Natural Product Synthesis

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The Leiodolide B Puzzle**

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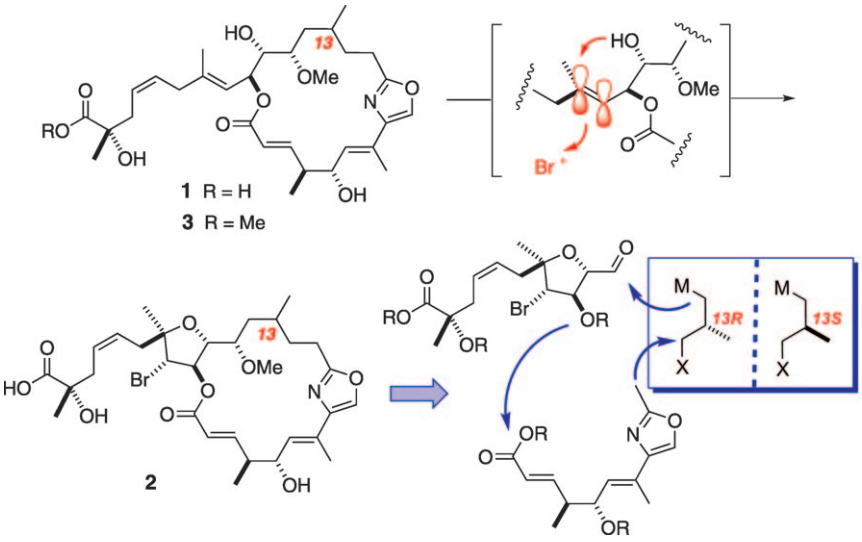
The quest for structurally novel and biologically significant lead compounds from marine sources is driving teams involved in the isolation of natural products to explore ever more remote locations. While the collection of diversified species in shallow waters by scuba diving is now well established, investigations into the deep sea environment are scarce for logistical reasons, even though they offer considerable promise.[1] During a campaign in Palau, Fenical and co-workers were able to collect sponges from the rare genus *Leiodermatium* at a depth of 220 m by using a manned submersible. Bioassay-guided fractionation of the methanol extracts led to the isolation of two unusual macrolides of apparently mixed polyketide/nonribosomal peptide synthetase origin termed leiodolide A (**1**) and B (**2**).[2,3] Both compounds, as well as the derived methyl ester **3**, showed significant cytotoxicity and appreciable selectivity in the NCI 60 tumor cell line assay.



Scheme 1. Proposed structures of and biosynthetic relationship between leiodolide A (**1**) and leiodolide B (**2**). Retrosynthetic analysis of **2** accounting for the unknown configuration at C13.

Being the more abundant of the two metabolites, **1** (8 mg, 0.001 % of the sponge's dry weight) was the primary subject of the structure-elucidation campaign. A combination of spectroscopic studies and degradation experiments led Fenical and co-workers to propose the structure shown in Scheme 1, in which the configuration of the stereogenic center at C13 remains unassigned.[2] Given the extremely limited supply of leiodolide B (**2**, 0.8 mg, 0.0001 % of the dry weight), its structure was inferred from that of **1** according to a proposed biosynthetic closure of the conspicuous brominated tetrahydrofuran ring.[2] This relationship also suggests that the α-hydroxy-α-methyl carboxylic acid terminus is *S*-configured in both compounds, although this aspect was rigorously established only for **1**.[4]

Intrigued by the architectural complexity and promising bioactivity, we embarked on a total synthesis of these unusual macrolides. In particular, our attention was caught by the complex tetrahydrofuran segment embedded in the northern sector of **2**, which contains five contiguous stereogenic centers, one of which is quaternary.[5] Moreover, the projected synthesis must account for the unknown configuration of C13 (Scheme 1).

We planned to forge the polysubstituted THF ring by a relay strategy which allows chiral information to be transmitted from a readily available epoxide to the exigent tertiary ether site at C23 via an axially chiral allene intermediate (Scheme 2). To this end, epoxide **8** was prepared by a Sonogashira coupling of **4** and **5**, followed by selective oxidation of the *Z*-alkene moiety in enyne **6** according to a protocol developed by Katsuki and co-workers.[6] Specifically, the reaction using catalytic amounts of $Ti(OiPr)_4$ and the well accessible salan ligand **7**[7] in combination with H_2O_2 under buffered biphasic conditions proceeded exceedingly well, furnishing the desired oxirane with an enantiomeric excess of 97 %. After protection of the primary alcohol, product **8** was subjected to conjugate epoxide opening. Although iron catalysis had previously been utilized to great advantage for similar purposes,[5,8] it was plagued in this particular case by a competitive direct opening of the oxirane ring. Gratifyingly

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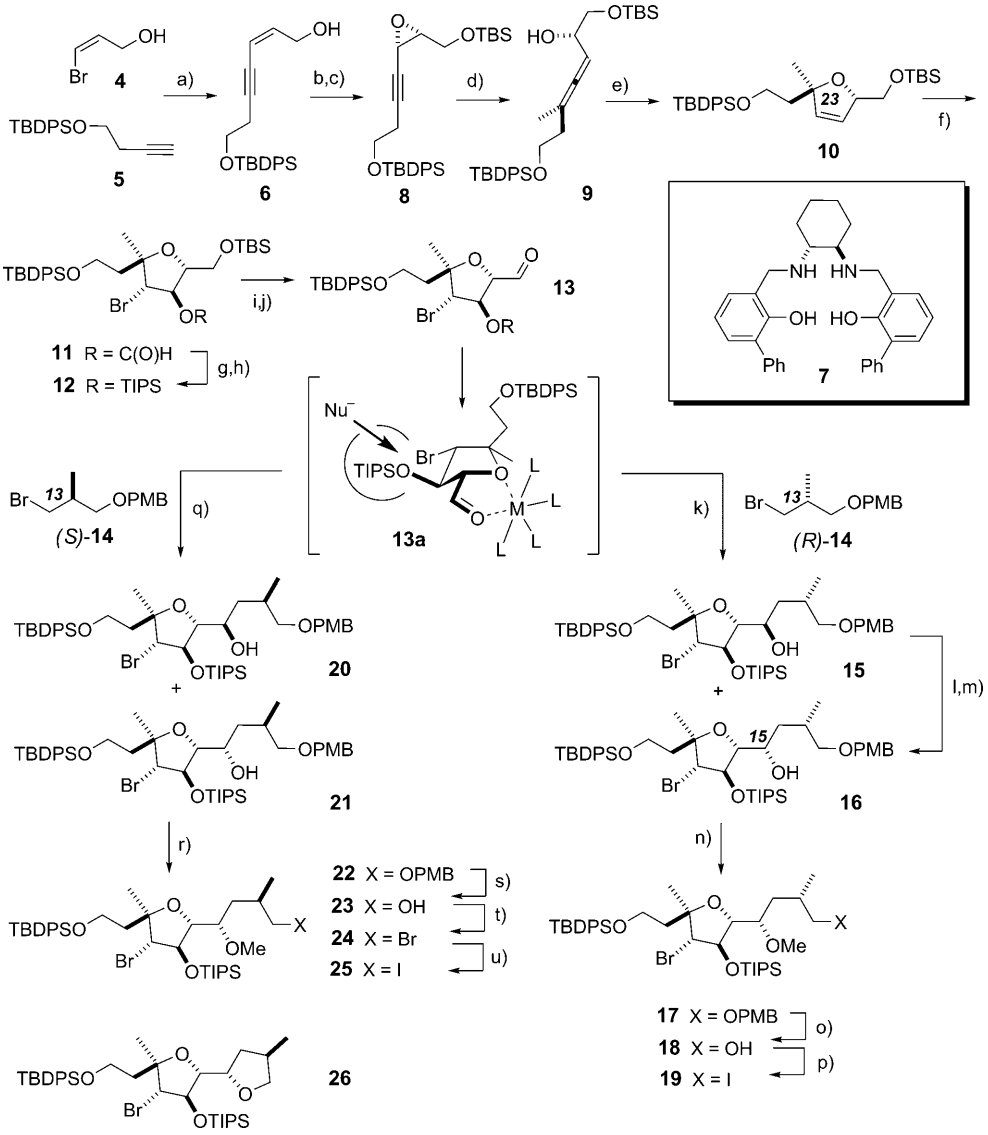


Scheme 2. a) $[Pd(PPh_3)_4]$ (2.2 mol%), CuI (15 mol%), Et_2NH, quant.; b) $Ti(OiPr)_4$ (10 mol%), **7** (12 mol%), aq H_2O_2, CH_2Cl_2, pH 7.4 buffer, 40°C, 99%, 97% *ee*; c) TBSCl, imidazole, cat. DMAP, CH_2Cl_2, 0°C→RT, 95%; d) MeMgBr, CuCN, $P(OPh)_3$, THF, −40°C→RT, 99%, d.r. > 95:5; e) $AgNO_3$, $CaCO_3$, acetone, H_2O, 91%; f) NBS, aq DMF, 10°C, 64%; g) $NaHCO_3$, $MeOH/H_2O$, 85%; h) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 93%; i) Cl_3CCOOH, THF/H_2O, 86%; j) DMP, pyridine, CH_2Cl_2, 0°C, 90%; k) (*R*)-**14**, *t*BuLi, Et_2O, −78°C, $MgBr_2$, then **13**, LiBr, CH_2Cl_2, 73%, d.r. = 4:1; l) DMP, pyridine, CH_2Cl_2, 0°C→RT, 74%; m) $NaBH_4$, $CeCl_3\cdot(7H_2O)$, MeOH, −70°C, 89%, d.r. = 3.5:1; n) LiHMDS, THF, MeOTf, −78°C→RT, 87%; o) DDQ, CH_2Cl_2/H_2O, 99%; p) I_2, PPh_3, imidazole, CH_2Cl_2, 92%; q) (*S*)-**14**, *t*BuLi, Et_2O, −78°C, $MgBr_2$, then **13**, LiBr, CH_2Cl_2, 85%, d.r. = 6.1:1; r) LiHMDS, THF, MeOTf, −78°C→RT; s) DDQ, CH_2Cl_2/H_2O, 0°C→RT, 93% (over both steps); t) CBr_4, PPh_3, benzene, 55°C, 97%; u) NaI, acetone, 88%. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone; DMAP = 4-dimethylaminopyridine; DMP = Dess–Martin periodinane; NBS = N-bromosuccinimide; LiHMDS = lithium hexamethyldisilazide; PMB = *para*-methoxybenzyl; TBDPS = *tert*-butyldiphenylsilyl; TBS = *tert*-butyldimethylsilyl; TIPS = tri(isopropyl)silyl; Tf = trifluoromethanesulfonyl.

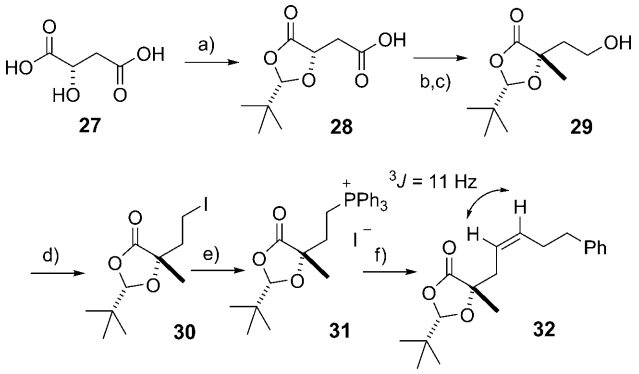
though, the reagent derived from MeMgBr, a stoichiometric amount of CuCN, and $P(OPh)_3$ cleanly afforded the desired allenol **9**.[9] The subsequent Ag^I-induced cyclization to the dihydrofuran **10** was high yielding under the conditions developed by Marshall and Pinney.[10] With the tertiary ether being properly set by this efficient chirality transfer process, a subsequent bromo-esterification with NBS in aqueous DMF provided compound **11** as a single isomer.[11] Standard protecting-group manipulations, including the chemoselective cleavage of the primary TBS group in the trisilylated intermediate **12**, and oxidation of the liberated alcohol gave aldehyde **13** in good overall yield.

With substantial amounts of **13** in hand, the stage was set for a chain extension with a C_3 building block embodying the as yet undefined stereocenter at C13 (leiodolide numbering). Although the addition of a nucleophile under Cram-chelation control was expected to lead to the correct configuration at C15,[12] aldehyde **13** turned out to be surprisingly unreactive. Presumably it is the bulky TIPS group which gets in the way of the incoming nucleophile (Nu^-) along the Burgi–Dunitz trajectory (see **13a**, Scheme 2). After extensive screening it was found that the reagent derived from bromide (*R*)-**14** by metal–halogen exchange with *t*BuLi in Et_2O followed by transmetalation with freshly prepared $MgBr_2$ gave well reproducible results,[13] provided that aldehyde **13** was administered in a 4 M solution of LiBr in CH_2Cl_2. Under these conditions, the isomeric alcohols **15** and **16** were obtained in 73% yield in a 1:4 ratio.[14] Not only were these compounds separable by careful flash chromatography, but the minor isomer **15** could be recycled by oxidation/Luche reduction to further the material throughput. The subsequent O-methylation of **16** proceeded well only with LiHMDS and precisely 1.05 equivalents of MeOTf. Oxidative cleavage of the PMB ether in **17** followed by conversion of the resulting alcohol **18** into the corresponding iodide **19** completed the preparation of the northern sector of **2** in one of the two possible diastereomeric forms.

Since the configuration of C13 in the leiodolides is unknown, it was mandatory to prepare the epimeric building

block as well. To this end, bromide (*S*)-**14** was added to aldehyde **13** under the optimized conditions; the stereochemical concord of this pair of reactants accounted for a higher yield and improved diastereoselectivity (85%, **20**/**21** = 1:6.1). Although the elaboration of **21** followed the tactics outlined above, the ultimate step leading to the primary iodide **25** was problematic. Whereas the use of I_2 in combination with PPh_3 and imidazole furnished substantial amounts of the tetrahydrofuran derivative **26**, a halide exchange sequence turned out to be viable.[15]

L-Malic acid (**27**) was the point of departure for the preparation of the side-chain sector (Scheme 3). Protection with pivaldehyde followed by diastereoselective methylation

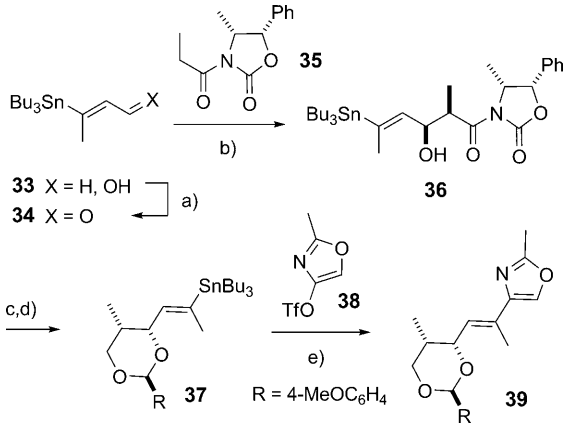


Scheme 3. a) Pivaldehyde, H_2SO_4 cat., pentane, reflux, 50%; b) LiHMDS, THF, MeI, −78°C→−20°C, 91%; c) $BH_3{\cdot}SMe_2$, THF, −20°C→RT; d) I_2, PPh_3, imidazole, CH_2Cl_2, 41% (over two steps); e) PPh_3, MeCN, microwave, 150°C, quant.; f) *n*BuLi, THF, 3-phenylpropanal, −78°C→RT, 80%.

of the dianion derived from **28**[16] and subsequent borane reduction gave alcohol **29**, which had to be converted without delay into the corresponding iodide **30**. The seemingly simple reaction of **30** with PPh_3 required forcing conditions under microwave irradiation. To avoid any surprise at a later stage of the project, the performance of the Wittig reagent derived from the phosphonium salt **31** was tested in a model reaction with 3-phenylpropanal. As expected for a nonstabilized ylide, the *Z*-alkene **32** was obtained as the only product in good yield (Scheme 3).

In parallel work, the known stannylated alcohol **33**[17,18] was oxidized with MnO_2 and the resulting aldehyde **34** subjected to an Evans boron-aldol reaction[19] to give compound **36** (Scheme 4). Reductive cleavage of the auxiliary and protection of the resulting diol as the *p*-methoxybenzylidene acetal gave product **37** in readiness for cross-coupling with the known oxazolyl triflate **38**.[20] This transformation failed under a variety of experimental conditions. Pleasingly, however, the modified procedure recently developed in our laboratory delivered product **39** in excellent yield and short reaction times, despite a very high catalyst loading being mandatory.[21,22]

The phase of fragment coupling commenced by alkylation of **39** with iodide **19** using Et_2NLi as the optimal base (Scheme 5).[23] Reductive opening of the PMB acetal released the primary alcohol **41** in preparation for the closure of the



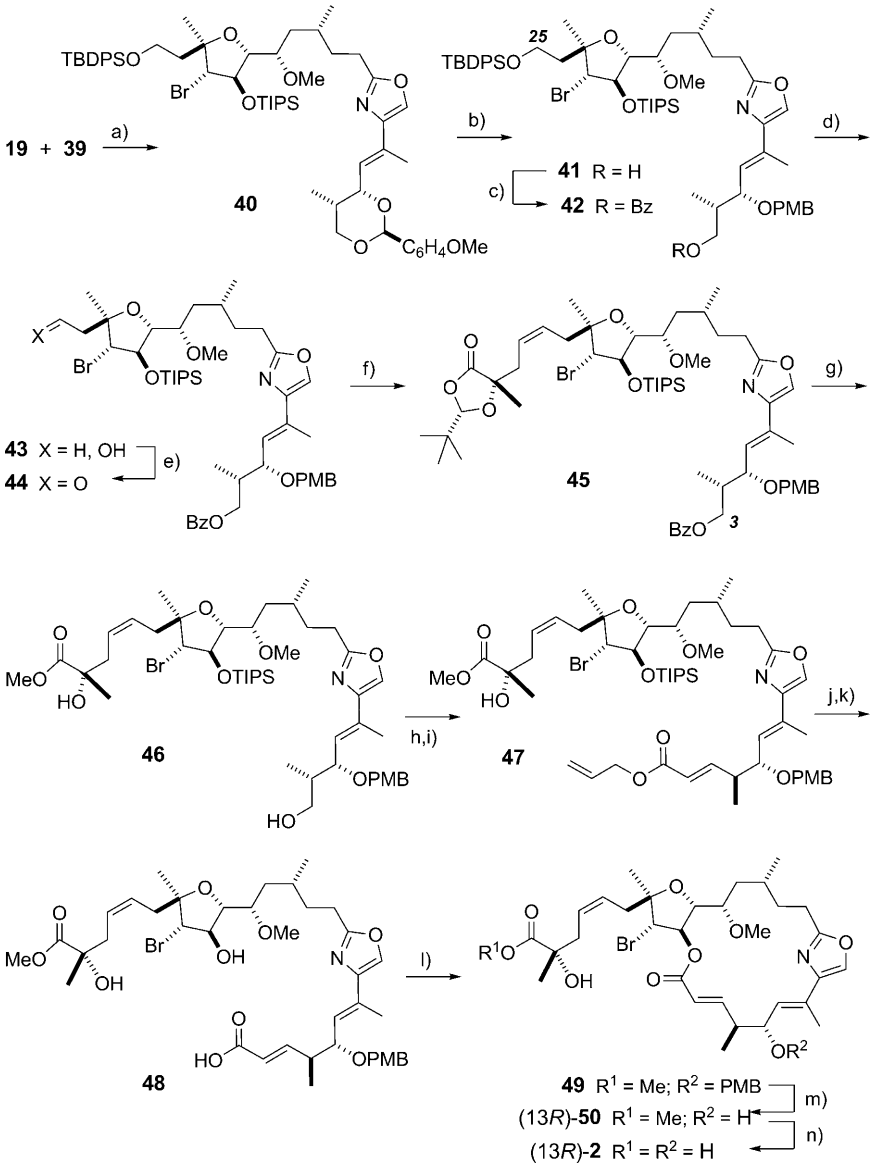
Scheme 4. a) MnO_2, CH_2Cl_2, 82%; b) Bu_2BOTf, Et_3N, CH_2Cl_2, −50°C, 95%; c) $LiBH_4$, THF, 0°C, 97%; d) 4-methoxybenzaldehyde dimethylacetal, cat. camphorsulfonic acid, DMF, 88%; e) $[Pd(PPh_3)_4]$ (70 mol%), copper thiophene-2-carboxylate, $[Bu_4N][Ph_2PO_2]$, DMF, 90%.

macrocyclic edifice. Exploratory studies, however, had shown that the installation of the side chain should be given priority

Table 1: Comparison of the ^{13}C NMR data of leiodolide B in $[D_4]$MeOH reported in the literature (75 MHz)[2] with the recorded data (150 MHz) for acid (13*R*)-**2** and the four diasteromeric esters **50** and **51** shown in Scheme 6.[a]

Position	Ref.	(13*R*)-**2**	(13*R*)-**50**	(13*S*)-**50**	(13*R*)-**51**	(13*S*)-**51**
1	166.6	166.7	166.7	166.7	166.6	166.9
2	122.8	121.5	121.5	121.5	121.8	121.7
3	153.1	153.1	153.2	153.5	153.3	153.5
4	45.1	44.7	44.7	44.5	45.6	46.2
5	71.7	72.0	72.0	72.0	71.9	71.6
6	131.2	128.3	128.3	128.0	128.9	129.5
7	125.5	128.4	128.4	129.2	129.1	128.4
8	143.3	143.4	143.1	143.6	143.7	143.5
9	134.5	135.2	135.2	135.1	134.8	135.5
10	166.4	166.5	166.5	166.5	166.6	167.1
11	25.7	25.8	25.8	25.1	25.2	26.0
12	33.9	33.9	33.9	34.0	34.5	35.6
13	30.5	29.4	29.4	30.4	29.2	31.5
14	36.7	37.0	37.0	38.7	36.7	39.9
15	78.0	77.9	77.9	79.0	78.3	79.6
16	80.5	80.9	80.9	83.7	80.9	83.7
17	78.4	78.7	78.5	79.2	78.3	77.8
18	16.3	15.5	15.5	15.6	15.9	16.7
19	13.7	14.1	14.1	14.3	14.4	14.2
20	20.7	20.9	20.9	20.2	20.9	21.1
21	58.0	58.0	58.0	59.1	58.0	59.9
22	56.2	56.1	55.9	56.0	55.8	55.4
23	84.0	84.5	84.5	84.7	84.4	84.2
24	37.6	37.4	37.3	37.3	37.5	37.8
25	126.5	127.8	127.9	127.9	127.9	127.8
26	130.4	128.6	128.4	128.4	128.5	128.5
27	39.2	39.1	39.2	39.2	39.2	39.2
28	76.4	75.4	75.7	75.7	75.8	75.7
29	182.7	179.1	177.5	177.5	177.5	177.5
30	26.0	25.9	25.9	26.1	26.0	26.4
31	26.4	26.0	25.9	25.9	25.9	25.9

[a] The heat map color-codes differences in chemical shift considered to be beyond the experimental error as follows: red: $\Delta\delta \geq 1$ ppm; blue: 0.5 ppm $\leq \Delta\delta < 1$ ppm; green: 0.3 ppm $\leq \Delta\delta < 0.5$ ppm. For a comparison of the ^1H NMR data, see the Supporting Information.



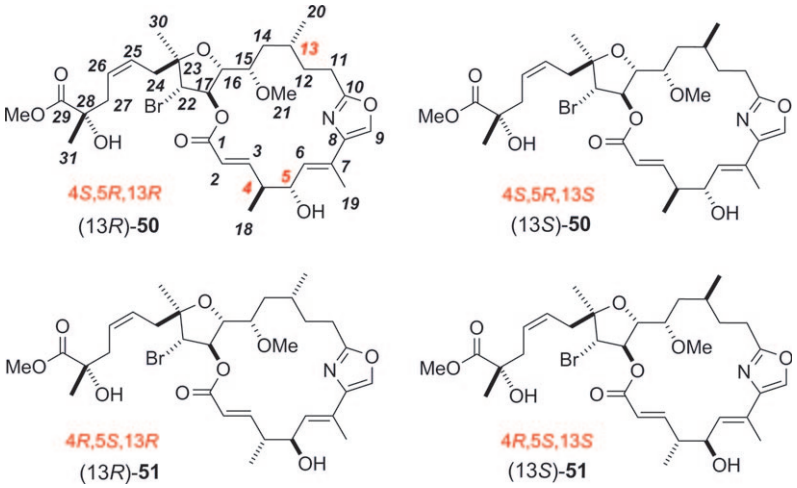
Scheme 5. a) **39**, Et_2NLi, THF, −78 °C, then **19**, 79%; b) DIBAL-H, toluene, −40 °C, 75%; c) benzoyl chloride, *i*PrNEt$_2$, DMAP, CH_2Cl_2, 80%; d) HF·pyridine, THF, pyridine, 0 °C, 72%; e) DMP, CH_2Cl_2, 0 °C→RT; f) **31**, *n*BuLi, THF, −78 °C→RT, 71% (over two steps); g) NaOMe, MeOH, 0 °C→RT, 75%; h) DMP, CH_2Cl_2, pyridine, 0 °C→RT; i) allyl diethyl phosphonoacetate, LiHMDS, THF, 72% (over two steps); j) HF·pyridine, THF, pyridine, 76%; k) 4-Me$C_6H_4SO_2Na$, [Pd(PPh$_3$)$_4$] (16 mol%), MeOH, THF; l) 2,4,6-trichlorobenzoyl chloride, toluene, Et_3N, then DMAP, 45 °C, 68% (over two steps); m) DDQ, CH_2Cl_2, H_2O, 0 °C→RT, 47%; h) Me_3SnOH, CH_2Cl_2, 60 °C, see text for further details. Bz = benzoyl; DIBAL-H = diisobutylaluminum hydride.

at this point. Therefore, **41** was temporarily protected as benzoate ester **42**, followed by selective removal of the TBDPS ether at C25 with buffered HF·pyridine.[24] Oxidation of **43** followed by reaction of the resulting aldehyde **44** with the ylide derived from **31** gave alkene **45** in respectable overall yield. Exposure to NaOMe in MeOH removed the benzoate at C3 and concomitantly converted the cyclic acetal at the acid terminus into the corresponding methyl ester. Dess–Martin oxidation of **46** followed by a Horner–Wadsworth–Emmons olefination gave product **47**, which comprises the complete carbon backbone of leiodolide B.

Buffered HF·pyridine at ambient temperature was the only reagent that would slowly deprotect the TIPS group in **47**, yet leave the fragile PMB group intact and not induce epoxide ring formation at the liberated bromohydrine site either. Palladium-catalyzed cleavage of the allyl ester followed by Yamaguchi lactonization[25] of the resulting *seco* acid **48** then gave the desired macrocycle **49** in 68% yield over both steps. Removal of the residual PMB group with DDQ completed the total synthesis of the putative leiodolide B methyl ester (13*R*)-**50**. The epimeric product (13*S*)-**50** was prepared analogously from **25** and **39** (for details see the Supporting Information). We were surprised, however, that neither of them matched the reported data of **2**, with small but non-negligible deviations being scattered over the entire framework (Table 1). Our NMR experiments indicated that different concentrations of the samples were not responsible for the observed deviances. Likewise, successive additions of CD_3COOD did not induce noticeable changes. Even though this experiment strongly suggested that the differences in the spectra are not caused by the fact that our synthetic samples were methyl esters whereas the natural product is a free carboxylic acid, attempts were made to rigorously clarify this point. Unfortunately, selective cleavage of the methyl ester in the presence of the macrolactone was troublesome, despite exploring several enzymatic and chemical methods. Nonetheless, we were able to obtain a very small quantity of the free acid (13*R*)-**2** by saponification of (13*R*)-**50** with excess Me_3SnOH[26] and subsequent purification by HPLC. In line with our expectations, this free acid and its methyl ester precursor had virtually identical spectra, differing only in the carboxylate terminus region (see Table 1 and the Supporting Information).

A closer inspection of the data showed stunning differences in the chemical shifts in the C2–C9 region of the molecule. We were apprehensive that the isolation team had been reasonably confident in assigning the 4*S*,5*R* configuration to the stereogenic centers in this sector, but had expressed a caveat that the recorded data were not totally unambiguous.[2] Therefore, we next rushed to prepare the enantiomeric oxazole building block *ent*-**39** (via *ent*-**35**). Its

incorporation into the macrocyclic frame then followed the assembly process outlined above for (13*R*)-**50**. Disappointingly, however, the data of the resulting products (13*R*)-**51** and (13*S*)-**51** (Scheme 6) did not match either, with even larger discrepancies encountered throughout the carbon skeleton (Table 1).



Scheme 6. Panel of diastereomeric products formed by total synthesis. The preparation of the individual isomers follows the sequence outlined for (13*R*)-**50** in the text; details are given in the Supporting Information. Arbitrary numbering Scheme used in Table 1.

To our dismay, we must hence conclude that none of the four isomers prepared during this investigation reproduces the published data of the natural product well enough to claim identity. The surprising scattering of the observed deviances makes it impossible at this point to localize the cause for the mismatch. Since the observed shift differences are small, the constitution originally assigned to leiodolide B is most likely correct and the variances must stem from a rather subtle structural detail.[27] We cannot even exclude that they are artifacts caused by the possible low resolution of the original spectra recorded on minute amounts of a not perfectly pure sample (the published ^{13}C NMR data were recorded at 75 MHz with 0.8 mg of material).[28] Since neither the original ^{13}C NMR spectra nor authentic leiodolide B could be made available to us, we have to leave this aspect open.[29,30] Yet, we are hopeful that the conquest of the more carefully characterized sister compound leiodolide A and its conversion into leiodolide B by a biomimetic path will resolve the puzzle.

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[24] More basic fluoride sources also cleave the TIPS ether and cause epoxide formation by intramolecular substitution of the adjacent bromide.

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[27] One possibility is that the α-hydroxy-α-methyl carboxylic acid terminus in **2** is *R* rather than *S* configured (see Ref. [4]), although it is not clear that this change would have an impact on the chemical shift of so many remote C atoms. Likewise, Table 1 shows both olefinic regions as "hotspots", but the chemical shift differences are not large enough to suggest misassigned geometries.

[28] The ^{1}H NMR spectrum of leiodolide B depicted in the Supporting Information of the isolation paper clearly shows the presence of an impurity (ca. 5–10%).

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