Enzyme-Assisted Asymmetric Total Synthesis of (−)-Podophyllotoxin and (−)-Picropodophyllin

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Described is the first *catalytic*, asymmetric synthesis of (−)-podophyllotoxin and its C_2-epimer, (−)-picropodophyllin. Asymmetry is achieved via the enzymatic desymmetrization of advanced meso diacetate **20**, through PPL-mediated ester hydrolysis. A second key feature of the synthesis is the strategically late introduction of the highly oxygenated natural ring E through an arylcopper species. The successful implementation of this approach augers well for the introduction of other *functionalized* rings E for future SAR work. The synthesis begins from piperonal, which is fashioned into isobenzofuran (IBF) precursor **14** in three steps (bromination, acetalization, and halogen−metal exchange/hydroxymethylation). Interestingly, treatment of **14** with HOAc in commerical dimethyl maleate (contains 5% dimethyl fumarate) leads to a nearly equimolar mixture of fumarate−(**15**) and maleate−IBF Diels−Alder adducts (**16** and **17**), indicating that IBF **11** reacts about 15 times faster with dimethyl fumarate than with dimethyl maleate. With scrupulously pure dimethyl maleate a 2.8:1 endo:exo mixture of maleate DA adducts is still obtained. On the other hand, the desired meso diester **16** is obtained pure and in nearly quantitative yield by employing neat dimethyl acetylene dicarboxylate as the dienophile, followed by catalytic hydrogenation. Reduction ($LiAlH_4$) of **16** provides meso diol **19**, which is then treated with Ac_2O, BzCl, and $PhCH_2COCl$ to provide the corresponding meso diesters, **20**−**22**. Screening of these meso benzoxabicyclo[2.2.1]heptyl substrate candidates across a battery of acyl transfer enzymes leads to an optimized match of diacetate **20** with PPL. Even on 10−20 g scales, asymmetry is efficiently introduced here, yielding the key chiral intermediate, monoacetate **25** (66% isolated yield, 83% corrected yield, 95% ee). Protecting group manipulation and oxidation (Swern) provide aldehyde **27b**, which undergoes efficient retro-Michael ring opening to produce dihydronaphthalene **30**, in which the C_3 and C_4 stereocenters are properly set. Following several unsuccessful approaches to the intramolecular delivery of ring E (via Claisen rearrangement, Heck-type cyclization, or radical cyclization), a highly diastereoselective, intermolecular conjugate addition of the arylcopper reagent derived from (3,4,5-trimethoxy)phenylmagnesium bromide and CuCN to acyl oxazolidinone **50** was developed (85% yield, only the required α-stereochemistry at C_1 is observed). The conjugate addition product is converted to (−)-picropodophyllin in two steps (lactonization, SEM deprotection) or to (−)-podophyllotoxin, in three steps, through the introduction of a C_2-epimerization step, under Kende conditions, prior to the final conjugate addition.

Introduction

(−)-Podophyllotoxin (**1**), an aryl tetralin lignan isolated from the American May apple tree (*Podophyllum peltatum*) and a related plant on the Indian subcontinent (*Podophyllum emodi*), is a potent antimitotic, binding to tubulin and inhibiting microtubule formation.[1] There has been renewed clinical interest in the natural product itself, particularly for the treatment of venereal warts.[2] Most notably, however, its glucosylated, 4-epi-derivative, etoposide (**2**), has seen extensive application as a chemotherapeutic, particularly for small cell lung cancer (SCLC), advanced testicular cancer, and Kaposi's sarcoma.[3,4] A recent report also raised the intriguing possibility of using epipodophyllotoxins as anti-HIV agents.[5] The semisynthetic drug apparently has a very different mechanism of action than its parent aglycon. Etoposide is known to stabilize the covalent enzyme-cleaved DNA complex that is normally present along the topoisomerase II reaction coordinate. This results in abnormally high concentrations of this species, actuating mutagenesis or cell death pathways.[6] Alternative mechanisms, several of which involve reactive species derived from oxidation

(1) King, L.; Sullivan, M. *Science* **1946**, *104*, 244−245.

(2) (a) Tyring, S.; Edwards, L.; Cherry, L. K.; Ramsdell, W. M.; Kotner, S.; Greenberg, M. D.; Vance, J. C.; Barnum, G.; Dromgoole, S. H.; Killey, F. P.; Toter, T. *Arch. Dermatol.* **1998**, *134*, 33−38. (b) Claesson, U.; Lassus, A.; Happonen, H.; Hogström, L.; Siboulet, A. *Int. J. STD AIDS* **1996**, *7*, 429−434. (c) Beutner, K. R. *Curr. Probl. Dermatol.* **1996**, *24*, 227−232.

(3) For reviews of the chemical, biological and clinical aspects of etoposide and related epipodophyllotoxins, see: (a) Imbert, T. F. *Biochimie* **1998**, *80*, 207−222. (b) Damayanthi, Y.; Lown, J. W. *Curr. Med. Chem.* **1998**, *5*, 205−252. (c) *Etoposide (VP-16). Current Status and New Developments*; Issell, B. F., Muggia, F. M., Carter, S. K., Eds.; Academic Press: New York, 1984.

(4) (a) Hande, K. R. *Biochim. Biophys. Acta* **1998**, *1400*, 173−184. (b) Pommier, Y.; Fesen, M. R.; Goldwasser, F. In *Cancer Chemotherapy and Biotherapy: Principles and Practice*; Chabner, B. A., Longo, S. L., Eds. Lippincoltt Raven: Philadephia, 1996; pp 435−461. (b) Smith, M. A. Rubinstein, L.; Cazenave, L.; Ungerleider, R. S.; Maurer, H. M.; Heyn, R.; Khan, F. M.; Gehan, E. *J. Natl. Cancer Inst.* **1993**, *85*, 554−558 and references therein.

(5) Lee, C. T.-L.; Lin, V. C.-K.; Zhang, S.-X.; Zhu, X.-K.; VanVliet, D.; Hu, H.; Beers, S. A.; Wang, Z.-Q.; Cosentino; L. M.; Morris-Natschke, S. L.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2897−2902.

(6) (a) Kingma, P, S,; Burden, D. A.; Osheroff, N. *Biochemistry* **1999**, *38*, 3457−3461. (b) Burden, D. A.; Osheroff, N. *Biochim. Biophys. Acta* **1998** *1400*, 139−154. (c) Burden, D. A.; Kingma, P. S.; Froelich-Ammon, S. J.; Bjornsti, M.-A.; Patchan, M. W.; Thompson, R. B.; Osheroff, N. *J. Biol. Chem.* **1996**, *271*, 29238−29244 and references therein.

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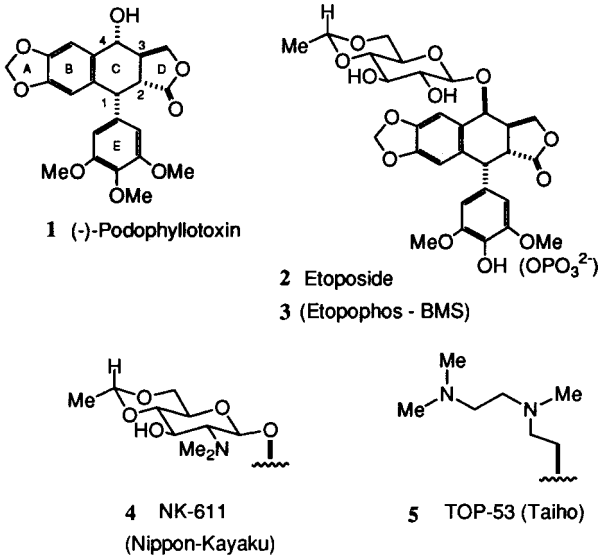
of ring E, have also been put forth.[7] Recently, several new members of the etoposide family have emerged as potentially superior chemotherapeutics, including the BMS prodrug, etopophos (**3**),[8] Nippon-Kayaku's NK-611 (**4**),[9] and Taiho's TOP-53 (**5**),[10] all of which have enhanced water solubility, and the latter of which may hold promise for NSCLC applications.



Owing both to its significant clinical role and to its intriguing structure (e.g., heavily oxygenated aromatic core, four contiguous chiral centers, pseudoaxial ring E, and facile epimerization at C_2 and C_4), podophyllotoxin has drawn considerable attention from synthetic chemists.[11−16] Nearly all first generation syntheses provided racemic product.[12] Meyers and co-workers recorded the first enantioselective synthesis of (−)-podophyllotoxin wherein all stereochemical information was elegantly derived from a chiral oxazoline-mediated construction of the $C_{1'}-C_1$ bond.[13a] More recently, both the Charlton and Jones groups have disclosed asymmetric Diels−Alder approaches, disconnecting at C_1-C_2 and at C_3-C_4 and employing a chiral ester auxiliary appended to the dienophile.[13b,c] The other enantioselective entry, due to the Vandewalle and Bhat groups, involves C_3-C_4 bond formation through conjugate addition of a sulfoxide- or dithiane-stabilized benzylic anion upon a ring D-butenolide, in which a resident chiral directing group on the butenolide[13d] or on the anion[13e] controls facial selectivity.

Philosophically, our approach[16] differs from these syntheses in two fundamental ways: (1) absolute stereochemistry is to be controlled catalytically, by means of an enzyme-catalyzed transformation upon an unnatural substrate,[17] and (2) ring E is introduced as late as possible in the synthesis. This latter strategem is designed to permit efficient structural variation in ring E as a tool for the study of its functional role in both the podophyllotoxin and etoposide series (Scheme 1). Retrosynthetically, then, ring E is disconnected first, with its installation envisioned to proceed either intramolecularly, via an aromatic Claisen rearrangement ($\Rightarrow X = H_2$, $Y = O$, $Z = H$) or a cyclization reaction (modified Heck[18] or radical 6-endo-trig $\Rightarrow X = CH_2$, O; $Y = O$, S; $Z = Br$, I) from **6**, or intermolecularly, via conjugate addition from **7**. The trans-disposed (3-alkoxymethyl-4-alkoxy)dihydronaphthalene core (**6** or **7**) would, in turn, arise via a retro-Michael ring opening from **8** or **9**.[19] If feasible, an isobenzofuran (IBF) Diels−Alder reaction from the sterically unprotected, electron-rich IBF **11** was envisioned to be the key step in assembling the benzoxabicyclo[2.2.1]-heptyl substructure.[20,21] This would lead to a family of advanced meso intermediates **10** to be enzymatically

(7) (a) Sakurai, H.; Miki, T.; Imakura, Y.; Shibuya, M.; Lee, K.-H. *Mol. Pharmacol.* **1991**, *40*, 965−973. (b) Sinha, B. K.; Eliot, H. M.; Kalayanaraman, B. *FEBS Lett.* **1988**, *227*, 240−244. (c) Van Maanen, J. M. S.; de Vries, J.; Pappie, D.; van der Akker, E.; Vincent, M.; Lafleur, M.; Retel, J.; van der Greef, J.; Pinedo, H. M. *Cancer Res.* **1987**, *47*, 4658−4662 and references therein.

(8) (a) de Jong, R. S.; Slijfer, E. A. M.; Uges, D. R. A.; Mulder, N. H.; de Vries, E. G. E. *Br. J. Cancer* **1997**, *76*, 1480−1483. (b) Soni, N.; Meropol, N. J.; Pendyala, L.; Noel, D.; Schacter, L. P.; Gunton, K. E.; Creaven, P. J. *J. Clin. Oncol.* **1997**, *15*, 766−772. (c). Kreis, W.; Budman, D. R.; Vinciguerra, V.; Hock, K.; Baer-Joann, I. R.; Schacter, L. P.; Fields, S. Z. *Cancer Chemother. Pharmacol.* **1996**, *38*, 378−384.

(9) (a) Rassmann, I.; Thodtmann, R.; Mross, M.; Huttmann, A.; Berdel, W. E.; Manegold, C.; Fiebig, H. H.; Kaeserfrolich, A.; Burk, K.; Hanauske, A. R. *Invest. New Drugs* **1998**, *16*, 319−324. (b) Mross, K.; Huettmann, A.; Herbst K.; Hanauske, A. R.; Schilling, T.; Manegold, C.; Burk, K.; Hossfeld, D. K. *Cancer Chemother. Pharmacol.* **1996**, *38* 217−224.

(10) Utsugi, T.; Shibata, J.; Sugimoto, Y.; Aoyagi, K.; Wierzba, K.; Kobunai, T.; Terada, T.; Oh-hara, T.; Tsuruo, T.; Yamada, Y. *Cancer Res.* **1996**, *56*, 2809−2814.

(11) For reviews of synthetic approaches to the *Podophyllum* lignans, see: (a) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75−96 and previous reviews in this series. (b) Ward, R. S. *Synthesis* **1992**, 719−730.

(12) For syntheses of (±)-podophyllotoxin, see: (a) Kraus, G. A.; Wu, Y. *J. Org. Chem.* **1992**, *57*, 2922−2925. (b) Peterson, J. R.; Hoang, D. D.; Rogers, R. D. *Synthesis* **1991**, 275−277 (c) Jones, D. W.; Thompson, A. M. *J. Chem. Soc., Chem. Commun.* **1987**, 1797−1798. (d) Kaneko, T.; Wong, H. *Tetrahedron Lett.* **1987**, *28*, 517−520. (e) Vyas, D. M.; Skonezny, P. M.; Jenks, T. A.; Doyle, T. W. *Tetrahedron Lett.* **1986**, *27*, 3099−3102. (f) Macdonald, D. I.; Durst, T. *J. Org. Chem.* **1986**, *51*, 4749−4750. (g) Jung, M. E.; Lowen, G. T. *Tetrahedron Lett.* **1986**, *27*, 5319−5322. (h) Jung, M. E.; Lam P. Y.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087−1105. (i) Van der Eycken, J.; De Clercq, P.; Vandewalle, M. *Tetrahedron Lett.* **1985**, *26*, 3871−3874. (j) Rajapaksa, D.; Rodrigo, R. *J. Am. Chem. Soc.* **1981**, *103*, 6208−6209. (k) Kende, A. S.; King, M. L.; Curran, D. P. *J. Org. Chem.* **1981**, *46*, 2826−2828. (l) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Chem. Commun.* **1980**, 262−263. (m) Kende, A. S.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 7082−7083. (n) Gensler, W. J.; Gastonis, C. G. *J. Org. Chem.* **1966**, *31*, 4004−4008.

(13) (a) Andrews, R. C.; Teague, S. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7854−7858. (b) Bush, E. J.; Jones, D. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 151−155. (c) Charlton, J. L.; Koh, K. *J. Org. Chem.* **1992**, *57*, 1514−1516. (d) Van Speybroeck, R.; Guo, H.; Van der Eycken, J.; Vandewalle, M. *Tetrahedron* **1991**, *47*, 4675−4682. (e) Hadimani, S. B.; Tanpure, R. P.; Bhat, S. V. *Tetrahedron Lett.* **1996**, *37*, 4791−4794.

(14) For recent asymmetric syntheses of building blocks toward (−)-podophyllotoxin, see: (a) Brinksma, J.; van der Deen, H.; van Oeveren, A.; Feringa, B. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4159−4163. (b) Lautens, M.; Rovis, T. *J. Org. Chem.* **1997**, *62*, 5246−5247. (c) Yoshida, S.; Yamanaka, T.; Miyake, T.; Moritani, Y.; Ohmizu, H.; Iwasaki, T. *Tetrahedron* **1997**, *53*, 9585−9598.

(15) For syntheses of 4-deoxypodophyllotoxin, isopodophyllotoxin, 4-deoxyisopodophyllotoxin, and epiisopodophyllotoxin, see: (a) Hanessian, S.; Ninkovic, S. *Can. J. Chem.* **1996**, *74*, 1880−1888. (b) Kuroda, T.; Takahashi, M.; Kondo, K.; Iwasaki, T. *J. Org. Chem.* **1996**, *61*, 9560−9563. (c) Bogucki, D. E.; Charlton, J. L. *J. Org. Chem.* **1995**, *60*, 588−593. (d) Pelter, A.; Ward, R. S.; Qianrong, L.; Pis, J. *Tetrahedron: Asymmetry* **1994**, *5*, 909−920. (e) Itoh, T.; Chika, J.-I.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1993**, *58*, 5717−5723. (f) Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron* **1993**, *49*, 1793−1806 (g) Choy, W. *Tetrahedron* **1990**, *46*, 2281−2286.

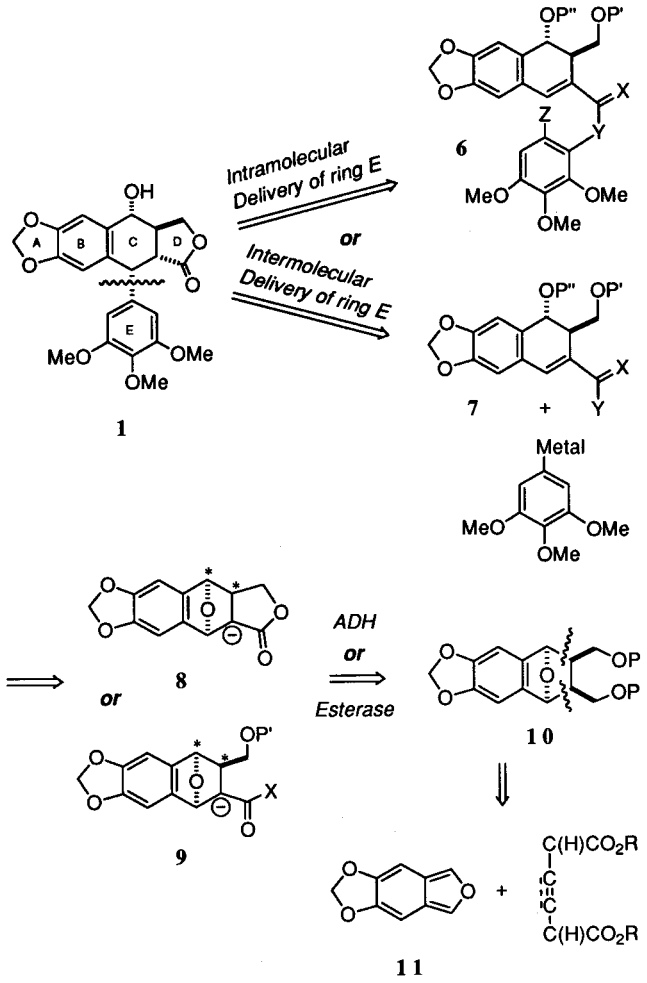
(16) Berkowitz, D. B.; Maeng, J.-H.; Dantzig, A. H., Shepard, R. L., Norman, B. H. *J. Am. Chem. Soc.* **1996**, *118*, 9426−9427.

(17) For discussions of chemoenzymatic natural product synthesis, see: (a) Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752-10765. (b) Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769−3826. (c) Mori, K. *Synlett* **1995**, 1097−1109.

(18) (a) Ishibashi, H.; Ito, K.; Hirano, T.; Tabuchi, M.; Ikeda, M. *Tetrahedron* **1993**, *49*, 4173−4182. (b) O'Connor, B.; Zhang, Y.; Negishi, E.-I.; Luo, F.-T.; Cheng, J.-W. *Tetrahedron Lett.* **1988**, *29*, 3903−3906.

(19) For examples of retro-Michael cycloreversions in oxabicyclo-[2.2.1]heptyl systems bearing an acidic hydrogen α to the bridgehead, see: (a) Keay, B. A.; Rajapaksa, D.; Rodrigo, R. *Can. J. Chem.* **1984**, *62*, 1093−1098. (b) Keay, B. A.; Rodrigo, R. *Tetrahedron* **1984**, *40*, 4597−4607.

Scheme 1

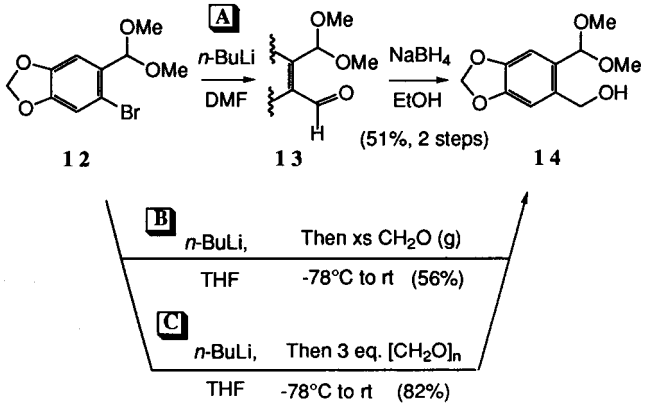


desymmetrized and then manipulated into the requisite enolate (**8** or **9**).

Results and Discussion

Given the projected instability of IBF **11**, we chose to target **14** as the IBF precursor from which **11** might be generated in situ.[22] Our synthesis emanates from piperonal and follows established procedures for its regiospecific bromination and subsequent acetalization to **12**.[23] The hydroxymethylation of **12** was examined under a variety of conditions. Initially, formaldehyde gas was employed as the electrophile, but less than satisfactory yields of **14** were obtained (Scheme 2). We then turned to an indirect approach, using dimethylformamide as a formyl cation equivalent, followed by borohydride reduction of aldehyde **13** (51%, two steps). In the end, the use of solid paraformaldehyde as formaldehyde source proved

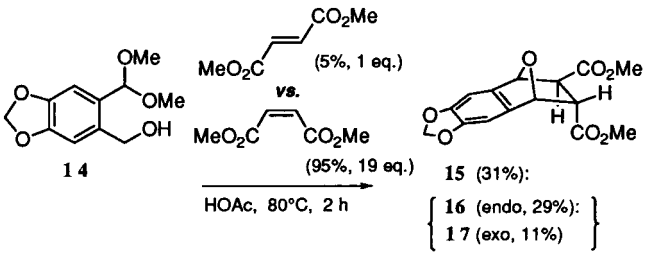
Scheme 2



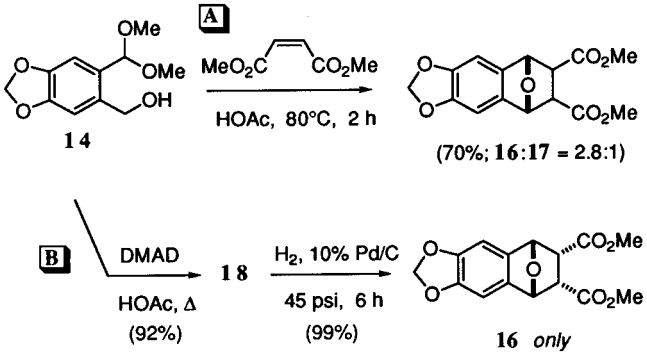
to be both the most convenient and the most efficient (82% isolated yield) procedure.

Interestingly, condensation of IBF precursor **14** with commercial dimethyl maleate (Aldrich, contains 5% dimethyl fumarate) under conditions of acid catalysis produces a nearly equimolar mixture of the undesired (chiral, racemic) fumarate cycloadduct **15** and the meso adducts **16** (endo) and **17** (exo), derived from maleate (Scheme 3). A control experiment established that none of the observed **15** arose from dienophile isomerization. Thus, careful fractional distillation of commercial dimethyl maleate removed all traces of the fumarate geometric isomer. Exposure of **14** to analytically pure dimethyl maleate produced only **16** and **17** (Scheme 4). So, one is led to the rather remarkable conclusion that IBF **11** generated in situ reacts about 15 times faster with dimethyl fumarate than with dimethyl maleate.

Scheme 3



Scheme 4



Aware that the endo product often predominates in IBF Diels−Alder reactions with dienophiles bearing carbonyl EWGs, we were somewhat disappointed with the 2.8:1 endo:exo ratio obtained. However, further examination of the literature reveals an apparent pattern of reactivity, whereby IBFs bearing unsaturated substituents at the 1- and/or 3-positions often give considerably

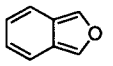
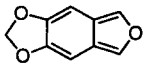
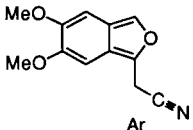
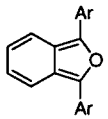
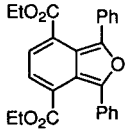
(20) This is to be contrasted with "sterically protected" IBFs such as 1,3-diphenyl-IBF that are much more easily handled yet reactive enough to trap alkenes with short lifetimes. For examples, see: Friedrichsen, W. *Adv. Hetereocycl. Chem.* **1980**, *26*, 135−241.

(21) For a review of the use of isobenzofurans in natural product synthesis, see: Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093-2135.

(22) Both acid- and base-catalyzed 1,4-elimination of alkoxydihydroisobenzofurans to the corresponding isobenzofurans are well-known: Tobia, D.; Rickborn, B. *J. Org. Chem.* **1987**, *52*, 2611−2615.

(23) Bromination (84% yield): (a) Conrad, P. C.; Kwiatkowski, P. L.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 586−591. Acetalization (96% yield): (b) Keay, B. A.; Plaumann, H. P.; Rajapaksa, D., Rodrigo, R. *Can J. Chem.* **1983**, *61*, 1987−1995.

Table 1. Endo/Exo Selectivity in IBF Diels–Alder Reactions with Dimethyl Maleate

IBF	Endo: Exo	Ref.
	2:1	24a
	2.8:1	This paper
	20:1	24b
	only endo[a,b]	24c
	only endo[a]	24d

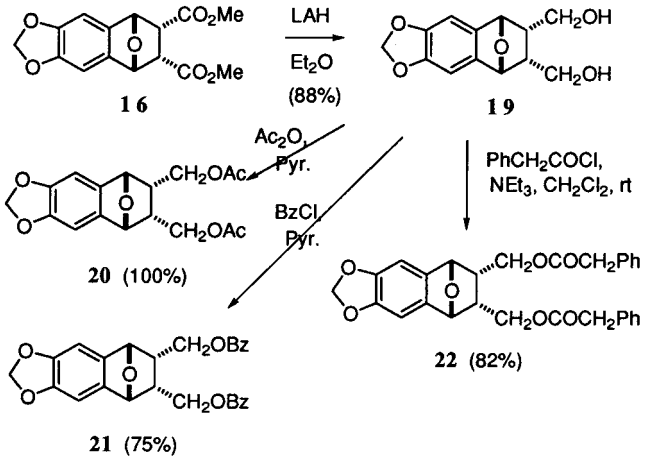
[a] In these cases, single crystalline products with sharp melting points were obtained. They are presumed to be endo. [b] Ar = 3,5-dibromo-4-hydroxyphenyl; diethyl maleate was used as dienophile in this case.

higher endo/exo ratios than their 1,3-unsubstituted counterparts (Table 1). This may be an indication that such 1,3-IBF substituents are capable of participating in favorable secondary orbital interactions with the carboxylate ester groups of the dienophile in endo IBF Diels–Alder transition states.

For our purposes, the endo/exo mixture could nicely be avoided by generating IBF **11** in neat dimethyl acetylenedicarboxylate (DMAD) under HOAc catalysis (Scheme 4), followed by catalytic hydrogenation. Under these conditions, excellent yields of cycloadduct **18** are reproducibly obtained, even on a 20 g scale (90%). The excess DMAD is routinely reclaimed by distillation and employed for subsequent cyclocondensation reactions. Catalytic hydrogenation occurs exclusively from the less hindered exo face in **18**, as expected, providing **16**, which may be cleanly reduced to diol **19**. Thus, diol **19** is obtained from piperonal in six steps and 53% overall yield.

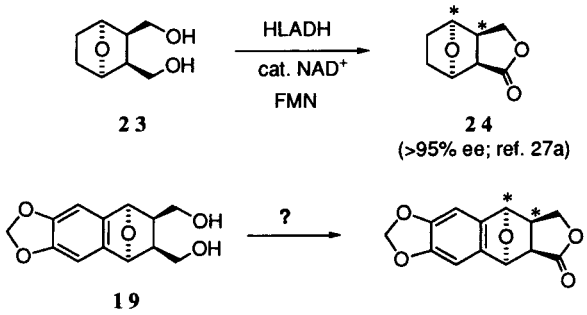
Enzymatic Desymmetrization. Though there are many examples of enzymatic resolutions and desymmetrizations of relatively simple mono- and bridged bicyclic substrates,[17b,c] there are few examples of enzymatic manipulations on polycyclic unnatural substrates, such as the series of meso tetracycles (in the $C_{13}O_5$–$C_{29}O_7$ range) being examined here (Scheme 5). We therefore took a "combinatorial" approach to the problem, whereby a battery of about a dozen predominantly acyl transfer enzymes would be screened with a range of potential ester and alcohol substrates.[25] Among the more attractive choices for acyl transferases were lipases GC (*Geotrichum candidum*)[26a] and P (*Pseudomonas cepacia*),[26b] RLE, PLE (rabbit and pig liver esterases),[26c] PPL (porcine pancreatic lipase),[26d] chymotrypsin,[26e] and penicillin acylase,[26f] all of which have demonstrably broad substrate specificity that includes at least monocyclic esters. It should be noted that substrates **21** and **22** were targeted toward chymotrypsin and penicillin acylase, respectively, reflecting the propensity of the former enzyme for cleavage of esters or amides derived from aromatic amino acids and the specificity of the latter enzyme for the arylacetyl groups.[26f]

Scheme 5. A Spectrum of Advanced meso Intermediates



We were also drawn to HLADH (horse liver alcohol dehydrogenase) through the elegant work of Jones and co-workers. The Toronto group has demonstrated that a rather diverse spectrum of meso diols, including nonbenzenoid, oxabicyclo[2.2.1]heptyl diol **23**, may be efficiently desymmetrized through HLADH-mediated four-electron oxidation, with the participation of a nicotinamide cofactor (Scheme 6).[27]

Scheme 6



Just over 100 screening experiments were performed among the five meso intermediates **16** and **19**–**22** and these eight enzymes. Among the variables examined were buffer, pH, temperature, weight equivalents of enzyme, enzyme stabilizers, and agitation method (shaking vs magnetic stirring vs mechanical stirring). Unfortunately,

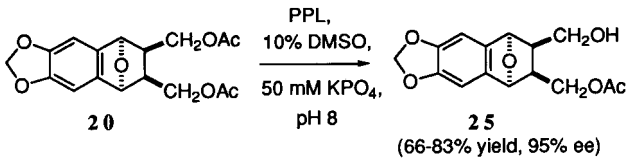
(24) (a) McCulloch, R.; Rye, A. R.; Wege, D. *Tetrahedron Lett.* **1969**, 5231–5234. (b) Meegalla, S. K.; Rodrigo, R. *J. Org. Chem.* **1991**, *56*, 1882–1888. (c) Weiss, R.; Mayer, F. *Monatsh. Chem.* **1937**, *71*, 6–9. (d) Freslon, G.; Lepage, Y. *Comptes Rendus Acad. Sci., Ser. C* **1975**, *280*, 961–963.

(25) For a detailed account of these enzymatic desymmetrizations, see: Berkowitz, D. B.; Maeng, J.-H. *Tetrahedron: Asymmetry* **1996**, *7*, 1577–1580.

(26) (a) Murata, M.; Ikoma, S.; Achiwa, K. *Chem. Pharm. Bull.* **1990**, *38*, 2329–2331. (b) Berkowitz, D. B.; Danishefsky, S. J. *Tetrahedron Lett.* **1991**, *32*, 5497–5500. (c) Bloch, R.; Guibe-Jampel, E.; Girard, C. *Tetrahedron Lett.* **1985**, *26*, 4087–4090. (d) Hemmerle, H.; Gais, H.-J. *Tetrahedron Lett.* **1987**, *28*, 3471–3474, (e) Jones, J. B. *Methods Enzymol.* **1976**, *44*, 831–856. (f) Holla, E. W. *J. Carbohydr. Chem.* **1990**, *9*, 113–119.

(27) (a) Jones, J. B.; Francis, C. J. *Can. J. Chem.* **1984**, *62*, 2578–2582. (b) Grunwald, J.; Wirz, B.; Scollar, M. P.; Klibanov, A. M. *J. Am. Chem. Soc.* **1986**, *108*, 6732–6734.

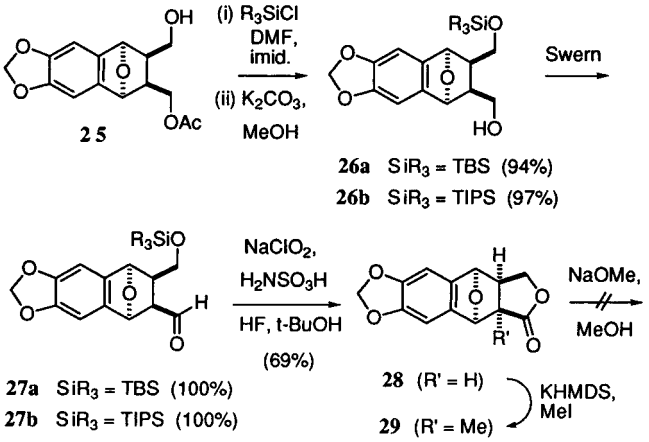
Scheme 7



HLADH (from both Sigma and Boehringer Mannheim) failed to accept diol **19** as substrate under a large variety of conditions, including those of Jones[27a] and of Klibanov.[27b]

However, acyl transfer chemistry was successful in both the acylation (lipases P and GC with diol **19** and vinyl acetate) and deacylation directions (RLE-, PLE-, and PPL-catalyzed hydrolyses of diacetate **20**).[25] In the end, the best match paired PPL with diacetate **20**. Under appropriate conditions, monoacetate **25** could be reproducibly obtained in 95% ee, even on 10−20 g scales (Scheme 7). It proved most convenient to terminate the reaction at about two-thirds conversion to minimize diol formation. Unreacted diacetate is then easily recycled. Taking into account the recovered starting diacetate, this procedure provides for an 83% yield of desymmetrized tetracycle **25**. Interestingly, the observed absolute stereochemistry for **25** is opposite to that predicted by the most comprehensive model for PPL hydrolyses of which we are aware.[25,28] This is probably because **20** is considerably more complex (higher carbon count, polycyclic) than those unnatural substrates upon which that model is based.

Scheme 8. The Lactone Enolate Fails to Ring Open



Elaboration of Chiral Monoacetate 25. Having established asymmetry, we next sought to convert the benzoxabicyclo[2.2.1]heptyl core of monoacetate **25** into the desired 4-hydroxydihydronaphthalene system via a retro-Michael ring opening. In the original retrosynthetic analysis (Scheme 1), lactone enolate **8** was to serve as the substrate for this transformation. Monoacetate **25** could be cleanly transformed into silyl ether(s) **26a**(**b**) (Scheme 8). Given the possibility for racemization via acetyl or silyl migration here, optical purity was examined by Mosher esterification. No loss of optical activity was observed, indicating that the seven-membered transition states required for these intramolecular migrations are not readily accessible, even under mildly basic conditions at room temperature. The ensuing Swern oxidation proceeds smoothly.

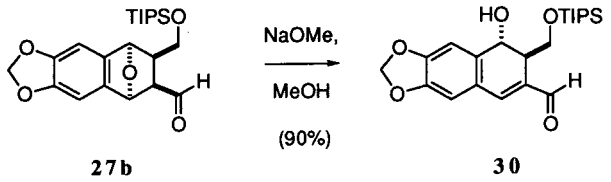
(28) Wimmer, Z. *Tetrahedron* **1992**, *48*, 8431−8436.

It was discovered fortuitously that one can conduct a sequential desilylation−hemiacetalization−oxidation sequence in one pot, under modified Lindgren oxidation conditions.[29] Indeed, under the original conditions of Lindgren,[29a] which include sulfamic acid as Cl_2 scavenger, one isolates some of the desired lactone. Noticing this, we chose to promote the desilylation by adding HF. In this way, lactone **28** may be isolated in very good yield directly from TBS-protected γ-hydroxyaldehyde **27a**. Unfortunately, however, the lactone fails to give the desired ring-opening reaction upon incubation with a variety of bases (NaOMe/MeOH; LDA/$BF_3\cdot Et_2O$; $AlBr_3$/THF; $[(CH_3)_3Si]_2NK$/18-Cr-6/THF; KOtBu/DMSO). That deprotonation indeed occurs could be established by trapping the lactone enolate with methyl iodide.

At this point, we turned to molecular mechanics (PC Model, MMX force field) to examine orbital overlap in this system. Minimization of the potassium enolate of lactone **28** gives a predicted geometry in which the π-system is nearly orthogonal to the C_1−O σ^* orbital (81° "dihedral" angle, where 0° corresponds to direct overlap of these orbitals). Hence, it appears that the geometric constraints imposed on an already somewhat rigid benzoxabicyclo[2.2.1]heptyl system, by confining the enolate carbonyl to a γ-lactone ring, prevent the retro-Michael reaction in **8**.

On the other hand, the MMX-minimized geometry of the corresponding "unconstrained" aldehyde-enolate (**9**) indicates considerably better $\pi-\sigma^*$ overlap (63° "dihedral" angle). In fact, treatment of **27** with base (LiHMDS, NaHMDS, KHMDS/18-Cr-6, NaOMe/MeOH) leads to retro-Michael ring opening. A TIPS protecting group (i.e., **27b**) is preferable to a TBS group, as the latter migrates to the C_4−O under some conditions. Reproducibly high yields are achieved with methoxide as base (Scheme 9).

Scheme 9. The Acyclic Enolate Retro-Michael Ring Opens



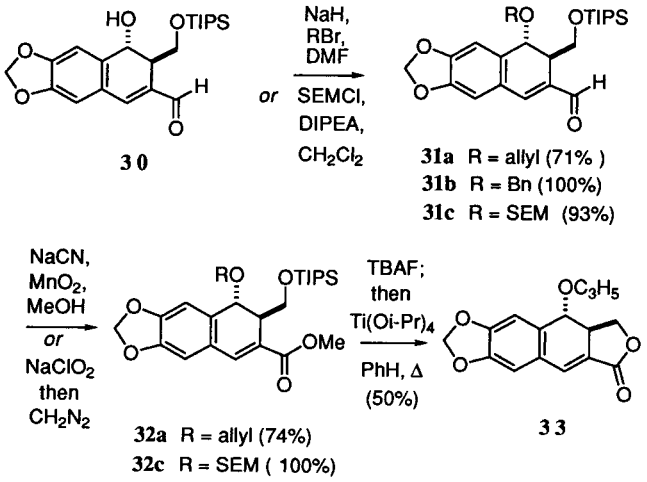
The proper stereochemistry for (−)-podophyllotoxin has now been set at both C_3 and C_4 in **30**. However, that stereochemical information is readily lost, as this 4-hydroxy-3-silyloxymethyl dihydronaphthalene intermediate is quite susceptible to aromatization via elimination under acidic conditions. Fortunately, **30** can be cleanly protected with ether- or acetal-type protecting groups provided that neutral to basic conditions are maintained (Scheme 10). Aldehyde **31** can be further transformed into several other potential Michael acceptors, with an eye toward installing ring E via conjugate addition. Thus, methyl ester **32** is obtained in a single step via allylic cyanohydrin oxidation under the Corey−Ganem conditions,[30] or in two steps via Lindgren oxidation[29] and treatment with diazomethane. Desilylation and transesterification under Ti(O-*i*-Pr)$_4$ catalysis[31] then provide α,β-unsaturated lactone **33**.

(29) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888−890. (b) Balkrishna, S. B.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096.

(30) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616−5617.

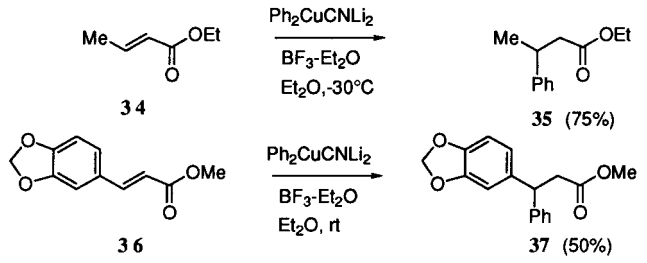
(31) Imwinkelried, R.; Schiess, M.; Seebach, D. *Org. Synth.* **1987**, *65*, 230−235.

Scheme 10. Elaboration to Potential Michael Acceptors

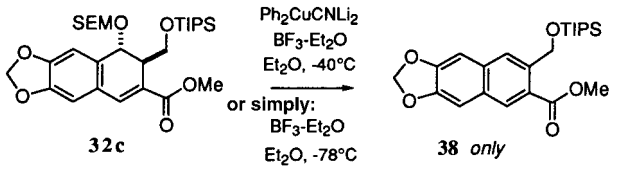


Approaches to the Introduction of Ring E. At this point, a model study was carried out to establish the best Michael acceptor and conditions for the projected conjugate addition. With the esters initially examined (Scheme 11), higher order cyanocuprates[32] perform best and addition of $BF_3 \cdot Et_2O$ is beneficial. Provided that freshly prepared phenyllithium is used,[33] conjugate addition of a higher order phenylcuprate to ethyl crotonate proceeds quite smoothly. The same conditions also lead to the desired 1,4-adduct with the methylenedioxy-substituted cinnamate ester **36**.[34] Conjugate addition was not observed in these systems using (i) higher order cuprates in the presence of TMSCl, (ii) higher order cuprates in the absence of $BF_3 \cdot Et_2O$, or (iii) lower order Gilman cuprates.

Scheme 11. Model Arylcuprate Conjugate Additions

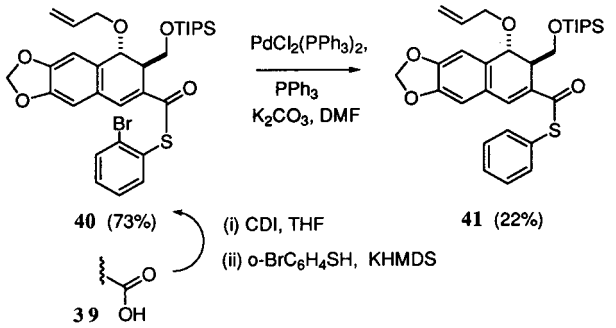


Scheme 12. Aromatization in the Presence of Activating Lewis Acids



Unfortunately, the same conditions that promote arylcopper addition in model system **36** lead to aromatization in α,β-unsaturated ester **32c** (Scheme 12). The realization that such (3,4-methylenedioxy)cinnamate esters (triply vinylogous carbonate esters) only sluggishly add arylcopper reagents led us to pursue several alternative approaches to the installation of ring E in parallel to these conjugate addition studies.

Scheme 13. Attempted 6-endo-trig Heck Cyclization



We were especially interested in the possibility of exploiting intramolecularity and chose to examine several potential cyclization routes. A Heck cyclization was attractive here as ring E might be brought in through an ester/thioester linkage to the C_2-carboxyl group. It might appear difficult to achieve such a cyclization as (i) the migratory insertion step would have to proceed in a 6-endo-trig mode and (ii) the β-hydride elimination would appear to be forbidden, as the Pd and the β-hydrogen would be trans-disposed following that migratory insertion. However, a Heck cyclization of this general class has been described by Ishibashi and co-workers,[19a] and Negishi's group has reported a couple of related 5-endo-trig Heck cyclizations.[19b] Ishibashi accounts for the β-hydride elimination by proposing an isomerization from the initial trans-Pd/β-H insertion complex to the cis complex through the intermediacy of a Pd-enolate. Alternatively, both authors use excess base, so an external base mediated elimination cannot logically be ruled out.

The model *o*-bromothioester **40** could be assembled from the corresponding acid via activation as the acyl imidazolide. Treatment of **40** under a variety of Heck conditions produced no cyclized products but rather gave modest yields of either reduced starting material (Scheme 13) or lactone **33** (10% $Pd(OAc)_2$, 20% PPh_3, $NaHCO_3$, DMF, 80 °C). It is worthy of note that Negishi's and Ishibashi's systems contain one and two sp^3-carbons, respectively, within the five- and six-membered transition states required for their Heck cyclizations. The σ-complex obtained after oxidative addition of PdL_2 to aryl bromide **40** may not be able to achieve a geometry that permits 6-endo-trig migratory insertion.

Along the same lines, it seemed reasonable to attempt a 6-endo-trig radical cyclization on a similar system. In light of the thiophilicity of trialkyltin radicals, we chose to move away from the thioester. Instead, *o*-bromophenyl ester **43** was constructed in a similar manner and subjected to standard radical cyclization conditions (Scheme 14). After 12 h at reflux, aside from recovered starting bromoester, reduced starting material was the only identifiable product. Apparently, hydrogen abstraction from $HSnBu_3$ by the intermediate aryl radical is faster than cyclization in this system.

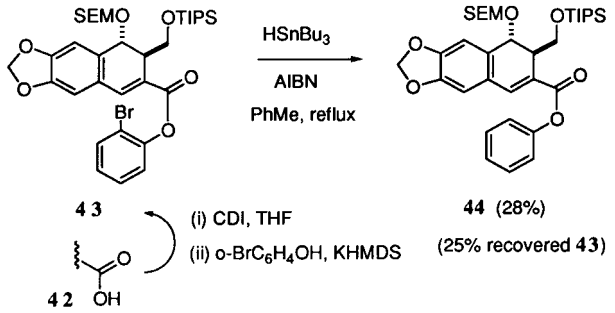
The feasibility of an aryl Claisen rearrangement was next investigated with *p*-methoxyphenyl ether **45**. The allylic alcohol precursor is obtained through reduction of α,β-unsaturated aldehyde **31b** with sodium trimethoxyborohydride. Williamson-type conditions (on the

(32) Lipshutz, B. H.; Moretti, R.; Crow, R. *Org. Synth.* **1990**, *69*, 80−88 and references therein.

(33) Schlosser, M.: Ladenberger, V. *J. Organomet. Chem.* **1967**, *8*, 193−197.

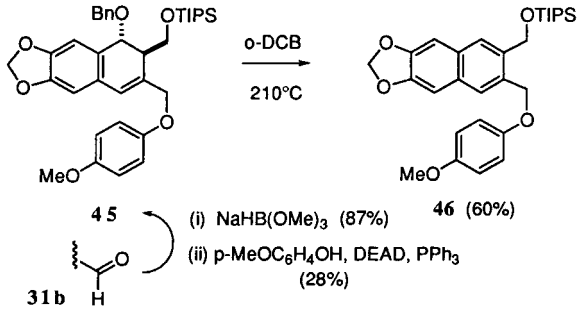
(34) The corresponding acid is commercially available, making this a convenient model system.

Scheme 14. Attempted 6-endo-trig Radical Cyclization



corresponding mesylate, with *p*-methoxyphenolate) failed to give the requisite allylic ether. Eventually **45** was produced in modest yield by a modified Mitsunobu protocol.[35] Upon attempting the Claisen rearrangement by heating **45** to 210 °C in 1,2-dichlorobenzene in a sealed tube, a 60% yield of aromatized product was obtained (Scheme 15). Apparently, the formal syn elimination of benzyl alchohol (leading to aromaticity) represents a more favorable reaction manifold than the Claisen rearrangement (requiring temporary loss of aromaticity) for this system at elevated temperatures. So, in both the intermolecular and intramolecular approaches to ring E installation, the sensitivity of our (4-alkoxy)dihydronaphthalene system to aromatization loomed large.

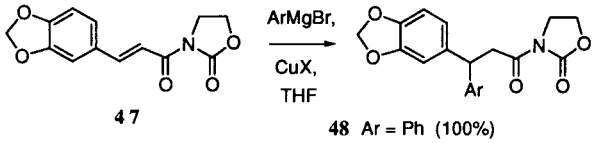
Scheme 15. Attempted Aromatic Claisen Rearrangement



A Solution for Stereocontrolled Conjugate Addition at C_1. Our model work in the intermolecular conjugate addition with conjugate additions to (3,4-methylenedioxy)cinnnamate esters had demonstrated the need for Lewis acid activation of the ester. However, with Michael acceptor **32c**, Lewis acids such as $BF_3 \cdot Et_2O$ promote elimination across C_3-C_4 (presumably by activating the C_4-leaving group) more efficiently than conjugate addition. Faced with this conundrum, we sought to modify the Michael-acceptor functionality so as to permit a more chemoselective activation. We surmised that an α,*β*-unsaturated acyl oxazolidinone, with its potential for bidentate metal chelation might well be activated with milder Lewis acids (e.g., MgX_2).

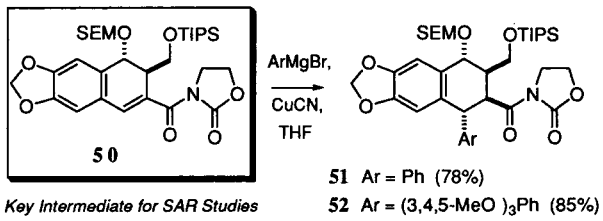
Indeed, treatment of model α,*β*-unsaturated acyl oxazolidinone **47** with Normant-type organocopper reagents (Scheme 16), formed from CuX and ArMgX (1:1 stoichiometry), produces excellent yields of the desired conjugate addition products, with both phenylmagnesium

Scheme 16. Acyl Oxazolinone Model Arylcuprate Conjugate Additions



bromide (CuBr-SMe_2) and (3,4,5-trimethoxy)phenylmagnesium bromide (CuCN). It is important to note that for the heavily oxygenated natural ring E, cuprate formation must be carried at a much higher temperature (−10 → 10 °C) than for the simple phenylcopper reagent (−78 °C suffices). If **50** is introduced into a mixture of ArMgBr and CuCN at lower temperatures (presumably prior to cuprate formation) the reaction is not clean and produces little to no conjugate addition product.

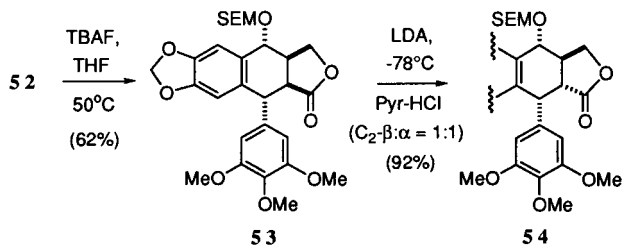
Scheme 17. Facile and Modular Introduction of Ring E



Apparently then, under the optimized conditions, the α,*β*-unsaturated acyl oxazolidinone in **50** is chemoselectively activated for 1,4-addition (Scheme 17). No aromatization products are observed. Importantly, the aryl group is introduced stereoselectively at C_1, with only the desired *re* face addition product being observed. This is presumably due, in large part, to the sterically demanding TIPS group, which is thought to block the *si* face from attack by ArCuMgBrX. The resulting enolate is apparently also protonated from the same sterically more accessible α-face in the workup to provide **51** or **52** with the correct relative and absolute stereochemistry for (−)-picropodophyllin.

As per design, only two steps (desilylative lactonization and SEM deprotection) separate conjugate addition product **52** from (−)-picropodophyllin (Schemes 18 and 19). Note that, with the natural E ring in place (i.e., **53**), only a small amount of thioether byproduct (**56**) accompanies the normal SEM deprotection product under these modified Kim conditions.[36]

Scheme 18

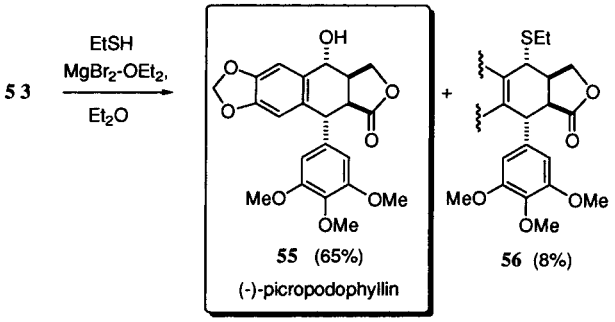


To access (−)-podophyllotoxin, a C_2 epimerization step is introduced immediately following lactonization. Penultimate epimerization to the thermodynamically less stable trans-lactone is a common feature of podophyllotoxin syntheses, from the earliest work of Gensler,[12n]

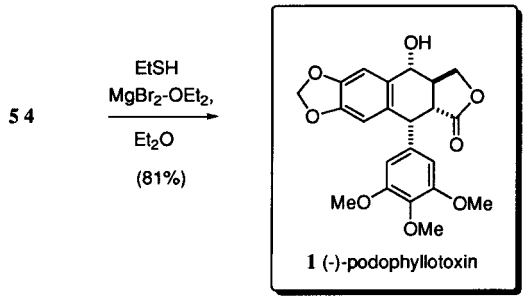
(35) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291−6292. (c) Petitou, M.; Duchaussoy, P.; Choey, J. *Tetrahedron Lett.* **1988**, *29*, 1389−1390.

(36) Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *Synlett* **1991**, 183−184.

Scheme 19



Scheme 20



through the approaches of Kende[12k] and Meyers.[13a] In our system, we find that the conditions of Kende (pyridinium chloride quench) provide the most satisfactory results, in terms of yield, trans:cis ratio, and reproducibility. In the case at hand, 4-*O*-SEM-podophyllotoxin (**53**) is readily separated from 4-*O*-SEM-picropodophyllin (**54**). The former acetal is then deprotected smoothly to provide a sample of the natural product that matches an authentic sample in all respects.

Conclusions

This report details the first catalytic, asymmetric synthesis of (−)-podophyllotoxin. An IBF Diels−Alder reaction is used to rapidly assemble a family of advanced, tetracyclic meso intermediates of the benzoxabicyclo-[2.2.1]heptyl variety. One of these, diacetate **20** is efficiently enzymatically desymmetrized (95% ee, 83% corrected yield) with PPL in a mixed organic (DMSO)/aqueous milieu. The need to synthesize, attach, and recover a chiral auxiliary is circumvented via the use of an inexpensive, commercially available enzyme. Key steps in the elaboration of enzymatic product **25** into the natural product include (i) the efficient retro-Michael ring opening of "unconstrained" enolate **9**, which unveils the (methylenedioxy)cinnamate core, and (ii) its chemoselective and stereoselective activation, as an acyl oxazolidinone (**50**), for the introduction of ring E. Most importantly, ring E is deliberately introduced late in the synthesis, only three steps from the final product. The efficient installation of the highly oxygenated natural ring E of podophyllotoxin described herein attests to the potential of this synthetic route for structure/function studies in this sector of the natural product.

Experimental Section

General. All reactions were conducted under an argon atmosphere using oven-dried glassware. For air- or water-sensitive reactions, glassware was flame-dried and then allowed to cool under an Ar atmosphere before use. Methylene chloride, pyridine, and diisopropylamine were distilled over CaH_2. THF, Et_2O, and benzene were distilled over sodium/benzophenone. Methanol was distilled over Mg/I_2. *n*-Butyllithium in hexanes was purchased from Aldrich and titrated before use. Mass spectra were acquired at the Nebraska Center for Mass Spectrometry (University of Nebraska-Lincoln) and are reported as *m*/*z* (relative intensity). Elemental analyses were carried out by M-H-W Labs (Phoenix, AZ) or Q-T-I Labs (Whitehouse, NJ).

4-(Dimethoxy)methyl-5-formyl(1,2-methylenedioxy)-benzene (13). To a solution of bromoacetal **12** (0.50 g, 1.8 mmol) in THF (8 mL) at −78 °C was added *n*-BuLi (1.45 mL, 1.8 mmol, 1.25 M in hexanes) dropwise via syringe. After stirring for 1 h at 0 °C, the resulting aryllithium solution was cooled to −78 °C,and DMF (0.87 mL, 11.2 mmol) was added. After slowly warming to room temperature and stirring for 2 h, the reaction was poured into H_2O-Et_2O. The water layer was extracted with two additional portions of Et_2O, and the combined organics were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (hexanes−Et_2O−NEt_3 66:33:0.5) provided aldehyde **13** (0.25 g, 61%): ^{1}H NMR (300 MHz, C_6D_6) δ 3.00 (s, 6 H), 5.17 (s, 2 H), 5.53 (s, 1 H), 7.15 (s, 1 H), 7.52 (s, 1 H), 10.4 (s, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 52.8, 100.6, 101.9, 107.8, 107.9, 129.8, 137.6, 148.5, 152.0, 188.7; HRMS (FAB, 3-NBA, NaI) calcd for $C_{11}H_{12}O_5Na$ 247.0582, obsd 247.0592.

4-(Dimethoxy)methyl-5-hydroxymethyl(1,2-methylenedioxy)benzene (14). Method A. Aldehyde **13** (0.25 g, 1.1 mmol) was dissolved in absolute EtOH (10 mL), and the solution was cooled to 0 °C. Sodium borohydride (0.1 g, 2.9 mmol) was added, and the reaction mixture was stirred overnight at room temperature. The reaction was quenched by pouring into ice/ethyl acetate, followed by acidification to pH 6.5 with 2 N HCl. The water layer was extracted with Et_2O, and the combined organics were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes−Et_2O−NEt_3 50:50:0.5) provided the product (0.21 g, 83%): ^{1}H NMR (200 MHz, C_6D_6) δ 2.47 (t, J = 6 Hz, 1 H), 2.97 (s, 6 H), 4.50 (d, J = 6 Hz, 2 H), 5.29 (s, 2 H), 5.31 (s, 1 H), 6.86 (s, 1 H), 7.27 (s, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 52.8, 62.6, 101.6, 101.8, 108.4, 110.1, 130.4, 134.8, 147.5, 148.4; HRMS (EI) calcd for $C_{11}H_{14}O_5$ 226.0841, obsd 226.0843. Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.39; H, 6.24. Found: C, 58.20; H, 6.07.

Method B. To a solution of bromoacetal **12** (10.0 g, 36.3 mmol) in THF (100 mL) at −78 °C was added *n*-BuLi (25.0 mL, 40.6 mmol, 1.6 M in hexanes) dropwise via syringe. After the solution was stirred for 1 h at 0 °C, a suspension of paraformaldehyde (3.30 g, 36.7 mmol) in THF (60 mL) was added via cannula. The reaction was warmed to room temperature, stirred for 2 h, and then quenched with H_2O/Et_2O. The aqueous layer was extracted with Et_2O, and the combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (50% EtOAc/hexanes) gave **14** (6.75 g, 82%) with spectral characteristics as before. On a larger scale, **12** (50 g, 182 mmol) gave **14** in 72% yield (29.7 g).

Dimethyl (1*R,2*S**,3*S**,4*S**)-1,4-Epoxy-6,7-methylenedioxy-1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylate (15) and *meso*-(1*R**,2*S**,3*R**,4*S**)-(*endo*)-isomer (16) and *meso*-(1*R**,2*R**,3*S**,4*S**)-(*exo*)-isomer (17).** IBF precursor **14** (250 mg, 1.1 mmol) was dissolved in dimethyl maleate (Aldrich, 3.19 g, 22.1 mmol; contains ∼1.1 mmol dimethyl fumarate and ∼21 mmol dimethyl maleate) and glacial AcOH (0.25 mL), and the mixture was stirred for 2 h at 80 °C. Excess dimethyl maleate was removed by vacuum distillation. Flash chromatography (33% EtOAc/hexanes) provided the major product **15** (105 mg, 31%) in a first fraction, followed by **16** (98 mg, 29%) and **17** (37 mg, 11%) in subsequent fractions. For **15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (d, J = 4 Hz, 1 H), 3.58 (s, 3 H), 3.78 (s, 3 H), 3.83 (dd, J = 4, 5 Hz, 1 H), 5.52 (d, J = 5 Hz, 1 H), 5.58 (s, 1 H), 5.93 (d, J = 2 Hz, 1 H), 5.96 (d, J = 2 Hz, 1 H), 6.68 (s, 1H), 6.82 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.2, 49.4, 52.1, 52.6, 80.4, 82.9, 101.4, 101.5, 102.5, 136.1, 137.9, 146.8, 147.1, 170.2, 172.3; HRMS (FAB, ONPOE) calcd for $C_{15}H_{14}O_7$ 306.0740 [M^+], obsd 306.0730.

For **16**: mp 96−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53 (s, 6H), 3.61 (dd, J = 2, 3 Hz, 2 H), 5.41 (dd, J = 2, 3 Hz, 2 H), 5.92 (d, J = 2 Hz, 1 H), 5.96 (d, J = 1 Hz, 1 H), 6.82 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.3, 52.3, 81.5, 101.9, 103.9, 137.2, 147.5, 170.5. Anal. Calcd for $C_{15}H_{14}O_7$: C, 58.83; H, 4.61. Found: C, 58.90; H, 4.71.

For **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (s, 2 H), 3.71 (s, 6 H), 5.57 (s, 2 H), 5.93 (d, J = 1 Hz, 1 H), 5.96 (d, J = 1 Hz, 1 H), 6.77 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.7, 52.3, 81.2, 101.4, 101.6, 138.1, 147.0, 171.5; HRMS (FAB, 3-NBA, NaI) calcd for $C_{15}H_{14}O_7Na$ 329.0637, obsd 329.0626.

In a control experiment, **14** (125 mg, 0.55 mmol) was treated with pure dimethyl maleate (398 mg, 2.76 mmol; obtained by fractional distillation) and HOAc (0.13 mL) under the above conditions to produce **16** (87 mg, 52%) and **17** (31 mg, 18%). No "fumarate adduct" **15** was observed in this experiment.

Dimethyl 1,4-Dihydro-1,4-epoxy-6,7-methylenedioxy-2,3-naphthalene-dicarboxylate (18). The substrate (23.7 g, 105 mmol) was dissolved in excess DMAD (251 g, 1.76 mol) and glacial AcOH (23.2 mL, 0.4 mol), and the mixture was stirred for 2 h at 80 °C. Excess DMAD was removed by vacuum distillation, and flash chromatography (30% EtOAc/hexanes) gave **18** (56.4 g, 90%) as a yellow solid. On a smaller scale, **14** (5.53 g, 24.1 mmol) gave **18** in 92% yield (13.6 g): mp 117−119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 6 H), 5.86 (s, 2 H), 5.90 (d, J = 1 Hz, 1 H), 5.95 (d, J = 1 Hz, 1 H), 6.95 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.0, 85.7, 102.2, 105.2, 141.4, 146.2, 152.5, 163.5. Anal. Calcd for $C_{15}H_{12}O_7$: C, 59.21; H, 3.98. Found: C, 59.27; H, 4.11.

Dimethyl *meso*-(1*R,2*S**,3*R**,4*S**)-1,4-Epoxy-6,7-methylenedioxy-1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylate (16).** IBF Diels−Alder product **18** (43.2 g, 0.14 mol) was dissolved in EtOAc (300 mL), and 10% Pd/C (1.5 g) was added. The reaction mixture was hydrogenated at 48 psi for 6 h. The reaction mixture was filtered through Celite and concentrated to give **16** as a white solid (43.1 g, 99%; identical to **16** produced independently, vide supra).

***meso*-(1*R**,2*R**,3*S**,4*S**)-2,3-Bis(hydroxymethyl)-1,4-epoxy-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (19).** To a solution of the dimethyl ester **16** (25.0 g, 82 mmol) in Et_2O (500 mL) at 0 °C was added $LiAlH_4$ (6.2 g, 0.16 mol), and the resulting reaction mixture was refluxed for 1 d. Quenching was carried out by the sequential addition of H_2O (6 mL; 30 min stirring), 6.4 mL of 15% NaOH (aqueous, 6 mL, 30 min stirring), and H_2O (19 mL; 30 min stirring). The mixture was neutralized with 1 N HCl solution (100 mL), followed by the addition of H_2O (2.5 L) and extraction with EtOAc (6.5 L). The organics were dried (Na_2SO_4) and concentrated to give **19** as a white solid (16.8 g, 82%). On a smaller scale, **16** (4.7 g, 15 mmol) provided an 88% yield of **19** (3.4 g): mp 177−179 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 2.65−2.68 (ddd, J = 4, 6, 9 Hz, 2 H), 2.77 (dd, J = 9, 10 Hz, 2 H), 3.15 (dd, J = 6, 10 Hz, 2 H), 5.24 (d, J = 4 Hz, 2 H), 5.90 (d, J = 1 Hz, 1 H), 5.94 (d, J = 1 Hz, 1 H), 6.85 (s, 2 H); ^{13}C NMR (125 MHz, C_5D_5N) δ 44.6, 60.1, 82.4, 101.6, 103.6, 138.2, 146.7. Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.26; H, 5.59.

***meso*-(1*R**,2*R**,3*S**,4*S**)-2,3-Bis(acetoxymethyl)-1,4-epoxy-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (20).** To a solution of **19** (57 g, 0.23 mol) and DMAP (1.4 g, 11.4 mmol) in pyridine (750 mL) at −10 °C was added Ac_2O (69.9 g, 0.68 mol). After the mixture stirred for 16 h at room temperature, EtOAc was added into the reaction mixture, and the organics were washed with saturated $NaHCO_3$ solution, 1 N HCl, and $CuSO_4$ (aqueous, saturated). Drying ($MgSO_4$) and concentration provided **20** (76 g, 100%): mp 120−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 6 H), 2.82−2.85 (m, 2 H), 3.24 (dd, J = 10, 11 Hz, 2 H), 3.75 (dd, J = 6, 11 Hz, 2 H), 5.26 (d, J = 4 Hz, 2 H), 5.94 (d, J = 1 Hz, 1 H), 5.99 (d, J = 1 Hz, 1 H), 6.76 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 40.6, 63.1, 82.2, 102.1, 103.8, 136.7, 147.6, 171.2; Anal. Calcd for $C_{17}H_{18}O_7$: C, 61.07; H, 5.43. Found: C, 61.20; H, 5.61.

***meso*-(1*R**,2*R**,3*S**,4*S**)-2,3-Bis(benzoyloxymethyl)-1,4-epoxy-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (21).** To a solution of diol **19** (100 mg, 0.40 mmol) in pyridine (2 mL) at 0 °C was added benzoyl chloride (0.1 mL, 0.88 mmol) dropwise via syringe. After 1 h at 0 °C, additional benzoyl chloride (50 μL, 0.44 mmol) and DMAP (5 mg, 0.04 mmol) were added. The resulting reaction mixture was allowed to warm to room temperature overnight, and saturated aqueous $NaHCO_3$ was added. The mixture was extracted with EtOAc, and the organics were washed with 1 N HCl and $CuSO_4$ (saturated aqueous). Drying ($MgSO_4$), filtration, concentration, and chromatography (33% EtOAc/hexanes) yields **21** (138 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07−3.12 (m, 2 H), 3.60 (dd, J = 10, 11 Hz, 2 H), 4.11 (dd, J = 5, 11 Hz, 2 H), 5.41 (d, J = 4 Hz, 2 H), 5.92 (d, J = 1 Hz, 1 H), 5.98 (d, J = 1 Hz, 1 H), 6.81 (s, 2 H), 7.25−8.12 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.1, 62.9, 81.7, 101.4, 103.2, 128.5, 129.6, 129.7, 136.1, 147.0, 166.0; HRMS (FAB, 3-NBA, NaI) calcd for $C_{27}H_{22}O_7Na$ 481.1263, obsd 481.1272.

***meso*-(1*R**,2*R**,3*S**,4*S**)-2,3-Bis[(2′-phenyl)acetoxymethyl]-1,4-epoxy-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (22).** To a solution of diol **19** (50 mg, 0.2 mmol) in CH_2Cl_2 (6 mL) and triethylamine (0.1 mL) at −35 °C was added phenylacetyl chloride (58 μL, 0.44 mmol) dropwise via syringe. The solution was warmed slowly to room temperature over 3 h and stirred at room temperature for 12 h. Saturated aqueous $NaHCO_3$ was added, and then the reaction mixture was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and chromatographed (80% EtOAc/hexanes) to give **22** (80 mg, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.76−2.80 (m, 2 H), 3.14 (t, J = 10 Hz, 2 H), 3.63 (s, 4H), 3.75 (dd, J = 5, 11 Hz, 2 H), 5.04 (d, J = 4 Hz, 2 H), 5.90 (d, J = 1 Hz, 1 H), 5.95 (d, J = 1 Hz, 1 H), 6.32 (s, 2 H), 7.27−7.40 (m, 10 H);^{13}C NMR (75 MHz, $CDCl_3$) δ 39.5, 41.3, 62.5, 81.2, 101.1, 102.8, 127.2, 128.6, 129.0, 133.7, 135.6, 146.5, 170.6; HRMS (FAB, 3-NBA, NaI) calcd for $C_{29}H_{26}O_7Na$ 509.1576, obsd 509.1594.

(1*R*,2*R*,3*S*,4*S*)-2-Acetoxymethyl-1,4-epoxy-3-hydroxymethyl-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (25). A 5 L RB flask was charged with PPL (263 g, crude, Sigma) and buffer solution (50 mM KPO_4, pH 7.8, 3.5 L). Diacetate **20** (20.0 g, 59.8 mmol) in DMSO (380 mL) was added via a sidearm while stirring with a mechanical stirrer. The reaction was quenched with 4 L of EtOAc after 2.5 h at room temperature. Following centrifugation to remove insoluble material, the organic layer was separated and washed with water. The organics were dried over $MgSO_4$ and concentrated. Flash chromatography (50−80% EtOAc/hexane) gave in the following order **20** (4.1 g, 21%); **25** [11.5 g, 66%; (83% based on recovered **20**)], and diol **19** (0.7 g, 5%). The monoacetate **25** was determined to be 95% ee by examination of the ^{1}H NMR spectrum of its derivative Mosher ester: mp 131−134 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.43−1.58 (br. s, 1 H), 2.06 (s, 3 H), 2.77−2.84 (ddd, J = 6, 9, 13 Hz, 2 H), 2.87 (dd, J = 9, 10 Hz, 1 H), 3.23 (dd, J = 10, 11 Hz, 1 H), 3.28 (dd, J = 6, 10 Hz, 1 H), 3.76 (dd, J = 6, 11 Hz, 1 H), 5.25 (d, J = 4 Hz, 1 H), 5.32 (d, J = 4 Hz, 1 H), 5.94 (d, J = 1 Hz, 1 H), 5.98 (d, J = 2 Hz, 1 H), 6.75 (s, 1 H), 6.83 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 40.3, 43.8, 61.0, 63.4, 82.3, 82.4, 102.0, 103.7, 103.8, 136.7, 137.2, 147.3, 147.4, 171.5; $[\alpha]^{24}_D$ = +52.6 ° (*c* 0.6, $CHCl_3$); HRMS (FAB, 3-NBA) calcd for $C_{15}H_{16}O_6$ 292.0947 [M^+], obsd 292.0952. Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.72; H, 5.65.

(1*S*,2*S*,3*R*,4*R*)-2-Acetoxymethyl-3-(*tert*-butyl)dimethylsilyloxymethyl-1,4-epoxy-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (57a). To a solution of **25** (1.0 g, 3.4 mmol) and imidazole (0.5 g, 7.5 mmol) in DMF (10 mL) at 0 °C was added a solution of TBSCl (0.57 g, 3.8 mmol) in DMF (10 mL), and the resulting mixture was stirred for 7 h at room temperature. Et_2O was added, and the mixture was washed with saturated aqueous $NaHCO_3$ and H_2O. The organics were dried ($MgSO_4$), filtered, and concentrated to produce **57a** (1.35 g, 97%) as an oil [on a large scale, **25** (8.8 g, 30 mmol) gave **57a** (11.5 g, 93%)]: ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.01 (s, 3 H), 0.00 (s, 3 H), 0.89 (s, 9 H), 2.07 (s, 3 H) 2.69−2.77 (m, 3 H), 3.10 (app t, J = 10 Hz, 1 H), 3.27 (dd, J = 2, 7 Hz, 1 H), 3.82 (dd, J = 5, 11 Hz, 1 H), 5.26 (d, J = 12 Hz, 1 H), 5.30 (d, J = 7 Hz, 1 H), 5.94 (d, J = 1 Hz, 1 H), 5.97 (d, J = 1 Hz, 1 H),

6.74 (s, 1 H), 6.79 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −4.8, 18.7, 21.4, 26.5, 40.3, 44.2, 61.3, 63.4, 82.4, 82.8, 101.9, 103.6, 104.0, 136.9, 137.5, 147.1, 147.2, 171.3; $[\alpha]^{24}{}_D = +9.5°$ (*c* 1.7, $CHCl_3$). Anal. Calcd for $C_{21}H_{30}O_6Si$: C, 62.04; H, 7.44. Found: C, 62.17; H, 7.04.

(1*S*,2*S*,3*R*,4*R*)-2-Acetoxymethyl-1,4-epoxy-6,7-methylenedioxy-3-triisopropylsilyloxymethyl-1,2,3,4-tetrahydronaphthalene (57b). From **25** (14.5 g, 49.6 mmol), imidazole (7.4 g, 0.11 mol), and TIPSCl (11.7 mL, 54.6 mmol) in DMF (155 mL) at 0 °C, by the procedure for **57a**, was obtained **57b** (22.3 g, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, J = 3 Hz, 18 H), 1.03−1.22 (m, 3 H), 2.06 (s, 3 H), 2.76−2.77 (m, 3 H), 3.14 (app t, J = 10 Hz, 1 H), 3.40−3.43 (m, 1 H), 3.78 (dd, J = 5, 11 Hz, 1 H), 5.24 (d, J = 4 Hz, 1 H), 5.33 (d, J = 3 Hz, 1 H), 5.94 (d, J = 1 Hz, 1 H), 5.97 (d, J = 1 Hz, 1 H), 6.74 (s, 1H), 6.83 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5, 18.6, 21.5, 40.2, 44.3, 61.8, 63.3, 82.3, 82.9, 101.8, 103.6, 104.1, 136.9, 137.5, 147.1, 147.2, 171.3; $[\alpha]^{24}{}_D = +3.0°$ (*c* 0.9, $CHCl_3$); HRMS (FAB, 3-NBA, LiI) calcd for $C_{24}H_{36}O_6SiLi$ 455.2442, obsd 455.2443.

(1*S*,2*S*,3*R*,4*R*)-3-(*tert*-Butyl)dimethylsilyloxymethyl-1,4-epoxy-2-hydroxymethyl-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (26a). To a solution of acetate **57a** (8.2 g, 20 mmol) in MeOH (82 mL) was added K_2CO_3 (557 mg, 4.0 mmol). The resulting suspension was stirred for 1.5 h at room temperature. Dowex 50 × 8 resin (H^+ form; 900 mg) was added, and stirring was continued for 30 min. Filtration, concentration, and flash chromatography (33% EtOAc/hexanes) yielded the alcohol **26a** (7.0 g, 95%). On a small scale, **57a** (850 mg, 2.1 mmol) gave the **26a** in 97% yield (740 mg,): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.87 (s, 9 H), 2.71−2.83 (m, 2 H), 3.01 (dd, J = 9, 10 Hz, 2 H), 3.12−3.17 (m, 1 H), 3.20 (dd, J = 6, 10 Hz, 1 H), 5.17 (d, J = 4 Hz, 1 H), 5.20 (d, J = 4 Hz, 1 H), 5.95 (d, J = 4 Hz, 2 H), 6.72 (s, 1 H), 6.76 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −4.8, 18.7, 26.4, 44.4, 44.6, 61.1, 61.8, 82.0, 82.1, 101.9, 103.3, 103.4, 137.4, 137.6, 147.0, 147.1; $[\alpha]^{24}{}_D = -78.8°$ (*c* 0.8, $CHCl_3$); HRMS (CI) calcd for $C_{19}H_{28}O_5Si$ $(MH)^+$ 365.1706, obsd 365.1785.

(1*S*,2*S*,3*R*,4*R*)-1,4-Epoxy-2-hydroxymethyl-6,7-methylenedioxy-3-triisopropylsilyloxymethyl-1,2,3,4-tetrahydronaphthalene (26b). From acetate **57b** (7.10 g, 15.8 mmol) and K_2CO_3 (438 mg, 3.17 mmol) in MeOH (60 mL), by the procedure for **57a**, was obtained alcohol **26b** (6.43 g, 100%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98−1.07 (m, 21 H), 2.79−2.85 (m, 2 H), 2.97−3.11 (m, 2 H), 3.17 (dd, J = 5, 11 Hz, 1 H), 3.31 (dd, J = 6, 10 Hz, 1 H), 5.19 (d, J = 4 Hz, 1 H), 5.20 (d, J = 5 Hz, 1 H), 5.96 (s, 2 H), 6.73 (s, 1 H), 6.76 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_12.4, 18.6, 44.4, 44.5, 61.1, 62.1, 82.0, 82.1, 101.9, 103.3, 103.4, 137.3, 137.6, 147.0, 147.1; IR (ATR) 3419 cm^{-1}; $[\alpha]^{24}{}_D = -26.8°$ (*c* 1.3, $CHCl_3$); HRMS (FAB, 3-NBA, LiI) calcd for $C_{22}H_{34}O_5SiLi$ 413.2336, obsd 413.2341.

(1*S*,2*R*,3*R*,4*R*)-3-(*tert*-Butyl)dimethylsilyloxymethyl-1,4-epoxy-2-formyl-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (27a). To a solution of oxalyl chloride (14.4 mL of a 2.0 M solution in CH_2Cl_2, 28.7 mmol) at −78 °C was added a solution of DMSO (2.3 mL, 32.6 mmol) in CH_2Cl_2 (9.8 mL) via cannula. After 10 min of stirring at −78 °C, a solution of **26a** (6.98 g. 19.1 mmol) in CH_2Cl_2 (9.8 mL) was added dropwise via cannula. After an additional 30 min at −78 °C, a solution of NEt_3 (8 mL, 57.5 mmol) in CH_2Cl_2 (7 mL) was added in the same manner. The resulting reaction was allowed to warm to −40 °C and kept there for 2 h. Et_2O (500 mL) was then added at −40 °C, and the reaction mixture was allowed to warm to room temperature. The mixture was washed with H_2O, aqueous NH_4Cl, and brine. The organics were dried (Na_2SO_4), filtered, and concentrated to produce the product **27a** (7.29 g, 100%): ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.02 (s, 3 H), −0.01 (s, 3 H), 0.86 (s, 9 H), 2.99 (dd, J = 10, 19 Hz, 1 H), 3.00−3.05 (m, 1 H), 3.20 (ddd, J = 3, 5, 8 Hz, 1 H), 3.37 (dd, J = 6, 9 Hz, 1 H), 5.33 (d, J = 4 Hz, 1 H), 5.37 (d, J = 5 Hz, 1 H), 5.95 (d, J = 1 Hz, 1 H), 5.97 (d, J = 2 Hz, 1 H), 6.81 (s, 1 H), 6.83 (s, 1 H), 9.06 (d, J = 4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −4.8, 18.7, 26.4, 47.1, 54.2, 62.1, 80.9, 82.6, 102.0, 103.8, 103.9, 137.0, 137.6, 147.4, 147.5, 202.5; $[\alpha]^{24}{}_D = -14.2°$ (*c* 6.4, $CHCl_3$); HRMS (FAB, 3-NBA, LiI) calcd for $C_{19}H_{26}O_5SiLi$ 369.1709, obsd 369.1719.

(1*S*,2*R*,3*R*,4*R*)-1,4-Epoxy-2-formyl-6,7-methylenedioxy-3-triisopropylsilyloxymethyl-1,2,3,4-tetrahydronaphthalene (27b). From **27a** (13.9 g, 34.2 mmol), oxalyl chloride (29.0 mL, 58.1 mmol, 2.0 M in CH_2Cl_2), DMSO (5.34 g, 68.4 mmol) and NEt_3 (11.8 g, 116 mmol), by the same procedure as for **27a**, was obtained aldehyde **27b** (14.3 g, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97−1.20 (m, 21 H), 2.99−3.12 (m, 2 H), 3.22 (ddd, J = 3, 5, 8 Hz, 1 H), 3.46−3.51 (m, 1 H), 5.38 (s, 1 H), 5.40 (s, 1 H), 5.96 (d, J = 1 Hz, 1 H), 5.98 (d, J = 1 Hz, 1 H), 6.84 (s, 1 H), 6.85 (s, 1 H), 9.07 (d, J = 3 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.6, 18.6, 47.3, 54.2, 62.8, 81.0, 82.7, 102.0, 103.9, 104.0, 136.9, 137.5, 147.4, 147.5, 202.5; $[\alpha]^{24}{}_D = -26.3°$ (*c* 0.8, $CHCl_3$); HRMS (FAB, 3-NBA, NaI) calcd for $C_{22}H_{32}O_5SiNa$ 427.1917, obsd 427.1925.

Lactone 28. To a solution of aldehyde **27a** (6.1 g, 16.8 mmol) and sulfamic acid (2.1 g, 21.9 mmol) in *t*-BuOH (195 mL) at room temperature was added a solution of sodium chlorite (2.0 g, 22.5 mmol) in H_2O (195 mL) followed by HF (1.6 g, concentrated aqueous). After being allowed to stir at room temperature for 14 h, the reaction mixture was extracted with EtOAc. The organics were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (50EnDash−75% EtOAc/hexanes) provided **28** (2.9 g, 69%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45−3.49 (m, 1 H), 3.61−3.70 (m, 2 H), 4.19 (dd, J = 8, 10 Hz, 1 H), 5.37 (d, J = 5 Hz, 1 H), 5.54 (d, J = 5 Hz, 1 H), 5.95 (d, J = 1 Hz, 1 H), 6.01 (d, J = 1 Hz, 1 H), 6.84 (s, 1 H), 6.85 (s, 1 H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 40.8, 48.3, 67.2, 79.5, 81.5, 101.2, 102.5, 103.4, 135.3, 136.3, 146.1, 146.2, 173.9; IR-(ATR) 1755 cm^{-1}; $[\alpha]^{24}{}_D = +135.9°$ (*c* 2.7, $CHCl_3$); HRMS (EI) calcd for $C_{13}H_{10}O_5$ 246.0525, obsd 246.0528.

α-Methylated Lactone 29. To a solution of **28** (100 mg, 0.41 mmol) in THF (1 mL) at −78 °C was added a solution of KHMDS (820 μL of a 0.5 M solution in toluene, 0.41 mmol) and 18-Cr-6 (108 mg, 0.41 mmol) in THF (1 mL) dropwise via cannula. After being allowed to stir for 12 h at −78 °C and an additional 11 h at −45 °C, ring opening was not observed by TLC, and CH_3I (255 μL, 4.1 mmol) was added. The reaction was quenched with aqueous $NaHCO_3$ and extracted with Et_2O. The organics were dried (Na_2SO_4), filtered, concentrated, and chromatographed (33% EtOAc/hexanes) to provide a sample of the clean methylated lactone: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.28 (ddd, J = 3, 6, 8 Hz, 1 H), 3.51 (s, 3 H), 3.58 (dd, J = 3, 10 Hz, 1 H), 4.23 (dd, J = 8, 10 Hz, 1 H), 5.34 (s, 1H), 5.41 (d, J = 5 Hz, 1 H), 5.95 (d, J = 1 Hz, 1 H), 6.00 (d, J = 1 Hz, 1 H), 6.82 (s, 2 H). Note: irradiation of the methyl group produced NOEs of 3.7% at the bridgehead (H_1) and of 6.6% at H_3, indicating that the lactone remains cis-endo with the methyl group occupying an exo position. ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.2, 55.0, 67.1, 83.4, 85.5, 93.6, 102.4, 103.8, 104.5, 134.4, 136.4, 148.3, 172.4.

(3*R*,4*R*)-2-Formyl-4-hydroxy-6,7-(methylenedioxy)-3-triisopropylsilyloxymethyl-3,4-dihydronaphthalene (30). To a solution of aldehyde **27b** (10.5 g, 26.0 mmol) in absolute MeOH (95 mL) at room temperature was added freshly prepared NaOMe in MeOH (300 mL of a 60 mM solution). After 24 h at room temperature, the reaction was monitored by TLC,and additional NaOMe (3 × 20 mL) was added at 2 h intervals, until no **27b** remained. H_2O (245 mL) was then added, and CO_2 was bubbled through the solution until the pH reached 8 (pH paper). MeOH was removed in vacuo, and the resulting aqueous layer was extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered, and evaporated to provide analytically **30** as a white solid (9.50 g, 90%): mp 87−89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93−1.03 (m, 21 H), 1.74 (d, J = 5 Hz, 1 H), 3.17 (app t, J = 10 Hz, 1 H), 3.34 (ddd, J = 2, 4, 6 Hz, 1 H), 3.80 (dd, J = 4, 10 Hz, 1 H), 4.97 (app t, J = 1 Hz, 1 H), 6.01 (s, 1 H), 6.02 (s, 1 H), 6.83 (s, 1 H), 6.93 (s, 1 H), 7.24 (s, 1 H), 9.61 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.5, 18.5, 43.4, 62.7, 70.0, 102.4, 109.8, 110.9, 125.3, 133.8, 136.0, 145.6, 148.8, 150.7, 192.9; IR (ATR) 3395, 1674, 1645 cm^{-1}; $[\alpha]^{24}{}_D = +82.0°$ (*c* 1.0, $CHCl_3$); HRMS (FAB, 3-NBA) calcd for $C_{22}H_{33}O_5Si$ [$(M + H)^+$] 405.2097, obsd

405.2096. Anal. Calcd for $C_{22}H_{32}O_5Si$: C, 65.31; H, 7.97. Found: C, 65.45; H, 7.98.

(3*R*,4*R*)-4-Allyloxy-2-hydroxymethyl-6,7-methylenedioxy-3-triisopropylsilyloxymethyl-3,4-dihydronaphthalene (31a). To a solution of aldehyde **30** (3.1 g, 7.74 mmol) in DMF (50 mL) at 0 °C was added NaH (372 mg of a 60% dispersion, 9.29 mmol) followed by allyl bromide (740 μL, 8.51 mmol) via syringe. The resulting mixture was allowed to stir for 3 h at 0 °C and an additional 0.5 h at room temperature. The reaction mixture was diluted in Et_2O and then washed with aqueous $NaHCO_3$ and H_2O. The organics were dried ($MgSO_4$), filtered, concentrated, and chromatographed (25% EtOAc/hexanes) to give **31a** (2.4 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93−1.03 (m, 21 H), 3.05 (app t, J = 10 Hz, 1 H), 3.45 (ddd, J = 1, 4, 6 Hz, 1 H), 3.69 (dd, J = 4, 10 Hz, 1 H), 3.97 (dd, J = 1, 6 Hz, 2 H), 4.69 (s, 1 H), 5.15−5.28 (m, 2 H), 5.78−5.92 (m, 1 H), 6.01 (d, J = 1 Hz, 1 H), 6.03 (d, J = 1 Hz, 1 H), 6.83 (s, 2 H), 9.59 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5, 18.6, 40.2, 61.8, 69.6, 75.2, 102.3, 109.9, 111.8, 118.2, 126.3, 131.0, 135.6, 136.4, 145.9, 148.7, 150.2, 193.0; HRMS (FAB, 3-NBA, NaI) calcd for $C_{25}H_{36}O_5SiNa$ 467.2230, obsd 467.2242.

(3*R*,4*R*)-4-Benzyloxy-2-formyl-6,7-methylenedioxy-3-triisopropylsilyloxymethyl-3,4-dihydronaphthalene (31b). To a solution of **30** (350 mg, 0.87 mmol) in DMF (5.5 mL) at −10 °C were added sequentially NaH (42 mg of a 60% dispersion, 1.04 mmol) and benzyl bromide (113 μL, 0.95 mmol). The resulting reaction mixture was allowed to warm to room temperature overnight. The mixture was diluted with Et_2O and then washed with aqueous $NaHCO_3$ and H_2O. The organics were dried ($MgSO_4$), filtered, and concentrated to produce **31b** (428 mg, 100%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.86−0.99 (m, 21 H), 3.05 (app t, J = 10 Hz, 1 H), 3.51−3.56 (m, 1 H), 3.69 (dd, J = 4, 10 Hz, 1 H), 4.50 (s, 2 H), 4.71 (s, 1 H), 6.02 (s, 1 H), 6.03 (s, 1 H), 6.71 (s, 1 H), 6.84 (s, 1 H), 7.24−7.33 (m, 6 H), 9.61 (s, 1 H).

(3*R*,4*R*)-2-Hydroxymethyl-6,7-methylenedioxy-3-triisopropylsilyloxy-methyl-4-(2′-trimethylsilylethoxy)methoxy-3,4-dihydronaphthalene (31c). To a solution of **30** (7.0 g, 17 mmol) in CH_2Cl_2 (140 mL) at 0 °C were added sequentially diisopropylethylamine (9.0 mL, 52 mmol) and SEM chloride (4.6 mL, 26 mmol). The resulting reaction mixture was allowed to warm slowly to room temperature overnight and then poured into aqueous $NaHCO_3$. The aqueous layer was further extracted with CH_2Cl_2. After drying ($MgSO_4$), filtering, and evaporating, the crude product was purified by SiO_2 chromatography (10% EtOAc/hexanes) to provide 13 (8.6 g, 93%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.00 (s, 9 H), 0.91−1.04 (m, 23 H), 3.07 (app t, J = 10 Hz, 1 H), 3.41 (ddd, J = 2, 4, 6 Hz, 1 H), 3.46−3.62 (m, 2 H), 3.70 (dd, J = 5, 10 Hz, 1 H), 4.58 (d, J = 7 Hz, 1 H), 4.65 (d, J = 7 Hz, 1 H), 4.98 (d, J = 1 Hz, 1 H), 6.01 (d, J = 2 Hz, 1 H), 6.02 (d, J = 1 Hz, 1 H), 6.84 (s, 1 H), 6.90 (s, 1 H), 7.23 (s, 1 H), 9.60 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.8, 12.5, 18.6, 18.7, 41.1, 61.8, 65.7, 72.3, 92.4, 102.4, 109.9, 112.1, 126.3, 130.7, 136.5, 145.7, 148.7, 150.2, 192.9; IR (ATR) 1674 cm^{-1}; $[\alpha]^{24}_D$ = +37.7° (*c* 0.9, $CHCl_3$). Anal. Calcd for $C_{28}H_{46}O_6Si_2$: C, 62.88; H, 8.67. Found: C, 63.00; H, 8.49.

Methyl (3*R*,4*R*)-4-Allyloxy-6,7-methylenedioxy-3-triisopropylsilyloxymethyl-3,4-dihydronaphthalene-2-carboxylate (32a). To a solution of **31a** (50 mg, 0.11 mmol) in MeOH (1.5 mL) at room temperature were added NaCN (30 mg, 0.60 mmol) and freshly prepared MnO_2 (207 mg, 2.39 mmol). The resulting reaction mixture was allowed to stir for 20 h. The reaction mixture was concentrated, and H_2O was added. The mixture was extracted with Et_2O, and the organics were dried ($MgSO_4$), filtered, concentrated, and chromatographed (25% EtOAc/hexanes) to yield **32a** (39 mg, 74%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.99−1.07 (m, 21 H), 3.04 (app t, J = 10 Hz, 1 H), 3.41 (ddd, J = 2, 4, 6 Hz, 1 H), 3.75 (dd, J = 4, 10 Hz, 1 H), 3.79 (s, 3 H), 3.91−3.99 (m, 2 H), 4.68 (d, J = 2 Hz, 1 H), 5.15−5.28 (m, 2 H), 5.83−5.90 (m, 1 H), 5.98 (d, J = 1 Hz, 1 H), 6.00 (d, J = 2 Hz, 1 H), 6.76 (s, 1 H), 6.80 (s, 1 H), 7.51 (s, 1 H).

(3*R*,4*R*)-6,7-Methylenedioxy-3-triisopropylsilyloxymethyl-4-(2′-trimethylsilylethoxy)methoxy-3,4-dihydronaphthalene-2-carboxylic Acid (42). To a solution of aldehyde **31c** (3.5 g, 6.5 mmol) in *t*-BuOH (130 mL) and 2-methyl-2-butene (35 mL) at room temperature was added a solution of $NaClO_2$ (5.4 g, 60 mmol) and NaH_2PO_4 (5.4 g) in H_2O (60 mL). After being allowed to stir at room temperature overnight, the reaction mixture was extracted with Et_2O, dried, and concentrated. Flash chromatography (10−30% EtOAc/hexanes) provided the title acid (3.6 g, 100%). [On a larger scale, **31c** (15.0 g, 28 mmol) gave the same acid in excellent yield (14.8 g, 95%).] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 9 H), 0.92−1.12 (m, 23 H), 3.13 (app t, J = 10 Hz, 1 H), 3.38 (ddd, J = 1, 5, 6 Hz, 1 H), 3.47−3.65 (m, 2 H), 3.78 (dd, J = 4, 10 Hz, 1 H), 4.61 (d, J = 7 Hz, 1 H), 4.67 (d, J = 7 Hz, 1 H), 4.97 (d, J = 2 Hz, 1 H), 5.99 (d, J = 1 Hz, 1 H), 6.01 (d, J = 1 Hz, 1 H), 6.80 (s, 1 H), 6.88 (s, 1 H), 7.63 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.8, 12.6, 18.6, 18.7, 43.2, 62.0, 65.7, 72.6, 92.4, 102.2, 109.9, 112.0, 125.8, 126.5, 129.4, 139.1, 148.6, 149.6, 172.9; IR (ATR) 3854, 1676 cm^{-1}; $[\alpha]^{24}_D$ = +78.3° (*c* 1.6, $CHCl_3$); HRMS (FAB, 3-NBA, NaI) calcd for $C_{28}H_{46}O_7Si_2Na$ 573.2680, obsd 573.2677.

Methyl (3*R*,4*R*)-6,7-Methylenedioxy-3-triisopropylsilyloxymethyl-4-(2′-trimethylsilylethoxy)methoxy-3,4-dihydronaphthalene-2-carboxylate (32c). To a solution of *N*-methyl-*N*-nitroso urea (4.26 g, 41.4 mol) in Et_2O (35 mL) was added a precooled (at 0 °C) solution of KOH (6.3 g, 108.6 mmol) in H_2O (18 mL). Then the Et_2O solution was warmed to 30−40 °C. The CH_2N_2 thereby formed was distilled directly into a solution of the acid **42** (1.44 g, 2.62 mmol) in Et_2O (50 mL) and MeOH (30 mL) at 0 °C for 40 min, followed by quenching of excess CH_2N_2 with HOAc. Concentration produced the methyl ester **32c** (1.48 g, 100%): ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.01 (s, 9 H), 0.91−1.05 (m, 23 H), 3.06 (app t, J = 10 Hz, 1 H), 3.37 (ddd, J = 2, 4, 6 Hz, 1 H), 3.46−3.51 (m, 1 H), 3.57−3.62 (m, 1 H), 3.74−3.80 (m, 4 H), 4.59 (d, J = 7 Hz, 1 H), 4.64 (d, J = 7 Hz, 1 H), 4.97 (s, 1 H), 5.97 (d, J = 1 Hz, 1 H), 5.99 (d, J = 2 Hz, 1 H), 6.77 (s, 1 H), 6.87 (s, 1 H), 7.52 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.8, 12.5, 18.6, 18.7, 43.5, 52.3, 62.0, 65.6, 72.6, 92.4, 102.1, 109.7, 112.0, 126.3, 126.7, 128.8, 137.1, 148.5, 149.2, 167.8; $[\alpha]^{24}_D$ = +97.3° (*c* 1.2, $CHCl_3$); HRMS (FAB, 3-NBA, NaI) calcd for $C_{29}H_{48}O_7Si_2Na$ 587.2836, obsd 587.2848.

Lactone 33. To a solution of **32a** (910 mg, 1.9 mmol) in THF (20 mL) at 0 °C was added TBAF (2.1 mL of a 1.0 M solution in THF, 2.1 mmol). After being allowed to stir for 4 h at 0 °C, the reaction mixture was quenched with aqueous $NaHCO_3$. The H_2O layer was extracted with Et_2O. The combined organics were dried ($MgSO_4$), filtered, and concentrated to produce an oil. A solution of this oil and titanium(IV) isopropoxide (116 μL, 0.38 mmol) in benzene (200 mL) was refluxed on a Dean Stark apparatus for 16 h. The reaction mixture was concentrated and chromatographed (25% EtOAc/hexanes) to produce **33** (268 mg, 50%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (ddd, J = 3, 9, 12 Hz, 1 H), 4.15−4.25 (m, 3 H), 4.61 (d, J = 14 Hz, 1 H), 4.81 (app t, J = 9 Hz, 1 H), 5.27−5.40 (m, 2 H), 5.94−5.99 (m, 1 H), 6.00 (d, J = 2 Hz, 1 H), 6.02 (d, J = 2 Hz, 1 H), 6.79 (s, 1 H), 7.10 (s, 1 H), 7.27 (d, J = 3 Hz, 1 H).

(±)-Ethyl 3-Phenylbutanoate (35). To a deoxygenated solution of CuCN (358 mg, 4.0 mmol) in Et_2O (6 mL) at −78 °C was added a solution of a freshly prepared PhLi (672 mg, 8.0 mmol) in Et_2O (4.8 mL). The resulting reaction mixture was allowed to stir for 1.5 h at −78 °C. $BF_3{\cdot}Et_2O$ (541 μL, 4.4 mmol) and ethyl *trans*-crotonate (**34**, 62 μL, 0.5 mmol) were added sequentially at −78 °C. The resulting mixture was allowed to warm to −30 °C overnight and then poured into aqueous NH_4Cl. The aqueous layer was further extracted with Et_2O. After drying ($MgSO_4$), filtering and evaporating, the crude product was purified by SiO_2 chromatography (33% EtOAc/hexanes) to provide **35** (72 mg, 75%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.10 (t, J = 7 Hz, 3 H), 1.22 (d, J = 7 Hz, 3 H), 2.48 (dd, J = 15, 29 Hz, 1 H), 2.51 (dd, J = 15, 28 Hz, 1 H), 3.15−3.25 (m, 1 H), 4.00 (q, J = 7 Hz, 2 H), 7.09−7.29 (m, 5 H).

Methyl (2*E*)-(3′,4′-Methylenedioxy)cinnamate (36). The title methyl ester **36** was obtained with freshly prepared CH_2N_2 as described for **32c**. (2*E*)-(3′,4′-Methylenedioxy)cinnamic acid (Aldrich, 2.7 g, 14.1 mmol) gave **36** in 99% yield (2.9 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3 H), 6.00 (s, 2 H) 6.25 (d, J = 16 Hz, 1 H), 6.80 (d, J = 8 Hz, 1 H), 6.98−7.02 (m, 2 H), 7.59 (d, J = 16 Hz, 1 H).

(±)-Methyl (3′,4′-Methylenedioxy)-3-phenyl-2,3-dihydrocinnamate (37). To a deoxygenated solution of CuCN (179 mg, 2.0 mmol) in Et_2O (3 mL) at −78 °C was added a solution of a freshly prepared PhLi (336 mg, 4.0 mmol) in Et_2O (3.1 mL). The reaction mixure was allowed to stir for 1.5 h at −35 °C. After the reaction mixture was cooled to −78 °C, $BF_3 \cdot Et_2O$ (271 μL, 2.2 mmol) and a solution of **36** (52 mg, 0.3 mmol) in Et_2O (2 mL) were added sequentially at −78 °C. The resulting reaction mixture was allowed to warm to −35 °C overnight and then stirred at room temperature for 12 h. Aqueous NH_4Cl was added, and the aqueous layer was extracted with Et_2O. The combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (33% EtOAc/hexanes) and MPLC (acetone/$CHCl_3$/hexanes 4:63:33) provided the adduct **37** (36 mg, 50%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.00 (d, J = 8 Hz, 2 H), 3.59 (s, 3 H), 4.47 (t, J = 8 Hz, 1 H), 5.89 (s, 2 H), 6.68 (s, 1 H), 6.71 (d, J = 1 Hz, 2 H), 7.15−7.30 (m, 5 H).

Methyl 6,7-Methylenedioxy-3-triisopropylsilyloxymethyl-naphthalene-2-carboxylate (38). Attempts to perform conjugate additions upon α,β-unsaturated ester **32c**, under the conditions used to synthesize **37** (or indeed, incubation of **32c** with $BF_3 \cdot Et_2O$ at −78 °C in Et_2O) led only to the isolation of aromatized product **38**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.6−1.19 (m, 21 H), 3.93 (s, 3 H), 5.30 (s, 2 H), 6.05 (s, 2 H), 7.14 (s, 1 H), 7.16 (s, 1 H), 8.11 (s, 1 H), 8.36 (s, 1 H).

(3*R*,4*R*)-4-Allyloxy-6,7-methylenedioxy-3-(triisopropylsilyloxy)methyl-3,4-dihydronaphthalene-2-carboxylic Acid (39). Following the same procedure as for the synthesis of **42** (vide supra) acid **39** (311 mg, 100%) was synthesized from aldehyde **31a** (300 mg, 0.67 mmol): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.97−1.08 (m, 21 H), 3.10 (app t, J = 10 Hz, 1 H), 3.41(ddd, J = 2, 5, 6 Hz, 1 H), 3.78 (dd, J = 5, 10 Hz, 1 H), 3.98 (app d, J = 6 Hz, 2 H), 4.68 (d, J = 1 Hz, 1 H), 5.16−5.29 (m, 2 H), 5.82−5.93 (m, 1 H), 6.00 (d, J = 2 Hz, 1 H), 6.01 (d, J = 1 Hz, 1 H), 6.79 (s, 1 H), 6.82 (s, 1 H), 7.62 (s, 1 H).

2′-Bromothiophenyl (3*R*,4*R*)-4-Allyloxy-6,7-methylenedioxy-3-triisopropylsilyloxymethyl-3,4-dihydronaphthalene-2-carboxylate (40). To a solution of **39** (100 mg, 0.22 mmol) in THF (500 μL) at room temperature was added carbonyl diimidazole (CDI, 39 mg, 0.24 mmol). The resulting reaction mixture was allowed to stir 2.5 h at room temperature and then concentrated. The crude product was dissolved in Et_2O and extracted with H_2O to remove imidazole. The organics were dried ($MgSO_4$), filtered, and concentrated to produce the imidazolide.

To a deoxygenated solution of 2-bromothiophenol (22 μL, 0.21 mmol) in THF (500 μL) at 0 °C was added KHMDS (430 μL of a 0.5 M solution in toluene, 0.21 mmol). The resulting reaction mixture was allowed to stir 1 h at 0 °C. Then a solution of the imidazolide in THF (500 μL) was added, via cannula. The reaction was stirred for 3.5 h at 0 °C and then quenched with aqueous $NaHCO_3$. The H_2O layer was extracted with Et_2O. The combined organics were dried, filtered, concentrated, and chromatographed (20% EtOAc/hexanes) to yield **40** (99 mg, 73%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.85−1.04 (m, 21 H), 3.15 (app t, J = 10 Hz, 1 H), 3.50 (ddd, J = 2, 5, 6 Hz, 1 H), 3.83 (dd, J = 5, 10 Hz, 1 H), 3.99 (app d, J = 6 Hz, 2 H), 4.71 (d, J = 2 Hz, 1 H), 5.16−5.30 (m, 2 H), 5.82−5.93 (m, 1 H), 6.01 (d, J = 2 Hz, 1 H), 6.03 (d, J = 2 Hz, 1 H), 6.82 (s, 1 H), 6.85 (s, 1 H), 7.25−7.72 (m, 4 H), 7.65 (s, 1 H).

Thiophenyl (3*R*,4*R*)-4-Allyloxy-6,7-methylenedioxy-3-triisopropylsilyloxymethyl-3,4-dihydronaphthalene-2-carboxylate (41). *o*-Bromothioester **40** (20 mg, 32 μmol) was incubated with $PdCl_2(PPh_3)_2$ (5 mg, 6 μmol), PPh_3 (10 mg, 38 μmol), and K_2CO_3 (9 mg, 64 μmol) in DMF (300 μL) under Ar at 75 °C for 24 h. After cooling to room temperature, the reaction mixture was partitioned between H_2O and Et_2O. The ether layer was dried ($MgSO_4$) and concentrated. Chromatography (25% EtOAc/hexanes) yielded reduction product **41** (4 mg, 22%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.96−1.12 (m, 21 H), 3.11 (app t, J = 10 Hz, 1 H), 3.48 (br dd, J = 6, 10 Hz, 1 H), 3.88 (dd, J = 6, 10 Hz, 1 H), 4.01−4.06 (m, 2 H), 4.78 (br s, 1 H), 5.21 (d, J = 10.5 Hz, 1 H),), 5.30 (d, J = 18 Hz, 1 H), 5.90 (m, 1 H), 6.02−6.07 (br s, 2 H), 6.81 (s, 1 H), 6.85 (s, 1 H), 7.41−7.54 (m, 3 H), 7.66 (s, 1 H), 7.68−7.75 (m, 2 H).

2″-Bromophenyl (3*R*,4*R*)-6,7-Methylenedioxy-3-triisopropylsilyloxymethyl-4-(2′-trimethylsilylethoxy)methoxy-3,4-dihydronaphthalene-2-carboxylate (43). To a solution of acid **42** (255 mg, 0.46 mmol) in THF (1 mL) at room temperature was added CDI (83 mg, 0.51 mmol). After 3 h at room temperature, the reaction mixture was partitioned between Et_2O and H_2O. The H_2O layer was back-extracted with Et_2O. The combined organics were dried and evaporated to provide the acyl imidazolide, which was taken forward without further purification. To a solution of 2-bromophenol (87 μL, 0.75 mmol) in THF (2 mL) at 0 °C was added KHMDS (1.5 mL of a 0.5 M solution in toluene, 0.75 mmol). The resulting mixture was allowed to stir 1 h at 0 °C prior to dropwise addition of a solution of acyl imidazolide (275 mg, 0.46 mmol) in THF (1 mL) via cannula. The reaction mixture was allowed to warm to room temperature over 7 h and then quenched with aqueous $NaHCO_3$. The H_2O layer was extracted with Et_2O. The combined organics were dried, filtered, concentrated, and chromatographed (25% EtOAc/hexanes) to produce **43** (63 mg, 20%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9 H), 0.96−1.02 (m, 23 H), 3.17 (app t, J = 10 Hz, 1 H), 3.46−3.67 (m, 3 H), 3.97 (dd, J = 4, 10 Hz, 1 H), 4.63 (d, J = 7 Hz, 1 H), 4.70 (d, J = 7 Hz, 1 H), 5.06 (d, J = 1 Hz, 1 H), 6.01 (d, J = 1 Hz, 1 H), 6.02 (d, J = 1 Hz, 1 H), 6.85 (s, 1 H), 6.91 (s, 1 H), 7.21−7.62 (m, 4 H), 7.82 (s, 1 H).

Phenyl (3*R*,4*R*)-6,7-Methylenedioxy-3-triisopropylsilyloxymethyl-4-(2′-trimethylsilylethoxy)methoxy-3,4-dihydronaphthalene-2-carboxylate (44). To a mixture of **43** (20 mg, 28 μmol) and AIBN (0.5 mg, 2.8 μmol) in dry PhMe (750 μL) was added Bu_3SnH (8.1 mg, 28 μmol) in dry PhMe (100 μL), and the resulting reaction mixture was refluxed for 12 h. The reaction was quenched with $NaHCO_3$ solution, extracted with Et_2O, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (20% Et_2O/hexanes) provided **44** (5 mg, 28%) and recovered **43** (5 mg, 25%). For **44**:^{1}H NMR (360 MHz, $CDCl_3$) δ −0.02−0.03 (br s, 9 H), 0.95−1.03 (br s, 23 H), 3.18 (app t, J = 9.5 Hz, 1 H), 3.44−3.51 (m, 1 H), 3.52−3.67 (m, 2 H), 3.87−3.93 (dd, J = 5, 10 Hz, 1 H), 4.65 (d, J = 7 Hz, 1 H), 4.71 (d, J = 7 Hz, 1 H), 5.05 (br s, 1 H), 6.01−6.04 (m, 2 H), 6.85 (s, 1 H), 6.93 (s, 1 H), 7.16 (d, J = 8 Hz, 2 H), 7.24 (app t, J = 8 Hz, 1 H), 7.40 (app t, J = 8 Hz, 2 H).

(3*R*,4*R*)-4-Benzyloxy-2-hydroxymethyl-6,7-methylenedioxy-3-triisopropylsilyloxymethyl-3,4-dihydronaphthalene (58). To a solution of **31b** (520 mg, 1.1 mmol) in EtOH (18 mL) at 0 °C was added $NaB(OCH_3)_3H$ (184 mg, 1.5 mmol). The resulting mixture was allowed to warm to room temperature over 9 h and then quenched with aqueous $NaHCO_3$. The mixture was extracted with Et_2O. The organic layers were dried ($MgSO_4$), filtered, and concentrated to produce the **58** (453 mg, 87%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.96−1.11 (m, 21 H), 2.40 (br., 1 H), 2.92−2.96 (m, 1 H), 3.28 (dd, J = 8, 10 Hz, 1 H), 3.56 (dd, J = 6, 10 Hz, 1 H), 4.25 (d, J = 1 Hz, 2 H), 4.42 (d, J = 2 Hz, 1 H), 4.49 (s, 1 H), 4.51 (s, 1 H), 5.95 (s, 2 H), 6.42 (s, 1 H), 6.64 (s, 2 H), 7.25−7.32 (m, 5 H).

(3*R*,4*R*)-4-Benzyloxy-2-(4′-methoxy)phenoxymethyl-6,7-methylenedioxy-3-triisopropylsilyloxymethyl-3,4-dihydronaphthalene (45). To a solution of **58** (30 mg, 0.06 mmol) in THF (1 mL) was added *p*-methoxyphenol (45 mg, 0.36 mmol), Ph_3P (41 mg, 0.16 mmol), and diethylazodicarboxylate (25 μL, 0.16 mmol). The resulting reaction mixture was heated to 80 °C for 13 h. The reaction mixture was cooled, concentrated, and chromatographed (25% EtOAc/hexanes) to give **45** (10 mg, 28%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.92−1.05 (m, 21 H), 2.98 (ddd, J = 2, 5, 7 Hz, 1 H), 3.73 (app t, J = 10 Hz, 1 H), 3.66−3.82 (m, 4 H), 4.48 (dd, J = 7 Hz, 2 H), 4.59 (d, J = 2 Hz, 1 H), 4.60 (d, J = 1 Hz, 2 H), 5.94 (d, J = 1 Hz, 1 H), 5.95 (d, J = 2 Hz, 1 H), 6.50 (s, 1 H), 6.64 (s, 1 H),

6.67 (s, 1 H), 6.79−6.90 (m, 4 H), 7.23−7.30 (m, 5 H); MS (FAB, 3-NBA, NaI) 625 (5, $[M + Na]^+$), 517 (10), 199 (100).

2-(4′-Methoxy)phenoxymethyl-6,7-(methylenedioxy)-3-triisopropylsilyloxymethyl-naphthalene (46). Aryl benzyl ether **45** (8 mg, 13 μmol) was heated to 210 °C in *o*-dichlorobenzene (600 μL) in a sealed vessel for 1.5 h. After evaporation of solvent, flash chromatography (25% EtOAc/hexanes) provided aromatized product **46** (4 mg, 60%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.95−1.14 (m, 21 H), 3.77 (s, 3 H), 4.99 (s, 2 H), 5.18 (s, 2 H), 6.04 (s, 2 H), 6.84 (d, J = 8 Hz, 1 H), 6.93 (d, J = 8 Hz, 1 H), 7.10 (s, 1 H), 7.13 (s, 1 H), 7.71 (s, 1 H), 7.78 (s, 1 H).

***N*-(3′,4′-Methylenedioxy)-(2*E*)-cinnamoyloxazolidinone (47).** To a solution of 3,4-(methylenedioxy)cinnamic acid (5.0 g, 26.0 mmol) in THF (70 mL) at room temperature was added CDI (4.6 g, 28.6 mmol). After being allowed to stir at room temperature overnight, the reaction mixture was concentrated. The organics were dissolved in EtOAc (100 mL), washed with H_2O (4 × 100 mL), concentrated, and used directly without further purification. To a solution of 2-oxazolidone (1.8 g, 20.6 mmol) in THF (80 mL) at −78 °C was added KHMDS (41 mL of a 0.5 M solution in PhMe, 20.6 mmol). The resulting reaction mixture was allowed to stir for 30 min at 78 °C. Then a solution of acyl imidazolide (3.8 g, 15.6 mmol) in CH_2Cl_2 (100 mL) was added via cannula at −78 °C. The resulting mixture was allowed to warm to room temperature slowly for 16 h and quenched with aqueous $NaHCO_3$. The H_2O layer was extracted once with CH_2Cl_2. The combined organic layers were dried, concentrated, and chromatographed (66% EtOAc/hexanes) to yield **47** (2.3 g, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (t, J = 8 Hz, 2 H), 4.42 (t, J = 8 Hz, 2 H), 5.99 (s, 2 H), 6.79 (d, J = 8 Hz, 1 H), 7.07 (dd, J = 2, 8 Hz, 1 H), 7.12 (d, J = 2 Hz, 1 H), 7.69 (d, J = 16 Hz, 1 H), 7.75 (d, J = 16 Hz, 1 H).

(±)-*N*-[3-(3′,4′-Methylenedioxy)phenyl-3-phenylpropanoyl]oxazolidinone (48). To a deoxygenated solution of CuBr-Me_2S (43 mg, 0.21 mmol) in THF (400 μL) and Me_2S (400 μL) at −78 °C was added PhMgBr (287 μL of a 1.0 M solution in THF, 0.29 mmol). The resulting mixture was allowed to stir for 1 h at 78 °C, whereupon a solution of **47** (24 mg, 0.09 mmol) in THF (450 μL) was added via cannula. After 2 h at −20 °C, aqueous NH_4Cl was added, followed by Et_2O. After further extraction of the aqueous layer wih Et_2O, the combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (50% EtOAc/hexanes) yielded **48** (30 mg, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (d, J = 8 Hz, 2 H), 3.91 (t, J = 8 Hz, 2 H), 4.33 (t, J = 8 Hz, 2 H), 4.60 (t, J = 8 Hz, 1 H), 5.90 (s, 2 H), 6.69−6.77 (m, 3 H), 7.24−7.30 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.7, 42.4, 45.9, 62.0, 100.9, 108.3, 108.4, 120.6, 126.5, 127.6, 128.5, 137.5, 143.6, 146.1, 147.7, 153.5, 171.3.

(±)-*N*-[3-(3′,4′-Methylenedioxy)phenyl-3-(3″,4″,5″-trimethoxy)phenylpropanoyl]oxazolidinone (49). To a suspension of CuCN (87 mg, 0.96 mmol) in THF (3 mL) at 5 °C was added 3,4,5-trimethoxyphenylmagnesium bromide[37] (3.26 mL of a 0.3 M solution in THF). The resulting mixture was allowed to stir for 1 h at 5 °C, whereupon a solution of **47** (63 mg, 0.24 mmol) in THF (5 mL) was added via cannula. After 0.5 h at 5 °C, aqueous NH_4Cl solution was added, followed by Et_2O. After further extraction of the aqueous layer with Et_2O, the combined organics were dried ($MgSO_4$), filtered, and evaporated. Chromatography (33% EtOAc/hexanes) yielded **49** (87 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (dd, J = 7, 17 Hz, 1 H), 3.76 (dd, J = 7, 17 Hz, 1 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 3,91 (t, J = 8 Hz, 2 H), 4.34 (t, J = 8 Hz, 2 H), 4.51 (t, J = 7 Hz, 1 H), 5.89 (s, 2 H), 6.47 (s, 2 H), 6.70−6.78 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) d 40.5, 42.4, 46.3, 56.0, 60.6, 61.9, 100.8, 104.6, 108.0, 108.1, 120.3, 136.4, 137.2, 139.1, 146.1, 147.6, 153.0, 153.5, 171.2; HRMS (FAB, 3-NBA, NaI) calcd for $C_{22}H_{23}NO_8Na$ 452.1321, obsd 452.1324.

(3*R*,4*R*)-6,7-Methylenedioxy-2-(*N*-oxazolidinonyl)carbonyl-3-triisopropylsilyloxymethyl-4-(2′-trimethylsilylethoxy)methoxy-3,4-dihydronaphthalene (50). To a solution of starting acid **42** (9.28 g, 16.9 mmol) in THF (45 mL) at room temperature was added CDI (3.01 g, 18.5 mmol), whereupon gas evolution was immediately observed. After 3 h at room temperature, the reaction mixture was partitioned between Et_2O and H_2O. The combined organics were dried and evaporated to provide the crude acyl imidazolide, which was taken forward without further purification. To a deoxygenated solution of 2-oxazolidinone (1.91 g, 21.9 mmol) in THF (100 mL) at −78 °C was added *n*-BuLi (17.7 mL of a 1.24 M solution in hexanes, 17.7 mmol). The resulting reaction mixture was allowed to stir for 1 h at −78 °C. Then a solution of acyl imidazolide (10.1 g, 16.9 mmol) in THF (80 mL) was added, dropwise, via cannula at −78 °C. After 4.5 h at −78 °C, the reaction mixture was diluted with Et_2O and then extracted with H_2O. The organic layer was dried ($MgSO_4$), filtered, concentrated, and chromatographed (hexanes/EtOAc/NEt_3 67:33:0.5) to yield **50** (6.66 g, 64%): mp 110−112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.01 (s, 9 H), 0.93−1.03 (m, 23 H), 3.22 (app t, J = 10 Hz, 1 H), 3.44 (ddd, J = 2, 6, 7 Hz, 1 H), 3.52 (app dt, J = 6, 10 Hz, 1 H), 3.61 (app dt, J = 6, 11 Hz, 1 H), 3.71 (app dd, J = 6, 10 Hz, 1 H), 3.95 (ddd, J = 6, 8, 10 Hz, 1 H), 4.09−4.15 (m, 1 H), 4.37−4.44 (m, 2 H), 4.60 (d, J = 7 Hz, 1 H), 4.68 (d, J = 7 Hz, 1 H), 4.94 (d, J = 2 Hz, 1H), 5.96 (d, J = 2 Hz, 1 H), 5.98 (d, J = 1 Hz, 1 H), 6.74 (s, 1 H), 6.86 (s, 1 H), 7.12 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.78, 12.5, 18.6, 18.7, 43.7, 44.7, 62.4, 62.8, 65.6, 71.7, 92.3, 102.2, 109.9, 112.0, 126.2, 127.1, 128.7, 138.0, 148.6, 149.4, 154.2, 170.2; IR (ATR) 1781, 1663 cm^{-1}; $[\alpha]^{24}_D$ = +69.9° (*c* 3.0, $CHCl_3$). Anal. Calcd for $C_{31}H_{49}NO_8Si_2$: C, 60.06; H, 7.97; N, 2.26. Found: C, 60.19; H, 7.70; N, 2.32.

(1*R*,2*S*,3*R*,4*R*)-6,7-Methylenedioxy-2-(*N*-oxazolidinonyl)-carbonyl-1-phenyl-3-triisopropylsilyloxymethyl-4-(2′-trimethylsilylethoxy)methoxy-1,2,3,4-tetrahydronaphthalene (51). To a suspension of CuCN (1.62 g, 18.1 mmol) in THF (17 mL) and Me_2S (17 mL) at −78 °C was added PhMgBr (21.5 mL of a 1.0 M solution in Et_2O). The resulting mixture was allowed to stir for 1.5 h at −78 °C, whereupon a solution of **50** (1.40 g, 2.26 mmol) in THF (12.5 mL) was added via cannula. After 3 h at −40 °C, aqueous NH_4Cl was added, followed by Et_2O. After further extraction of the aqueous layer with Et_2O, the combined organics were dried (M_8SO_4), filtered, and evaporated. Chromatography (25% EtOAc/hexanes) yielded **51** (1.23 g, 78%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.04 (s, 9 H), 0.96−1.06 (m, 23 H), 2.70−2.75 (m, 1H), 3.49 (dd, J = 9, 10 Hz, 1 H), 3.60−3.67 (m, 1 H), 3.75 (dd, J = 5, 11 Hz, 1 H), 3.81−3.91 (m, 3 H), 4.19−4.31 (m, 2 H), 4.44 (d, J = 11 Hz, 1 H), 4.80−4.86 (m, 2 H), 4.87 (d, J = 3 Hz, 1 H), 4.93 (d, J = 7 Hz, 1 H), 5.81 (d, J = 1 Hz, 1 H), 5.86 (d, J = 1 Hz, 1 H), 6.22 (s, 1 H), 6.73 (s, 1 H), 7.21−7.23 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.7, 12.6, 18.6, 18.8, 42.4, 43.4, 44.0, 45.6, 61.5, 62.4, 65.7, 73.0, 93.1, 101.5, 110.0, 110.6, 127.1, 127.8, 129.0, 130.2, 133.6, 145.7, 146.7, 148.3, 153.2, 174.4; IR (ATR) 1784, 1695 cm^{-1}; $[\alpha]^{24}_D$ = −106.9° (*c* 3.6, $CHCl_3$). Anal. Calcd for $C_{37}H_{55}NO_8Si_2$: C, 63.67; H, 7.94; N, 2.01. Found: C, 63.72; H, 7.78; N, 1.86.

(1*R*,2*S*,3*R*,4*R*)-6,7-Methylenedioxy-2-(*N*-oxazolidinonyl)-carbonyl-3-triisopropylsilyloxymethyl-1-(3′,4′,5′-trimethoxy)phenyl-4-(2″-trimethylsilylethoxy)methoxy-1,2,3,4-tetrahydronaphthalene (52). To a suspension of CuCN (0.52 g, 5.81 mmol) in THF (10 mL) at 10 °C was added (3,4,5-trimethoxy)phenylmagnesium bromide[37] (19.3 mL of a 0.3 M solution in THF). The resulting mixture was allowed to stir for 1 h at 10 °C, whereupon a solution of **50** (0.45 g, 0.73 mmol) in THF (10 mL) was added via cannula. After 2.5 h at 10 °C, the reaction was worked up as for **51**. Chromatography (10−30% EtOAc/hexanes) yielded **52** (0.49 g, 85%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 9 H), 0.97−1.01 (m, 5 H), 0.98 (d, J = 4 Hz, 18 H), 2.63−2.67 (m, 1 H), 3.50 (dd, J = 9, 10 Hz, 1 H), 3.62 (dt, J = 7,10 Hz, 1H), 3.76 (s, 6 H), 3.80 (s, 3 H), 4.28−4.32 (m, 3 H), 4.81 (d, J = 7 Hz, 1 H), 4.87−4.90 (m, 3 H), 5.85 (d, J = 1 Hz, 1 H), 5.88 (d, J = 1 Hz, 1 H), 6.32 (s, 1 H), 6.44 (s, 2 H), 6.75 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.4, 12.0, 17.9, 18.1, 41.8, 42.8, 44.0, 44.4, 56.1, 60.8, 61.7, 65.1, 72.7, 92.6, 100.9, 106.5, 109.1, 110.0, 127.3, 132.4, 136.5, 140.2,

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146.2, 147.6, 152.6, 153.0, 173.8; IR (ATR) 1783, 1693 cm^{-1}; $[\alpha]^{24}_D = -98.1°$ (*c* 1.02, $CHCl_3$). Anal. Calcd for $C_{40}H_{61}NO_{11}Si_2$: C, 60.96; H, 7.80; N, 1.78. Found: C, 60.55; H, 7.59; N, 1.52.

(1*R*,2*S*,3*R*,4*R*)-4-*O*-(2-Trimethylsilylethoxy)methylpicropodophyllin (53). To a solution of **52** (285 mg, 362 μmol) in THF (5 mL) at room temperature was added TBAF (0.92 mL of a 1.0 M solution in THF). The resulting reaction mixture was heated at 40−50 °C for 5 h. After cooling to room temperature, the volatiles were evaporated in vacuo. The residue was taken up in dry PhH−$CHCl_3$ (1:1; 10 mL) and concentrated to azeotropically remove H_2O and promote the lactonization of any γ-hydroxy acid present. This procedure was repeated twice. Then the crude product was partitioned between CH_2Cl_2 and aqueous NH_4Cl. After further extraction of the aqueous layer with CH_2Cl_2, the crude product was subjected to SiO_2 chromatography (10−30% EtOAc/hexanes) to provide **53** (123 mg, 62%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 9 H), 0.90−1.01 (m, 2 H), 2.91−2.96 (m, 1 H), 3.24 (dd, *J* = 5, 10 Hz, 1 H), 3.60 (dt, *J* = 7,10 Hz 1 H), 3.71−3.76 (m, 1 H), 3.79 (s, 6H), 3.82 (s, 3H), 4.14 (d, *J* = 5 Hz, 1 H), 4.32 (dd, *J* = 4, 10 Hz, 1 H), 4.41 (dd, *J* = 7, 10 Hz, 1 H), 4.51 (d, *J* = 7 Hz, 1 H), 4.76 (d, *J* = 7 Hz, 1 H), 4.79 (d, *J* = 7 Hz, 1 H), 5.91 (d, *J* = 1 Hz, 1 H), 5.92 (d, *J* = 1 Hz, 1 H), 6.40 (s, 1 H), 6.44 (s, 2 H), 6.85 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.5, 18.1, 40.9, 44.7, 45.2, 56.1, 60.8, 65.9, 70.1, 74.9, 94.1, 101.2, 105.7, 107.1, 109.5, 129.0, 131.2, 136.9, 139.0, 146.8, 147.6, 153.3, 178.0; IR (ATR) 1773 cm^{-1}; $[\alpha]^{24}_D = +61.3°$ (*c* 0.75, $CHCl_3$). Anal. Calcd for $C_{28}H_{36}O_9Si$: C, 61.74; H, 6.66. Found: C, 61.53; H, 6.91.

(1*R*,2*R*,3*R*,4*R*)-4-*O*-(2′-Trimethylsilylethoxy)methylpodophyllotoxin (54). A solution of LDA (4.15 mL of a 0.27 M solution in THF, 1.1 mmol) was prepared at 0 °C and then cooled to −78 °C. A solution of **53** (200 mg, 0.37 mmol) in THF (5 mL) was then added dropwise via cannula at −78 °C. After this solution stirred for 90 min at −78 °C, a suspension of freshly prepared pyridinium hydrochloride (297 mg, 2.57 mmol) in THF (3 × 2 mL) was added. The transfer was effected in three portions owing to the limited solubility of the salt in THF. After allowing the reaction mixture to come to room temperature, it was poured into saturated NH_4Cl (aqueous, 10 mL) and $CHCl_3$ (20 mL). Following a second extraction with $CHCl_3$, the organics were dried ($MgSO_4$), filtered, concentrated, and chromatographed (10−30% EtOAc/hexanes) to give **54** (93 mg, 47%), in a first fraction, followed by diastereomeric lactone **53** (91 mg, 46%). For **54**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 9 H), 0.91−0.97 (m, 2 H), 2.81 (dd, *J* = 5, 14 Hz, 1 H), 2.86−2.95 (m, 1H), 3.68 (dt, *J* = 1, 8 Hz, 2 H), 3.73 (s, 6 H), 3.79 (s, 3 H), 4.11 (appt, *J* = 9 Hz, 1 H), 4.56 (d, *J* = 5 Hz, 1 H), 4.60 (dd, *J* = 7, 9 Hz, 1 H), 4.68 (d, *J* = 9 Hz, 1 H), 4.83 (d, *J* = 8 Hz, 1 H), 4.89 (d, *J* = 8 Hz, 1 H), 5.94 (s, 1 H), 5.95 (s, 1 H), 6.37 (s, 2 H), 6.49 (s, 1 H), 6.98 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.5, 18.1, 38.9, 43.9, 45.6, 56.1, 60.7, 66.1, 71.9, 79.4, 94.9, 101.4, 107.1, 108.0, 109.6, 131.1, 131.7, 135.3, 136.9, 147.5, 147.7, 152.5, 174.2; IR (ATR) 1779 cm^{-1}; $[\alpha]^{24}_D = -95.7°$ (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{28}H_{36}O_9Si$: C, 61.74; H, 6.66. Found: C, 61.43; H, 6.59. HRMS (FAB, 3-NBA) calcd for $C_{28}H_{36}O_9Si$ 544.2128 [M^+], obsd 544.2148.

(−)-Picropodophyllin (55). *cis*-Lactone **53** (75 mg, 0.14 mmol) was taken up in Et_2O (4 mL) and PhH (1 mL). $MgBr_2\cdot Et_2O$ complex (64 mg, 0.25 mmol) was added under Ar atmosphere in a glovebag. To the resulting solution at 0 °C was added EtSH (31 μL, 0.41 mmol) dropwise, via syringe. After 2 h at 0 °C and 6 h at room temperature, additional $MgBr_2\cdot Et_2O$ (32 mg, 0.13 mmol) and EtSH (15 μL, 0.2 mmol) were added, as before. After 3 h (0 °C → room temperature), the reaction was quenched by the addition of aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (25−50% EtOAc/hexanes) gave **56** (4 mg, 8%) in a first fraction and **55** (30 mg, 65%) in a second fraction. For **55**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (bs, 1 H), 2.68−2.73 (m, 1 H), 3.21 (dd, *J* = 5, 9 Hz, 1 H), 3.80 (s, 6 H), 3.84 (s, 3 H), 4.07 (d, *J* = 5 Hz, 1 H), 4.40 (dd, *J* = 6, 10 Hz, 1 H), 4.46 (d, *J* = 9 Hz, 1 H), 4.50 (dd, *J* = 2, 10 Hz, 1 H), 5.90 (d, *J* = 1 Hz, 1 H), 5.92 (d, *J* = 1 Hz, 1 H), 6.34 (s, 1 H), 6.44 (s, 2 H), 7.03 (s, 1 H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 42.6, 44.0, 45.4, 56.2, 60.9, 69.3, 69.8, 101.2, 105.4, 105.8, 109.1, 130.6, 132.2, 137.1, 139.3, 147.0, 147.3, 153.6, 177.9; IR (ATR) 3472, 1769 cm^{-1}; $[\alpha]^{24}_D = -10.0°$ (*c* 0.3, $CHCl_3$); HRMS (FAB, 3-NBA) calcd for $C_{22}H_{22}O_8$ 414.1315 [M^+], obsd 414.1324. For **56**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (t, *J* = 8 Hz, 3 H), 2.61 (br q, *J* = 2, 8 Hz, 2 H), 2.89−2.98 (m, 1 H), 3.11 (dd, *J* = 4, 8 Hz, 1 H), 3.73 (d, *J* = 8 Hz, 1 H), 3.79 (s, 6 H), 3.83 (s, 3 H), 4.25 (d, *J* = 4 Hz, 1 H), 4.37−4.40 (m, 2H), 5.91 (d, *J* = 1 Hz, 1 H), 5.93 (d, *J* = 1 Hz, 1 H), 6.40 (s, 2 H), 6.41 (s, 1 H), 7.18 (s, 1 H); IR (ATR) 1770 cm^{-1}; $[\alpha]^{24}_D = 139.2°$ (*c* 0.05, $CHCl_3$); HRMS (FAB, 3-NBA) calcd for $C_{24}H_{26}O_7S$ 458.1399 [M^+], obsd 458.1399.

(−)-Podophyllotoxin (1). *trans*-Lactone **54** (71 mg, 0.13 mmol) was taken up in Et_2O (4 mL) and PhH (1 mL). $MgBr_2\cdot Et_2O$ complex (61 mg 0.24 mmol) was added under Ar. To the resulting solution at 0 °C was added EtSH (29 μL, 0.39 mmol) dropwise, via syringe. After 2 h at 0 °C and 6 h at room temperature, additional $MgBr_2\cdot Et_2O$ (30 mg, 0.12 mmol) and EtSH (15 μL, 0.2 mmol) were added, as before. After 3 h, the reaction was quenched by the addition of aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (25−50% EtOAc/hexanes) gave **1** (44 mg, 81%), identical in all respects to an authentic sample of the natural product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (bs, 1 H), 2.72−2.80 (m, 1 H), 2.83 (dd, *J* = 4, 14 Hz, 1 H), 3.75 (s, 6 H), 3.80 (s, 3 H), 4.08 (appt, *J* = 10 Hz, 1 H), 4.58−4.61 (m, 2 H), 4.76 (d, *J* = 10 Hz, 1 H), 5.96 (d, *J* = 1 Hz, 1 H), 5.98 (d, *J* = 1 Hz, 1 H), 6.36 (s, 2 H), 6.50 (s, 1 H), 7.10 (s, 1 H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 40.8, 44.1, 45.3, 56.3, 60.7, 71.3, 72.8, 101.4, 106.3, 108.5, 109.8, 131.2, 133.2, 135.4, 137.4, 147.7, 147.8, 152.6, 174.4; IR (ATR) 3710, 1770 cm^{-1}; $[\alpha]^{24}_D = -101.7°$ (*c* 0.55, EtOH) {lit. $[\alpha]^{24}_D = -102.1°$ (*c* 0.529, EtOH)[13b] and $[\alpha]^{22}_D = -104$ (*c* 0.36, EtOH)[13a]}; HRMS (FAB, 3-NBA) calcd for $C_{22}H_{22}O_8$ 414.1315 [M^+], obsd 414.1299.

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Supporting Information Available: Copies of the ^{1}H NMR spectra for compounds **13**−**22**; **25**; **26a,b**; **27a,b**; **28**−**30**; **31c**; **32a,c**; **33**; **35**−**44**; **46**−**56**; **57a,b**; and **58**, as well as comparison spectra of synthetic and authentic (−)-podophyllotoxin (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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