

Catalytic enantioselective synthesis of macrolides via asymmetric alkylation

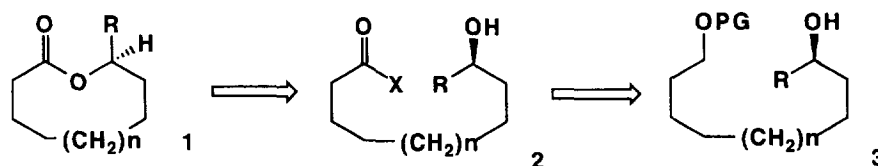
Graham B. Jones,* Robert S. Huber and Brant J. Chapman

Department of Chemistry and Laboratory of Medicinal Chemistry, Clemson University, Clemson, SC 29634-1905, USA

Abstract: Catalytic enantioselective syntheses of the macrolides (*R*)-(–) phoracantholide and (*R*)-(+)-lasiodiplodin have been achieved. Stereochemistry was introduced in using an arene chromium tricarbonyl derived catalyst, which mediated the enantioselective addition of dimethyl zinc to a functionalized aldehyde. © 1997 Elsevier Science Ltd

Introduction

The pursuit of natural products synthesis has remained a fertile area for the development of a number of important general synthetic methods. A classic example was seen in the 1980s with emergence of new methods for macrolactonisation, driven by total syntheses of complex target molecules including the erythronolide and tylosin families.¹ General conditions have been prescribed for these ring closures, rendering the disconnection of lactones **1** to activated hydroxyacids **2** a routine transform, for $n=2-8$ (Scheme 1).²



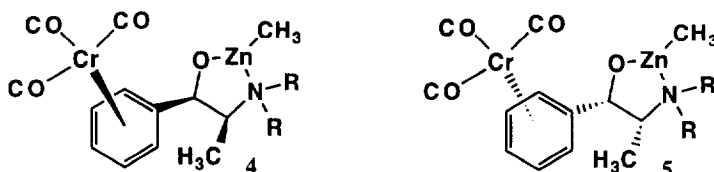
Scheme 1. Linear diol analysis to macrolactone synthesis.

There has been a recent surge in interest in the *asymmetric* synthesis of macrolactones, driven in part by the rapid growth in new asymmetric methodologies.³ For simple macrolactones, an attractive strategy is to synthesize diols **3**, bearing both the desired asymmetric center and a masked carboxyl function (OPG) which can be converted to the carboxyl derivative as required (Scheme 1). Based on our prior work on the development of novel catalyst systems,⁴ we wished to demonstrate a catalytic enantioselective route to diols **3**, hence lactones **1**, based on aldehyde *alkylation strategy*.

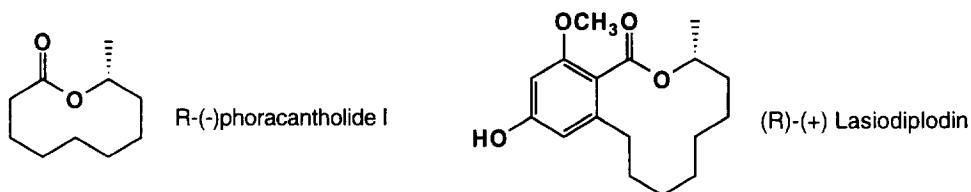
Results and discussion

Though a vast number of catalytic alkylation catalysts have been reported in the last few years, little attention has been devoted to incorporation of such methodology in total synthesis. From our own observations, many catalysts which function effectively for the enantioselective alkylation of popular test substrates, including benzaldehydes, or unsubstituted aliphatic aldehydes, often perform poorly when used with functionalized substrates, precluding their use in synthesis. In 1992 we reported two new catalysts derived from the norephedrine *viz*: **4** and **5**.⁴ These catalysts are capable of mediating asymmetric alkylation of aldehydes with very high enantioselectivity (up to 99% e.e.) using various dialkyl zincs, and a mechanistic argument has been advanced to explain the origin of their selectivity.⁵ Routinely, catalysts **4** give rise to *R* product alcohols and catalysts **5** the *S* alcohols.

* Corresponding author. Email: graham@clemson.edu

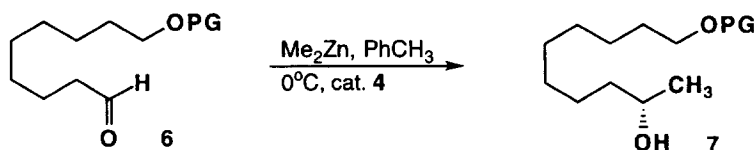


Both catalysts perform well on a multigram scale, and, following reaction, a single crystallization of the product alcohol often results in enantiomeric enrichment, providing a versatile catalytic route to multigram quantities of optically pure secondary alcohols. Based on the above considerations, we elected to demonstrate synthesis of representative [C10–12] macrolactones using our catalytic approach, and identified two potential targets—phoracantholide and lasiodiplodin, neither of which has yet succumbed to *catalytic* asymmetric synthesis.



Phoracantholide I

Phoracantholide I, a defensive secretion of the longicorn *Pholacantha synonyma*, and has been the focus of a number of synthetic approaches, and represented an ideal model target to test our methods.⁶ Successful synthesis would involve preparation of a suitable *R* 1,9-diol **7** via enantioselective alkylation of **6** using catalysts **4** (Scheme 2).



Scheme 2.

For substrate compatibility, we surveyed three commonly available protecting groups, and a variety of different catalytic conditions (Table 1). Optimum conditions were found using 5 mol% of the *N,N* dibutyl catalyst **4** (*R*=Bu), and the trityloxy protecting group (entry 3). As is typically the case,^{4,5} far inferior enantioselectivities were observed using catalyst devoid of the arene chromium tricarbonyl group (entry 5). These results illustrate the stereodirective benefit the metal carbonyl group imparts for alkylation control, and the effect of subtle changes both in catalyst and substrate architecture. Marginal improvements were possible by increasing the amount of catalyst (entry 4), and also when conducting the reactions on sub-millimolar scale, in which case e.e.s close to 95% are possible. However, for practical purposes, we opted to employ 5 mol% catalyst, which gave reproducible results on a multigram scale.

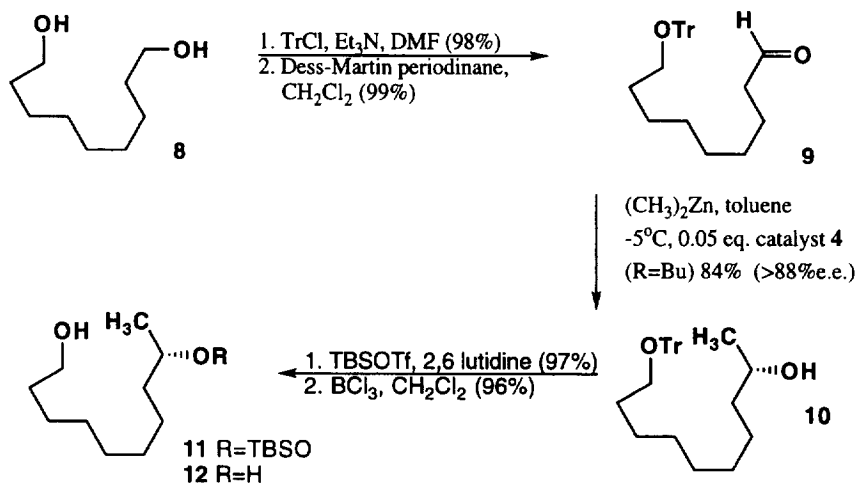
Our eventual synthesis of *R*-(–) phoracantholide I is outlined in Scheme 3, commencing with the commercially available 1,9 nonanediol **8**. Following monoprotection, oxidation of the residual alcohol to the corresponding aldehyde **9** was best achieved using the Dess–Martin reagent,⁷ then allowing enantioselective methylation using the optimized conditions (Table 1) to give **10**. Hydroxy protection was then followed by selective (trityloxy) deprotection. Conventional deprotection protocol using either formic acid in ether^{8a} or diethyl aluminum chloride in methylene chloride^{8b} proved unsatisfactory, giving mixtures of deprotected alcohols **10**, **11**, and **12**. This problem was finally overcome by using

Table 1. Enantioselective methylation of aldehydes **6** using 1*R*,2*S* norephedrine derived catalysts **4**[#]

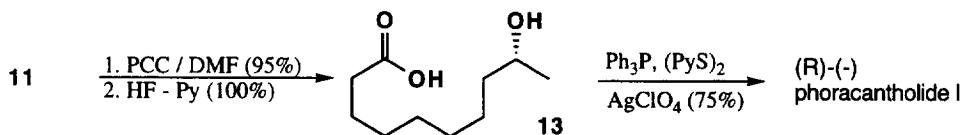
Entry	catalyst	mol %	PG	%yield 7 [^]	%e.e. 7
1	4 R=Bu	5	Bn	89	70
2	4 R=Bu	5	TBDPS	82	84
3	4 R=Bu	5	Tr	84	88
4	4 R=Bu	20	Tr	88	91
5	4 R=Bu (uncomplexed)*	20	Tr	67	59
6	4 R=Me	5	Tr	91	79
7	4 R=-(CH ₂) ₅ -	5	Tr	86	84

* 1*R*, 2*S* *N,N* dibutyl norephedrine. [^] Yields refer to isolated products. [#] All reactions conducted in toluene at 0°C

boron trichloride, selective deprotection ensuing in 30 min at -10°C, to give desired carboxylate precursor **11** in excellent yield.⁹

**Scheme 3.**

The exposed primary alcohol **11** was transformed to the corresponding carboxylic acid using PCC in DMF, thence the chiral secondary alcohol deprotected to allow macrolactonisation of the resulting hydroxyacid **13**, best achieved using the pyridyl-thioester protocol (Scheme 4).¹⁰ Synthetic phoracantholide I was spectroscopically identical with reported data, and the optical rotation confirmed that racemization had not taken place during the closing stages of synthesis.¹¹

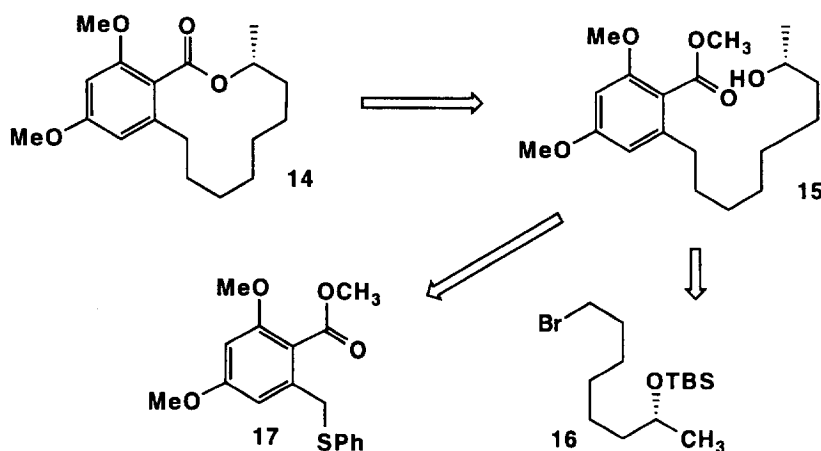
**Scheme 4.**

A variety of structurally related C-10 macrolides of this class have been identified, many of which show interesting biological activity,¹² suggesting this general approach may prove useful for structure-activity studies within sub-families.

Lasiodiplodin

(*R*)-(+)-Lasiodiplodin, a major metabolite of *Lasiodiplodia theobromae*, has been the subject of several synthetic investigations due to earlier reports of its purported ability to function as a plant growth inhibitor.¹³ Subsequent studies revealed however that another metabolite, jasmonic acid was responsible for the inhibitory activity.¹⁴ Besides from racemic syntheses,¹³ only two enantioselective routes have been reported, one requiring a chiral pool precursor,^{15a} and the other requiring the stoichiometric use of an asymmetric controller group, and subsequent purification of a diastereomeric mixture.^{15b}

Conventional analysis of lasiodiplodin or its dimethyl ether **14** invites macrolactonization of **15**, which we reasoned could be, in turn, assembled by coupling a stabilized lithio anion derived from **17** with C₈ chiral carbinol **16** (Scheme 5). Several possible enantioselective routes to fragment **16** could be envisaged. However, as was subsequently revealed, separation of the enantiomeric alcohols corresponding to the protected diol **18** using our preferred analytical method [chiral HPLC, Daicel OD column] proved unacceptable, precluding rapid optimization of the alkylation step. The *tert*-butyldiphenylsilyl ether **19** however gave baseline separation, and was thus employed.

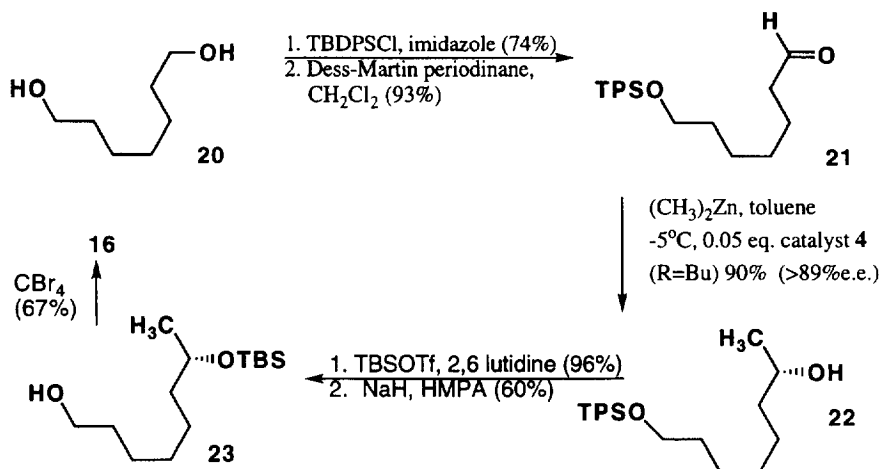


Scheme 5. Retrosynthetic analysis of (*R*)-(+)-lasiodiplodin.

Accordingly, aldehyde **21** was prepared from 1,7 heptanediol **20** without incident, and was subjected to enantioselective methylation using dimethyl zinc in the presence of catalyst **4** (R=Bu), 5 mol% (Scheme 6). The methylation proceeded in high yield giving (*R*) alcohol **22** in excellent yield and 89% e.e., suggesting that the increase in substrate chain length results in a decrease of unfavorable substrate–catalyst interactions (c.f. entry 2, Table 1). The *sec*-alcohol was protected, then the primary alcohol selectively deprotected using the procedure of Shekhani to give C-8 alcohol **23**.¹⁶ Mild bromination then completed the formation of the desired chiral side chain **16** (Scheme 6).

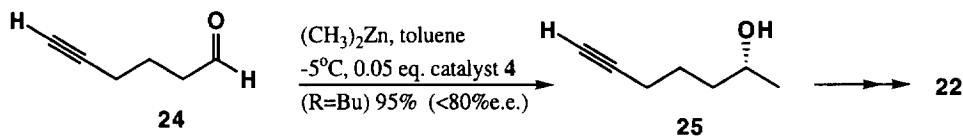


In an effort to improve the enantioselectivity of the alkylation process yet further, an additional route to **22** was also investigated. Under the notion that the remote silyloxy group of the substrate (**21**) may potentially associate with the metal carbonyl group of the catalyst, we investigated alkylation of aldehyde **24**, readily available from 5-hexyn-1-ol (Scheme 7). The resulting C-7 synthon **25** could



Scheme 6.

potentially be converted to **22** via alkynyl hydroxymethylation, followed by concomitant acetylene reduction.



Scheme 7.

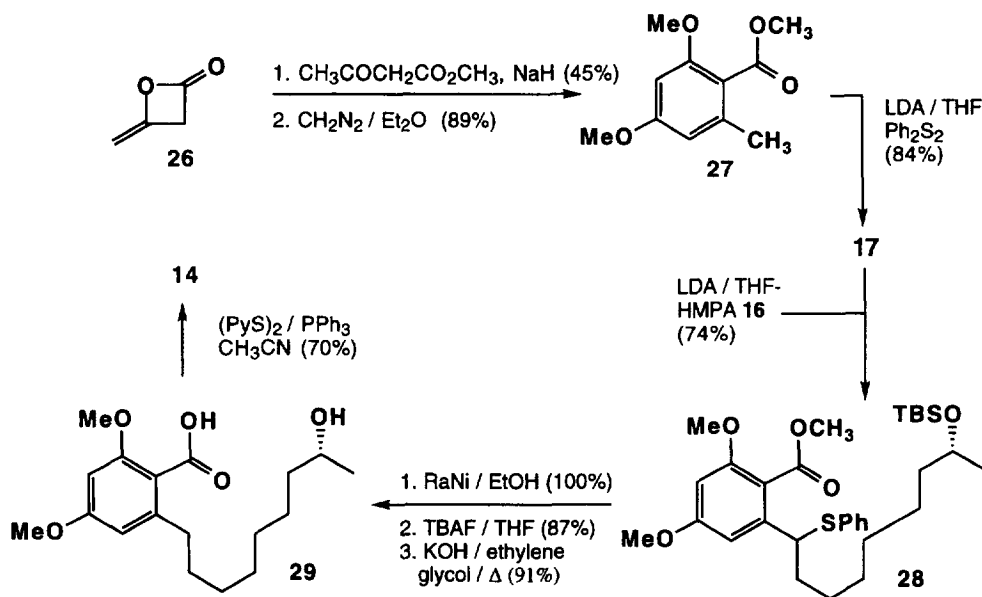
In any event, though the chemical yield of **25** was surprisingly high for this unmasked alkynyl substrate, the maximum level of enantioexcess attainable for alkylation was far below that for substrate **21**, hence the route outlined in Scheme 6 was adopted for large scale synthesis.

The known arene **17** was synthesized using a modification of the excellent procedure popularized by Tsuji, involving diketene **26** and methylacetoacetate which produces a bis phenol,¹⁷ which was then subjected to one pot dimethylation to give **27**, and followed by attachment of the phenylsulfide group using LDA/diphenylsulfide (Scheme 8). Deprotonation of **17**, followed by slow addition of bromoalkane **16** gave a 74% yield of the coupled alkane **28** which was subjected to desulfurization (Ra-Ni), silyl deprotection, then saponification to give advanced precursor **29** (Scheme 8). Lactonization using conventional conditions gave (*R*)-(+)-lasiodiplodin methyl ether **14**,¹⁸ spectroscopically identical with reported data,¹⁵ and which can be transformed into the natural product using ethylthiolate.^{15a}

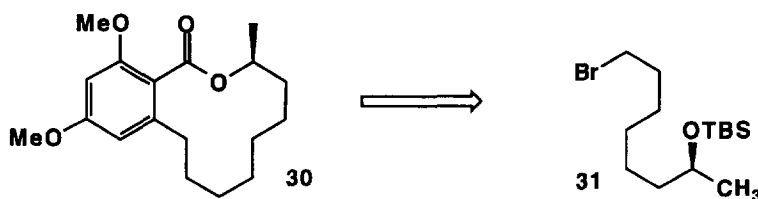
A catalytic enantioselective route to the antipode **30** could also be envisioned (Scheme 9). To demonstrate this possibility, the desired synthon **31** was prepared in an analogous manner to **16** using the route outlined in Scheme 6, instead employing the 1*R*,2*S* derived catalyst **5** (R=Bu). The alkylation proceeded in similarly high e.e., and the product carbinol was transformed into **16** without incident.

Conclusion

The catalytic enantioselective synthesis of two macrolides has been achieved. Stereochemistry was introduced using an asymmetric Lewis acid catalyst designed to mediate stereoselective alkylation of functionalized aldehydes. Since either enantiomeric form of alcohol can be obtained by appropriate choice of catalyst and the method is amenable to a multigram scale, it compares favorably with alternative approaches.¹⁵ Application of this methodology in the enantioselective synthesis of related C-10 and C-12 macrolides thus appears an attractive possibility.



Scheme 8.



Scheme 9. Retrosynthetic analysis of methyl (S)-(-) lasiodiplodin.

Experimental methods

General information

^1H (300 MHz) and ^{13}C NMR (75 MHz) were obtained using a Bruker Model AC300. Elemental analyses were carried out by Atlantic Microlab, Inc., Atlanta, GA. Optical rotations were obtained using a Horiba Model SEPA-200 Polarimeter. Enantiomeric excesses were determined using an ISCO model 2350 HPLC pump, V⁴ Absorbance detector, and a Hewlett Packard Series II Integrator; Racemic mixtures of the compounds studied were prepared by conventional methods in every case studied. Ether and THF were distilled from sodium-benzophenone ketyl. Hexane, benzene, and toluene were dried over sodium wire and distilled from calcium hydride. Dichloromethane was distilled from phosphorus pentoxide before use. DMF was dried by stirring with barium oxide for 12 h at room temperature, followed by distillation from alumina at reduced pressure. All handling of air and moisture sensitive reagents was conducted under an atmosphere of dry nitrogen using needles and cannula dried in an oven at 120°C for at least 12 h and the tips flame dried immediately prior to use. Syringes were either dried in an oven at 120°C for 12 h and allowed to cool under a stream of dry nitrogen, or dried in an evacuated drying pistol for 12 h and used immediately upon removal. Gas leakage through the septa was minimized by wrapping of Teflon tape at the septum-glass boundary and by the application of a light coating of stopcock grease to the septa at the point of cannula penetration. Unless otherwise stated, all reagents were purchased from the Aldrich Chemical Company and used as supplied. Arene

chromium carbonyl species (**4**, **5**) were prepared⁵ and manipulated using appropriate caution to prevent decomposition.¹⁹

9-Hydroxynonyl-1-triphenylmethylether

To a stirred solution of 1,9-nonanediol (15.0 g, 93.6 mmol), triphenylmethyl chloride (26.2 g, 94 mmol), and dimethylaminopyridine (1.22 g, 10 mmol) in DMF (150 mL) at 0°C was added triethylamine (27.9 mL, 200 mmol) *via* syringe. The resulting solution was allowed to warm to 25°C over 12 hours. The solution was poured into water, and extracted with ethyl acetate. The organic phase was washed with 1% HCl, water and brine. Silica gel chromatography (7:3 hexanes:EtAOc) yielded the title compound (16.2 g, 43%) [98% based on recovered diol] as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.7–7.2 (m, 15 H), 3.7 (br, 2H), 3.04 (t, J=6.6 Hz, 2H), 1.8–0.8 (m, 14H); IR (neat, cm⁻¹) 3346 (br), 3085, 3057, 3022, 2924, 2853, 1489, 1440, 1222, 1068, 1032; MS 402 (M⁺); C₂₈H₃₄O₂: calcd C, 83.54, H, 8.51; found: C, 83.62, H 8.59.

9-Trityloxynonanal **9**

To a solution of Dess–Martin periodinane (16.2 g, 38.3 mmol) in CH₂Cl₂ (100 mL) was added 9-hydroxynonyl-1-triphenylmethylether (14.0 g, 34.8 mmol) in CH₂Cl₂ (30 mL) *via* syringe. The resulting solution was stirred at 25°C for 6 hours. The solution was poured into 200 mL of a 1:1 saturated solution of NaHCO₃/NaHSO₃. The mixture was diluted with ether (200 mL), and the ethereal solution was washed with saturated NaHCO₃ (50 mL), brine (50 mL), and filtered through silica. The solvent was removed *in vacuo* to yield **9** as a pale yellow oil (13.8 g, 99% yield). ¹H NMR δ 9.75 (t, J=1.8 Hz, 1H), 7.46–7.19 (m, 15H), 3.03 (t, J=6.6 Hz, 2H), 2.40 (t, J=1.8 Hz, 2H) 1.7–0.85 (m, 12H); ¹³C NMR δ 203.0, 144.5, 128.7, 127.7, 126.8, 86.3, 63.6, 43.9, 31.6, 30.0, 29.3, 29.1, 26.2, 22.1; IR (neat, cm⁻¹) 1721; C₂₈H₃₂O₂: calcd C, 83.96, H, 8.05; found: C, 83.77, H 8.16.

1-Trityloxy-(R)-decan-9-ol **10**

To a solution of tricarbonyl chromium(0) (1*R*,2*S*) *N,N*-dibutylnorephedrine⁴ (0.23 g, 0.56 mmol) in toluene (10 mL) at 0°C was added Me₂Zn (2 M in toluene, 25 mL, 50 mmol) dropwise, followed by aldehyde **9** (4.5 g, 11.3 mmol) in toluene (15 mL). The resulting solution was stirred at 4°C for 6 days. The solution was poured over ice and extracted with ether (3×125 mL). The ethereal solution was washed with 1% HCl (3×50 mL), saturated NaHCO₃ (50 mL), and water (2×50 mL). Column chromatography (95:5 to 85:15 hexanes:EtOAc) yielded **10** (3.94 g, 84%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.5–7.2 (m, 15H), 3.83 (br. s, 1H), 3.65 (br. m, 1H), 3.13 (t, J=6.5 Hz, 2H), 1.8–0.97 (m, 17H); ¹³C NMR (75 MHz, CDCl₃) δ 144.4, 128.6, 127.6, 126.7, 86.2, 67.9, 63.6, 39.2, 30.0, 29.5, 29.5, 29.4, 26.2, 25.7, 23.4; IR (neat) 3388 (br), 3050, 2924, 2848, 1489, 1440, 1363, 1243, 1068 cm⁻¹; MS (m/e) 412 (M⁺); HPLC: Daicel OD column; 99:1 hexane:isopropyl alcohol eluent; flow rate 1.0 mL/min; R=18.20 mins, S=18.96 mins; [α]_D=+19.0 (c=0.5, CHCl₃); C₂₉H₃₆O₂: calcd C, 83.61, H, 8.71; found: C, 83.82, H 8.69.

1-Trityloxy-9-*t*-butyldimethylsilyloxydecanediol

To a solution of **10** (3.75 g, 9.01 mmol) in CH₂Cl₂ (15 mL) at –10°C was added *via* syringe TBDMS-OTf (2.07 mL, 9.01 mmol) followed by 2,6-lutidine (2.6 mL, 22.5 mmol). The resulting solution was stirred at –10°C for 20 minutes. The solution was poured over ice, and extracted with CH₂Cl₂ (3×50 mL). The organic phase was washed with 1% HCl (2×50 mL), water (50 mL), and brine (50 mL). Solvent evaporation afforded the title compound as a colorless oil (4.64 g, 97%). ¹H NMR (300 MHz, CDCl₃) δ 7.5–7.2 (m, 15H), 3.79 (m, 1H), 3.07 (t, 2H, J=6.6 Hz), 1.7–1.2 (m, 14H), 1.15 (d, 3H, J=6 Hz), 0.93 (s, 9H), 0.13 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 144.5, 128.7, 127.7, 126.8, 86.3, 68.7, 63.7, 39.8, 30.1, 29.7, 29.6, 29.5, 26.3, 26.1, 25.9, 23.9, 18.3, –4.3; IR (neat, cm⁻¹) 3057, 2924, 2860, 1447, 1370, 1250, 1068; [α]_D=+18.94 (c=0.22 CHCl₃); C₃₅H₅₀O₂Si: calcd C, 79.19, H, 9.49; found: C, 79.34, H 9.71.

(R)-9-tert-Butyldimethylsilyloxy-1-decanol 11

To a solution of 1-trityloxy-9-*t*-butyldimethylsilyloxydecane-1,9-diol (4.5 g, 8.49 mmol) in CH₂Cl₂ (850 mL) at -10°C was added BCl₃ (1 M in CH₂Cl₂, 8.5 mL, 8.5 mmol) dropwise *via* syringe. After 20 minutes at -10°C, the solution was poured over icy saturated NaHCO₃ (100 mL), and extracted with CH₂Cl₂ (2×50 mL). The organic phase was washed with water (2×75 mL) and filtered through a small plug of silica gel. Solvent evaporation afforded **11** as a colorless oil (2.35 g, 96%). ¹H NMR (300 MHz, CDCl₃) δ 3.75 (m, 1H), 3.62 (t, J=6.6 Hz, 2H), 1.6–1.2 (m, 14H), 1.10 (d, J=6 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 68.7, 63.0, 39.7, 32.8, 29.6, 29.6, 29.4, 26.0, 25.8, 25.7, 23.8, 18.2, -4.4; IR (neat) 3339 (br), 2938, 2853, 1461, 1384, 1250, 1138, 1046 cm⁻¹; MS (m/e) 287 (M⁺); [α]_D²⁰=+1.26 (c=0.5, CHCl₃); C₁₆H₃₆O₂Si: calcd C, 66.60, H, 12.58; found: C, 66.88, H 12.46.

9-tert-Butyldimethylsilyloxydecanoic acid

To a suspension of PDC (15.04 g, 40 mmol) in DMF (30 mL) was added a solution of **11** (2.3 g, 7.99 mmol) in DMF (5 mL). The resulting solution was stirred at 25°C for 23 hours. The solution was poured into water (500 mL), and extracted with Et₂O (3×100 mL). Filtration of the ethereal solution followed by solvent evaporation and dry flash chromatography (50:50:1 hexanes:Et₂O:AcOH) followed by solvent evaporation *in vacuo* yielded the title compound as a pale yellow oil (2.29 g, 95%) ¹H NMR (300 MHz, CDCl₃) δ 3.70 (m, 1H), 2.30 (t, 2H, J=7.4 Hz), 1.2–1.6 (m, 12H), 1.06 (d, 3H, J=6 Hz), 0.86 (s, 9H), 0.05 (s, 6H); IR (neat, cm⁻¹) 2931, 2860, 1707, 1468, 1250, 1046 [α]_D²⁰=+74.51 (c=0.3 CHCl₃); C₁₆H₃₄O₃Si: calcd C, 63.52, H, 11.33; found: C, 63.81, H 11.45.

9-Hydroxydecanoic acid 13

To a solution of 9-*tert*-butyldimethylsilyloxydecanoic acid (1.81 g, 5.98 mmol) in CH₃CN (50 mL) at 0°C was added pyridine (2 mL) followed by HF/pyridine (2 mL) *via* syringe. The resulting solution was stirred at 23°C for 1 hour. The solution was poured into 1% HCl (10 mL), and extracted with EtOAc (3×50 mL). The organic solution was washed with brine (25 mL) and the solvent evaporated to yield known **13** as a colorless oil (1.11 g, 100%) spectroscopically identical to known compound.⁶ ¹H NMR (300 MHz, CDCl₃) δ 3.78 (m, 1H), 2.28 (t, 2H, J=7.4 Hz), 1.2–1.6 (m, 12H), 1.17 (d, J=6.2 Hz, 3H); [α]_D²⁰=-7.0 (c=0.1 CHCl₃) Lit^{6c} [α]_D²⁰=-7.2 (c=1 THF).

9-Decanolide (Phoracanthrolide I)

To a solution of **13** (1.03 g, 5.47 mmol) in benzene (30 mL) was added di-(2-pyridyl)disulfide (1.45 g, 6.60 mmol) and triphenylphosphine (4.72 g, 18 mmol). The solution was then stirred at 25°C for 1.5 hours. The resulting solution was diluted with dry CH₃CN (250 mL) and added over the course of 3 hours to a refluxing solution of AgClO₄·H₂O (6.76 g, 30 mmol) in CH₃CN (250 mL). Following the addition, the resulting solution was heated to 160°C for 1.5 hours. Upon cooling to 25°C, the solvents were removed *in vacuo* and the oil taken up in benzene (100 mL) and washed with 1 M NaCN solution (25 mL). The organic phase was then dried over MgSO₄, filtered through a plug of silica, and the solvents removed *in vacuo* to yield (*R*)-(-) phoracanthrolide I as a colorless oil (0.70 g, 75%) spectroscopically identical with known material. ¹H NMR (300 MHz, CDCl₃) δ 4.21 (m, 1H), 0.80–2.2 (br m, 14H), 0.90 (d, J=7.3 Hz, 3H); [α]_D²⁰=-31.0 (c=0.1, CHCl₃) Lit^{6b} [α]_D²⁰=-32.1 (c=0.56, CHCl₃).

Methyl 2,4-dihydroxy-6-methylbenzoate

A modification of Tsuji's procedure was employed.¹⁷ Sodium hydride (0.60 g of 80% dispersion in oil, 20 mmol) was placed in a flame dried solid addition funnel and the oil was removed with several portions of pentane. The funnel was quickly attached to a flame dried 100 mL round bottom flask equipped with a 25 mL dropping funnel and to the flask was added methyl acetoacetate (2.32 g, 2.16 mL, 20 mmol) and THF (20 mL). The dropping funnel was charged with diketene (1.68 g, 1.54 mL, 20 mmol) and 20 mL of THF. The flasked was immersed in an ice-salt bath, after which the sodium

hydride was added portionwise over the course of 5 min. Following the sodium hydride addition, the diketene solution was added dropwise over the course of five min. The resulting solution was allowed to stir for 1.0 h at -5°C , after which it was allowed to warm to 25°C and stir for an additional 3.0 h. The reaction mixture was then diluted with water and 10% HCl was added until the solution was acidic. The organic material was extracted into ethyl acetate and the organic layer was separated and treated with water and brine and dried over MgSO_4 . Removal of the solvents *in vacuo* gave a dark oily residue comprised of the desired product and the corresponding O-alkylated product. Column chromatography (silica gel; 1:4 EtOAc:hexanes eluent) gave 1.64 g (45% yield) of the title compound as colorless needles.¹⁷ ^1H NMR (300 MHz, CDCl_3) δ 11.79 (s, 1H, OH), 6.28 (d, $J=2.55$ Hz, 1H), 6.23 (d, $J=2.55$ Hz, 1H), 5.47 (s, 1H, OH), 3.92 (s, 3H), 2.48 (s, 3H).

Methyl 2,4-dimethoxy-6-methylbenzoate

Methyl 2,4-dihydroxy-6-methylbenzoate (1.0 g, 5.50 mmol) was dissolved in 60 mL of diethyl ether and the resulting solution was cooled to 0°C . A soln of CH_2N_2 (50 mL of 0.3 M in Et_2O , 15 mmol) was then added *via* cannula. After 3.0 h of stirring at 0°C , TLC (1:4 EtOAc:hexanes, anisaldehyde staining solution) and ^1H NMR of a small aliquot revealed the reaction mixture to be comprised mostly of mono-methylated material (2-hydroxy-4-methoxy). The reaction flask was thus allowed to stand for 7.0 days at $+5^{\circ}\text{C}$, after which time both hydroxyl groups were found to be methylated. The reaction was quenched by the dropwise addition of glacial acetic acid (0°C) until gas evolution ceased and the solution became colorless, after which the product solution was treated with saturated NaHCO_3 and brine and dried over MgSO_4 . Concentration and column chromatography (silica gel, 1:4 EtOAc:hexanes eluent) of the resulting oil gave 1.03 g (89%).¹⁷ ^1H NMR (300 MHz, CDCl_3) δ 6.30 (s, 2H), 3.87 (s, 3H), 3.79 (s, 6H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 168.6, 161.4, 158.2, 138.2, 116.4, 106.7, 96.2, 55.9, 55.3, 51.9, 19.9.

Methyl 2,4-dimethoxy-6-(thiophenyl) methyl benzoate 17

A 100 mL round bottom flask was flame dried and charged with 50 mL of THF and 1.16 mL of diisopropylamine (0.84 g, 8.30 mmol). The solution was cooled to 0°C and *n*-BuLi (2.56 mL of 2.55 M, 6.52 mmol) was added. After 10 min, the reaction mixture was cooled to -78°C and benzoate **27** was added. A deep rust-orange coloration developed immediately on benzoate addition. The anion solution was allowed to stir for 1.0 h at -78°C , after which a solution of 1.94 g (8.89 mmol) of Ph_2S_2 in THF (15 mL) was added dropwise, resulting in a clear, pale yellow solution. The reaction mixture was allowed to warm to room temperature overnight, after which it was diluted with EtOAc and treated with 50 mL of 10% HCl solution. The layers were separated and the organic layer was treated again with 10% HCl, followed by saturated NaHCO_3 and brine and dried over MgSO_4 . Silica gel chromatography (3:7 EtOAc:hexane) afforded 1.58 g of **17** as yellow needles (84% yield).¹⁷ ^1H NMR (300 MHz, CDCl_3) δ 7.26 (m, 5H), 6.35 (s, 2H), 4.12 (s, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.9, 161.4, 158.6, 138.5, 135.8, 132.1, 130.5, 128.8, 126.6, 115.7, 106.2, 97.8, 56.0, 55.3, 52.2, 37.4; MS (EI) *m/e* 318, 209.

7-tert-Butyldiphenylsiloxy-1-heptanol

A 10 mL round bottom flask was flame dried and charged with 1,7-heptandiol (0.529 g, 0.56 mL, 4.0 mmol) and DMF (0.75 mL). *t*-Butyldiphenylsilyl chloride (1.045 g, 0.99 mL, 3.8 mmol) was added, and imidazole (0.68 g, 10 mmol) was then added in small portions. The reaction mixture was allowed to stir for 24 h at 25°C , after which it was poured into water and extracted with ethyl acetate. The layers were separated and the organic layer was treated with saturated NaHCO_3 and brine and dried over MgSO_4 . Column chromatography (silica gel, 1:4 EtOAc:hexanes eluent) afforded 1.048 g (74% yield) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 7.72 (m, 4H), 7.43 (m, 6H), 3.70 (t, $J=6.5$ Hz, 2H), 3.65 (t, $J=6.6$ Hz, 2H), 1.78 (s, $J=\text{OH}$ Hz, 1H), 1.59 (m, 4H), 1.37 (m, 6H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 135.5, 134.1, 129.4, 127.5, 63.9, 62.9, 32.7, 32.4, 29.1, 26.8, 25.7, 25.6, 19.2; IR (neat) 3355, 1112 cm^{-1} ; MS (EI) *m/e* 370.

7-tert-Butyldiphenylsiloxy-1-heptanal 21

7-*tert*-Butyldiphenylsiloxy-1-heptanol (2.081 g, 5.61 mmol) was stirred with 3.6 g (8.49 mmol) of Dess–Martin periodinane in 60 mL of CH₂Cl₂ for 12 h at 25°C. After this time, the solution was poured into 150 mL of saturated NaHCO₃ and 10 g of Na₂S₂O₃ and shaken vigorously for five min. The layers were separated and the organic layer was treated with brine, dried over MgSO₄, and finally concentrated *in vacuo*. Filtration through a short plug of silica with CH₂Cl₂ furnished **21** as a colorless oil (1.921 g; 93% yield). ¹H NMR (300 MHz, CDCl₃) δ 9.76 (t, J=1.7 Hz, 1H), 7.69 (m, 4H), 7.41 (m, 6H), 3.67 (t, J=6.4 Hz, 2H), 2.41 (dt, J=1.7, 7.3 Hz, 2H), 1.59 (m, 4H), 1.42–1.28 (m, 4H), 1.07 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 202.8, 135.5, 134.1, 129.5, 127.6, 63.7, 43.8, 32.3, 28.8, 26.8, 25.5, 22.0, 19.2; MS (EI) *m/e* 368, 353; C₂₃H₃₂SiO₂: calcd C, 74.95; H, 8.75; found: C, 74.88; H, 8.69.

(R)-(+)-8-tert-Butyldiphenylsiloxy-2-octanol 22

A solution of 7-*tert*-butyldiphenylsiloxy-1-heptanal (2.768 g, 7.51 mmol) in toluene (5 mL) was added dropwise to a precooled (0°C) solution of (1*R*,2*S*) *N,N*-dibutyl norephedrine tricarbonyl (η⁶ arene) chromium(0) complex (0.15 g, 0.38 mmol)⁴ and dimethyl zinc (15 mL, 30 mmol; 2.0 M in toluene) in dry toluene (20 mL). The reaction was stirred for 36 h at 5°C, then quenched by cannulating the mixture onto a slurry of crushed ice and saturated aqueous ammonium chloride (10g). The crude mixture was extracted into ether (3×20 mL). The ethereal extracts were dried (MgSO₄), filtered, then the solvent was removed *in vacuo*, and the product carbinol purified by flash chromatography (8:2 hexanes:ethyl acetate eluent) to give **22** (2.6 g, 90%) as a colorless oil. R_F 0.55 (50:50-hexane:ethyl acetate); ¹H NMR (300 MHz, CDCl₃) δ 7.68 (m, 4H), 7.41 (m, 6H), 3.79 (m, 1H), 3.66 (t, J=6.4 Hz, 2H), 1.56 (m, 2H), 1.41–1.31 (m, 9H), 1.19 (d, J=5.6 Hz, 3H), 1.05 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 135.5, 134.1, 129.4, 127.5, 68.1, 63.9, 39.2, 32.5, 29.3, 26.8, 25.71, 25.70, 23.4, 19.2; IR (neat) 3355, 1112, 700 cm⁻¹; MS (EI) *m/e* 384, 369; [α]_D +14.6° (c=1, CHCl₃); HPLC; Daicel OD column, 0.5% IPA 99.5% hexanes eluent; flow rate 1.0 mL/min, (*R*)-(+)-enantiomer=17.6 mins, (*S*)-(–)-enantiomer=19.6 mins; C₂₄H₃₆SiO₂: calcd C, 74.95, H, 9.43; found: C, 74.83, H, 9.46.

(R)-8-tert-Butyldiphenylsiloxy-2-octanol, tert-butyldimethylsilyl ether

Alcohol **22** (1.99 g, 5.17 mmol) was dissolved in 6 mL of CH₂Cl₂ and 2,6-lutidine (1.66 g, 15.52 mmol) was added. The solution was cooled to –78°C, after which TBDMS-OTf (2.05 g, 7.76 mmol) was added. After 4.0 h at –78°C, TLC analysis indicated completion and the reaction mixture was allowed to warm to 25°C. A saturated solution of NaOH (20 mL) was added, and the product extracted into CH₂Cl₂. The organic layers were treated with 10% HCl (20 mL), followed by saturated NaHCO₃ (20 mL) and brine (20 mL), and then dried over K₂CO₃. Column chromatography of the resulting oil (silica gel, 1:9 EtOAc:hexanes) afforded the title compound (2.48 g) as a colorless oil (96% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.69 (m, 4H), 7.41 (m, 6H), 3.77 (m, 1H), 3.67 (t, 2H), 1.58 (quin, 2H), 1.43–1.20 (m, 8H), 1.13 (d, J=6.08 Hz, 3H), 1.07 (s, 9H), 0.91 (s, 9H), 0.06 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 135.6, 134.2, 129.5, 127.6, 68.6, 64.0, 39.7, 32.6, 29.4, 26.9, 25.9, 25.8 (2), 23.8, 19.2, 18.2, –4.4, –4.7; IR (neat) 1255, 1113, 834, 773, 702 cm⁻¹; MS (EI) *m/e* 498, 483, 468; [α]_D +3.9° (c=1, CHCl₃); C₃₀H₅₀Si₂O₂: calcd C, 72.22, H, 10.10; found: C, 72.46, H, 10.32.

(R)-7-tert-Butyldimethylsiloxy-1-octanol 23

Sodium hydride (0.568 g, 23.7 mmol) was suspended in 6 mL HMPA and 1.0 mL of THF was added. The resulting suspension was brought to 0°C and 2.0 g (4.01 mmol) of **22** was added. The resulting slurry was stirred for 8.0 h at 0°C, until TLC analysis indicated the reaction had halted, at which point anhydrous methanol was added dropwise *via* cannula at 0°C. The methanol addition was continued until a clear solution resulted, at which point saturated NH₄Cl was added and the product extracted into Et₂O. The combined ethereal extracts were treated with 10% HCl soln (3×20 mL), followed by NaHCO₃ (1×20 mL) and brine (1×20 mL) and dried over Na₂SO₄. Column chromatography (silica gel, 1:4 EtOAc:hexanes) afforded 0.6465 g of **23** as a viscous oil (60% yield). ¹H NMR (300 MHz,

CDCl_3) δ 3.76 (m, 1H), 3.62 (t, $J=6.63$ Hz, 2H), 1.69 (s, 1H, broad OH), 1.55 (quin, 2H), 1.38–1.24 (m, 8H), 1.10 (d, $J=6.07$ Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 68.6, 62.9, 39.6, 32.7, 29.5, 25.9, 25.7 (2), 23.8, 18.1, -4.4, -4.7; IR (neat) 3355, 1112, 773 cm^{-1} ; MS (EI) m/e 260, 215, 230; $[\alpha]_{\text{D}} +12.2^\circ$ ($c=1$, CHCl_3).

(R)-1-Bromo-7-tert-butyltrimethylsilyloxy-octane 16

Alcohol **23** (0.5258 g, 2.019 mmol) was dissolved in 10 mL of CH_2Cl_2 and the solution was cooled to 0°C . CBr_4 (1.004 g, 3.028 mmol) was added, followed by Ph_3P (1.588 g, 6.056 mmol). After 1.0 h of stirring at 0°C , the cold solution was diluted with hexanes and filtered through a plug of silica. Solvent removal, followed by a second filtration through a silica plug (with hexanes) afforded 0.4393 g (67%) of bromide **16** as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 3.76 (m, 1H), 3.41 (t, 2H), 1.85 (quin, 2H), 1.48–1.29 (m, 8H), 1.11 (d, $J=6.07$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 68.52, 39.57, 33.94, 32.78, 28.83, 28.16, 25.89, 25.56, 23.81, 18.00, -4.40, -4.72; IR (neat) 1258, 836, 773 cm^{-1} ; MS (EI) m/e 324, 322, 309, 307; $[\alpha]_{\text{D}} +17.9^\circ$ ($c=1$, CHCl_3); $\text{C}_{14}\text{H}_{31}\text{BrSiO}$: calcd C, 52.00, H, 9.66; found: C, 52.26, H, 9.73.

5-Hexynal

Dess–Martin periodinane (5.2 g) was dissolved in 80 mL of CH_2Cl_2 and pyridine (2.2 mL) was added as a buffering agent. 5-Hexyn-1-ol (1.0 g, 1.12 mL, 10.19 mmol) was then added and the reaction mixture allowed to stir for 4.0 h at 25°C , after which a solution of 13 g of $\text{Na}_2\text{S}_2\text{O}_3$ in NaHCO_3 (saturated) was added. The product was extracted into CH_2Cl_2 and the organic layer was separated and treated with 10% HCl soln (to remove the pyridine), followed by saturated NaHCO_3 and brine. Silica gel chromatography (1:4 Et_2O :pet. ether) afforded 0.6660 g (68% yield) of the aldehyde **24** as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 9.80 (t, $J=1.3$ Hz, 1H), 2.61 (dt, $J=1.3, 7.2$ Hz, 2H), 2.27 (dt, $J=2.6, 6.9$ Hz, 2H), 1.98 (t, $J=2.6$ Hz, 1H), 1.85 (pent, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 201.7, 83.2, 69.3, 42.5, 20.8, 17.8.

(R)-6-Heptyn-2-ol

A solution of 5-hexyn-1-ol (32.8 mg, 0.3412 mmol), (1*R*,2*S*)-*N,N*-dibutyl norephedrine tricarbonyl (η^6 arene) chromium(0) complex (13.6 mg, 0.034 mmol),⁴ and dimethyl zinc (0.85 mL, 1.7 mmol; 2.0 M in toluene) in toluene (0.5 mL) was stirred for 72 h at 5°C , then quenched by cannulating the mixture onto a slurry of crushed ice and saturated aqueous ammonium chloride (10g). The crude mixture was extracted into ether (3×10 mL). The ethereal extracts were dried (MgSO_4), filtered, then the solvent was removed *in vacuo*, and the product carbinol purified by flash chromatography (8:2 hexanes:ethyl acetate eluent) to give **25** (36.3 mg, 95%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 3.81 (sextet, 1H), 2.21 (m, 2H), 1.95 (t, $J=2.7$ Hz, 1H), 1.67–1.51 (m, 5H), 1.19 (d, $J=6.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 84.3, 68.5, 67.6, 38.1, 24.6, 23.6, 18.3; IR (neat) 3302, 2128 cm^{-1} ; MS (EI) m/e 112; $[\alpha]_{\text{D}}^{20} +14.2^\circ$ ($c=4.7$, CHCl_3).

(R)-Methyl 2,4-dimethoxy-6-(1-thiophenyl-8-tert-butyltrimethylsilyloxy) benzoate 28

A 20 mL round bottom flask was flame dried and charged with 4.0 mL of THF and 0.11 mL (0.794 mmol) of diisopropylamine. The solution was cooled to -78°C and *n*-BuLi (0.466 mL of 1.55 M, 0.722 mmol) was added. After 20 min, a solution of benzoate **17** (0.2298 g, 0.722 mmol) in 1.5 mL THF was added *via* cannula and the resulting orange anion solution was made to stir for 1.0 h at -78°C before HMPA (0.628 mL, 5.0 equiv.) was added. A solution of bromide **16** (0.233 g, 0.7204 mmol) in 2.0 mL of THF was then cooled to -78°C and added dropwise to the anion solution *via* a cannula. The reaction mixture was allowed to warm to room temperature overnight, after which it was diluted with EtOAc and treated with 20 mL of 10% HCl solution. The layers were separated and the organic layer was treated again with 10% HCl, followed by saturated NaHCO_3 and brine and dried over MgSO_4 . Filtration through a plug of silica afforded 0.2989 g (74% yield) of **28** as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 7.30–7.27 (m, 2H), 7.21–7.17 (m, 3H), 6.65 (d, $J=2.16$ Hz, 1H),

6.32 (d, $J=2.16$ Hz, 1H), 4.27 (t, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.73 (m, 1H), 1.87 (m, 2H), 1.39–1.29 (m, 10H), 1.10 (d, $J=6.05$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 168.2, 161.6, 157.6, 143.0, 135.1, 131.7, 128.6, 126.8, 116.3, 103.4, 97.3, 68.6, 55.8, 55.3, 52.0, 49.9, 39.6, 37.0, 29.4, 29.3, 27.4, 25.9, 25.7, 23.7, 18.1, -4.5 , -4.7 ; IR (neat) 1731, 1602, 1578, 1256, 1156, 772 cm^{-1} ; MS (CI) m/e 560, 545, 451; Anal. calcd for $\text{C}_{31}\text{H}_{48}\text{O}_5\text{SSi}$: C, 66.39; H, 8.63; found: C, 66.21; H, 8.64.

(R)-Methyl 2,4-dimethoxy-6-(8-*tert*-butyldimethylsiloxy nonyl) benzoate

A 100 mL round bottom flask was charged with 50 mL of ethanol (95%) and to this was added approximately 4.0 mL of an aqueous suspension of Raney Nickel. Compound **28** (0.1203 g, 0.2144 mmol) was dissolved in 10 mL of ethanol and this solution was added to the suspension of RaNi. The resulting suspension was left to stir vigorously for 2.0 h at 25°C, after which time the reaction was judged to be complete by TLC analysis. The suspension was poured through a pad of celite with excess ethanol to remove the metal, and the celite pad was immersed in dilute aqueous HCl to ensure any unreacted Raney Nickel was destroyed. Removal of the ethanol *in vacuo*, followed by the azeotropic removal of residual water with benzene, afforded 99.3 mg (100% yield) of the title compound as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 6.32 (m, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.77 (m, 1H), 2.53 (m, 2H), 1.56 (m, 2H), 1.28 (m, 10H), 1.10 (d, $J=6.1$ Hz, 3H), 0.88 (s, 9H), 0.040 (s, 3H), 0.037 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 168.8, 161.3, 157.9, 143.0, 116.2, 105.8, 96.1, 68.6, 55.8, 55.3, 52.0, 39.7, 33.9, 31.2, 29.6, 29.5, 29.4, 25.9, 25.8, 23.8, 18.1, -4.4 , -4.7 ; IR (neat) 1731, 1602, 1578, 1256, 1156, 1098, 770 cm^{-1} ; MS (EI) m/e 452 (M^+), 437, 422.

(R)-Methyl 2,4-dimethoxy-6-(8-hydroxynonyl) benzoate

(R)-Methyl 2,4-dimethoxy-6-(8-*tert*-butyldimethylsiloxy nonyl) benzoate (89 mg, 0.1966 mmol) was dissolved in 3 mL of THF and TBAF (1.0 mL of 1.0 M in THF) was added at 0°C. The reaction mixture was allowed to warm to room temperature overnight, and after 16 h of stirring an additional 1.0 mL of TBAF was added (bringing the total to 10.0 equiv.). The reaction mixture was left to stir for an additional 24 h, at which point TLC analysis revealed that the reaction had halted. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was separated and treated with water and brine, after which it was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was applied to a preparative TLC plate and eluted with 1:1 EtOAc:hexanes. Recovery following preparative plate separation was 41.4 mg (62% yield, 87% yield based on recovered starting material) of the desired title compound. ^1H NMR (300 MHz, CDCl_3) δ 6.30 (m, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.75 (m, 1H), 2.51 (m, 2H), 1.55 (m, 2H), 1.41–1.26 (m, 11H), 1.16 (d, $J=6.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 168.8, 161.3, 157.9, 142.9, 116.2, 105.7, 96.0, 68.0, 55.8, 55.3, 52.0, 39.3, 33.9, 31.1, 29.4, 29.3 (2C), 25.7, 23.4; IR (neat) 3450, 1725, 1610, 1280, 1165 cm^{-1} ; MS (EI) m/e 338 (M^+), 291, 210; $[\alpha]_{\text{D}} -2.5^\circ$ ($c=0.8$, CHCl_3), $\text{Lit}^{15\text{a}}$ -1.60 (*R*) ($c=0.6$, EtOH). $\text{Lit}^{15\text{b}}$ $+2.7$ (*S*) ($c=1$, CHCl_3).

(R)-2,4-Dimethoxy-6-(8-hydroxynonyl) benzoic acid **29**

(R)-Methyl 2,4-dimethoxy-6-(8-hydroxynonyl) benzoate (40 mg, 0.12 mmol) was saponified in 2.0 mL of ethylene glycol and 0.12 mL of 10 N KOH at 165°C for 4.0 h (according to the procedure of Solladie). Benzene (4.0 mL) and 10 N KOH (10 mL) were added and the layers were separated. The organic phase was further treated with 10 N KOH (3 \times 1 mL), after which the organic phase was discarded and the combined aqueous phases were made acidic to pH paper by the addition of conc. HCl. The acidic aqueous phase was then extracted with benzene (3 \times 5 mL) and the combined benzene layers were washed with water (2.0 mL) and dried over Na_2SO_4 . Filtration and solvent removal afforded 35 mg **29** (91%) as a viscous oil. ^1H NMR (300 MHz, CDCl_3) δ 6.36 (AB, 2H), 5.70 (s, $J=\text{OH}$ Hz, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 3.84 (m, 1H), 2.72 (m, 2H), 1.70–1.10 (m, 12H), 1.17 (d, $J=6.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.7, 161.3, 158.1, 144.1, 115.2, 106.4, 95.9, 68.0, 55.8,

55.1, 38.6, 33.9, 30.9, 29.0 (2C), 28.9, 25.3, 22.9; IR (neat) 3445, 1710, 1610, 1265, 1165 cm^{-1} ; MS (EI) m/e 324 (M^+), 306, 207, 196; $[\alpha]_{\text{D}} -3.1^\circ$ ($c=1$, CHCl_3); Lit^{15b} $[\alpha]_{\text{D}} +3.5$ (S) ($c=1.0$, CHCl_3).

Methyl-(R)-(+)-lasiodiplodin 14

To a solution of the hydroxyacid **29** (35 mg, 0.11 mmol) in 1.0 mL of benzene was added di-(2-pyridyl) disulfide (35 mg, 0.15 mmol) and triphenylphosphine (41 mg, 0.36 mmol). After 1.0 h, the resulting solution was diluted with dry CH_3CN (4 mL) and added over the course of 4.0 h to a refluxing solution of AgClO_4 (0.55 mmol) in CH_3CN (10 mL). Following the addition, the resulting solution was heated to 160°C for 0.5 h, after which the solvents were removed *in vacuo* and the oil taken up in 20 mL of benzene and washed with 1.0 M NaCN solution. The organic phase was then dried over Na_2SO_4 , filtered through a plug of silica, and the solvents removed *in vacuo*. Silica gel chromatography (75:25 hexane:EtOAc) afforded 23.1 mg (70%) of **14** as an oil. ^1H NMR (300 MHz, CDCl_3) δ 6.31 (AB, 2H), 5.28 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.64 (m, 2H), 1.98–1.21 (m, 12H), 1.32 (d, $J=6.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 168.5, 161.1, 157.7, 142.7, 118.1, 105.9, 96.3, 72.0, 55.8, 55.3, 32.3, 30.6, 30.1, 26.4, 25.4, 24.2, 21.2, 19.4; IR (neat) 1722, 1610, 1275, 1210, 1168, 1100 cm^{-1} ; MS (EI) m/e 306 (M^+), 196, 191, 152; $[\alpha]_{\text{D}} +7.6$ ($c=0.6$, CHCl_3). Lit^{15b} $[\alpha]_{\text{D}} -8.5$ (S) ($c=1$, CH_3OH); $[\alpha]_{\text{D}} +9.0$ (R) ($c=1$, CHCl_3); Lit^{15a} $[\alpha]_{\text{D}} +4.2$ (R) ($c=0.18$, EtOH).

Acknowledgements

We thank the Donors of the Petroleum Research Fund (Administered by the American Chemical Society) for financial support of this work (25958-G1, 28706-AC1).

References

1. Representative examples: Masamune, S.; Lu, L. D.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523; Stork, G.; Rychnovsky, S. *J. Am. Chem. Soc.* **1987**, *109*, 1565.
2. Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley, New York, 1989.
3. For review see: Roxburgh, C. J.; *Tetrahedron* **1995**, *51*, 9767.
4. Jones, G. B.; Heaton, S. B. *Tetrahedron Lett.* **1992**, *33*, 1693.
5. Jones, G. B.; Heaton, S. B. *Tetrahedron: Asymmetry* **1993**, *4*, 261.
6. For representative syntheses see: (a) Gerlach, H.; Kunzler, P.; Oertle, K. *Helv. Chim. Acta.* **1978**, *61*, 1226; (b) Nagumo, S.; Suemune, H.; Sakai, K. *Tetrahedron.* **1992**, *48*, 8667; (c) Fouque, E.; Rousseau, G. *Synthesis* **1989**, 661.
7. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. For improved preparation of this reagent see: Ireland, R. E.; Liu, L.; *J. Org. Chem.* **1993**, *58*, 2899.
8. (a) Bessodes, M.; Komiotis, D.; Antonakis, K. *Tetrahedron Lett.* **1986**, *27*, 579; (b) Koster, H.; Sinha, N. D. *Tetrahedron Lett.* **1982**, *23*, 2641.
9. Jones, G. B.; Chapman, B. J.; Huber, R. S.; Beaty, R. *Tetrahedron: Asymmetry* **1994**, *5*, 1199.
10. Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.
11. Kitahara, T.; Koseki, K.; Mori, K. *Agric. Biol. Chem.* **1983**, *47*, 389.
12. Drager, G.; Kirschning, A.; Thiericke, R.; Zerlin, M. *Nat. Prod. Reps.* **1996**, *13*, 365.
13. Gerlach, H.; Thalman, A. *Helv. Chim. Acta.* **1977**, *60*, 2866; Takahashi, T.; Kasuga, K.; Tsuji, J. *Tetrahedron Lett.* **1978**, 4917; Danishefsky, S. J.; Etheredge, S. J. *J. Org. Chem.* **1979**, *44*, 4716.
14. Aldridge, D. C.; Galt, S.; Giles, D.; Turner, W. B. *J. Chem. Soc. (C)* 1971, 1623.
15. (a) Braun, M.; Mahler, U.; Houben, S. *Liebigs Ann. Chem.* **1990**, 513; (b) Solladie, G.; Rubio, A.; Carreno, M. C.; Ruano, J. L. *Tetrahedron: Asymmetry* **1990**, *1*, 187.
16. Shekhani, M. S.; Khan, K. M.; Mahmood, K.; Shah, P. M.; Malik, S. *Tetrahedron Lett.* **1990**, *31*, 1669.
17. Kato, T.; Hozumi, T. *Chem. Pharm. Bull.* **1972**, *20*, 1574.
18. Jones, G. B.; Huber, R. S. *Synlett.* **1993**, 367.
19. Jones, G. B.; Mathews, J. E. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 93.

(Received in USA 1 April 1997)