a range of functionalized molecules. As can be seen in Scheme 1, our approach to this intermediate relied on two key reactions: an Evans aldolization to establish the absolute configurations at C4 and C5, and a ring-closing metath-

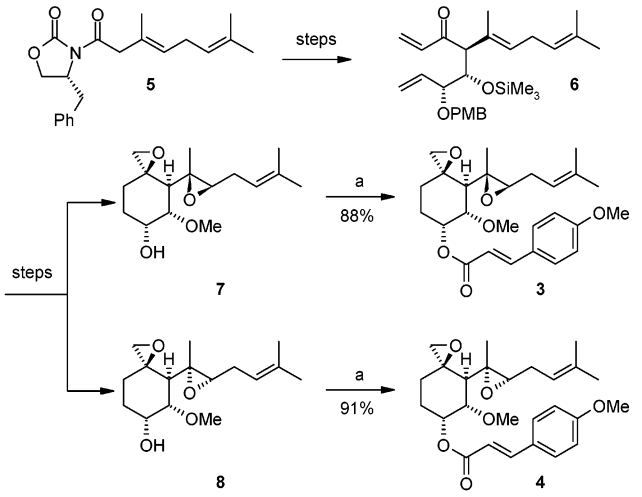
(9) Han, C. K.; Ahn, S. K.; Choi, N. S.; Hong, R. K.; Moon, S. K.; Chun, H. S.; Lee, S. J.; Kim, J. W.; Hong, C. I.; Kim, D.; Yoon, J. H.; No, K. T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 39−43.

(10) The validity of this approach has already been demonstrated in a preliminary communication (ref 5f).

SCHEME 1



SCHEME 2[a]



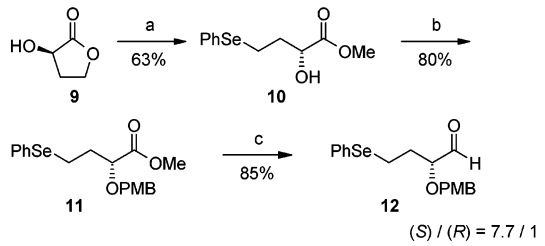
[a] Key: (a) *p*-methoxycinnamic acid (8−10 equiv), DCC (8−10 equiv), DMAP (8−10 equiv), CH_2Cl_2, 20 °C, 5 h.

esis (RCM) to form the cyclohexenyl ring. The configuration at C6 was secured using a chiral α-alkoxyaldehyde[10] at the aldolization step.

1. Synthesis of *p*-Methoxycinnamyl Ester (3) and Its (1′*S*,2′*S*)-Isomer (4). Our first task was to prepare the *p*-methoxycinnamyl ester of fumagillol **3** as the best available standard according to the literature. For this we needed fumagillol, which was conveniently prepared as recently described in a preliminary communication (Scheme 2).[5f] Briefly, the aldol obtained by condensation of the chiral isogeranyl-derived oxazolidine **5** and the chiral aldehyde **12** was converted in a few steps to the key intermediate **6**. RCM of **6** yielded a substituted cyclohexenone which was functionalized, eventually leading to fumagillol **7** and its (1′*S*,2′*S*)-isomer **8**. Treatment of fumagillol with *p*-methoxycinnamic acid and DCC/DMAP afforded our target molecule **3** in excellent yield. For comparison purposes, the (1′*S*,2′*S*)-isomer **4** was prepared from **8** in the same way.

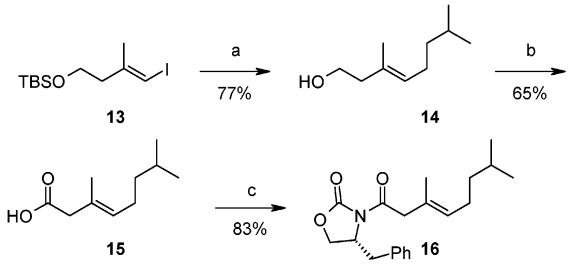
Two minor modifications of our original protocol proved to be beneficial (Scheme 3). In the original procedure, opening of lactone **9** was effected by treatment with $NaBH_4$/PhSeSePh. Although this method generally provided good yields of ester **10**, we sometimes had disappointing results when performing large-scale preparations, resulting in material loss and formation of side products. Reliability could be greatly improved using "naked" NaSePh obtained by cleavage of PhSeSePh by NaH in THF. A more annoying phenomenon was the high sensitivity of aldehyde **12** to basic or acidic conditions which manifested itself during the reduction step **11** →

SCHEME 3[a]



[a] Key: (a) (i) PhSeNa (1.8 equiv), 18-crown-6 (0.05 equiv), THF, 20 °C, 2 h, (ii) HCl (1 M), then extract with AcOEt, (iii) CH_2N_2 (excess), Et_2O, 20 °C; (b) PMBOC(CCl_3)═NH, camphorsulfonic acid (0.2 equiv), 20 °C, 20 h; (c) DIBAL-H, toluene, −78 °C, 20 min.

SCHEME 4[a]



[a] Key: (a) (i) isopentylZnCl (2.1 equiv), $Pd(PPh_3)_4$ (0.02 molar equiv), THF, 20 °C, 16 h, (ii) NBu_4F (1.1 equiv), THF, 20 °C, 2 h; (b) CrO_3 (3 equiv), H_2SO_4/H_2O/acetone, 0 °C, 15 min; (c) (i) $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C, 1 h → 20 °C, 3 h, (ii) (*R*)-(+)-4-benzyl-2-oxazolidinone (Li salt) (1 equiv), −78 °C, 20 min.

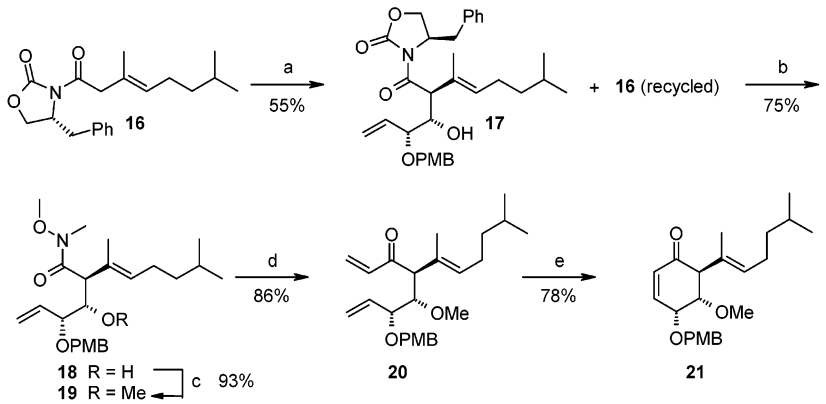
12. Although the reduction was always clean as judged by TLC and ^{1}H NMR, we observed α_D's ranging from +6° to +30° in different experiments, an obvious sign that racemization had occurred, further confirmed by ^{1}H NMR studies using the chiral shift reagent Eu(hfc)$_3$.

The reaction workup involves the formation of a gel by careful addition of methanol to the reaction mixture. This was supposed to facilitate removal of inorganic aluminum species by filtration but the result was quite disappointing. In fact this procedure led to partial racemization whose extent could be linked to the time taken for filtering-off the gel. Switching to a more classical workup (addition of methanol at −78 °C, then brine, and rapid extraction with non polar solvents such as cyclohexane) partly solved the problem, reducing racemization to an acceptable level (77% ee as measured by ^{1}H NMR), the corresponding α_D being +50°.

2. Side-Chain Modification. We did not intend to embark on extensive structure−activity relationship studies of the fumagillin side chain. Our aim, in this part of the work, was limited to: (a) clarifying the role of the side-chain epoxide and (b) identifying an alternative side chain compatible with biological activity but easier to work with than the unstable 1,4-dienic system used in our previous work on fumagillol (see Scheme 2). Our synthesis commences with the preparation of oxazolidine **16** (Scheme 4). The known vinyl iodide **13**[11] was treated with isopentyl zinc chloride in the presence of tetrakis-triphenylphosphine palladium and subsequently with TBAF to afford alcohol **14**.[12] Oxidation with CrO_3 gave

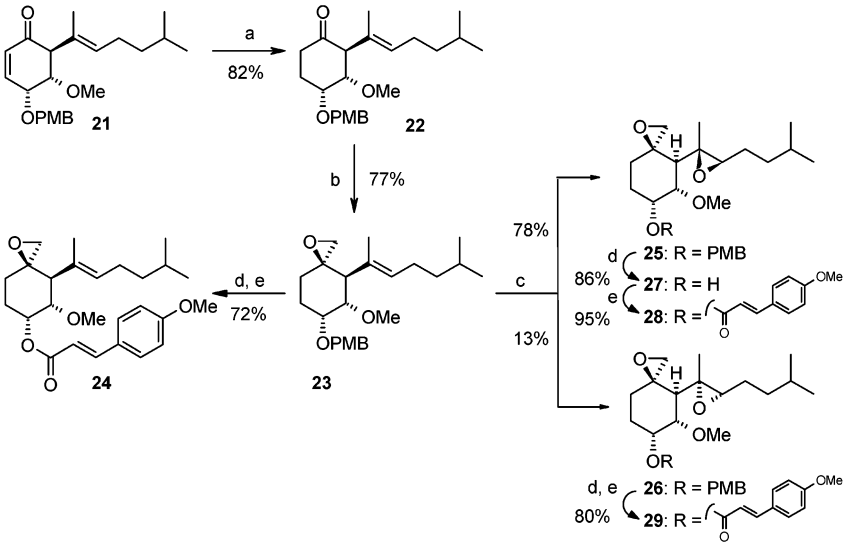
(11) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093−4096.

SCHEME 5[a]



[a] Key: (a) (i) LDA (1 equiv), THF, −78 °C, 30 min, (ii) **12** (1.1 equiv), −78 °C, 1.5 h, (iii) evaporate, (iv) NBu_4IO_4 (2 equiv), $CHCl_3$, 60 °C, 2 h; (b) $AlMe_3$ (3.5 equiv), *N*,*O*-dimethylhydroxylamine hydrochloride (3.5 equiv), THF, 20 °C, 24 h; (c) MeI (18 equiv), Ag_2O (5 equiv), Et_2O, reflux, 8 h; (d) CH_2═$CHMgBr$ (5 equiv), THF, 20 °C, 12 h; (e) Grubbs II (0.10 molar equiv), toluene, 70 °C, 45 min.

SCHEME 6[a]



[a] Key: (a) RaNi, THF, 0 °C, 20 min; (b) $Me_3S^+OI^-$ (15 equiv), NaH (10 equiv), LiI (12 equiv), DMSO/THF (1:1), 0 °C → 20 °C, 30 min; (c) *m*-CPBA (1.5 equiv), $NaHCO_3$ (6 equiv), CH_2Cl_2, 0 °C, 1 h, separate; (d) DDQ (1.1 equiv), CH_2Cl_2/H_2O, 20 °C, 1 h; (e) *p*-methoxycinnamic acid (10 equiv), DCC (10 equiv), DMAP (10 equiv), CH_2Cl_2, 20 °C, 48 h.

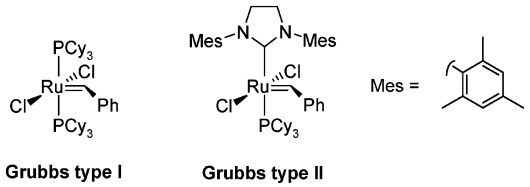


FIGURE 4. Structure of Ru-based RCM catalysts.

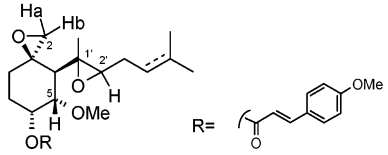
the corresponding carboxylic acid which was converted to oxazolidine **16** (Scheme 4).

We next proceeded to the preparation of the key cyclohexenone **21** (Scheme 5), from which all analogues modified in the side chain or the C7−C8 region were to be prepared. Condensation between oxazolidine **16** and aldehyde **12** afforded a single adduct **17** in fair yield,[13] to which the configuration shown in Scheme 5 was attributed on the basis of our earlier work on fumagillol.[5f] Cleavage of the chiral auxiliary by *N*,*O*-dimethylhydroxylamine/$AlMe_3$ and sequential treatment of the resulting *N*,*O*-dimethylhydroxylamide with vinylmagnesium bromide afforded the α,*β*-unsaturated ketone **20** which was submitted to RCM. Using the conditions developed earlier (Grubbs type I catalyst, $Ti(OiPr)_4$), cyclohexenone **21** was obtained in 48% yield, a value close to the 53% obtained in our fumagillol synthesis. In the

(12) Weissberger, E.; Stockis, A.; Carr, D. D.; Gienfried, J. *Bull. Soc. Chim. Belg.* **1980**, *89*, 281−288.

(13) Although aldehyde **12** is a 7.7: 1 mixture of (*R*) and (*S*) enantiomers, we could isolate only one aldol product, after deselenylation. This unexpected result has also been observed in the course of our fumagillol synthesis (see ref 5f) as well as with other similar condensations using aldehyde **12** and oxazolidinones bearing branched, *β*,*γ*-unsaturated acyl groups (unpublished results). A possible explanation is that of preferential condensation of these oxazolidinones with (*S*)-**12** possibly due to "matched" double-asymmetric induction, whereas reaction with (*R*)-**12** would be kinetically strongly disfavoured. Although we are not aware of literature reports fully supporting our tentative explanation, a related behavior of oxazolidinone boron enolates was described: Sibi, M. P.; Lu, J.; Talbacka, C. L. *J. Org. Chem.* **1996**, *61*, 7848−7855. In this report, however, the differences in yields were not as marked as in the present work.

TABLE 1. Comparison of ^{1}H NMR Signals for Cinnamyl Esters 3, 4, 28, and 29



	(1′*R*,2′*R*)-**3**	(1′*S*,2′*S*)-**4**	(1′*R*,2′*R*)-**28**	(1′*S*,2′*S*)-**29**
H-2′	δ 2.62 (t, J = 6.4 Hz)	δ 2.70 (t, J = 6.5 Hz)	δ 2.59 (dd, J = 8, 4.4 Hz)	δ 2.62 (m)
H-2a	δ 2.54 (d, J = 4.3 Hz)	δ 2.66 (d, J = 4.5 Hz)	δ 2.61 (d, J = 4.3 Hz)	δ 2.66 (d, J = 4.5)
H-2b	δ 3.00 (d, J = 4.3 Hz)	δ 3.34 (d, J = 4.5 Hz)	δ 2.91 (d, J = 4.3 Hz)	δ 3.30 (d, J = 4.5)
H-5	δ 3.70 (dd, 11.1, 2.8 Hz)	δ 3.54 (dd, 11.5, 2.8 Hz.)	δ 3.71 (dd, 11.1, 2.8 Hz.)	δ 3.55 (dd, 11.3, 2.7 Hz)

present case, however, considering the central role of **21** in our synthetic strategy, higher yields were highly desirable. In this respect, switching to Grubbs type II catalyst (Figure 4) proved to be very beneficial, raising the RCM yield to a satisfactory 78%. This very good result almost came as a surprise, considering the complete lack of success of these RCM conditions when applied to the synthesis of fumagillol itself. We hypothesize that the increased reactivity of Grubbs type II catalyst as compared to Grubbs type I allowed the trisubstituted (4′,5′) double bond in the fumagillol series to participate to the RCM process, either via RCM or cross-metathesis.

With cyclohexenone **21** in hand, we moved on to the synthesis of our first series of side-chain-modified analogues (Scheme 6). Selective reduction of the conjugated double bond in **21** was very cleanly effected with Raney nickel.[14] The resulting cyclohexanone **22** was converted in good yield to a single isolated epoxide **23** by treatment with the ylide derived from trimethylsulfoxonium iodide, in the presence of LiI.[5f,15] Oxidative removal of the PMB protecting group and acylation by *p*-methoxycinnamic acid yielded the *p*-methoxycinnamate **24**, our first target molecule. It should be noted that all cinnamyl derivatives described in this work (**24**, **28**, **29**, **32**, **39**, **45**, **51**, and **60**) contain predominantly (*E*) isomers but are always contaminated by small amounts (ca. 10%) of the (*Z*) isomer. This is of limited relevance with regard to biological results, however. Previous work from Han has shown that (*Z*)-6-cinnamyl analogues of fumagillin are 4 orders of magnitude less active than the (*E*)-isomers.[9] From **23**, epoxidation using *m*-CPBA led to the formation of two epoxides, **25** and **26**. Based upon literature precedents, we attributed the (1′*R*,2′*R*) configuration to the major isomer **25**.[16] Treatment of epoxide **25** with DDQ and acylation of the resulting alcohol by *p*-methoxycinnamic acid/DCC/DMAP afforded the (1′*R*,2′*R*) cinnamyl ester **28**. Similar treatment of the minor, (1′*S*,2′*S*) epoxide **26** gave the corresponding ester **29**. The ^{1}H NMR spectra of **28** and **29** were compared to those of their unsaturated analogues **3** and **4** obtained from fumagillol and (1′*S*,2′*S*)-fumagillol, respectively, thus confirming the structures of **28** and **29** and the validity of our earlier structure assignment to **25** and **26** (Table 1).

TABLE 2. MetAP-2 Inhibition by Fumagillin and Side-Chain-Modified Analogues

	2	**3**	**4**	**24**	**28**	**29**
IC_{50} (nM)	10 ± 2	35 ± 10	≫2500	15 ± 5	17 ± 3	≫2500

The synthesis of **28**, as compared to that of the standard molecule **3** offers several distinct advantages: (a) The highly efficient Grubbs II catalyst could be used for the RCM of **20**, leading to shorter reaction times and improved yields (78% yield as compared to 53% for **6**). (b) The spiroepoxide **23** was obtained in 77% yield (53% for the corresponding spiroepoxide in the synthesis of **3**).[5f] (c) The presence of a single double bond in **23** allowed us to use a simple, high yielding, stereoselective *m*-CPBA-based epoxidation procedure for installing the side chain epoxide instead of the regioselective but poorly stereoselective hydroxyl-directed epoxidation required for the synthesis of **3**. At this point, the inhibitory activity against MetAP-2 of the standard molecule **3** and its dihydro analogue **28** were compared. To our pleasure, both molecules showed similar potencies (35 nM vs 17 nM, respectively) (Table 2).[17−19]

In addition, we found out that epoxide **28** and olefin **24** were equally active, supporting Han's observations.[9] The most striking finding, however, was the complete lack of activity of compound **29** (and analogue **4**) (Table 2).

Although it is too early for drawing firm conclusions, the data derived from this work added to available information from the literature indicate that, in addition to being directly involved in binding with MetAP-2, the 1′−2′ epoxide may play a role in optimizing the orienta-

(14) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Meneses, R. *Synlett* **1999**, 1663−1666.

(15) Amano, S.; Ogawa, M.; Ohtsuka, M.; Childa, N. *Tetrahedron* **1999**, *55*, 2205−2224.

(16) In related side chain-modified fumagillin analogues, epoxidation always occurs on the *re-re* face of the 1′,2′ olefinic double bond to afford the (1′*R*,2′*R*) epoxide in large excess. See refs 4, 5a, 5b.

(17) Briefly, recombinant human MetAP-2 was obtained and purified to homogeneity according to the method decribed by X. Li and Y.-H. Chang (see ref 18). All the assays were performed in buffer A (10 mM Hepes buffer-pH 7.4 containing 10% glycerol and 0.5 mM $CoCl_2$) with MET-ALA-SER as the substrate (K_m = 0.7 mM).[1] To an appropriate amount of each enzyme sample, the substrate solution was added at a final concentration of 1 mM and the reaction mixture was incubated at 37 °C for 10−30 min. The reaction was stopped by adding 100 mM EDTA or by placing the samples in a boiling bath for 2 min. The release of the N-terminal methionine was quantified by measuring the absorbance at 450 nm developed by incubation with the following color reagent (see ref 19): 10 mM Hepes buffer, pH 7.4 (buffer B) containing 70 μg/mL of amino acid oxidase, 10 μg/mL of horseradish peroxidase and 1 mM o-dianisidine for 30−60 min at 37 °C. Activities were expressed as μmols of methionine produced by using the conversion factor of 1 μmol of Met per mL = 8.6 A_{450}. IC_{50} were determined by incubating the enzyme and its substrate (following the experimental conditions described above) with increasing concentrations of inhibitor.

(18) Li, X.; Chang, Y.-H. *Biochem. Biophys. Res. Commun.* **1996**, *227*, 152−159

(19) Ben-Bassat, A.; Bauer, K.; Chang, S. Y.; Myambo, K.; Boosman, A.; Chang, S. *J. Bacteriol.* **1987**, *169*, 751−757.

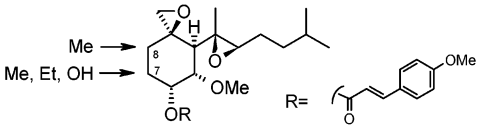
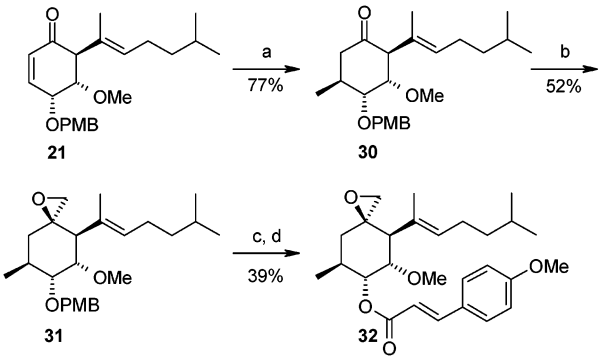


FIGURE 5. Planned modification at C7 and C8 of the fumagillin skeleton.

SCHEME 7[a]



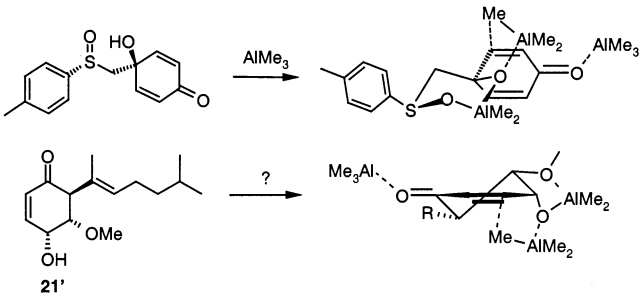
[a] Key: (a) Me_2CuLi (1.1 equiv), Et_2O, 0 °C, 1 h; (b) CH_2I_2 (5 equiv), BuLi (5 equiv), THF, −78 °C, 1 h → 20 °C, 1.5 h; (c) DDQ (1.1 equiv), CH_2Cl_2/H_2O, 20 °C, 1 h; (d) *p*-methoxycinnamic acid (10 equiv), DCC (10 equiv), DMAP (10 equiv), CH_2Cl_2, 20 °C, 24 h.

tion of the side chain within the enzyme's recognition site. If this is true, it is easy to see on a simple model that superimposing the "wrong" (1′*S*,2′*S*) and "correct" (1′*R*,2′*R*) epoxides within the recognition site places the lipophilic side chain in completely different locations. If no epoxide is present, the side chain is free from constraints due to hydrogen bonding involving the 1′−2′ epoxide and can locate itself optimally. Although confirmation of this proposal will obviously require additional work, the MetAP-2 inhibition data led us to continue our studies in the structurally simpler dihydro series i.e., starting from cyclohexenone **21**.

3. Cyclohexane Ring Modification. Having succeeded in identifying a simplified side chain for our studies, we directed our research efforts to the modification of the cyclohexane ring. Our aim at that stage was not to extensively study structure−activity relationships in the "western" part of the fumagillin molecule, a region which we felt could be important for interaction with MetAP-2, but rather to develop the methodologies needed for accessing C7 and C8. For this purpose, the introduction of simple lipophilic (methyl, ethyl) or polar (hydroxyl) groups was planned (Figure 5).

We first studied the introduction of alkyl groups at C7. Cuprate chemistry is classically used for this type of transformation. Accordingly, addition of Me_2CuLi to the cyclohexenone **21** afforded a single (within ^1H NMR detection limits) product **30** to which the structure indicated in Scheme 7 was attributed on the basis of conclusive ^1H NMR data (see Figure 6). The high stereoselectivity of the cuprate conjugate addition was expected and formation of a major isomer can be simply rationalized on the basis of steric effects as shown in Figure 6. Disappointingly, initial epoxidation attempts using Corey's dimethylsulfoxonium methylide failed completely, leading only to the formation of cyclopropane derivatives resulting from elimination of the β-methoxy group in **30**.

SCHEME 8



Switching to the Matteson's method was successful, giving the desired spiroepoxide **31**—resulting from an expected equatorial attack on the carbonyl group—(see Figure 6 for structural proof) which was converted to cinnamate **32**.

Although the complete stereoselectivity of the reaction **21** → **30** was welcome from the synthetic standpoint, it also meant that access to the—for us equally interesting—(7*R*) isomer of **30** was not possible by the cuprate method. Some years ago, Liotta, Maryanoff, et al. had shown that deprotonated *p*-quinols undergo specific Michael addition of Grignard compounds, whereby the newly introduced alkyl or vinyl group ends up cis to the directing hydroxyl group.[20] Unfortunately, attempted treatment of cyclohexenone **21′** with BuLi (to form the lithium alkoxide) and then vinylmagnesium bromide failed (no 1,4-addition was observed and **21′** was left unchanged).

More recently, Carreño et al. described a diastereoselective, sulfoxide-aided Michael addition of alkyl groups to (*R*)-4-hydroxy-4-[(p-tolylsulfinyl)methyl]-2,5-cyclohexadienones using excess trialkylalanes.[21] The proposed mechanism involves the transition state shown in Scheme 8, in which a first equivalent of trialkylalane is consumed to form an aluminum alcoolate, further chelated by the sulfoxyl oxygen, a second equivalent coordinates and activates the carbonyl group toward nucleophilic addition while a third equivalent forms a complex with the aluminum alkoxide moiety and transfers an alkyl group with total facial selectivity. We reasoned that cyclohexenone **21′** features a similar pattern of potential complexing groups suggesting that the method could be applied to our problem.

To our delight, as shown in Scheme 9, this proved to be the case and treatment of **21′** with excess trimethylaluminum cleanly led to the stereoselective formation of **33**, along with carbinol **34**, formed by the alternative 1,2-addition on the carbonyl group. Our belief that the mechanism indicated in Scheme 8 is operative is conforted by two observations: no significant reaction was observed when less than 3 equiv of trimethyl aluminum were used and there is no conjugate addition when **21** is used as a substrate. Trimethylsilylation of the free hydroxyl group in **33** was followed by spiroepoxide formation which, in this case, proceeded in high yield.[22]

(20) (a) Solomon, M.; Jamison, W. C. L.; McCormick, M.; Liotta, D. C.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C A. *J. Am. Chem. Soc.* **1988**, *110*, 3702−3704. (b) Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Synthesis* **1992**, 127−131.

(21) (a) Carreño, M. C.; Perez-Gonzalez, M.; Ribagorda, M.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 3687−3693. (b) Carreño M. C.; Perez-Gonzalez, M.; Ribagorda M.; Fisher, J. *J. Org. Chem.* **1996**, *61*, 6758−6759.

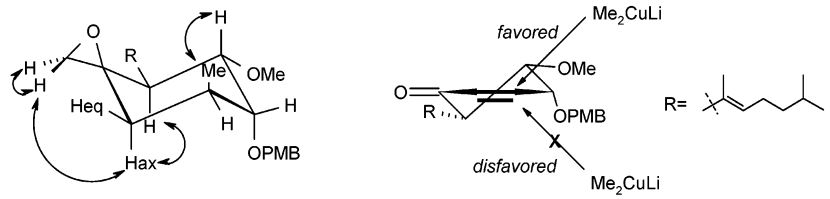
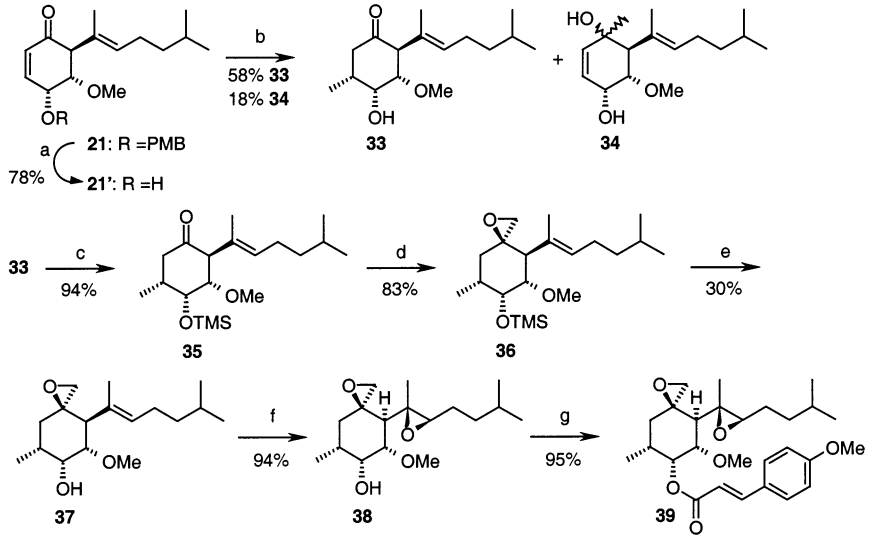


FIGURE 6. NOESY data for cyclohexyl part of **31** and rationale for the preferential formation of **30**.

SCHEME 9[a]



[a] Key: (a) DDQ (1.1 equiv), CH_2Cl_2/H_2O, 20 °C, 8 h; (b) $AlMe_3$ (10 equiv), CH_2Cl_2, 20 °C, 4 h; (c) TMSCl (2.5 equiv), NEt_3 (10 equiv), DMAP (3 molar equiv), CH_2Cl_2, 20 °C, 1 h; (d) $Me_3S^+OI^-$ (15 equiv), NaH (10 equiv), LiI (12 equiv), DMSO/THF (1:1), 0 → 20 °C, 2 h; (e) PPTS (0.1 molar equiv), MeOH/H_2O (20:1), 20 °C, 24 h; (f) *m*-CPBA (1.5 equiv), $NaHCO_3$ (6 equiv), CH_2Cl_2, 0 °C, 1 h; (g) *p*-methoxycinnamic acid (10 equiv), DCC (10 equiv), DMAP (10 equiv), CH_2Cl_2, 20 °C, 16 h.

Removal of the TMS group was sluggish, probably due to steric hindrance of the trimethylsilyloxy group by the two neighboring substituents, affording alcohol **37** in modest (30%) yield. Epoxidation of the 1′,2′-double bond proceeded exceedingly well leading to a single epoxide **38** which was converted to cinnamyl ester **39** as described previously.

To obtain some preliminary information about steric requirements at C7, we also wanted to prepare the 7-ethyl analogue of **3**. The synthesis, depicted in Scheme 9, is similar to that of **39** but, following introduction of the ethyl group, the free hydroxyl was converted to the corresponding benzoate which had been shown by Taber to be compatible with the basic conditions of Corey's epoxidation.[5b] This modification was positive, leading to a higher yield at the deprotection step. The other steps in the synthetic sequence proceeded particularly well providing the cinnamate **45** in good overall yield (Scheme 10).

Our method for introducing an hydroxyl group at C7 which is shown in Scheme 11, is based upon previous Miyashita's work on the organoselenium-mediated reduction of α,β-epoxyketones.[23] Epoxidation of the conjugated C7−C8 double bond in **21** was best effected using H_2O_2/K_2CO_3 in methanol[24] and proceeded with complete stereoselectivity to afford epoxide **46**.[25] Upon treatment by the reagent prepared in situ from $(PhSe)_2$ and $NaBH_4$, **46** underwent regioselective opening leading to β-hydroxyketone **47**. Protection of the hydroxyl group in **47** was followed by formation of the spiroepoxide. At that point, inspection of the ^1H NMR spectrum confirmed the 7 (*S*) configuration in **49** (see Figure 7 for relevant ^3J values. In particular, note the lack of large axial-axial coupling between H-7 and one of the H-8's). Finally, treatment with cinnamic acid in the presence of DCC and DMAP and removal of the silyl protecting groups yielded the 7-hydroxy analogue **51**.

Finally, to complete our synthetic studies, we wanted to establish methods allowing the preparation of C8-substituted analogues of **3**. Our approach was to introduce an hydroxymethyl group at that position—which seemed to be feasible via a Baylis-Hillman reaction—and to use the hydroxyl group as a starting point for further modification. This approach, which proved to be fruitful, although in an unexpected way, is shown in Scheme 12.

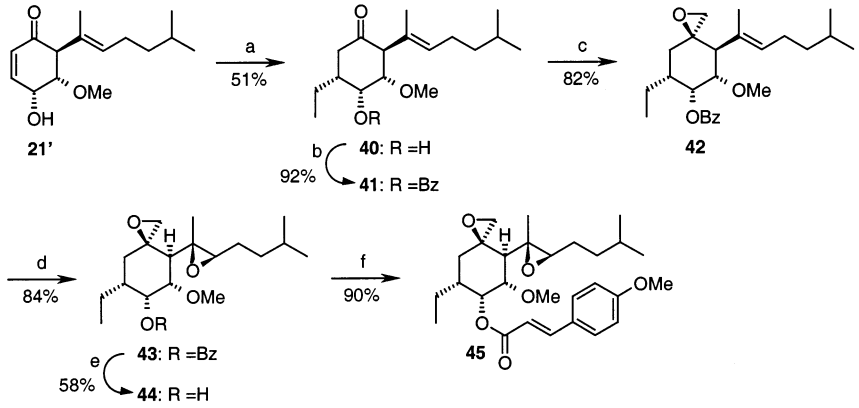
(22) Attempted epoxidation of alcohol **33** led to the exclusive formation of a cyclopropyl ketone as observed earlier. Facile intramolecular deprotonation by the alcoolate derived from OH-6 followed by β-elimination of the methoxy group may explain this result. During this work, this type of β-elimination constantly constituted a potential problem which required particular attention.

(23) Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron* **1997**, *53*, 12469−12486.

(24) The alternative TBHP/triton B method led to erratic results (yields ranging from 25% to 75%) the major problem being the oxidation of the PMB group to the corresponding *p*-methoxybenzoate.

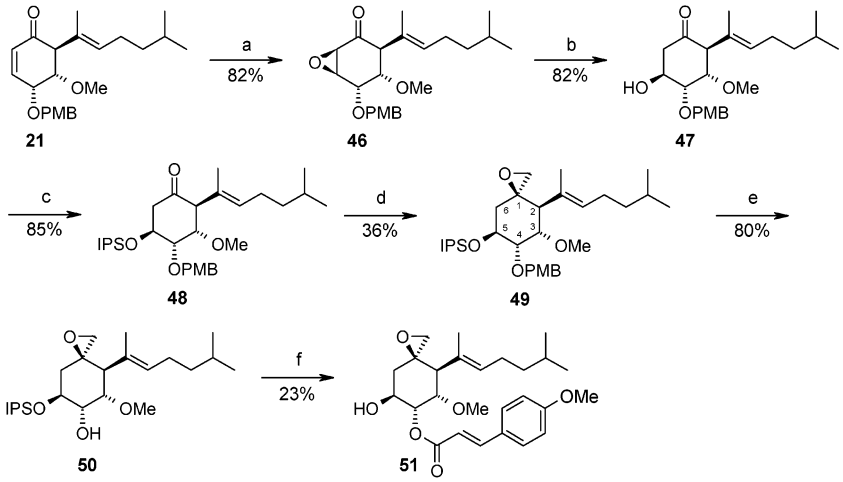
(25) On the basis of literature precedents, the epoxide function was expected to be located trans to the OPMB group: Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Org. Chem.* **1997**, *62*, 3984−3988.

SCHEME 10[a]



[a] Key: (a) $AlEt_3$ (10 equiv), CH_2Cl_2, 20 °C, 4 h; (b) Benzoic acid (10 equiv), DCC (10 equiv), DMAP (10 equiv), CH_2Cl_2, 20 °C, 16 h; (c) $Me_3S^+OI^-$ (15 equiv), NaH (10 equiv), LiI (12 equiv), DMSO/THF (1:1), 0 → 20 °C, 2 h; (d) *m*-CPBA (1.5 equiv), $NaHCO_3$ (6 equiv), CH_2Cl_2, 20 °C, 1 h; (e) K_2CO_3, MeOH, 20 °C, 16 h; (f) *p*-methoxycinnamic acid (12 equiv), DCC (12 equiv), DMAP (12 equiv), CH_2Cl_2, 20 °C, 16 h.

SCHEME 11[a]



[a] Key: (a) H_2O_2 (3 equiv), K_2CO_3, (0.1 equiv), MeOH, 0 °C, 30 min; (b) $(PhSe)_2$ (1.5 equiv), $NaBH_4$ (3 equiv), AcOH (0.5 equiv), 0 °C, 15 min; (c) ^{i}Pr(Me)$_2$SiCl (1.5 equiv), DMAP (2 equiv), DMF/THF (1/1: v/v), 20 °C, 1 h; (d) CH_2I_2 (5 equiv), BuLi (5 equiv), −78 °C, 1 h → 20 °C, 1.5 h; (e) DDQ (1.2 equiv), CH_2Cl_2/H_2O, 20 °C, 2 h; (f) (i) *p*-methoxycinnamic acid (10 equiv), DCC (10 equiv), DMAP (10 equiv), CH_2Cl_2, 20 °C, 36 h, (ii) TBAF (1 equiv), 20 °C, 30 min.

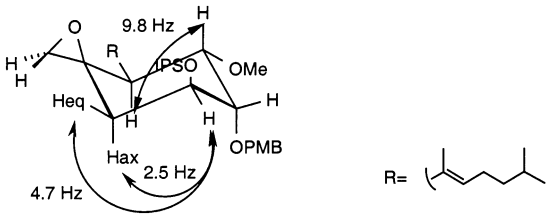


FIGURE 7. Coupling constants in spiroepoxide **49**.

The synthesis commences by the treatment of cyclohexenone **21** with formaldehyde, in the presence of tributylphosphine to give the hydroxymethylated derivative **52** in good yield.[26] We had initially planned to reduce the conjugated system in **53** by RaNi, a reaction which had proved very reliable when applied to **21**. Unfortunately, **53** was unreactive under a variety of conditions. Reduction of the conjugated double could be effected, however, using Et_3SiH (TESH) in the presence of Wilkinson's catalyst, affording silyl enol ether **54**.[27] Our plans were then to remove the TES group, form the spiroepoxide and introduce further functionality based on the hydroxyl group modification. In fact, formation of the desired α-hydroxymethyl cyclohexanone was never observed. Instead, cleavage of the TES group by fluoride treatment led to double elimination of the TBS and (again) the methoxy group to afford an α,β−α′,β′ doubly unsaturated ketone, while acidic treatment of **54** cleanly afforded the α,β-unsaturated ketone **55**. Although the expected intermediate was not obtained, **55** fulfils our requirements even better. For example, RaNi reduction led to a mixture of the two C8 derivatives **56** and **57**. We found that only ketone **57** underwent epoxidation, using Matteson's conditions to give a single epoxide **58** in 54% yield probably reflecting the increased steric hindrance on both faces of the carbonyl group in **56**, relative to **57**. The synthesis

(26) (a) Kabat, M. M.; Kiegel, J.; Cohen, N.; Toth, K.; Wovkulich, P. M.; Uskokovíc, M. R. *J. Org. Chem.* **1996**, *61*, 118−124. (b) Taylor, R. J. K.; Thorsten, G. *Tetrahedron Lett.* **2002**, *43*, 3573−3576.

(27) Liu, H.-J.; Browne, E. N. C. *Can. J. Chem.* **1980**, *59*, 601−607.

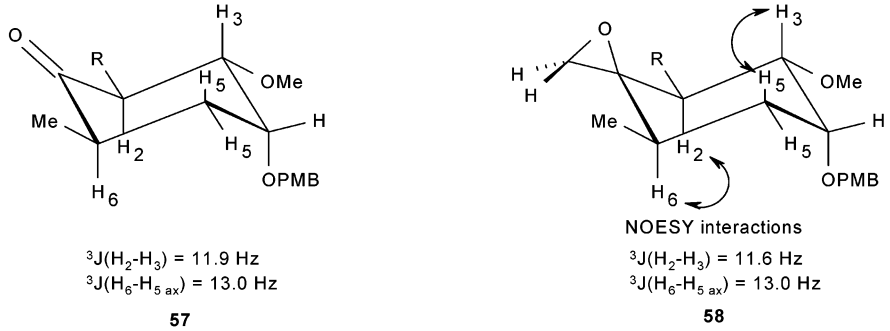
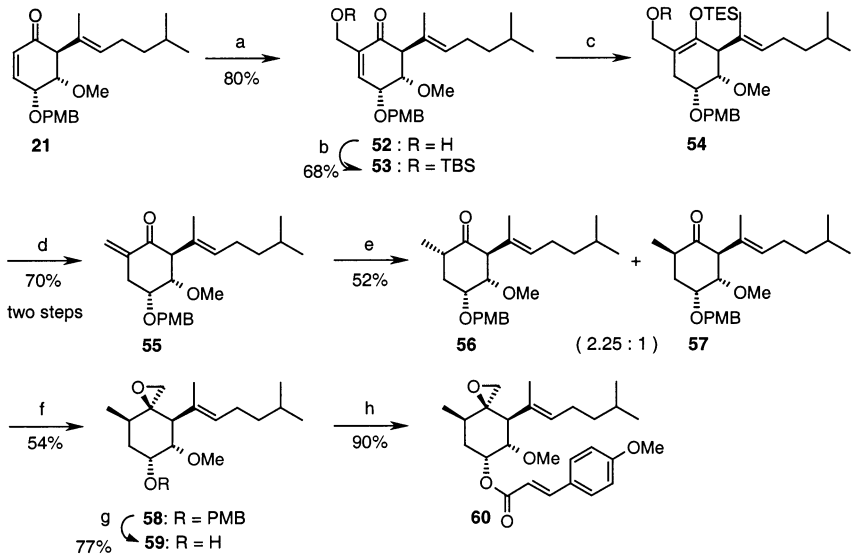


FIGURE 8. Structure determination of ketone **57** and epoxide **58**: relevant NMR data.

SCHEME 12[a]



[a] Key: (a) PBu_3 (0.85 equiv), HCHO, (40% in water, 2.6 equiv), THF, 20 °C, 16 h; (b) TBSCl (1.1 equiv), DMAP (1.5 equiv), THF, 20 °C, 4 h; (c) Et_3SiH (35 equiv), $RhCl(PPh_3)_3$ (0.03 molar equiv), toluene, 65 °C, 4 h; (d) TFA (1 M, 1 molar equiv), THF/H_2O (1/1 v/v), 20 °C, 1.5 h; (e) RaNi, THF, 0 °C, 2 h; (f) CH_2I_2 (5 equiv), BuLi (5 equiv), −78 °C, 45 min → 20 °C, 1.5 h; (g) DDQ (1.2 equiv), CH_2Cl_2/H_2O, 20 °C, 1 h; (h) *p*-methoxycinnamic acid (10 equiv), DCC (10 equiv), DMAP (10 equiv), CH_2Cl_2, 20 °C, 16 h.

TABLE 3. MetAP-2 Inhibition by Fumagillin and Ring-modified Analogues

	2	**3**	**32**	**39**	**45**	**51**	**60**
IC_{50} (nM)	10 ± 2	35 ± 10	250	95 ± 5	>2500	35	70

was completed to give our last target molecule, the cinnamate **60** (see structure determination in Figure 8).

The results obtained in the inhibition assay are shown in Table 3. As can be seen, introduction of substituents at positions 7 or 8 of the fumagillin skeleton is compatible with biological activity in the MetAP-2 assay. The possibilities for modification in this area of the molecule, however, appear to be limited as shown by the sharp decrease of activity when replacing H by Me, then Et at position 7 (compare **3**, **39**, and **45**). Introduction of a hydroxyl group at the same position is also possible, as well as a methyl group at position 8. None of these modifications, however, led to an improvement of the biological activity as compared to the standard compounds **2** and **3**.

4. Conclusion. In summary, we have demonstrated the validity of the RCM-based approach for the synthesis of new types of modified fumagillin analogues. Our strategy was 2-fold: in the first part of the work, we identified a simplified side chain compatible with biological activity. In the second part, methods were developed aimed at modifying a precise, difficult to access, part of the fumagillin molecule and a series of simple analogues were prepared.

In the course of our synthesis, a new (to the best of our knowledge), efficient, and stereoselective conjugate addition of organoaluminum compounds to highly functionalized α,*β*-unsaturated ketones was discovered. In our case, the method, whose scope we have not yet examined, nicely complemented the conjugate addition of cuprates. We have also developed a mild one-pot reduction/elimination sequence of α-hydroxymethyl-α,*β*-unsaturated ketones which may be of general usefulness for the formation of sensitive α-methylene ketones.

The results obtained with the side-chain-modified analogues **24**, **28**, and **29** show that the side-chain epoxide is dispensable, in line with Liu's observations. However, the striking difference between the two epoxides **28** and **29** suggests that, besides its possible role as H-bond acceptor, the 1′−2′ epoxide may help correctly orientating the side chain of fumagillin and analogues

for recognition by MetAP-2. More research to check the validity of this hypothesis is warranted.

Preliminary results obtained with the C7−C8-modified compounds suggest that modification in this part of the fumagillin skeleton is limited to the introduction of small substituents. This, of course would have to be confirmed in more detailed studies which should include other type of small polar, acidic, or basic substituents.

Experimental Section

General Methods. All manipulations were carried out in dry solvents under an atmosphere of dry Ar. Commercially available reagents were used without further purification. Et_2O and THF were freshly distilled from Na/benzophenone prior to use. DMF, CH_2Cl_2, and toluene were distilled from CaH_2. Evaporations of solvents were done with a rotary evaporator. Flash chromatography was conducted on silica gel (230−400 mesh). ^{1}H NMR were performed at 250 or 400 MHz and ^{13}C NMR at 62.9 or 100 MHz and calibrated on residual solvents signals.

***p*-Methoxycinnamic Acid (3*R*,4*S*,5*S*,6*R*)-5-Methoxy-4-[(1*R*,2*R*)-1,2-epoxy-1,5-dimethylhexyl]-1-oxaspiro[2.5]oct-6-yl Ester (3).** *p*-Methoxycinnamic acid (70 mg, 396 μmol, 8 equiv), followed by DMAP (48 mg, 396 μmol, 8 equiv) and DCC (50 mg, 396 μmol, 8 equiv) were added to a solution of fumagillol (14 mg, 49 μmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 5 h at 20 °C, and then the solvent was removed in vacuo and the residue passed over a short pad of silica gel (cyclohexane/AcOEt 1/1). Chromatography on preparative TLC (hexane/ethyl acetate, 8/2) afforded pure **3** (19.7 mg, 88%) as a colorless oil. $[\alpha]^{20}_D = -45$ ($c = 95$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 7.62 (d, $J = 16$ Hz, 1H); 7.46 and 6.89 (2d, $J = 8.8$ Hz, 4H); 6.36 (d, $J = 16$ Hz, 1H); 5.74 (m, 1H); 5.21 (tm, $J = 7.4$ Hz, 1H); 3.83 (s, 3H); 3.70 (dd, $J = 2.8$, 11.1 Hz, 1H); 3.45 (s, 3H); 3.00 (d, $J = 4.3$ Hz, 1H); 2.62 (t, $J = 6.4$ Hz, 1H); 2.54 (d, $J = 4.3$ Hz, 1H); 2.37 (m, 1H); 2.23−1.80 (m, 4H); 2.05 (d, $J = 11.1$ Hz, 1H); 1.74 (s, 3H); 1.65 (s, 3H); 1.23 (s, 3H); 1.10 (ddd, $J = 2.7$, 4.6, 13.4 Hz, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 166.9, 161.3, 144.5, 134.8, 129.7, 127.2, 118.6, 115.9, 114.3, 79.2, 66.2, 61.0, 59.5, 58.5, 56.6, 55.3, 50.9, 48.3, 29.4, 27.4, 25.7, 25.7, 18.0, 13.9.

***p*-Methoxycinnamic Acid (1*R*,4*S*,5*S*,6*R*)-5-Methoxy-4-[(1*S*,2*S*)-1,2-epoxy-1,5-dimethylhexyl]-1-oxaspiro[2.5]oct-6-yl Ester (4).** *p*-Methoxycinnamic acid (75 mg, 425 μmol, 10 equiv) followed by DMAP (52 mg, 425 μmol, 10 equiv) and DCC (87 mg, 425 μmol, 10 equiv) were added to a solution of 1′,2′-*epi*-fumagillol (12 mg, 42 μmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 5 h at 20 °C, and then the solvent was removed in vacuo and the residue passed over a short pad of silica gel (cyclohexane/AcOEt 1/1). Chromatography on preparative TLC (hexane/ethyl acetate, 7/3) afforded **4** (16.7 mg, 91%), which contains 10% of the *Z*-isomer. $[\alpha]^{20}_D = -184$ ($c = 0.825$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 7.63 (d, $J = 16$ Hz, 1H); 7.48 and 6.90 (2d, $J = 8.8$ Hz, 4H); 6.32 (d, $J = 16$ Hz, 1H); 5.70 (m, 1H); 5.17 (tm, $J = 7.0$ Hz, 1H); 3.84 (s, 3H); 3.54 (dd, $J = 2.8$, 11.5 Hz, 1H); 3.37 (s, 3H); 3.33 (d, $J = 4.5$ Hz, 1H); 2.70 (t, $J = 6.5$ Hz, 1H); 2.66 (d, $J = 4.5$ Hz, 1H); 2.34−1.81 (m, 5H); 2.02 (d, $J = 11.5$ Hz, 1H); 1.69 (s, 3H); 1.60 (s, 3H); 1.24 (s, 3H); 1.08 (ddd, $J = 2.7$, 4.0, 13.3 Hz, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 166.6, 161.4, 144.6, 133.6, 129.8, 127.0, 118.9, 115.7, 114.3, 79.6, 66.2, 64.3, 59.8, 59.3, 56.8, 55.4, 51.9, 48.0, 29.4, 27.4, 25.9, 25.8, 18.0, 13.3.

Methyl (2*R*)-2-Hydroxy-4-phenylselanylbutanoate (10). To a solution of diphenyl diselenide (13.7 g, 44 mmol, 0.9 equiv) in THF (60 mL) was added NaH (60% in oil, 3.49 g, 87.3 mmol, 1.8 equiv). The mixture was stirred for 1 h at 60 °C, then cooled to 0 °C. 18-C-6 crown ether (650 mg, 2.5 mmol, 0.05 equiv) was added, followed by a solution of (*R*)-(+)-α-hydroxybutyrolactone (5.00 g, 49 mmol) in THF (10 mL). The mixture was stirred for 2 h at 20 °C, quenched at 0 °C with 1 M HCl, and extracted with AcOEt. The organic layers were combined, washed with brine, and dried over Na_2SO_4, and the solvent was evaporated in vacuo. The residue was dissolved in ether (50 mL) and treated with excess CH_2N_2. Solvent removal and chromatography (SiO_2, cyclohexane → cyclohexane/AcOEt 8/2) afforded pure **10** (8.42 g, 63%) as a colorless oil. $[\alpha]^{20}_D = +7$ ($c = 1.74$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.49 (m, 2 H); 7.26 (m, 3 H); 4.32 (ddd, $J = 8.0$, 5.3, 4.0 Hz, 1 H); 3.77 (s, 3 H); 3.01 (dd, $J = 8.0$, 7.2 Hz, 2 H); 2.79 (d, $J = 5.3$ Hz, 1 H); 2.16 and 2.03 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): 175.0, 132.4, 129.6, 129.0, 126.8, 69.7, 52.5, 34.5, 22.6.

Methyl (2*R*)-2-*p*-Methoxybenzyloxy-4-phenylselanylbutanoate (11). Camphorsulfonic acid (3.2 g, 13.7 mmol) was added to a solution of **10** (18.7 g, 68.5 mmol) and freshly prepared *p*-methoxybenzyl trichloroacetimidate (38.7 g, 137 mmol) in dichloromethane (150 mL). The mixture was stirred at 20 °C for 24 h and quenched with a saturated solution of $NaHCO_3$. The mixture was partitioned between ethyl acetate and water, and the organic layer was dried and concentrated in vacuo. The residue was chromatographed (SiO_2, eluent/cyclohexane/AcOEt 8/2) to afford pure **11** (18.94 g, 70%). $[\alpha]^{20}_D = +67$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 7.47 (m, 2H); 7.26 (m, 5H); 6.86 (d, $J = 8.5$ Hz, 2H); 4.62 and 4.29 (2d, $J = 11.0$ Hz, 2H); 4.10 (dd, $J = 4.5$, 8.0 Hz, 1H); 3.80 (s, 3H); 3.75 (s, 3H); 2.97 (m, 2H); 2.10 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 172.9, 159.4, 132.6, 129.7, 129.3, 129.0, 126.9, 113.7, 76.6, 72.1, 55.2, 51.9, 33.4, 23.3. Anal. Calcd for $C_{19}H_{22}O_4Se$: C, 58.02; H, 5.64. Found: C, 58.12. H, 5.65.

(2*R*)-2-*p*-Methoxybenzyloxy-4-phenylselanylbutanal (12). A solution of DIBAL-H (1.5 M in toluene, 1 mL, 1.5 mmol, 1.5 equiv) was added at −78 °C to a solution of ester **11** (400 mg, 1.02 mmol, 1 equiv) in 2 mL of toluene. The mixture was stirred 20 min at −78 °C, anhydrous methanol (1 mL) was added, and the cold bath was removed, allowing the reaction to reach room temperature. Cyclohexane (40 mL) followed by 40 mL of brine were added. The two-phase mixture was separated, and the aqueous phase was extracted six times with cyclohexane. The combined organic phases were dried over $MgSO_4$, filtered, and evaporated in vacuo. **12** (250 mg, 68%) was obtained as a slightly yellow oil, which was used for the next step without further purification (this unstable material readily epimerizes when exposed to silica gel chromatography). $[\alpha]^{20}_D = +50$ ($c = 1.6$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 9.64 (d, 1H, $J = 1.6$); 7.48 (d, $J = 8.8$ Hz, 2H); 7.25 (m, 5H); 6.88 (d, $J = 8.8$ Hz Hz, 2H); 4.48 and 4.44 (2d, $J = 11.3$ Hz, 2H); 3.93 (ddd, $J = 7.0$, 5.2, 1.6 Hz, 1H); 3.80 (s, 3H); 2.99 (m, 2H); 2.02 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 203.0, 159.5, 132.7, 129.7, 129.1, 129.0, 127.0, 113.9, 82.2, 72.3, 55.2, 30.6, 22.8. Anal. Calcd for $C_{18}H_{20}O_3Se$: C, 59.51; H, 5.55. Found: C, 58.91. H, 5.55.

((3*E*)-4-Iodo-3-methylbut-3-enyloxy)trimethylsilane (13). Butyn-1-ol (5 mL, 66 mmol) was slowly added (ca. 3 h) to a cold (0 °C) solution containing Cp_2ZrCl_2 (7.5 g, 25 mmol, 0.4 equiv) and $AlMe_3$ (2 M in toluene, 100 mL, 200 mmol) in 1,2-dichloroethane (150 mL). The mixture was stirred at 20 °C for 24 h, and a solution of iodine (20 g, 78 mmol, 1.2 equiv) in THF (75 mL) was slowly added while keeping the internal temperature at −30 °C. The cold bath was removed, allowing the temperature to reach 0 °C, and the mixture was cannulated to a saturated aqueous $NaHCO_3$ solution. The mixture was extracted four times with a mixture of cyclohexane and ether (2/1), the organic layers were combined, washed with brine, and dried, and the solvent was removed. The residue was dissolved in THF (100 mL) and treated with imidazole (20 g, 290 mmol, 4.5 equiv) and TBSCl (9 g, 60 mmol, 0.9 equiv). The mixture was stirred at 20 °C for 1 h, quenched (NH_4Cl), and extracted with ether. The organic layers were combined, washed with brine, and dried, and the solvent was removed. The residue was filtered through silica gel with ether as eluent. **13** (16.7 g, 78%) was obtained as a slightly yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): 5.92 (m, 1H); 3.68 (t, $J = 6.6$ Hz, 2H); 2.41 (td, $J = 6.6$, 1.1 Hz, 2H); 1.85 (s, 3H); 0.89 (s,

9H); 0.04 (s, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 145.0, 76.4, 61.3, 42.6, 25.9, 24.3, 18.2, −5.2.

(3*E*)-3,7-Dimethyloct-3-enol (14). To a suspension of magnesium (965 mg, 39.7 mmol, 2.4 equiv) in THF (20 mL) was slowly added a solution of 1-bromo-3-methylbutane (3.96 mL, 33.0 mmol, 2 equiv) in THF (15 mL). After nearly all the magnesium has been consumed, the mixture was heated for 1 h at 70 °C. The mixture was then cooled to 0 °C, and a THF solution of $ZnCl_2$ (1 M, 35 mL, 35 mmol, 2.1 equiv) was added. The mixture was stirred for 1 h at 20 °C, cooled to 0 °C, and treated with $Pd(PPh_3)_4$ (350 mg, 0.34 mmol, 0.02 equiv), and then a solution of compound **13** (5 g, 15.3 mmol) in THF (25 mL) was added. The mixture was stirred overnight at 20 °C, quenched (NH_4Cl), and extracted with cyclohexane. The combined organic layers were dried, solvent was removed, and the residue was filtered through cotton wool. This oil was then dissolved in THF (50 mL) and treated with TBAF (1 M in THF, 16 mL, 16 mmol, 1.1 equiv) for 2 h at 20 °C. The reaction was stopped (NH_4Cl solution) and extracted with ether. The combined organic layers were dried over Na_2SO_4, and the solvent was removed in vacuo. Chromatography (SiO_2, cyclohexane/AcOEt 98/2 → 75/25) finally yielded pure **14** (1.84 g, 77%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): 5.22 (br t, J = 7 Hz, 1H); 3.63 (t, J = 6.2 Hz, 2H); 2.22 (t, J = 6.2 Hz, 2H); 1.99 (br q, J = 7.5 Hz, 2H); 1.61 (s, 3H); 1.53 (m, 1H); 1.22 (m, 2H); 0.86 (d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 130.7, 128.2, 60.1, 42.6, 38.9, 27.6, 25.6, 22.4, 15.6. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.68. H, 12.89.

(3*E*)-3,7-Dimethyloct-3-enoic Acid (15). A cold (0 °C) solution of CrO_3 (8.84 g, 88.4 mmol, 3 equiv) in water (25 mL) and 95% H_2SO_4 (8.2 mL) was added to a solution of alcohol **14** (4.6 g, 29.5 mmol) in acetone (250 mL) while keeping the temperature at 0 °C. The mixture was stirred a further 15 min at 0 °C, quenched with water (250 mL), and extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was removed in vacuo. Chromatography (SiO_2, cyclohexane/AcOEt 95/5 → 75/25) finally gave pure **15** (3.26 g, 65%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): 7.5 (br s, 1H); 5.30 (br t, J = 6.6 Hz, 1H); 3.01 (s, 2H); 2.03 (br q, J = 7.5 Hz, 2H); 1.70 (s, 3H); 1.55 (m, 1H); 1.22 (m, 2H); 0.88 (d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 177.9, 130.5, 127.3, 44.7, 38.5, 27.6, 25.9, 22.5, 16.2.

(4*R*)-4-Benzyl-3-[3(*E*)-(3,7-dimethylocta-3-enoyl)]-oxazolidin-2-one (16). Acid **15** (5.72 g, 33.6 mmol) was dissolved in CH_2Cl_2 (60 mL) and treated with oxalyl chloride (3.12 mL, 37.0 mmol, 1.1 equiv) and a few drops DMF at 0 °C. Stirring was continued for 1 h at 0 °C and for another 3 h at 20 °C, after which the solvent was evaporated in vacuo. Meanwhile, (*R*)-(−)-4-benzyl-2-oxazolidinone (6.85 g, 38.6 mmol, 1.15 equiv) was dissolved in THF (80 mL) and treated at −78 °C with BuLi (1.6 M in hexanes, 25.2 mL, 40.2 mmol, 1.2 equiv) for 30 min. The crude acid chloride was dissolved in THF (100 mL) and added to the lithio oxazolidinone at −78 °C. Stirring was continued for 2 h at −78 °C and overnight at 0 °C. The solution was poured into aqueous NH_4Cl solution and extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. Chromatography (SiO_2, cyclohexane/AcOEt 95/5 → 8/2) gave **16** (9.16 g, 83%) as a colorless oil. $[\alpha]^{20}_D$ = −53 (c = 1.02, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 7.37−7.20 (m, 5H); 5.30 (tm, J = 6.7 Hz, 1H); 4.67 (dddd, J = 3.0, 3.5, 7.0, 10.0 Hz, 1H); 4.18 (ABX, 2H); 3.62 (AB, 2H); 3.32 (dd, J = 3.3, 13.3 Hz, 1H); 2.75 (dd, J = 9.8, 13.3 Hz, 1H); 2.06 (br q, J = 7.4 Hz, 2H); 1.72 (s, 3H); 1.55 (m, 1H); 1.24 (m, 2H); 0.88 (d, J = 6.5 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 171.6, 153.3, 135.3, 130.2, 129.4, 128.9, 127.6, 127.3, 66.1, 55.2, 45.4, 38.6, 37.8, 27.6, 25.9, 22.5, 16.6.

(4*R*)-4-Benzyl-3-[(2*S*)-2-[(1*S*,2*R*)-1-hydroxy-2-*p*-methoxybenzyloxybut-3-enyl]-3,7-dimethylocta-3-enoyl]oxazolidin-2-one (17). To a cold (0 °C) solution of diisopropylamine (2.88 mL, 20.56 mmol) in THF (10 mL) was added BuLi (1.6 M in hexanes, 12.85 mL, 20.56 mmol). The mixture was stirred for 15 min at 0 °C and then cooled to −78 °C, and a solution of **16** (6.76 g, 20.56 mmol) in THF (10 mL) was added. The mixture was stirred for 30 min, and aldehyde **12** (8.28 g, 22.62 mmol) in THF (10 mL) was added. The mixture was stirred for 1 h at −78 °C, quenched with ammonium chloride, allowed to reach 20 °C, and extracted with ether. The combined organic layers were dried and the solvent was removed in vacuo. The residue was dissolved in $CHCl_3$ (60 mL) and treated with tetrabutylammonium periodate (19.6 g, 45.2 mmol, 2 equiv) for 2 h at 60 °C. Solvent removal and chromatography (SiO_2, cyclohexane/AcOEt 9/1 → 8/2) afforded diastereomerically pure **17** (5.83 g, 55%). $[\alpha]^{20}_D$ = −129 (c = 1.45, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 7.37−7.20 (m, 5H); 7.11 (m, 2H); 6.83 (d, J = 8.6 Hz, 2H); 5.92 (ddd, J = 8.0, 10.3, 17.2 Hz, 1H); 5.56 (tm, J = 7.0 Hz, 1H); 5.43 and 5.34 (2dd, J = 1.8, 10.3 Hz and J = 1.8, 17.2 Hz, 2H); 4.77 (d, J = 8.7 Hz, 1H); 4.54 (d, J = 10.8 Hz, 1H); 4.43 (m, 1H); 4.31 (ddd, J = 3.6, 6.3, 8.7 Hz, 1H); 4.26 (d, J = 10.8 Hz, 1H); 4.01 (m, 2H); 3.75 (m, 1H); 3.69 (s, 3H); 3.08 (dd, J = 3.1, 13.2 Hz, 1H); 2.19 (d, J = 3.6 Hz, 1H); 2.05 (br q, J = 7.3 Hz, 2H); 1.86 (dd, J = 10.9, 13.2 Hz, 1H); 1.73 (s, 3H); 1.50 (m, 1H); 1.21 (m, 2H); 0.85 (d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 171.8, 159.2, 152.7, 135.8, 135.7, 133.7, 130.1, 130.0, 129.4, 128.8, 127.1, 120.3, 113.7, 83.3, 72.0, 70.4, 65.6, 55.9, 55.1, 53.8, 38.4, 37.0, 27.7, 26.1, 22.5, 22.4, 14.6.

(2*S*)-2-[(1*S*,2*R*)-1-Hydroxy-2-*p*-methoxybenzyloxybut-3-enyl]-3,7-dimethylocta-3-enoic Acid Methoxymethylamide (18). A solution of trimethylaluminum in toluene (2 M, 19 mL, 37.9 mmol, 3.5 equiv) was added to a cold (0 °C) suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (3.70 g, 37.9 mmol, 3.5 equiv) in THF (20 mL). The mixture was stirred at 20 °C for 30 min and then cooled to 0 °C. A solution of aldol **17** (5.79 g, 10.8 mmol) in THF (10 mL) was added. The mixture was stirred overnight at 20 °C and then poured slowly onto a cold aqueous solution of tartaric acid (25%). Extraction with AcOEt and chromatography (SiO_2, cyclohexane/AcOEt 85/15 → 8/2) afforded **18** (3.41 g, 75%) as a colorless oil. $[\alpha]^{20}_D$ = −125 (c = 0.975, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 7.25 and 6.87 (2d, J = 8.6 Hz, 4H); 5.89 (ddd, J = 8.1, 10.3, 17.2 Hz, 1H); 5.39 (dd, J = 2.0, 10.3 Hz, 1H); 5.36 (m, 1H); 5.30 (dd, J = 2.0, 17.2 Hz, 1H); 4.52 and 4.26 (2d, J = 11.0 Hz, 2H); 4.18 (dt, J = 2.1, 6.2 Hz, 1H); 3.80 (s, 3H); 3.79 (m, 1H); 3.70 (br m, 1H); 3.61 (s, 3H); 3.31 (br s, 1H); 3.12 (s, 3H); 2.06 (br q, J = 7.1 Hz, 2H); 1.73 (s, 3H); 1.54 (m, 1H); 1.22 (m, 2H); 0.87 (d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 159.0, 135.5, 131.8, 130.5, 129.6, 129.3, 119.7, 113.7, 81.2, 72.9, 69.7, 61.0, 55.2, 51.3, 38.6, 32.0, 27.7, 26.0, 22.5, 22.4, 15.2.

(2*S*)-2-[1*S*,2*R*)-1-Methoxy-2-*p*-methoxybenzyloxybut-3-enyl]-3,7-dimethylocta-3-enoic Acid Methoxymethylamide (19). To a suspension of Ag_2O (8 g, 35 mmol, 5 equiv) and activated 4 Å molecular sieves (2 g) in Et_2O (10 mL) were added alcohol **18** (2.96 g, 7 mmol) and MeI (8 mL). The suspension was stirred overnight at 45 °C and then filtered through Celite. The residue was chromatographed (SiO_2, cyclohexane/AcOEt 9/1) to afford pure **19** (2.8 g, 93%) as a colorless oil. $[\alpha]^{20}_D$ = −121 (c = 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 7.26 and 6.85 (2d, J = 8.6 Hz, 4H); 5.92 (ddd, J = 8.1, 10.3, 17.3 Hz, 1H); 5.36 (br t, J = 7.1 Hz, 1H); 5.31 (dd, J = 2.1, 10.3 Hz, 1H); 5.20 (dd, J = 2.0, 17.3 Hz, 1H); 4.51 and 4.34 (2d, J = 11.4 Hz, 2H); 3.98 (dd, J = 3, 9.9 Hz, 1H); 3.80 (m, 1H); 3.79 (s, 3H); 3.58 (s, 3H); 3.49 (br m, 1H); 3.46 (s, 3H); 3.07 (s, 3H); 2.00 (br q, J = 7.4 Hz, 2H); 1.72 (s, 3H); 1.53 (m, 1H); 1.23 (m, 2H); 0.86 (d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 158.8, 135.4, 130.9, 130.7, 129.9, 129.0, 119.2, 113.5, 82.9, 82.8, 69.9, 61.0, 60.9, 55.2, 52.0, 38.5, 32.3, 27.6, 25.9, 22.5, 22.5, 15.3. Anal. Calcd for $C_{25}H_{39}NO_5$: C, 69.25; H, 9.07; N, 3.23. Found: C, 68.99. H, 9.24. N, 3.15.

(4*S*)-4-((1*S*,2*R*)-1-Methoxy-2-*p*-methoxybenzyloxybut-3-enyl)-5,9-dimethyldeca-1,5-dien-3-one (20). To a cold (0 °C) solution of amide **19** (877 mg, 2.02 mmol) in THF (5 mL)

was added vinylmagnesium bromide (1 M in THF, 10 mL, 10 mmol, 5 equiv). After being stirred for 12 h at 20 °C, the mixture was cannulated onto 20 mL of a 2:1 (v/v) mixture of saturated ammonium chloride and THF. After extraction (ether) and chromatography (SiO_2, cyclohexane/AcOEt 95/5), pure **20** was obtained (689 mg, 86%). $[\alpha]^{20}_D = -293$ ($c = 1.07$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 7.24 and 6.86 (2d, J = 8.6 Hz, 4H); 6.35 (dd, J = 10.1, 17.4 Hz, 1H); 6.18 (dd, J = 1.8, 17.4 Hz, 1H); 5.88 (ddd, J = 8.2, 10.3, 17.3 Hz, 1H); 5.64 (dd, J = 1.8, 10.1 Hz, 1H); 5.36 (tm, J = 7.0 Hz, 1H); 5.31 (dm, J = 10.3 Hz, 1H); 5.15 (dm, J = 17.4 Hz, 1H); 4.49 and 4.28 (2d, J = 11.4 Hz, 2H); 4.01 (dd, J = 3.8, 9.1 Hz, 1H); 3.80 (s, 3H); 3.70 (dd, J = 3.8, 9.1 Hz, 1H); 3.47 (s, 3H); 3.46 (d, J = 9.1 Hz, 1H); 2.03 (br q, J = 7.6 Hz, 2H); 1.60 (s, 3H); 1.51 (m, 1H); 1.21 (m, 2H); 0.86 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 198.0, 158.9, 135.5, 135.5, 132.7, 130.7, 129.3, 129.1, 127.8, 119.5, 113.6, 82.5, 81.4, 69.9, 61.4, 60.7, 55.2, 38.4, 27.6, 26.2, 22.5, 22.5, 14.4. HRMS (FAB): *m/z* found 407.2794, calcd for $C_{25}H_{36}O_4Li$ *m/z* 407.2774.

(4*R*,5*S*,6*S*)-5-Methoxy-4-*p*-methoxybenzyloxy-6-[(*E*)-1,5-dimethylhex-1-enyl]cyclohex-2-enone (21). To a solution of **20** (38 mg, 95 μmol) in toluene (3 mL) was added dropwise a solution of Grubbs type II catalyst (8 mg, 9.5 μmol, 0.1 equiv) in toluene (0.5 mL). The mixture was stirred for 45 min at 70 °C and quenched with pH 7 buffer. Extraction with ether and chromatography (SiO_2, cyclohexane/AcOEt 6/4) afforded **21** (27.1 mg, 78%) as a colorless oil. $[\alpha]^{20}_D = -86$ ($CHCl_3$, $C = 1.8$). ^{1}H NMR (250 MHz, $CDCl_3$): 7.30 and 6.89 (2d, J = 8.7 Hz, 4H); 6.78 (ddd, J = 10.1, 3.7, 1.0 Hz, 1H); 6.06 (dd, J = 10.1, 1.5 Hz, 1H); 5.13 (tm, J = 7.0 Hz, 1H); 4.65 (AB, 2H); 4.31 (dt, J = 3.4, 1.5 Hz, 1H); 3.81 (s, 3H); 3.75 (ddd, J = 6.8, 3.2, 1.1 Hz, 1H); 3.42 (d, J = 6.8, 1H); 3.41 (s, 3H); 2.00 (br q, J = 7.2 Hz, 2H); 1.58 (s, 3H); 1.50 (m, 1H); 1.19 (m, 2H); 0.86 (d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 199.0, 159.4, 145.5, 130.8, 130.2, 129.9, 129.6, 128.9, 113.9, 80.0, 71.6, 70.6, 58.6, 57.7, 55.3, 38.4, 27.6, 25.9, 22.5, 22.5, 15.3. HRMS (FAB): *m/z* found 379.2462, calcd for $C_{23}H_{32}O_4Li$ *m/z* 379.2461.

(4*R*,5*S*,6*S*)-6-(1,5-Dimethylhex-1-enyl)-4-hydroxy-5-methoxycyclohex-2-enone (21′). A solution of **21** (20 mg, 53 μmol) in CH_2Cl_2 (2 mL) containing water (65 μL) was treated with DDQ (13 mg, 59 μmol, 1.1 equiv) for 7 h at 20 °C. The reaction was stopped with saturated $NaHCO_3$ solution (0.5 mL) and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was filtered through a short pad of silica gel (eluent: cyclohexane/AcOEt 6/4) to afford **21′** (white solid, 10.5 mg, 78%). Mp = 46−47 °C. $[\alpha]^{20}_D = -43$ ($c = 1.02$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 6.78 (ddd, J = 1.3, 3.1, 10.1 Hz, 1H); 6.07 (dd, J = 1.7, 10.1 Hz, 1H); 5.15 (tm, J = 7.0 Hz, 1H); 4.51 (m, 1H); 3.77 (ddd, J = 1.3, 3.7, 5.1 Hz, 1H); 3.44 (s, 3H); 3.39 (d, J = 5.2 Hz, 1H); 3.84 (s, 1H); 2.02 (br q, J = 7.1 Hz, 2H); 1.68 (s, 3H); 1.52 (m, 1H); 1.19 (m, 2H); 0.86 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 198.4, 147.3, 130.4, 130.0, 128.7, 81.2, 64.8, 57.4, 57.3, 38.5, 27.6, 26.0, 22.5, 22.4, 15.8.

(2*S*,3*S*,4*R*)-3-Methoxy-4-*p*-methoxybenzyloxy-2-[(*E*)-1,5-dimethylhex-1-enyl]cyclohexanone (22). Under vigorous stirring, 15 drops of a 50% suspension of RaNi in water were added to a cold (0 °C) solution of **21** (45 mg, 0.121 mmol) in THF (1.5 mL). The mixture was stirred for 20 min at 0 °C. Ether (2 mL) was added and the mixture was extracted with ethyl acetate. Chromatography (SiO_2, cyclohexane/AcOEt 8/2) afforded pure **22** (colorless oil, 37 mg, 82%). $[\alpha]^{20}_D = -10$ ($CHCl_3$, $C = 1.0$). ^{1}H NMR (250 MHz, $CDCl_3$): 7.33 and 6.88 (2d, J = 8.6 Hz, 4H); 5.16 (tm, J = 7.0 Hz, 1H); 4.67 (AB, 2H); 4.11 (dt, J = 2.2, 4.6 Hz, 1H); 3.80 (s, 3H); 3.49 (d, J = 10.7 Hz, 1H); 3.43 (dd, J = 2.2, 10.7 Hz, 1H); 3.33 (s, 3H); 2.60 (m, 1H); 2.26−2.14 (m, 2H); 2.06 (m, 2H); 1.65−1.46 (m, 2H); 1.57 (s, 3H); 1.19 (m, 2H); 0.87 (d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 209.1, 159.2, 130.8, 130.5, 129.2, 129.0, 113.7, 81.9, 71.1, 70.3, 61.9, 57.4, 55.3, 38.6, 35.8, 27.6, 25.9, 24.5, 22.5, 22.5, 14.1.

(3*R*,4*S*,5*S*,6*R*)-4-[-(*E*)-1,5-Dimethylhex-1-enyl]-5-methoxy-6-*p*-methoxybenzyloxy-1-oxaspiro[2.5]octane (23). To a suspension of NaH (40 mg, 1.01 mmol, 10 equiv) in DMSO (1 mL) was added trimethylsulfoxonium iodide (334 mg, 1.52 mmol, 15 equiv). The mixture was stirred at 20 °C for 1 h. THF (1 mL) and lithium iodide (163 mg, 1.21 mmol, 12 equiv) were added to the mixture, and stirring was continued for further 40 min. A solution of **22** (38 mg, 101 μmol) in DMSO/THF (1/1, 1 mL) was added at 0 °C. The mixture was stirred for 30 min at 20 °C and quenched with ether (5 mL) and pH 7 buffer (5 mL). Extraction with ether and chromatography (SiO_2, cyclohexane/AcOEt 9/1) afforded pure **23** (colorless oil, 30 mg, 77%). $[\alpha]^{20}_D = -68$ ($c = 0.85$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 7.32 and 6.87 (2d, J = 8.6 Hz, 4H); 5.21 (tm, J = 7.4 Hz, 1H); 4.62 (s, 2H); 4.07 (dt, J = 2.3, 4.5 Hz, 1H); 3.80 (s, 3H); 3.49 (dd, J = 2.6, 11.2 Hz, 1H); 3.30 (s, 3H); 2.99 (d, J = 11.2 Hz, 1H); 2.65 and 2.42 (2d, J = 5.0 Hz, 2H); 2.23 (dt, J = 4.3, 13.5, 13.5 Hz, 1H); 2.11−1.94 (m, 3H); 1.69−1.47 (m, 2H); 1.54 (s, 3H); 1.29−1.15 (m, 2H); 1.06 (ddd, J = 2.8, 4.0, 13.5 Hz, 1H); 0.87 and 0.86 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 159.0, 131.7, 131.0, 130.7, 129.2, 113.6, 81.0, 70.7, 70.4, 60.9, 56.6, 55.2, 51.4, 48.6, 38.8, 28.5, 27.7, 25.7, 25.0, 22.6, 22.5, 14.1.

***p*-Methoxycinnamic Acid (3*R*,4*S*,5*S*,6*R*)-5-Methoxy-4-[(*E*)-1,5-dimethylhex-1-enyl]-1-oxaspiro[2.5]oct-6-yl Ester (24).** A solution of spiroepoxide **23** (17 mg, 43.8 μmol) in CH_2Cl_2 (2 mL) containing water (65 μL) was treated with DDQ (11 mg, 48 μmol, 1.1 equiv) for 1.5 h at 20 °C. The reaction was stopped with saturated $NaHCO_3$ solution (0.5 mL) and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was filtered through a short pad of silica gel (cyclohexane/AcOEt 6/4) to afford **23′** (10.5 mg, 90%), which was used without further purification for the next step. ^{1}H NMR (250 MHz, $CDCl_3$) (**23′**): 5.22 (tm, J = 7.6 Hz, 1H); 4.34 (dt, J = 6.0, 3.0 Hz, 1H); 3.51 (dd, J = 3.0, 11.2 Hz, 1H); 3.38 (s, 3H); 2.80 (d, J = 11.2 Hz, 1H); 2.62 and 2.44 (2d, J = 5.0 Hz, 2H); 2.33 (br s, 1H); 2.26 (td, J = 13.6, 4.5 Hz, 1H); 2.10−1.96 (m, 3H); 1.76 (tm, J = 13.9 Hz, 1H); 1.56 (s, 3H); 1.53 (m, 1H); 1.19 (m, 2H); 1.03 (ddd, J = 2.5, 4.5, 13.6 Hz, 1H); 0.87 (2d, J = 6.6 Hz, 6H).

A solution of alcohol **23′** (10.5 mg) in CH_2Cl_2 (2 mL) was treated with *p*-methoxycinnamic acid (61 mg, 390 μmol, 10 equiv), followed by DMAP (48 mg, 390 μmol, 10 equiv) and DCC (80 mg, 390 μmol, 10 equiv). The mixture was stirred for 48 h at 20 °C, and then the solvent was removed in vacuo and the residue purified on preparative TLC (SiO_2 hexane/AcOEt 8/2). Pure **24** (13.5 mg, 80%) was obtained, which contains 10% of the *Z*-isomer. $[\alpha]^{20}_D = -118$ (c = 0.67, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) (**24**): 7.66 (d, J = 16 Hz, 1H); 7.48 and 6.90 (2d, J = 8.8 Hz, 4H); 6.38 (d, J = 16 Hz, 1H); 5.72 (dt, J = 2.6, 3.9 Hz, 1H); 5.26 (tm, J = 7.2 Hz, 1H); 3.84 (s, 3H); 3.63 (dd, J = 2.8, 11.2 Hz, 1H); 3.37 (s, 3H); 2.93 (d, J = 11.2 Hz, 1H); 2.70 and 2.49 (2d, J = 5 Hz, 2H); 2.22 (dt, J = 4.5, 13.6 Hz, 1H); 2.12−1.99 (m, 3H); 1.89 (tdd, J = 13.6, 2.4, 4.2 Hz, 1H); 1.58 (s, 3H); 1.54 (m, 1H); 1.26−1.17 (m, 2H); 1.18 (ddd, J = 2.5, 4.1, 13.8 Hz, 1H); 0.87 and 0.86 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$) (**24**): 166.9, 161.3, 144.5, 131.0, 130.8, 129.7, 127.2, 115.9, 114.3, 79.2, 66.7, 60.6, 57.0, 55.3, 51.4, 49.4, 38.8, 28.8, 27.7, 25.8, 25.7, 22.6, 22.4, 14.1. HRMS (FAB): *m/z* found 435.2710, calcd for $C_{26}H_{36}O_5Li$ *m/z* 435.2723.

(3*R*,4*S*,5*S*,6*R*)-4-[(1*R*,2*R*)-1,2-Epoxy-1,5-dimethylhexyl]-5-methoxy-6-*p*-methoxybenzyloxy-1-oxaspiro[2.5]-octane (25) and (3*R*,4*S*,5*S*,6*R*)-4-[(1*S*,2*S*)-1,2-Epoxy-1,5-dimethylhexyl]-5-methoxy-6-*p*-methoxybenzyloxy-1-oxaspiro[2.5]octane (26). To a cold (0 °C) mixture of **23** (40 mg, 103 μmol) and $NaHCO_3$ (52 mg, 618 μmol, 6 equiv) in CH_2Cl_2 (2 mL) was added *m*-CPBA (70%, 37 mg, 154 μmol, 1.5 equiv). The mixture was stirred for 1 h at 0 °C and then 1 h at 20 °C. The mixture was quenched with a saturated aqueous

$NaHCO_3$ solution (5 mL) and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. Chromatography (SiO_2, cyclohexane/AcOEt 8/2) afforded **26** (5.7 mg, 13%) followed by **25** (32.5 mg). **25.** $[\alpha]^{20}_D = -54$ (c = 0.95, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 7.31 and 6.86 (2d, J = 8.6 Hz, 4H); 4.61 (AB, 2H); 4.07 (dt, J = 2.2, 2.2, 4.4 Hz, 1H); 3.80 (s, 3H); 3.55 (dd, J = 2.5, 10.9 Hz, 1H); 3.37 (s, 3H); 2.85 and 2.55 (2d, J = 4.4 Hz, 2H); 2.52 (dd, J = 4.6, 7.4 Hz, 1H); 2.14 (dt, J = 4.4, 13.4, 13.4 Hz, 1H); 2.12 (d, J = 10.9 Hz, 1H); 1.95 (dq, J = 4.3, 13.8 Hz, 1H); 1.68−1.17 (m, 6H); 1.17 (s, 3H); 1.01 (dt, J = 4.0, 13.5 Hz, 1H); 0.89 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 159.0, 131.0, 129.2, 113.6, 81.3, 70.9, 70.1, 61.5, 60.0, 58.5, 56.4, 55.2, 51.1, 47.7, 35.6, 29.1, 27.9, 26.0, 25.3, 22.6, 22.4, 14.1. HRMS (FAB): m/z found 411.2722, calcd for $C_{24}H_{36}O_5Li$ m/z 411.2723. **26.** ^{1}H NMR (250 MHz, $CDCl_3$): 7.29 and 6.87 (2d, J = 8.6 Hz, 4H); 4.60 (s, 2H); 4.05 (m, 1H); 3.80 (s, 3H); 3.43 (dd, J = 2.5, 11.2 Hz, 1H); 3.32 (s, 3H); 3.28 (d, J = 4.5 Hz, 1H); 2.68 (t, J = 6.0 Hz, 1H); 2.60 (d, J = 4.5 Hz, 1H); 2.12−2.04 (m, 3H); 1.69−1.18 (m, 6H); 1.18 (s, 3H); 0.98 (m, 1H); 0.88 (2d, J = 6.6 Hz, 6H).

(−)-Dihydrofumagillol (27). A solution of spiroepoxide **25** (38 mg, 94 μmol) in CH_2Cl_2 (2 mL) containing water (65 μL) was treated with DDQ (24 mg, 103 μmol, 1.1 equiv) for 1.5 h at 20 °C. The reaction was stopped with a saturated $NaHCO_3$ solution (0.5 mL) and extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Preparative TLC (SiO_2, cyclohexane/AcOEt 1/1) afforded (−)-dihydrofumagillol **27** (23 mg, 86%). $[\alpha]^{20}_D = -44$ (c = 1.15, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 4.35 (br m, 1H); 3.61 (dd, J = 2.7, 11.1 Hz, 1H); 3.48 (s, 3H); 2.83 and 2.57 (2d, J = 4.3 Hz, 2H); 2.54 (dd, J = 4.4, 7.4 Hz, 1H); 2.37 (d, J = 2.0 Hz, 1H); 2.20 (dt, J = 4.5, 13.5, 13.5 Hz, 1H); 2.00 (ddt, J = 2.5, 2.5, 4.1, 14.2 Hz, 1H); 1.92 (d, J = 11.1 Hz, 1H); 1.82−1.22 (m, 6H); 1.18 (s, 3H); 0.98 (ddd, J = 2.5, 4.5, 13.5 Hz, 1H); 0.88 (2d, J = 6.5 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 80.9, 64.1, 62.0, 59.9, 58.5, 56.5, 50.9, 47.2, 35.6, 28.4, 27.9, 26.5, 26.0, 22.6, 22.3, 13.9.

***p*-Methoxycinnamic Acid (3*R*,4*S*,5*S*,6*R*)-5-Methoxy-4-[(1*R*,2*R*)-1,2-epoxy-1,5-dimethylhexyl]-1-oxaspiro[2.5]oct-6-yl Ester (28).** A solution of alcohol **27** (20 mg, 70 μmol) in CH_2Cl_2 (2 mL) was treated with *p*-methoxycinnamic acid (215 mg, 704 μmol, 10 equiv), followed by DMAP (85 mg, 704 μmol, 10 equiv) and DCC (145 mg, 704 μmol, 10 equiv). The mixture was stirred overnight at 20 °C, and then the solvent was removed in vacuo and the residue passed through a pad of silica gel (eluent: cyclohexane/AcOEt 1/1). Preparative TLC (SiO_2, hexane/AcOEt 8/2) afforded **28** (30 mg, 95%), containing 10% of the *Z*-isomer. $[\alpha]^{20}_D = -56.5$ ($CHCl_3$, C = 0.92). ^{1}H NMR (250 MHz, $CDCl_3$): 7.63 (d, J = 16 Hz, 1H); 7.46 and 6.89 (2d, J = 8.7 Hz, 4H); 6.36 (d, J = 16 Hz, 1H); 5.73 (m, 1H); 3.83 (s, 3H); 3.71 (dd, J = 2.8, 11.0 Hz, 1H); 3.45 (s, 3H); 2.0.91 and 2.61 (2d, J = 4.3 Hz, 2H); 2.59 (dd, J = 4.4, 8.0 Hz, 1H); 2.13 (dt, J = 4.3, 13.3, 13.3 Hz, 1H); 2.05 (d, J = 11.0 Hz, 1H); 2.07−1.82 (m, 2H); 1.68−1.20 (m, 5H); 1.20 (s, 3H); 1.13 (dt, J = 3.0, 3.0, 13.2 Hz, 1H); 0.90 (2d, J = 6.5 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 166.9, 161.3, 144.5, 129.7, 127.2, 115.9, 114.3, 79.1, 66.3, 61.7, 59.6, 58.5, 56.6, 55.3, 51.1, 48.4, 35.6, 29.3, 27.8, 26.0, 25.7, 22.6, 22.3, 13.9. HRMS (FAB): m/z found 451.2663, calcd for $C_{26}H_{36}O_6Li$ m/z 451.2672.

***p*-Methoxycinnamic Acid (3*R*,4*S*,5*S*,6*R*)-5-Methoxy-4-[(1*S*,2*S*)-1,2-epoxy-1,5-dimethylhexyl]-1-oxaspiro[2.5]oct-6-yl Ester (29).** A solution of spiroepoxide **26** (7.7 mg, 19 μmol) in CH_2Cl_2 (0.5 mL) containing water (30 μL) was treated with DDQ (5 mg, 21 μmol, 1.1 equiv) for 1.5 h at 20 °C. The reaction was stopped with saturated $NaHCO_3$ solution (0.5 mL) and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (0.5 mL) and successively treated with *p*-methoxycinnamic acid (34 mg, 190 μmol, 10 equiv), DMAP (24 mg, 190 μmol, 10 equiv), and DCC (40 mg, 190 μmol, 10 equiv). The mixture was stirred overnight at 20 °C, and then the solvent was removed in vacuo and the residue filtered through a short pad of silica (eluent: cyclohexane/AcOEt 1/1). Preparative TLC (SiO_2 hexane/AcOEt 8/2) afforded **29** (6.8 mg, 80%), containing 10% of the *Z*-isomer. ^{1}H NMR (250 MHz, $CDCl_3$): 7.63 (d, J = 16 Hz, 1H); 7.48 and 6.90 (2d, J = 8.7 Hz, 4H); 6.33 (d, J = 16 Hz, 1H); 5.71 (m, 1H); 3.84 (s, 3H); 3.55 (dd, J = 2.7, 11.3 Hz, 1H); 3.38 (s, 3H); 3.34 and 2.66 (2d, J = 4.5 Hz, 2H); 2.62 (m, 1H); 2.14 (dt, J = 4.4, 13.3 Hz, 1H); 2.02 (d, J = 11.4 Hz, 1H); 2.06−1.83 (m, 2H); 1.63−1.23 (m, 5H); 1.23 (s, 3H); 1.13 (ddd, J = 2.4, 4.0, 13.5 Hz, 1H); 0.86 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 166.6, 161.4, 144.6, 129.7, 127.0, 115.7, 114.3, 79.7, 66.2, 65.2, 59.8, 59.2, 56.8, 55.4, 51.9, 48.1, 35.0, 29.4, 27.9, 26.0, 25.9, 22.6, 22.3, 13.2.

(2*S*,3*S*,4*R*,5*S*)-2-(1,5-Dimethylhex-1-enyl)-3-methoxy-4-*p*-methoxybenzyloxy-5-methylcyclohexanone (30). A suspension of CuI (56 mg, 290 μmol, 1.1 equiv) in Et_2O (1 mL) was treated with MeLi (1.4 M in Et_2O, 422 μL, 590 μmol, 2.2 equiv) at 0 °C. After 1 h, a solution of enone **21** (100 mg, 270 μmol, 1 equiv) in Et_2O (0.5 mL) was added. The mixture was stirred at 0 °C for 1 h, quenched with saturated NH_4Cl (2 mL), and extracted with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification on preparative TLC (hexane/ethyl acetate, 4/1) provided **30** as a colorless oil (80 mg, 77%). $[\alpha]^{20}_D = +43$ (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 6.81 and 7.24 (2d, J = 8.4 Hz, 4H), 5.03 (t, J = 7.0 Hz, 1H), 4.56 and 4.63 (2d, AB, J = 11.8 Hz, 2H), 3.73 (s, 3H)), 3.65 (dd, J = 6.0, 2.0 Hz, 1H), 3.60 (dd, J = 8.5, 2.0 Hz, 1H), 3.31 (m, 1H), 3.28 (s, 3H), 2.57 (dd, J = 14.5, 6.0 Hz, 1H), 2.36 (m, 1H), 2.05 (m, 3H), 1.50 (s, 3H), 1.46 (m, 1H), 1.15 (m, 2H), 0.92 (d, J = 7.2 Hz, 3H), 0.81 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 15.11, 18.8, 22.9, 26.3, 28.1, 31.8, 39.0, 44.2, 55.7, 58.0, 62.3, 72.1, 77.4, 79.4, 114.1, 129.7, 130.4, 131, 159.6, 210.0. HRMS (FAB): m/z found 395.2790, calcd for $C_{24}H_{36}O_4Li$ m/z 395.2774.

(3*R*,4*S*,5*S*,6*R*,7*S*)-4-[(*E*)-1,5-Dimethyl-hex-1-enyl]-5-methoxy-6-*p*-methoxybenzyloxy-7-methyl-1-oxaspiro[2.5]-octane (31). A solution of ketone **30** (65 mg, 167 μmol, 1.0 equiv) and CH_2I_2 (68 μmol, 835 μmol, 5 equiv) in THF (1 mL) was treated with BuLi (1.6 M in hexanes, 520 μL, 835 μmol, 5.0 equiv) at −78 °C. The mixture was stirred for 1 h at −78 °C and then for 1.5 h at 20 °C. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification on preparative TLC (hexane/ethyl acetate, 4/1) afforded pure **31** as a colorless oil (35 mg, 52%). $[\alpha]^{20}_D = -12$ (c = 1.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 6.87 and 7.29 (2d, J = 8.3 Hz, 4H), 5.29 (m, 1H), 4.58 (2d, AB, J = 11.8 Hz, 2H), 3.80 (s, 3H), 3.70 (dd, J = 8.3, 2.0 Hz, 1H), 3.54 (br d, J = 4.3 Hz, 1H), 3.34 (s, 3H), 2.71 (d, J = 8.0 Hz, 1H), 2.38 and 2.54 (2d, J = 5.0 Hz), 2.26 (m, 1H), 2.02 (m, 2H), 1.93 (dd, J = 13.7, 5.0 Hz, 1H), 1.57 (s, 3H), 1.54 (m, 1H), 1.32 (dd, J = 13.7, 5.8 Hz, 1H), 1.22 (m, 2H), 1.04 (d, J = 7.0 Hz, 3H), 0.88 and 0.89 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 159.1, 131, 130.0, 129.2, 113.7, 78.0, 77.7, 71.4, 58.8, 57.0, 55.3, 51.0, 49.5, 38.8, 35.6, 31.7, 27.8, 25.9, 22.5 and 22.6, 18.1, 14.9).

(3*R*,4*S*,5*S*,6*R*,7*S*)-4-[(*E*)-1,5-Dimethyl-hex-1-enyl]-5-methoxy-7-methyl-1-oxaspiro[2.5]octan-6-ol (31′). A solution of spiroepoxide **31** (35 mg, 87 μmol) in CH_2Cl_2 (3 mL) was treated with DDQ (22 mg, 96 μmol, 1.1 equiv) in the presence of H_2O (85 μL) for 1.5 h at 20 °C. The reaction was stopped with saturated $NaHCO_3$ solution (0.5 mL) and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification on preparative TLC (hexane/ethyl acetate, 4/1) afforded pure **31′** as colorless oil (20 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): 5.28 (t, J = 7.0 Hz, 1H), 3.89 (m, 1H), 3.68 (dd, J = 9.0, 2.5 Hz, 1H), 3.39 (s, 3H), 2.66 (d, J = 9.0 Hz, 1H), 2.36 and 2.51 (2d, J = 5.2 Hz, 2H), 2.34 (br s, 1H), 2.18 (m, 1H), 1.95−2.10 (m, 3H), 1.60 (s, 3H), 1.53 (m, 1H), 1.22 (m, 3H), 1.10 (d, J = 7.6 Hz, 3H), 0.88 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 130.7, 130.4,

79.3, 70.7, 58.9, 57.1, 50.0, 48.5, 38.8, 33.6, 33.4, 27.7, 25.9, 22.6, 22.5, 17.8, 15.11.

***p*-Methoxycinnamic Acid (3*R*,4*S*,5*S*,6*R*,7*S*)-4-[(*E*)-1,5-Dimethyl-hex-1-enyl]-5-methoxy-7-methyl-1-oxaspiro-[2.5]oct-6-yl Ester(32).** *p*-Methoxycinnamic acid (185 mg, 1.04 mmol, 12 equiv) followed by DMAP (127 mg, 1.04 mmol, 12 equiv) and DCC (215 mg, 1.04 mmol, 12 equiv) were added to a solution of alcohol **31′** (25 mg, 87 μmol) in CH_2Cl_2 (2 mL). The mixture was stirred overnight at 20 °C, and then the solvent was removed in vacuo and the residue passed over a short pad of silica gel (cyclohexane/AcOEt 1/1). Chromatography on preparative TLC (hexane/ethyl acetate, 85/15) afforded pure **32** containing ca. 10% of the *Z*-isomer as a colorless oil (18 mg, 49%). $[\alpha]^{20}_D = -49$ (c = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.66 (d, J = 16.0 Hz, 1H), 6.91 and 7.48 (2d, J = 8.8 Hz, 4H), 6.38 (d, J = 16.0 Hz, 1H), 5.40 (t, J = 6.8 Hz, 1H), 5.25 (m, 1H), 3.87 (m, 1H), 3.83 (s, 3H), 3.36 (s, 3H), 2.70 (d, J = 8.3 Hz, 1H), 2.44 and 2.60 (2d, J = 5.0 Hz, 2H), 2.32 (m, 1H), 2.05 (m, 2H), 1.98 (dd, J = 13.5, 4.5 Hz, 1H), 1.65 (s, 3H), 1.55 (m, 1H), 1.45 (dd, J = 13.5, 5.6 Hz, 1H), 1.26 (m, 2H), 1.13 (d, J = 7.2 Hz, 3H), 0.89 (d, 6H, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 166.9, 161.4, 144.6, 129.8, 130.5, 130.3, 127.2, 115.8, 114.3, 77.3, 73.0, 58.6, 57.5, 55.3, 50.7, 50.0, 38.8, 35.5), 32.0, 27.8, 25.9, 22.5, 17.9, 14.8. HRMS (FAB): *m*/*z* found 443.2793, calcd for $C_{27}H_{39}O_5$ *m*/*z* 443.2797.

(2*S*,3*S*,4*R*,5*R*)-4-Hydroxy-3-methoxy-5-methyl-2-[(*E*)-1,5-dimethyl-hex-1-enyl]cyclohexanone (33). To a cold (0 °C) solution of **21′** (42 mg, 166 μmol) in CH_2Cl_2 (0.8 mL) was added $AlMe_3$ (2 M in toluene, 800 μL, 1.6 mmol, 10 equiv). The mixture was stirred for 4 h at 20 °C and then slowly transferred onto a 20% aqueous tartaric acid solution. The mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by preparative TLC (SiO_2, cyclohexane/AcOEt 7/3) to afford **33** (26.5 mg, 58%) as a white solid. Mp = 33−34 °C. $[\alpha]^{20}_D = +22$ (c = 0.95, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 5.18 (tm, J = 6.9 Hz, 1H); 4.14 (br s, 1H); 3.41 (s, 3H); 3.39 (dd, J = 2.6, 11.2 Hz, 1H); 3.26 (d, J = 11.2 Hz, 1H); 2.55 (t, J = 13.9 Hz, 1H); 2.37 (s, 1H,); 2.15−2.04 (m, 3H); 1.83 (m, 1H); 1.61 (s, 3H); 1.57 (m, 1H); 1.26 (m, 2H); 1.17 (d, J = 6.7 Hz, 3H); 0.86 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 208.3, 131.4, 128.7, 82.2, 68.4, 60.5, 57.6, 42.8, 38.6, 32.0, 27.6, 25.9, 22.6, 22.5, 17.7, 14.2. HRMS (FAB): *m*/*z* found 275.2200, calcd for $C_{16}H_{28}O_3Li$ *m*/*z* 275.2198.

(2*S*,3*S*,4*R*,5*R*)-4-Trimethylsilyloxy-3-methoxy-5-methyl-2-[(*E*)-1,5-dimethyl-hex-1-enyl]cyclohexanone (35). TMSCl (29 μL, 233 μmol, 2.5 equiv) was added to a solution of alcohol **33** (25 mg, 93 μmol), DMAP (34 mg, 279 μmol, 3.0 equiv), and triethylamine (130 μL, 0.93 mmol, 10 equiv) in CH_2Cl_2 (2 mL). The mixture was stirred for 1 h at 20 °C and then quenched with a saturated aqueous NH_4Cl solution. Extraction with ether, solvent removal, and preparative TLC (SiO_2, cyclohexane/AcOEt 9/1) afforded **35** (29.8 mg, 94%) as a colorless oil. $[\alpha]^{20}_D = -4.3$ (c = 1.40, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 5.12 (tm, J = 6.9 Hz, 1H); 4.10 (br s, 1H); 3.33 (s, 3H); 3.32 (d, J = 11.4 Hz, 1H); 3.22 (dd, J = 1.9, 11.4 Hz, 1H); 2.44 (t, J = 13.9 Hz, 1H); 2.13−2.02 (m, 3H,); 1.76 (m, 1H); 1.58 (s, 3H); 1.57 (m, 1H); 1.25 (m, 2H); 1.01 (d, J = 6.6 Hz, 3H); 0.87 (2d, J = 6.9 Hz, 6H); 0.16 (s, 9H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 209.3, 131.0, 129.0, 82.8, 70.5, 60.6, 57.7, 43.4, 38.7, 32.6, 27.7, 25.9, 22.6, 22.6, 18.1, 14.3, 0.6.

(3*R*,4*S*,5*S*,6*R*,7*R*)-4-[(*E*)-1,5-Dimethylhex-1-enyl]-5-methoxy-7-methyl-6-trimethylsilyloxy-1-oxaspiro[2.5]-octane (36). To a suspension of NaH (31 mg, 790 μmol, 10 equiv) in DMSO (1 mL) was added trimethylsulfoxonium iodide (261 mg, 1.19 mmol, 15 equiv). The mixture was stirred at 20 °C for 1 h. THF (1 mL) and lithium iodide (127 mg, 0.95 mmol, 12 equiv) were added to the mixture, and stirring was continued for 40 min. A solution of **35** (25 mg, 73 μmol) in DMSO/THF (1/1, 1 mL) was added at 0 °C. The mixture was stirred for 2 h at 20 °C and quenched with ether (5 mL) and pH 7 buffer (5 mL). Extraction with ether and chromatography (SiO_2, cyclohexane/AcOEt 9/1) afforded pure **36** (colorless oil, 21.6 mg, 83%). $[\alpha]^{20}_D = -55$ (c = 1.52, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 5.16 (tm, J = 6.7 Hz, 1H); 4.07 (br s, 1H); 3.34 (dd, J = 2.1, 11.6 Hz, 1H); 3.33 (s, 3H); 2.85 (d, J = 11.5 Hz, 1H); 2.62 and 2.38 (2d, J = 5.1 Hz, 2H); 2.11−1.79 (m, 3H); 2.05 (t, J = 12.9 Hz, 1H); 1.54 (s, 3H); 1.53 (m, 1H); 1.20 (m, 2H); 0.92 (d, J = 6.6 Hz, 3H); 0.87 and 0.86 (2d, J = 6.6 Hz, 6H); 0.85 (m, 1H); 0.16 (s, 9H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 131.2, 130.6, 82.4, 70.6, 60.6, 57.1, 51.0, 47.1, 38.9, 36.1, 32.8, 27.7, 25.8, 22.6, 22.5, 18.2, 14.6, 0.6. HRMS (FAB): *m*/*z* found 361.2755, calcd for $C_{20}H_{38}O_3SiLi$ *m*/*z* 361.2750.

(3*R*,4*S*,5*S*,6*R*,7*R*)-6-Hydroxy-5-methoxy-7-methyl-4-[(*E*)-1,5-dimethylhex-1-enyl]-1-oxaspiro[2.5]octane (37). A solution of epoxide **36** (28 mg, 79 μmol, 1.0 equiv) in THF (2 mL) containing water (0.1 mL) was treated with PPTS (2 mg, 7.9 μmol, 10 mol %) for 24 h at 20 °C. The reaction was stopped with saturated aqueous $NaHCO_3$ and extracted with ether. Solvent removal and preparative TLC (SiO_2, cyclohexane/AcOEt 7/3) afforded **37** (6.6 mg, 30%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): 5.21 (tm, J = 7.6 Hz, 1H); 4.13 (br s, 1H); 3.50 (dd, J = 2.7, 11.4 Hz, 1H); 3.39 (s, 3H); 2.77 (d, J = 11.4 Hz, 1H); 2.62 and 2.43 (2d, J = 5.0 Hz, 2H); 2.16 (br s, 1H); 2.09 (t, J = 13.0 Hz, 1H); 2.08−1.93 (m, 3H); 1.56 (s, 3H); 1.53 (m, 1H); 1.19 (m, 2H); 1.08 (d, J = 6.6 Hz, 3H); 0.94 (dd, J = 3.6, 13.1 Hz, 1H); 0.88 and 0.87 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 130.9, 81.4, 68.5, 60.4, 56.8, 50.9, 47.3, 38.8, 35.6, 31.7, 27.7, 25.7, 22.6, 22.5, 17.7, 14.5.

5-(*R*)-5-Methyldihydrofumagillol (38). To a cold (0 °C) solution of **37** (6.6 mg, 21 μmol) and $NaHCO_3$ (10 mg, 126 μmol, 6 equiv) in CH_2Cl_2 (2 mL) was added *m*-CPBA (70%, 8 mg, 31 μmol, 1.5 equiv). The mixture was stirred for 1 h at 0 °C and then 1 h at 20 °C. The mixture was quenched with a saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. Preparative TLC (SiO_2, cyclohexane/AcOEt 7/3) afforded **38** (6.0 mg, 94%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): 4.16 (br s, 1H); 3.62 (dd, J = 2.5, 11.3 Hz, 1H); 3.50 (s, 3H); 2.85 and 2.57 (2d, J = 4.9 Hz, 2H); 2.54 (dd, J = 4.5, 7.4 Hz, 1H); 2.04 (t, J = 13.5 Hz, 1H); 1.92 (m, 1H); 1.90 (d, J = 11.4 Hz, 1H); 1.66−1.20 (m, 6H); 1.18 (s, 3H); 1.08 (d, J = 6.6, 3H); 0.90 (2d, J = 6.6 Hz, 6H); 0.89 (m, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 81.5, 68.1, 62.0, 59.5, 58.4, 56.4, 50.6, 46.5, 36.1, 35.6, 31.7, 27.9, 26.0, 22.6, 22.3, 17.5, 13.9.

***p*-Methoxycinnamic acid (3*R*,4*S*,5*S*,6*R*,7*R*)-5-Methoxy-7-methyl-4-[(1*R*,2*R*)-1,2-epoxy-1,5-dimethylhexyl]-1-oxaspiro[2.5]oct-6-yl Ester (39).** A solution of alcohol **38** (6 mg, 20 μmol) in CH_2Cl_2 (2 mL) was successively treated with *p*-methoxycinnamic acid (35 mg, 200 μmol, 10 equiv), DMAP (25 mg, 200 μmol, 10 equiv), and DCC (41 mg, 200 μmol, 10 equiv). The mixture was stirred overnight at 20 °C, and then the solvent was removed in vacuo and the residue filtered through a short pad of silica gel (eluent: cyclohexane/AcOEt 1/1). Preparative TLC (SiO_2, *n*-hexane/AcOEt 8/2) afforded **39** (7.9 mg, 95%), containing 15% of the *Z*-isomer. $[\alpha]^{20}_D = -43$ (c = 0.39, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 7.62 (d, J = 15.9 Hz, 1H); 7.47 and 6.90 (2d, J = 8.7 Hz, 4H); 6.36 (d, J = 15.9 Hz, 1H); 5.90 (br s, 1H); 3.83 (s, 3H); 3.70 (dd, J = 2.7, 11.5 Hz, 1H); 3.48 (s, 3H); 2.92 and 2.60 (2d, J = 4.4 Hz, 2H); 2.57 (m, 1H); 2.10 (m, 1H); 1.99 (t, J = 13.0 Hz, 1H); 1.97 (d, J = 11.4 Hz, 1H); 1.67−1.16 (m, 5H); 1.18 (s, 3H); 1.00 (m, 1H); 0.94 (d, J = 6.6 Hz, 3H); 0.89 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 167.1, 161.3, 144.6, 129.8, 127.3, 115.9, 114.3, 79.7, 69.3, 61.7, 59.3, 58.4, 56.8, 55.4, 50.7, 47.7, 37.5, 35.7, 31.4, 27.9, 26.0, 22.6, 22.3, 17.2, 13.9. HRMS (FAB): *m*/*z* found 465.2823, calcd for $C_{27}H_{38}O_6Li$ *m*/*z* 465.2828.

(2*S*,3*S*,4*R*,5*R*)-4-Hydroxy-3-methoxy-5-ethyl-2-[(*E*)-1,5-dimethyl-hex-1-enyl]cyclohexanone (40). To a cold (0 °C) solution of **21′** (14 mg, 55.5 μmol) in CH_2Cl_2 (0.8 mL) was added $AlEt_3$ (1 M in hexane, 550 μL, 550 μmol, 10 equiv). The mixture was stirred for 2 h at 20 °C, then slowly transferred onto a 20% aqueous tartaric acid solution. The mixture was extracted with ethyl acetate. The combined organic layers were dried

over Na_2SO_4 and evaporated in vacuo. The residue was purified on preparative TLC (SiO_2, cyclohexane/AcOEt 7/3) to afford **40** (8.0 mg, 51%) as a colorless oil. $[\alpha]^{20}_D = +20$ (c = 1.05, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 5.18 (tm, J = 7.0 Hz, 1H); 4.25 (br s, 1H); 3.41 (s, 3H); 3.38 (dd, J = 2.4, 11.2 Hz, 1H); 3.29 (d, J = 11.3 Hz, 1H); 2.49 (t, J = 13.4 Hz, 1H); 2.35 (br s, 1H); 2.20 (dd, J = 3.8, 13.8 Hz, 1H); 2.09 (br q, J = 7.3 Hz, 2H); 1.71−1.45 (m, 4H); 1.61 (s, 3H); 1.24 (m, 2H); 0.96 (t, J = 7.0 Hz, 3H); 0.88 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 208.3, 131.3, 128.8, 82.3, 66.4, 61.0, 57.7, 41.2, 38.7, 38.6, 27.6, 25.9, 25.0, 22.6, 22.5, 14.2, 11.6. HRMS (FAB): m/z found 289.2354, calcd for $C_{17}H_{30}O_3Li$ m/z 289.2355.

(2*S*,3*S*,4*R*,5*R*)-4-Benzoyloxy-3-methoxy-[(*E*)-1,5-dimethyl-hex-1-enyl]cyclohexanone (41). A solution of alcohol **40** (20 mg, 71 μmol) in CH_2Cl_2 (2 mL) was successively treated with benzoic acid (86 mg, 0.71 mmol, 10 equiv), DMAP (86 mg, 0.71 mmol, 10 equiv), and DCC (146 mg, 0.71 mmol, 10 equiv). The mixture was stirred overnight at 20 °C. The solvent were removed in vacuo and the residue filtered through a short pad of silica gel (eluent: cyclohexane/AcOEt 1/1). Preparative TLC (SiO_2, *n*-hexane/AcOEt 8/2) finally gave pure **41** (26 mg, 92%) as a colorless oil. $[\alpha]^{20}_D = -45$ (c = 1.25, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 8.05 (d, J = 7.0 Hz, 2H); 7.58 and 7.46 (2m, 3H); 5.99 (br s, 1H); 5.18 (tm, J = 6.9 Hz, 1H); 3.54 (dd, J = 2.6, 11.6 Hz, 1H); 3.43 (s, 3H); 3.39 (d, J = 11.6 Hz, 1H); 2.53 (t, J = 14.6 Hz, 1H); 2.43 (dd, J = 4.7, 14.6 Hz, 1H); 2.07 (m, 2H); 1.83 (m, 1H); 1.60 (s, 3H); 1.60−1.20 (m, 5H); 0.97 (t, J = 7.4 Hz, 3H); 0.86 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 207.5, 165.8, 133.2, 132.8, 131.6, 130.0, 129.7, 128.5, 80.6, 68.0, 62.2, 57.7, 42.5, 38.6, 38.1, 27.6, 25.9, 25.0, 22.5, 22.5, 13.9, 11.5.

(3*R*,4*S*,5*S*,6*R*,7*R*)-6-Benzoyloxy-4-[(*E*)-1,5-dimethylhex-1-enyl]-5-methoxy-7-methyl-1-oxaspiro[2.5]octane (42). To a suspension of NaH (60% in oil, 25 mg, 620 μmol, 10 equiv) in DMSO (1 mL) was added trimethylsulfoxonium iodide (204 mg, 0.93 mmol, 15 equiv). The mixture was stirred at 20 °C for 1 h. THF (1 mL) and lithium iodide (99 mg, 0.74 mmol, 12 equiv) were added to the mixture, and stirring was continued for further 40 min. A solution of **41** (25 mg, 62 μmol) in DMSO/THF 1/1 (1 mL) was added at 0 °C. The mixture was stirred for 2 h at 20 °C and quenched with ether (5 mL) and pH 7 buffer (5 mL). Extraction with ether and chromatography (SiO_2, cyclohexane/AcOEt 8/2) afforded pure **42** (colorless oil, 21 mg, 82%). $[\alpha]^{20}_D = -72$ (c = 1.05, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): 8.04 (m, 2H); 7.55 (m, 1H); 7.41 (m, 2H); 5.95 (br s, 1H); 5.22 (tm, J = 6.6 Hz, 1H); 3.65 (dd, J = 2.7, 11.6 Hz, 1H); 3.42 (s, 3H); 2.93 (d, J = 11.6 Hz, 1H); 2.73 and 2.51 (2d, J = 5.0 Hz, 2H); 2.14 (t, J = 13.2 Hz, 1H); 2.11−1.86 (m, 3H); 1.56 (s, 3H); 1.55−1.15 (m, 6H); 0.94 (t, J = 7.4 Hz, 3H); 0.86 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 166.0, 132.9, 131.2, 130.8, 130.5, 129.7, 128.3, 80.1, 68.8, 60.2, 57.2, 51.2, 49.2, 38.8, 38.3, 35.4, 27.7, 25.7, 24.8, 22.6, 22.4, 14.0, 11.6.

(3*R*,4*S*,5*S*,6*R*,7*R*)-6-Benzyloxy-4-[(1*R*,2*R*)-1,2-epoxy-1,5-dimethyl-hexyl]-7-ethyl-5-methoxy-1-oxaspiro[2.5]-octane (43). To a cold (0 °C) solution of **42** (19 mg, 45 μmol) and $NaHCO_3$ (50 mg) in CH_2Cl_2 (2 mL) was added *m*-CPBA (70%, 16 mg, 68 μmol, 1.5 equiv). The mixture was stirred for 1 h at 0 °C and then 1 h at 20 °C. The mixture was quenched with a saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. Preparative TLC (SiO_2, cyclohexane/AcOEt 7/3) afforded **43** (16.6 mg, 84%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): 7.98 (m, 2H); 7.54 (m, 1H); 7.41 (m, 2H); 5.97 (br s, 1H); 3.73 (dd, J = 2.7, 11.5 Hz, 1H); 3.52 (s, 3H); 2.96 and 2.64 (2d, J = 4.5 Hz, 2H); 2.56 (dd, J = 4.0, 7.0 Hz, 1H); 2.07 (t, J = 13.0 Hz, 1H); 2.01 (d, J = 11.5 Hz, 1H); 1.91 (m, 1H); 1.68−1.18 (m, 7H); 1.19 (s, 3H); 1.13 (dd, J = 3.5, 13.0 Hz); 0.93 (t, J = 7.3 Hz, 3H); 0.89 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 166.0, 132.8, 130.4, 129.7, 128.3, 80.1, 68.3, 61.7, 59.2, 58.2, 57.0, 50.8, 48.3, 38.4, 36.0, 35.7, 27.8, 26.0, 24.6, 22.6, 22.3, 13.9, 11.5.

5-(*R*)-5-Ethyldihydrofumagillol (44). To a solution of **43** (16 mg, 37 μmol) in MeOH (1 mL) was added potassium carbonate (50 mg). The mixture was stirred for 24 h at 20 °C, quenched with a saturated aqueous NH_4Cl solution, and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed (SiO_2, cyclohexane/AcOEt 6/4) to afford **44** (7 mg) as a colorless oil which was directly used for the next step. ^{1}H NMR (250 MHz, $CDCl_3$): 4.27 (br s, 1H); 3.60 (dd, J = 2.6, 11.3 Hz, 1H); 3.50 (s, 3H); 2.86 and 2.58 (2d, J = 4.3 Hz, 2H); 2.54 (dd, J = 4.4, 7.5 Hz, 1H); 2.19 (br s, 1H); 1.98 (t, J = 12.9 Hz, 1H); 1.92 (d, J = 11.3 Hz, 1H); 1.68−1.20 (m, 8H); 1.18 (s, 3H); 0.97 (t, J = 7.4 Hz, 3H); 0.96 (m, 1H); 0.89 (2d, J = 6.6 Hz, 6H).

***p*-Methoxycinnamic Acid (3*R*,4*S*,5*S*,6*R*,7*R*)-5-Methoxy-7-ethyl-4-[(1*R*,2*R*)-1,2-epoxy-1,5-dimethylhexyl]-1-oxaspiro[2.5]oct-6-yl Ester (45).** A solution of alcohol **44** (9 mg, 28.8 μmol) in CH_2Cl_2 (2 mL) was successively treated with *p*-methoxycinnamic acid (62 mg, 350 μmol, 12 equiv), DMAP (43 mg, 350 μmol, 12 equiv), and DCC (72 mg, 350 μmol, 12 equiv). The mixture was stirred overnight at 20 °C, and then the solvent was removed in vacuo and the residue filtered through a short pad of silica gel (eluent: cyclohexane/AcOEt 1/1). Preparative TLC (SiO_2, *n*-hexane/AcOEt 8/2) afforded **45** (12.3 mg, 52% for two steps), which contained 10% of the *Z*-isomer. $[\alpha]^{20}_D = -43$ ($CHCl_3$, C = 0.6). ^{1}H NMR (250 MHz, $CDCl_3$): 7.61 (d, J = 16.0 Hz, 1H); 7.46 and 6.89 (2d, J = 8.7 Hz, 4H); 6.32 (d, J = 16.0 Hz, 1H); 5.85 (br s, 1H); 3.83 (s, 3H); 3.68 (dd, J = 2.7, 11.5 Hz, 1H); 3.49 (s, 3H); 2.93 and 2.61 (2d, J = 4.4 Hz, 2H); 2.56 (dd, J = 4.2, 7.5 Hz, 1H); 1.99 (d, J = 11.3 Hz, 1H); 1.98 (t, J = 12.7 Hz, 1H); 1.86 (m, 1H); 1.67−1.18 (m, 7H); 1.20 (s, 3H); 1.08 (dd, J = 3.0, 12.9 Hz, 1H); 0.92 (t, J = 7.3 Hz, 3H); 0.89 (2d, J = 6.6 Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 166.9, 161.3, 144.5, 129.7, 127.3, 115.9, 114.3, 80.0, 67.5, 61.7, 59.3, 58.4, 56.9, 55.4, 50.8, 48.0, 38.3, 35.8, 35.7, 27.9, 26.0, 24.6, 22.6, 22.3, 13.8, 11.5. HRMS (FAB): m/z found 479.2981, calcd for $C_{28}H_{40}O_6Li$ m/z 479.2985

(1*R*,3*S*,4*S*,5*R*,6*S*)-3-[(*E*)-1,5-Dimethyl-hex-1-enyl]-4-methoxy-5-*p*-methoxybenzyloxy-7-oxabicyclo[4.1.0]heptan-2-one (46). To a solution of enone **21** (32 mg, 86 μmol) in MeOH (1 mL) at 0 °C was added K_2CO_3 (20% solution in H_2O (w/w), 5 μL, 8 μmol, 0.1 equiv) followed by H_2O_2 (30% solution, 30 μL, 260 μmol, 3 equiv). The mixture was stirred for 2 h at 0 °C, stopped with a NH_4Cl solution, and extracted with AcOEt. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification on preparative TLC (hexane/ethyl acetate, 85/15) provided pure **46** as a colorless oil (27 mg, 82%). $[\alpha]^{20}_D = -46$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 6.89 and 7.28 (2d, J = 8.5 Hz, 4H), 5.37 (t, 1H, J = 7.2 Hz), 4.59 and 4.87 (2d, AB, J = 11.8 Hz, 2H), 4.45 (dd, J = 3.6, 2.7 Hz, 1H), 3.81 (s, 3H), 3.78 (dd, J = 10.1, 2.5 Hz, 1H), 3.47 (t, J = 3.8 Hz, 1H), 3.37 (s, 3H), 3.27 (d, J = 3.8 Hz, 1H), 3.10 (d, J = 10.1 Hz, 1H), 2.06 (m, 2H), 1.43 (s, 3H), 1.20−1.29 (m, 3H), 0.89 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 204.6, 159.5, 132.4, 130.3, 129.5, 129.3, 114.0, 73.5, 70.4, 59.9, 58.4, 55.3, 54.6, 54.5, 38.5, 27.6, 26.0, 22.6, 22.5, 14.4.

(2*S*,3*S*,4*R*,5*S*)-2-[(*E*)-1,5-Dimethyl-hex-1-enyl]-5-hydroxy-3-methoxy-4-*p*-methoxybenzyloxycyclohexanone (47). To a solution of PhSeSePh (109 mg, 350 μmol, 1.5 equiv) in ethanol (4 mL) was added $NaBH_4$ (26.2 mg, 700 μmol, 3 equiv) at 20 °C. After 15 min, this solution was cooled to 0 °C, and AcOH (6 μl, 0.5 equiv) was added, followed by a solution of epoxide **46** (90 mg, 231 μmol) in ethanol (3 mL). After 15 min, the reaction was diluted with AcOEt and washed with brine. The aqueous phase was further extracted with AcOEt, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was passed over a short pad of silica gel (cyclohexane/AcOEt 1/1). After purification on preparative TLC (SiO_2, *n*-hexane/ethyl acetate, 75/25), pure **47** was obtained as a yellow oil (74 mg, 82%). $[\alpha]^{20}_D = +34$ (c = 1.48, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 6.89 and 7.30

(2d, J = 8.3 Hz, 4H), 5.13 (t, J = 6.6 Hz, 1H), 4.63 and 4.80 (2d, AB, J = 11.6 Hz, 2H), 4.22 (m, 1H), 3.96 (dd, J = 5.8, 2.5 Hz, 1H), 3.85 (dd, J = 8.8, 2.5 Hz, 1H), 3.81 (s, 3H), 3.40 (m, 1H), 3.37 (s, 3H), 2.82 (dd, J = 14.8, 3.8 Hz, 1H), 2.37 (dd, J = 14.8, 5.3 Hz, 1H), 2.05 (m, 2H), 1.58 (s, 3H), 1.53 (m, 1H), 1.22 (m, 2H), 0.88 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 208.0, 159.4, 131.9, 131.0, 130.0, 129.5, 113.8, 78.5, 75.7, 72.8, 67.9, 61.9, 57.9, 55.3, 45.0, 38.6, 27.7, 26.0, 22.5, 14.6.

(2*S*,3*S*,4*R*,5*S*)-2-[(*E*)-1,5-Dimethyl-hex-1-enyl]-5-(isopropyldimethylsilanyloxy)-3-methoxy-4-*p*-methoxybenzyloxycyclohexanone (48). Isopropyldimethylsilyl chloride (37 μL, 237 μmol, 1.5 equiv) was added to a solution of alcohol **47** (62 mg, 158 μmol) and DMAP (38 mg, 316 μmol, 2 equiv) in THF/DMF 1:1 (1 mL). The mixture was stirred for 1 h at 20 °C. After quenching (ammonium chloride), extraction (cyclohexane), and preparative TLC (hexane/AcOEt 9/1), pure **48** (59 mg, 76%) was obtained as a colorless oil. $[\alpha]^{20}_D = +19$ (c = 0.65, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 6.90 and 7.30 (2d, J = 8.8 Hz, 4H), 5.19 (t, J = 6.9 Hz, 1H), 4.60 and 4.84 (2d, AB, J = 11.8 Hz, 2H), 4.08 (dt, J = 4.5, 3.3 Hz, 1H), 3.88 (m, 1H), 3.81 (s, 3H), 3.80 (dd, J = 10.7, 2.8 Hz, 1H), 3.36 (d, J = 10.7 Hz, 1H), 3.35 (s, 3H), 2.76 (dd, J = 14.7, 3.4 Hz, 1H), 2.24 (ddd, J = 14.7, 3.3, 0.9 Hz, 1H), 2.08 (m, 2H), 1.56 (m, 4H), 1.24 (m, 2H), 0.88 (m, 12H), 0.70 (m, 1H), −0.02 and −0.01 (s, 6H). Anal. Calcd for $C_{28}H_{46}O_5Si$: C, 68.53; H, 9.45. Found: C, 68.29. H, 9.11.

(3*R*,5*S*,6*R*,7*S*,8*S*)-8-[(*E*)-1,5-Dimethyl-hex-1-enyl]-7-methoxy-6-*p*-methoxybenzyloxy-1-oxaspiro[2.5]oct-5-yloxy]-isopropyldimethylsilane (49). A solution of ketone **48** (59 mg, 120 μmol, 1.0 equiv) and CH_2I_2 (49 μL, 600 μmol, 5 equiv) in THF (1 mL) was treated with BuLi (1.6 M in hexanes, 375 μL, 600 μmol, 5.0 equiv) at −78 °C. The mixture was stirred for 1 h at −78 °C and then for 1.5 h at 20 °C. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by preparative TLC (hexane/ethyl acetate, 9/1) provided **49** as a colorless oil (22 mg) which was directly used for the next step. ^{1}H NMR (400 MHz, $CDCl_3$): 6.87 and 7.29 (2d, J = 8.8 Hz, 4H), 5.21 (t, J = 6.9 Hz, 1H), 4.57 and 4.70 (2d, AB, J = 12.1 Hz, 2H), 4.01 (m, 1H), 3.84 (dd, J = 9.8, 2.5 Hz, 1H), 3.81 (s, 3H), 3.74 (dd, J = 5.0, 2.3 Hz, 1H), 3.34 (s, 3H), 2.79 (d, J = 9.8 Hz, 1H), 2.24 and 2.49 (2d, AB, J = 5.3 Hz, 2H), 2.15 (dd, J = 13.8, 2.5 Hz, 1H), 1.96 (m, 2H), 1.54 (s, 3H), 1.35 (dd, J = 13.8, 4.7 Hz, 1H), 1.20 (m, 2H), 0.93 and 0.94 (2d, 6H), 0.86 and 0.88 (2d, J = 6.6 Hz Hz, 6H), 0.76 (m, 1H), 0.00 and 0.01 (s, 6H).

(3*R*,4*S*,5*S*,6*R*,7*S*)-4-[(*E*)-1,5-Dimethyl-hex-1-enyl]-7-(isopropyldimethylsilanyloxy)-5-methoxy-1-oxaspiro[2.5]-octan-6-ol (50). DDQ (7 mg, 31 μmol, 1.2 equiv) was added to a solution of epoxide **49** (13 mg, 26 μmol) in CH_2Cl_2 (1 mL) containing water (25 μL). The mixture was stirred for 2 h at 20 °C and then stopped by addition of saturated $NaHCO_3$ and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification on preparative TLC (SiO_2, CH_2Cl_2) provided **50** (8 mg) as a colorless oil which was directly used for the next step. ^{1}H NMR (400 MHz, $CDCl_3$): 5.27 (t, J = 7.8 Hz, 1H), 4.09 (m, 1H), 3.97 (m, 1H), 3.86 (dd, J = 9.0, 2.8 Hz, 1H), 3.39 (s, 3H), 2.62 (d, J = 9.0 Hz, 1H), 2.32 (d, J = 2.0, 1H), 2.30 and 2.49 (2d, AB, J = 4.5 Hz, 2H), 2.00 (m, 2H), 1.62 (s, 3H), 1.53 (m, 1H), 1.46 (dd, J = 14.1, 5.0 Hz, 1H), 1.23 (m, 2H), 0.97 (d, J = 6.8 Hz, 6H), 0.88 and 0.87 (d, J = 6.4 Hz, 6H), 0.82 (m, 1H), 0.08 and 0.07 (2 s, 6H).

***p*-Methoxycinnamic Acid (3*R*,4*S*,5*S*,6*R*,7*S*)-4-[(*E*)-1,5-Dimethyl-hex-1-enyl]-7-hydroxy-5-methoxy-1-oxaspiro-[2.5]oct-6-yl Ester (51).** *p*-Methoxycinnamic acid (35 mg, 200 μmol, 10 equiv) followed by DMAP (24 mg, 200 μmol, 10 equiv) and DCC (41 mg, 200 μmol, 10 equiv) were added to a solution of alcohol **50** (8 mg, 20 μmol) in CH_2Cl_2 (2 mL). The mixture was stirred overnight at 20 °C, and then the solvent was removed in vacuo and the residue passed over a short pad of silica gel (cyclohexane/AcOEt 1/1). The residue obtained was dissolved in THF (1 mL) and treated with TBAF (1 M in THF, 20 μL, 20 μmol) for 0.5 h. The reaction was stopped with saturated NH_4Cl and extracted with AcOEt. Combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Two successive purifications by preparative TLC on silica gel ((1) hexane/ethyl acetate, 3/2; (2) CH_2Cl_2/ethyl acetate, 9/1) afforded **51** as a 7:3 mixture of *E*/*Z* cinnamates (2 mg, 7% from **48**). ^{1}H NMR (400 MHz, $CDCl_3$): *E*-Isomer: 7.67 (d, J = 16.0, 1H), 7.48 and 6.91 (2d, J = 8.8 Hz, 4H), 6.35 (d, J = 16.0 Hz, 1H), 5.62 (m, 1H), 5.33 (t, J = 7.2 Hz, 1H), 4.20 (m, 1H), 4.02 (dd, J = 10.0, 2.8 Hz, 1H), 3.85 (s, 3H), 3.39 (s, 3H), 2.84 (d, J = 10.4 Hz, 1H), 2.57 (d, J = 6.4 Hz, 1H), 2.66 and 2.47 (2d, AB, J = 4.8 Hz, 2H), 2.37 (dd, J = 14.6, 3.3 Hz, 1H), 2.05 (m, 2H), 1.61 (s, 3H), 1.61−1.48 (m, 2H), 1.23 (m, 2H), 0.89 and 0.88 (d, J = 6.4 Hz, 6H). Z-Isomer: 6.90 (d, J = 12.4 Hz, 1H), 7.68 and 6.88 (2d, J = 8.8 Hz, 4H), 5.88 (d, J = 12.4 Hz, 1H), 5.59 (m, 1H), 5.28 (t, J = 7.2 Hz, 1H), 4.00 (m, 1H), 3.98 (dd, J = 10.0, 2.8 Hz, 1H), 3.83 (s, 3H), 3.38 (s, 3H), 2.75 (d, J = 10.4 Hz, 1H), 2.55 (d, J = 6.4 Hz, 1H), 2.62 and 2.42 (2d, AB, J = 4.8 Hz, 2H), 2.22 (dd, J = 14.6, 3.3 Hz, 1H), 2.05 (m, 2H), 1.59 (s, 3H), 1.61−1.48 (m, 2H), 1.23 (m, 2H), 0.89 and 0.88 (d, J = 6.4 Hz, 6H). HRMS (FAB): *m*/*z* found 451.2704, calcd for $C_{26}H_{36}O_6Li$ *m*/*z* 451.2672.

(4*R*,5*S*,6*S*)-6-[(*E*)-1,5-Dimethyl-hex-1-enyl]-2-hydroxymethyl-5-methoxy-4-*p*-methoxybenzyloxycyclohex-2-enone (52). To a solution of enone **21** (230 mg, 618 μmol) in THF (5 mL) at 20 °C was added tri-*n*-butylphosphine (130 μl, 530 μmol, 0.85 equiv) followed by formaldehyde (40% aqueous solution, 130 μL, 1.62 mmol, 2.6 equiv). The mixture was stirred overnight, diluted with H_2O, and extracted with AcOEt. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed (SiO_2, cyclohexane/ethyl acetate, 7/3) to afford pure **52** (200 mg, 80%) as a colorless oil. $[\alpha]^{20}_D = -116$ (c = 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.28 and 6.88 (2d, J = 8.8 Hz, 4H), 6.75 (m, 1H), 5.12 (t, J = 7.0 Hz, 1H), 4.68 and 4.64 (2d, AB, J = 11.6 Hz, 2H), 4.36 (m, 2H), 4.18 (d, J = 14.4 Hz, 1H), 3.80 (s, 3H), 3.74 (m, 1H), 3.45 (d, J = 6.4 Hz, 1H), 3.40 (s, 3H), 2.00 (m, 2H), 1.56 (s, 3H), 1.50 (m, 1H), 1.15 (m, 2H), 0.85 (d, J = 6.4 Hz, 6H). RMN ^{13}C (100 MHz, $CDCl_3$): 199.5, 159.5, 140.6, 139.6, 130.4, 129.9, 129.5, 128.9, 113.9, 80.1, 71.6, 69.7, 61.1, 58.8, 57.7, 55.3, 38.4, 27.7, 26.0, 22.5, 15.2.

(4*R*,5*S*,6*S*)-2-(*tert*-Butyldimethylsilanyloxymethyl)-6-[(*E*)-1,5-dimethyl-hex-1-enyl]-5-methoxy-4-*p*-methoxybenzyloxycyclohex-2-enone (53). TBSCl (80 mg, 530 μmol, 1.5 equiv) was added to a solution of alcohol **52** (195 mg, 485 μmol) and DMAP (89 mg, 728 μmol, 2 equiv) in THF (3 mL). The mixture was stirred for 4 h at 20 °C. After quenching (ammonium chloride), extraction (cyclohexane), and chromatography (SiO_2, cyclohexane/AcOEt 9/1), pure **53** (170 mg, 68%) was obtained as a colorless oil. $[\alpha]^{20}_D = -74$ (c = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.30 and 6.88 (2d, J = 8.0 Hz, 4H), 6.84 (br s, 1H), 5.13 (t, J = 7.0 Hz, 1H), 4.66 (s, 2H), 4.34 (m, 3H), 3.81 (s, 3H), 3.71 (m, 1H), 3.46 (d, J = 6.4 Hz, 1H), 3.40 (s, 3H), 2.03 (m, 2H), 1.56 (s, 3H), 1.52 (m, 1H), 1.19 (q, J = 7.6 Hz, 2H), 0.92 (s, 9H), 0.86 (d, J = 6.8 Hz, 6H), 0.08 and 0.06 (2s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 198.2, 159.4, 140.2, 138.5, 130.5, 130.3, 129.5, 129.0, 113.9, 80.1, 71.5, 70.2, 59.8, 58.9, 57.5, 55.2, 38.4, 27.6, 25.9, 22.5, 18.3, 15.0, −4.6. HRMS (FAB): *m*/*z* found 523.3429, calcd for $C_{30}H_{48}O_5LiSi$ *m*/*z* 523.3431.

(2*S*,3*S*,4*R*)-2-[(*E*)-1,5-Dimethyl-hex-1-enyl]-3-methoxy-4-*p*-methoxybenzyloxy-6-methylenecyclohexanone (55). To a solution of **53** (135 mg, 261 μmol) in toluene (1.5 mL) was added Et_3SiH (1.5 mL) followed by Wilkinson's catalyst $RhCl(PPh_3)_3$ (6 mg, 7 μmol, 0.03 equiv). The mixture was heated to 65 °C for 4 h, and then the solvent was removed in vacuo and the residue filtered through a short pad of silica (cyclohexane → cyclohexane/AcOEt 9/1) to yield 176 mg of crude **54**, which were dissolved in THF/H_2O (1/1), and treated

with TFA (1M in THF, 260 μl, 260 μmol, 1 equiv). The reaction was stirred for 1.5 h, quenched with H_2O, and extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed (SiO_2, cyclohexane/ethyl acetate, 9/1) to afford pure **55** (70 mg, 70%) as a colorless oil. $[\alpha]^{20}_D = -5.6$ (c = 1.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.27 and 6.87 (2d, J = 8.8 Hz, 4H), 5.98 (s, 1H), 5.21 (d, J = 1.5 Hz, 1H), 5.17 (t, J = 7.0 Hz, 1H), 4.60 (s, 2H), 4.08 (m, 1H), 3.81 (s, 3H), 3.60 (dd, J = 8.6, 1.5 Hz, 1H), 3.42 (d, J = 8.6 Hz, 1H), 3.38 (s, 3H), 2.92 (dd, J = 16.0, 6.4 Hz, 1H), 2.53 (dd, J = 16.0, 2.8 Hz, 1H), 2.03 (m, 2H), 1.57 (s, 3H), 1.55 (m, 1H), 1.23 (m, 2H), 0.87 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 200.0, 159.2, 141.2, 131.2, 130.5, 130.0, 129.2, 123.2, 113.9, 113.8, 80.7, 71.1, 70.7, 60.9, 57.6, 55.3, 32.5, 27.6, 26.0, 22.5, 14.8.

(2*S*,3*S*,4*R*,6*S*)-2-[(*E*)-1,5-Dimethyl-hex-1-enyl]-3-methoxy-4-*p*-methoxybenzyloxy-6-methyl-cyclohexanone (56) and (2*S*,3*S*,4*R*,6*R*)-2-[(*E*-1,5-Dimethyl-hex-1-enyl]-3-methoxy-4-*p*-methoxybenzyloxy-6-methylcyclohexanone (57). Under vigorous stirring, 10 drops of a 50% suspension of Raney Nickel in water were added to a cold (0 °C) solution of enone **55** (70 mg, 106 μmol) in THF (1 mL). After 2 h, the mixture was diluted with ether and filtered through Celite. The residue was chromatographed on preparative TLC (SiO_2, *n*-hexane/AcOEt 9/1) to afford pure **56 (**25 mg, 36%) alongside with pure **57** (11 mg, 16%). **56.** $[\alpha]^{20}_D = +50$ (c = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.30 and 6.89 (2 d, J = 8.4 Hz, 4 H), 4.98 (t, J = 7.0 Hz, 1 H), 4.61 and 4.54 (2 d, AB, J = 12.0 Hz, 2 H), 4.03 (ddd, J = 10.1, 4.3, 2.0 Hz, 1 H), 3.90 (br s, 1 H), 3.81 (s, 3 H), 3.42 (s, 3 H), 3.30 (m, 1 H), 2.39 (m, 1 H), 1.99−1.92 (m, 4 H), 1.53 (s, 3 H), 1.49 (m, 1 H), 1.13 (m, 2 H), 1.06 (d, J = 6.4 Hz, 3 H), 0.86 (d, J = 6.8 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): 211.9, 159.3, 130.6, 130.0, 129.3, 128.0, 113.8, 80.8, 73.4, 70.5, 60.6, 57.9, 55.3, 40.2, 38.5, 33.5, 27.8, 25.9, 22.5, 15.6, 15.1. **57.** $[\alpha]^{20}_D = -16$ (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.34 and 6.88 (2d, J = 8.4 Hz, 4H), 5.18 (t, J = 6.8 Hz, 1H), 4.63 (2d, AB, J = 11.6 Hz, 2H), 4.11 (m, 1H), 3.82 (s, 3H), 3.57 (d, J = 11.9 Hz, 1H), 3.35 (dd, J = 11.9, 2.5 Hz, 1H), 3.30 (s, 3H), 2.75 (d quint, J = 13.0, 6.6 Hz, 1H), 2.20 (ddd, J = 14.4, 5.8, 4.0 Hz, 1H), 2.08 (m, 2H), 1.59 (s, 3H), 1.55 (m, 1H), 1.28−1.17 (m, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 209.7, 159.2, 130.8, 130.7, 129.4, 129.3, 117.1, 82.7, 71.4, 70.4, 61.8, 57.2, 55.3, 38.7, 38.5, 33.9, 29.7, 27.7, 25.9, 22.6, 13.9. HRMS (FAB): m/z found 395.2768, calcd for $C_{24}H_{36}O_4Li$ m/z 395.2774.

(3*R*,4*S*,5*S*,6*R*,8*R*)-4-[(*E*)-1,5-Dimethyl-hex-1-enyl]-5-methoxy-6-*p*-methoxybenzyloxy-8-methyl-1-oxaspiro[2.5]-octane (58). A solution of ketone **57** (20 mg, 51 μmol) and CH_2I_2 (20 μL, 250 μmol, 5 equiv) in THF (0.3 mL) was treated with BuLi (1.6 M in hexanes, 160 μL, 250 μmol, 5 equiv) at −78 °C. The mixture was stirred for 45 min at −78 °C and then for 1.5 h at 20 °C. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification on preparative TLC (SiO_2, *n*-hexane/ethyl acetate, 9/1) provided pure **58** (11 mg, 54%) as a colorless oil. $[\alpha]^{20}_D = -53$ (c = 0.55, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.32 and 6.87 (2d, J = 8.8 Hz, 4H), 5.21 (t, J = 6.6 Hz, 1H), 4.67 and 4.61 (2d, AB, J = 12.0 Hz, 2H), 4.06 (br s, 1H), 3.81 (s, 3H), 3.46 (dd, J = 11.6, 2.4 Hz, 1H), 3.29 (s, 3H), 3.01 (d, J = 11.6 Hz, 1H), 2.61 and 2.47 (2d, AB, J = 4.8 Hz, 2H), 2.34 (dtd, J = 13.0, 6.8, 3.8 Hz, 1H), 2.01 (m, 2H), 1.89 (dt, J = 14.0, 3.8 Hz, 1H), 1.54 (s, 3H), 1.52 (m, 1H), 1.37 (td, J = 13.0, 2.0 Hz, 1H), 1.22 (m, 3H), 0.88 and 0.87 (2d, J = 6.4 Hz, 6H), 0.67 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 159.1, 131.3, 130.6, 129.2, 114.8, 81.1, 70.0, 56.6, 55.3, 49.8, 47.9, 38.9, 34.4, 28.4, 27.7, 25.8, 22.6 and 22.5, 13.8.

(3*R*,4*S*,5*S*,6*R*,8*R*)-4-[(*E*-1,5-Dimethyl-hex-1-enyl]-5-methoxy-8-methyl-1-oxaspiro[2.5]octan-6-ol (59). DDQ (8 mg, 33 μmol, 1.2 equiv) was added to a solution of epoxide **58** (11 mg, 27 μmol) in CH_2Cl_2 (0.5 mL) containing water (30 μL). The mixture was stirred for 1 h at 20 °C and then stopped by addition of saturated $NaHCO_3$ and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification on preparative TLC (SiO_2, *n*-hexane/AcOEt 9/1) afforded **59** (6 mg) as a colorless oil which was directly used for the next step. ^{1}H NMR (400 MHz, $CDCl_3$): 5.22 (t, J = 6.9 Hz, 1H), 4.33 (m, 1H), 3.49 (dd, J = 11.3, 2.8 Hz, 1H), 3.38 (s, 3H), 2.80 (d, J = 11.3 Hz, 1H), 2.51 and 2.64 (2d, AB, J = 4.5 Hz, 2H), 2.37 (m, 2H), 2.04 (m, 2H), 1.93 (dt, J = 14.1, 3.7 Hz, 1H), 1.57 (s, 3H), 1.52 (m, 1H), 1.22 (m, 2H), 0.87 and 0.89 (d, J = 6.4 Hz, 6H), 0.69 (d, J = 6.8 Hz, 3H).

***p*-Methoxycinnamic Acid (1*R*,4*S*,5*S*,6*R*,8*R*)-4-[(*E*)-(1,5-Dimethyl-hex-1-enyl]-5-methoxy-8-methyl-1-oxaspiro-[2.5]oct-6-yl Ester (60).** *p*-Methoxycinnamic acid (44 mg, 250 μmol, 10 equiv) followed by DMAP (30 mg, 250 μmol, 10 equiv) and DCC (51 mg, 250 μmol, 10 equiv) were added to a solution of alcohol **59** (6 mg, 87 μmol) in CH_2Cl_2 (1 mL). The mixture was stirred overnight at 20 °C, and then the solvent was removed in vacuo and the residue passed over a short pad of silica gel (cyclohexane/AcOEt 7/3). Chromatography on preparative TLC (SiO_2, *n*-hexane/AcOEt 9/1) afforded pure **60** (8 mg, 69% from **58**) containing ca.0.13% of the *Z*-cinnamate. $[\alpha]^{20}_D = -90$ (c = 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.66 (d, J = 16 Hz, 1H), 6.91 and 7.48 (2d, J = 8.8 Hz, 4H), 6.38 (d, J = 16 Hz, 1H), 5.40 (t, J = 6.8 Hz, 1H), 5.25 (m, 1H), 3.87 (m, 1H), 3.83 (s, 3H), 3.36 (s, 3H), 2.70 (d, J = 8.3 Hz, 1H), 2.44 and 2.60 (2d, J = 5.0 Hz, 2H), 2.32 (m, 1H), 2.05 (m, 2H), 1.95 (dt, J = 14.6, 3.8 Hz, 1H), 1.64 (td, J = 13.7, 2.0 Hz, 1H), 1.53 (m, 1H), 1.26 (m, 2H), 0.89 and 0.88 (d, J = 6.6 Hz, 6H), 0.71 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 166.9, 161.4, 144.5, 132.1, 130.8, 129.8, 127.3, 116.1, 114.4, 79.1, 66.9, 62.7, 57.0, 55.3, 50.5, 47.9, 38.8, 34.6, 28.9, 27.7, 25.7, 22.5, 22.6, 13.6. HRMS (FAB): m/z found 443.2790, calcd for $C_{27}H_{39}O_5$ m/z 443.2797.

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Supporting Information Available: ^{13}C NMR spectra of compounds **4**, **10**−**12**, **14**−**21**, **21′**, **22**−**25**, **27**−**31**, **31′**, **32**, **33**, **35**−**43**, **45**−**47**, **52**, **53**, **55**−**58**, and **60**. This material is available free of charge via the Internet at http://pubs.acs.org.

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