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Chagosensine: A Riddle Wrapped in a Mystery Inside an Enigma

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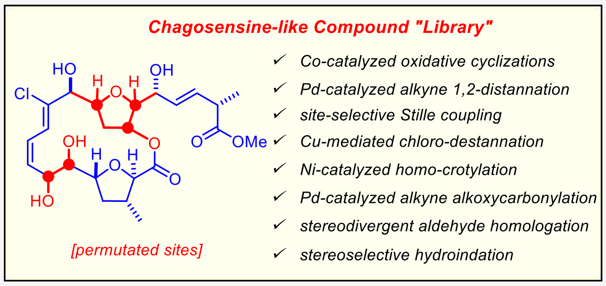

ABSTRACT: The marine macrolide chagosensine is supposedly distinguished by a (*Z*,*Z*)-configured 1,3-chlorodiene contained within a highly strained 16-membered lactone ring, which also incorporates two *trans*-2,5-disubstituted tetrahydrofuran (THF) rings; this array is unique. After our initial synthesis campaign had shown that the originally proposed structure is incorrect, the published data set was critically revisited to identify potential mis-assignments. The "northern" THF ring and the *anti*-configured diol in the "southern" sector both seemed to be sites of concern, thus making it plausible that a panel of eight diastereomeric chagosensine-like compounds would allow the puzzle to be solved. To meet the challenge, the preparation of the required building blocks was optimized, and a convergent strategy for their assembly was developed. A key role was played by the cobalt-catalyzed oxidative cyclization of alken-5-ol derivatives ("Mukaiyama cyclization"), which is shown to be exquisitely chemoselective for terminal alkenes, leaving even terminal alkynes (and other sites of unsaturation) untouched. Likewise, a palladium-catalyzed alkyne alkoxycarbonylation reaction with formation of an α-methylene-γ-lactone proved instrumental, which had not found application in natural product synthesis before. Further enabling steps were a nickel-catalyzed "Tamaru-type" homocrotylation, stereodivergent aldehyde homologations, radical hydroindation, and palladium-catalyzed alkyne-1,2-bis-stannation. The different building blocks were assembled in a serial fashion to give the idiosyncratic chlorodienes by an unprecedented site-selective Stille coupling followed by copper-mediated tin/chlorine exchange. The macrolactones were closed under forcing Yamaguchi conditions, and the resulting products were elaborated into the targeted compound library. Yet, only one of the eight diastereomers turned out to be stable in the solvent mixture that had been used to analyze the natural product; all other isomers were prone to ring opening and/or ring expansion. In addition to this stability issue, our self-consistent data set suggests that chagosensine has almost certainly little to do with the structure originally proposed by the isolation team.

■ INTRODUCTION

In a recent Communication, we reported the total synthesis of the methyl ester of nominal chagosensine (**2aa**).[1] Even though our route had passed through the free acid itself, which supposedly represents the natural product,[2] synthetic **1**—unlike chagosensine—proved highly unstable and had to be instantly protected on treatment with diazomethane. This stability issue was not the only major divergence with the original literature report:[2] rather, massive spectral mismatch between synthetic **2aa** and the documented methyl ester derived from the isolated material[2] was on record (Scheme 1).[1] Since the deviations were scattered over the entire framework, it was by no means obvious which substructure(s) might have been mis-assigned by the isolation team.

The original spectra of the natural product and its derivatives were neither deposited nor made available to us by the authors upon request, thus preventing any reinspection. This somewhat frustrating situation limited us to a critical re-evaluation of the published data[2] in order to identify potentially questionable assignments. This extra effort seemed justified, given the fact that chagosensine is "first-in-class":[3] to the best of our knowledge, this macrolide isolated from the calcareous bright yellow sponge *Leucetta chagosensis* collected in the Gulf of Aqaba is the only natural product known comprising a (*Z*,*Z*)-configured 1,3-chlorodiene.[4] Equally remarkable is the presence of a 16-membered lactone with two inscribed *trans*-2,5-disubstituted tetrahydrofuran (THF) rings that impart massive strain onto the core. The high level of oxidation of the entire carbon perimeter decorated with 11 stereogenic centers and an extra olefin in the side chain are yet other captivating structural attributes.

Although these features render chagosensine unique, tangible relationships with a small cohort of other (marine) natural products deserve careful consideration; though less complex, these compounds had been subject to intense

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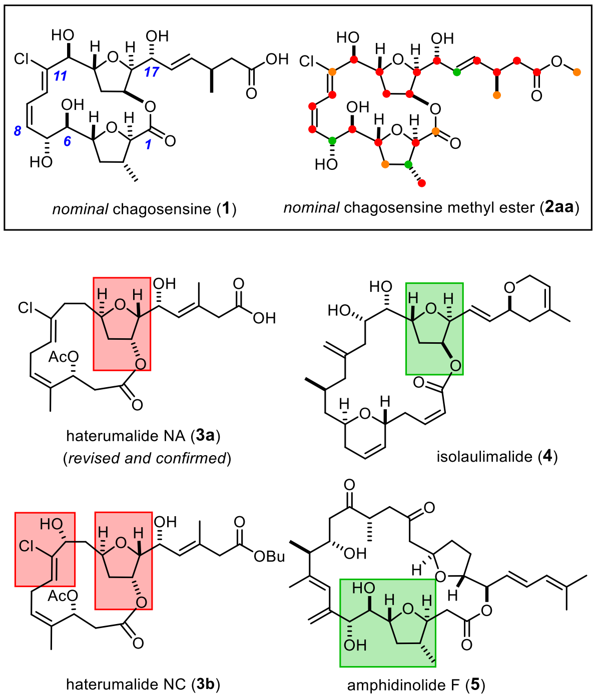
Scheme 1. Nominal Chagosensine and the Corresponding Methyl Ester[a]



[a]The dots overlaid over the C atoms indicate shift differences between the signals of synthetic **2aa** and the data reported in the literature (red: $\Delta\delta > 1$ ppm; orange: $1 \geq \Delta\delta \geq 0.5$ ppm; green: $\Delta\delta < 0.5$ ppm). Comparison with related natural products of confirmed constitution and stereochemistry.

scrutiny in the past (Scheme 1).[5] Actually, chagosensine appears almost like a composite; the many conformities, in turn, suggested that the mis-assignment is likely stereochemical rather than constitutional in nature. A more detailed comparison confirmed this notion in that the relative configuration of the "northern" THF ring appeared to be a major point of concern. The configuration of this subunit had been deduced by the isolation team from nuclear Overhauser effect spectroscopy (NOESY) correlations and the *J*-coupling pattern,[2] which is a priori risky given the floppiness of saturated five-membered rings. Moreover, the authors claimed an analogy to the tetrahydrofuran subunit of the haterumalides (and biselides),[6] even though for us the juxtaposition is not compelling (see the Supporting Information). The real issue, however, arises from the fact that the isolation team had compared chagosensine with the structure *originally* assigned to haterumalide NA (**3a**),[7] which is definitely incorrect. Shortly before their paper was published, it had been proven by total synthesis that the *trans*-2,5-disubstituted THF comprised in **3a** actually features the "*inverted*" configuration as depicted in Scheme 1.[8,9] Admittedly though, the substructure proposed for chagosensine does find exact correspondence in isolaulimalide (**4**); while the stereostructure of this natural product is unambiguous,[10] the *J*-coupling pattern is again at variance (see the Supporting Information). When seen against this backdrop, one cannot help but conclude that the assignment of the northern THF ring is questionable; an inverted array seems equally plausible, which might well account for the mismatch between the data of synthetic **2aa** and the isolated natural product.

The stereostructure of the "southern" sector, as proposed by the isolation team,[2] might not be definitive either. Specifically, the *anti*-diol unit at C6/C7 was assigned with the help of the circular dichroic exciton chirality method applied to the derived bis-cinnamate ester.[2] This analytical tool works well for fairly rigid compounds but must be applied with greatest care to more flexible systems, because conformational changes can reverse the helicity of the interacting chromophores.[11] There is no evidence in the original chagosensine publication that this caveat had been taken into account.[2] In this context, however, it is important to note that the southern hemisphere of chagosensine bears great similarity to a substructure of amphidinolide C and F (except for the missing methylene group between the carboxylate and the tetrahydrofuran ring),[12−14] even though the *J*-values are again at variance (see the Supporting Information). Anyway, this overall situation leaves serious doubt: if the configuration of the 1,2-diol stereochemistry is downgraded to "unsecure", four possible isomers of the southern segment must be taken into consideration. When combined with the two conceivable northern hemispheres referred to above, this makes up for an ensemble of eight diastereomeric chagosensine-like compounds, which was deemed necessary to solve the puzzle.

■ RESULTS AND DISCUSSION

Strategic Considerations. In view of the size, strain, and complexity of the target, only a highly convergent, robust, and flexible approach can provide access to the required compound collection without undue effort (Figure 1). We conjectured that our first-generation synthesis of nominal chagosensine methyl ester **2aa** actually meets this strategic precondition well:[1] Specifically, we had devised a new entry into the idiosyncratic chloro-1,3-diene unit of the target, after a number of other options had been ruled out.[1,15,16] The successful sequence commenced with a palladium-catalyzed *vic*-distannation of a propargylic alcohol **E** to afford a synthon of type **D** (Scheme 2).[17,18] Upon proper choice of the catalyst and the reaction conditions, only the less-hindered terminal C−Sn moiety of **D** engages in a Stille reaction with a (*Z*)-configured alkenyl halide partner **C**; such site-selective cross coupling of 1,2-bistannylalkenes had been essentially unknown before.[19−21] The resulting product **B** lends itself to chlorodemetalation with retention of configuration to give the desired chlorodiene product **A**.[22−24] This sequence is inherently modular and hence deemed adequate for the preparation of the envisaged chagosensine "library" in a serial manner from the fragments **6** and **7** (Figure 1).

The other cornerstone of our original approach to be retained in the second-generation synthesis concerns the formation of the 16-membered ring by macrolactonization.[25] The strain imparted onto the macrocycle by the two inscribed 2,5-*trans*-configured THF rings and the rigid chlorodiene is the likely cause why all our attempts to use alternative cyclization reactions had failed, despite considerable experimentation;[15] this includes ring closing metathesis of olefins or alkynes.[26,27] The effect of ring strain surfaced even in the lactonization of the diol derivative **8aa**, which led to the 12-membered ring **9** incorporating a single THF ring rather than to the desired—but obviously less favorable—16-membered ring comprising both THF entities (Scheme 3).[1] To rectify the outcome, the C12-OH group was blocked with a MOM-group; for this choice, our original approach to **2aa** converged to acetal protecting groups only in macrolactone **10aa**, all of which

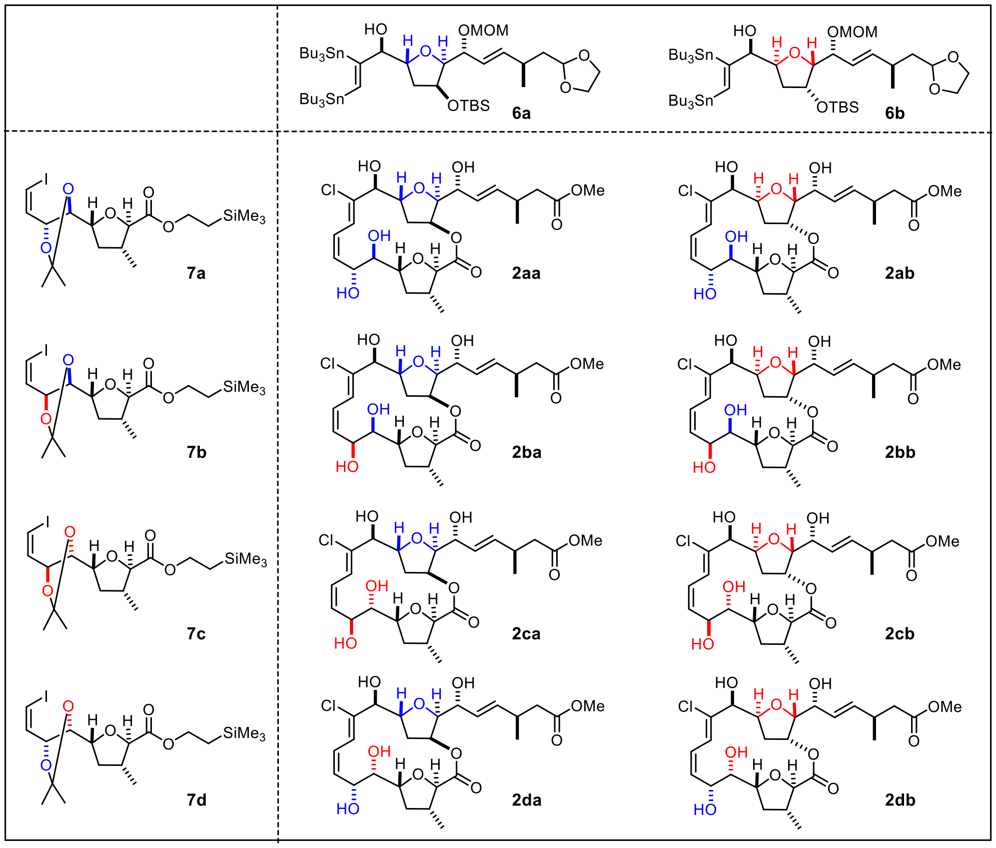
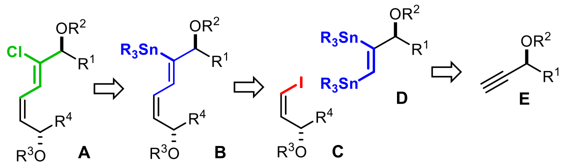


Figure 1. Matrix of conceived building blocks and chagosensine-like target compounds.

Scheme 2[a]

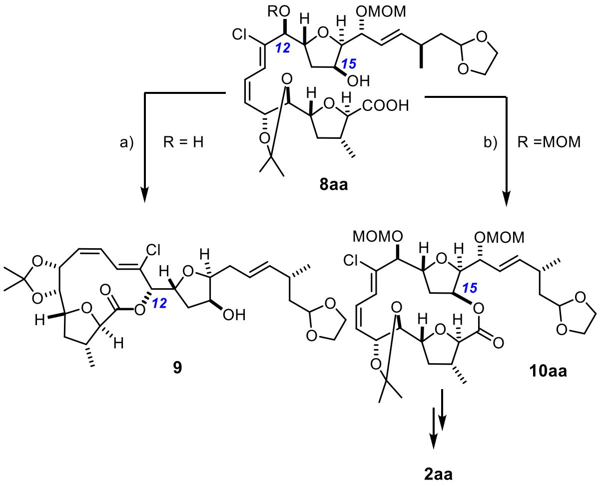


[a]Disconnection of the (*Z*,*Z*)-configured 1,3-chlorodiene subunits that hold the promise of being sufficiently flexible for the preparation of the envisaged chagosensine library.

could be removed with excess Me_2BBr in a single operation at the very end of the synthesis,[28−30] despite the fragile nature of the released product. Therefore this protecting group strategy was deemed yet another design element worth to be maintained.

Preparation of the Northern Segment in Two Diastereomeric Formats. With the overall strategy defined, we carefully reconsidered the preparation of the building blocks. (*S*)-Citronellal (**11**) served as the point of departure for the preparation of the northern sector. The derived acetal formed on treatment with ethylene glycol, triethyl orthoformate, and catalytic camphorsulfonic acid in CH_2Cl_2 was ozonolyzed to furnish aldehyde **12** in readiness for a modified Saegusa-type oxidation to give enal **13**, which worked nicely on scale with catalytic $Pd(OAc)_2$ and diethyl allyl phosphate as the final oxidant (Scheme 4).[31] Parenthetically we note that the corresponding dimethylacetal of this very enal had previously been made in nine steps,[32] whereas the current route furnished **13** in only three simple operations with at least 55% overall yield (6 g scale).

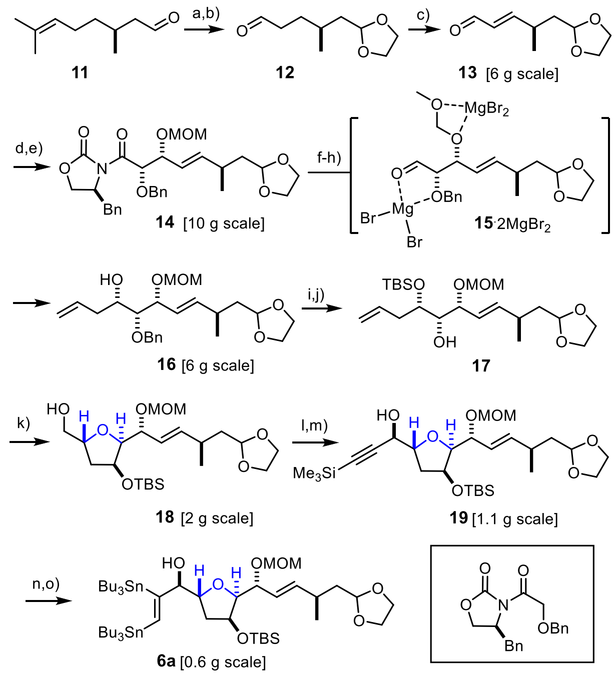
Scheme 3. Exploration of the Lactonization and Protecting Group Strategy[a]



[a]Reagents and conditions: (a) *N*-ethyl-2-bromopyridinium tetrafluoroborate, $NaHCO_3$, 1,2-dichloroethane, 80 °C, 30% (80% brsm); (b) 2,4,6-trichlorobenzoyl chloride, $(iPr)_2NEt$, THF, then 4-dimethylaminopyridine (DMAP), toluene, reflux, 40% (+ ca. 6% (epimer) + 13% (lactide)).

This compound was subjected to an auxiliary-controlled *syn*-selective glycolate aldol reaction,[33] and the resulting product **14** was elaborated into the corresponding aldehyde. We reasoned that chain extension by asymmetric allylation might not require a chiral catalyst or auxiliary; rather, substrate control should lead to the required *syn*,*syn*-configured triol

Scheme 4[a]



[a]Reagents and conditions: (a) ethylene glycol, $(EtO)_3CH$, camphorsulfonic acid (5 mol %), CH_2Cl_2, 98%; (b) O_3, Sudan red III, CH_2Cl_2, then Me_2S, −78 °C → RT, 97%; (c) $Pd(OAc)_2$ (4 mol %), diethyl allyl phosphate, $NaHCO_3$, THF, 86 °C, 58%; (d) (*S*)-4-benzyl-3-(2-(benzyloxy)acetyl)oxazolidin-2-one, *n*Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C → 0 °C, dr = 12:1, 80% (pure isomer); (e) MOMCl, tetrabutylammonium iodide (TBAI) (1 mol %), (*i*Pr)$_2$NEt, CH_2Cl_2, 0 °C → RT, quant; (f) $LiBH_3(OH)$, Et_2O, 0 °C, 88%; (g) [SO_3·pyridine], (*i*Pr)$_2$NEt, dimethyl sulfoxide (DMSO), CH_2Cl_2, −30 °C → 0 °C, quant; (h) $MgBr_2\cdot(OEt_2)$, allyltrimethylsilane, CH_2Cl_2, 0 °C → RT, dr = 14:1, 92% (pure isomer); (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 88%; (j) DDQ, CH_2Cl_2/pH 7.4 buffer (1:1), 50 °C, 70%; (k) $Co(nmp)_2$ (10 mol %), *t*BuOOH (10 mol %), O_2 (1 atm), *i*PrOH, 55 °C, dr ≥20:1, 69% (pure isomer); (l) [SO_3·pyridine], (*i*Pr)$_2$NEt, DMSO, CH_2Cl_2, −30 °C → −20 °C; (m) trimethylsilylacetylene, $Zn(OTf)_2$, (−)-*N*-methylephedrine, (*i*Pr)$_2$NEt, toluene, dr = 11:1, 65% (over two steps); (n) K_2CO_3, MeOH, 85%; o) $(Bu_3Sn)_2$, [(*t*BuNC)$_2$PdCl$_2$] (10 mol %), THF, 93%.

derivative **16**. This notion was based on the observation that **15** did not react with allyl trimethylsilane when only 1 equiv of $MgBr_2\cdot(OEt_2)$ was added as the promotor; sequestration of the Lewis acid by the methoxymethyl (MOM)-acetal is the most likely cause for this resilience. Under this premise, addition of a second equivalent of $MgBr_2\cdot(OEt_2)$ should entail formation of a reactive complex of type [**15**·2MgBr$_2$], which is expected to deliver **16** with a *syn,syn*-triol unit as the major product via a "Cram-chelate" transition state.[34] This anticipation proved correct in that the desired isomer was obtained with a diastereomer ratio (dr) ≥14:1; pure **16** was isolated in 92% yield on greater than 6 g scale (single largest batch).[35]

With a practical and scalable approach to **16** in place, our attention shifted to the formation of the conspicuous 2,5-*trans*-configured tetrahydrofuran ring via an oxidative Mukaiyama cyclization using $Co(nmp)_2$ as the catalyst.[36−39] Even though the appropriate alcohol **17** contains two different alkenes, the desired product **18** was formed in high yield and with excellent diastereoselectivity (dr ≥20:1), again on a (multi)gram scale; only traces of what seemed to be a regioisomeric product derived from reaction with the internal double bond were detected in the crude mixture. This favorable outcome may simply reflect a kinetic preference for the 5-*exo-trig* cyclization leading to **18**; however, it has been suggested in the literature that ligand exchange is actually rate-determining:[40] in such an "inner-sphere" *syn*-attack mechanism, the terminal alkene outcompetes the more hindered disubstituted olefin, because it binds more rapidly to the catalytically active cobalt center, which would also be in line with the observed result. What the selective formation of **18** does not support is a scenario triggered by single electron transfer (SET),[37] since oxidation of the more electron-rich internal olefin should be faster (or at least competitive).

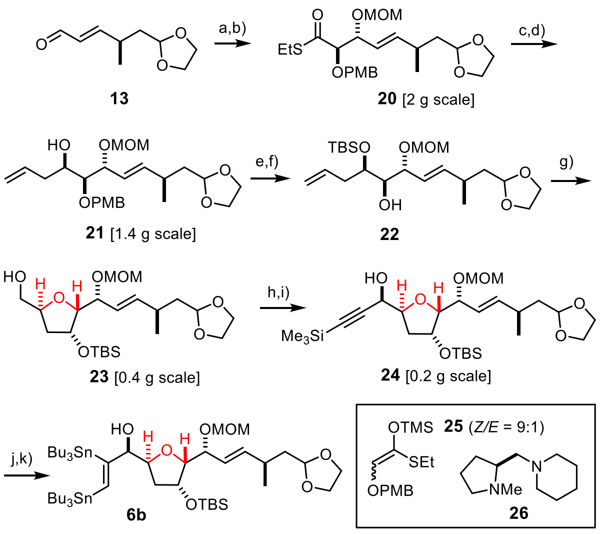
Oxidation of the primary alcohol in **18** to the corresponding aldehyde was performed under modified Parikh-Doering conditions,[41] in which the commonly used Et_3N was replaced by (*i*Pr)$_2$NEt to prevent epimerization from occurring. The crude aldehyde proved very sensitive and was therefore directly used in the subsequent asymmetric alkynylation with trimethylsilylacetylene, which proceeded well on gram scale provided that all components had been scrupulously dried prior to use.[35,42] Selective cleavage of the C-silyl group of **19** with K_2CO_3 in MeOH followed by palladium-catalyzed bis-stannylation[17] of the released terminal alkyne completed the synthesis of the northern fragment **6a** in the format corresponding to the originally assigned structure of chagosensine.

For the preparation of the diastereomeric building block **6b** with the inverted *trans*-tetrahydrofuran ring, an *anti*-glycolate aldol reaction had to be implemented in the first place (Scheme 5). This goal was attained via the tin/diamine-mediated Mukaiyama-Kobayashi protocol.[43,44] Although the required silyl enol ether **25** consists of a mixture of isomers (*Z*/*E* = 9:1), it could be used as such, since only (*Z*)-**25** reacts with enal **13** in the presence of $Sn(OTf)_2$, $Bu_2Sn(OAc)_2$, and chiral diamine **26**.[45] Inspection of the crude product showed a dr ≈ 20:1, from which the desired *anti*-configured compound **20** was isolated in analytically pure form in up to 66% yield.[35]

Adjustment of the protecting groups followed by Fukuyama reduction of the thiolester[46] set the stage for chain extension. Once again, a chelate-Cram controlled allylation provided a convenient solution,[34] furnishing the targeted *syn,anti*-configured triol derivative **21** in good yield. The subsequent cobalt-catalyzed oxidative cyclization of the derived alcohol **22** was just as selective and productive as that of compound **16**, in that basically no isomers but the desired product **23** were detected in the crude mixture; this gratifying outcome implies that remote stereocenters have little, if any, impact on the course of the reaction. After formation of the corresponding aldehyde, however, we had to learn that the asymmetric alkynylation[42] required a large excess of trimethylsilylacetylene, $Zn(OTf)_2$, and ligand to avoid competing self-aldolization. Apparently, the present setting constitutes the mismatched case, in which unfavorable substrate bias needs to be overruled by driving the desired transformation forward with excess reagents. Desilylation of the alkyne unit of **24** followed by palladium-catalyzed *vic*-distannation[17] then furnished the isomeric northern building block **6b** with high overall yield.

The Diastereomeric Southern Segments. The preparation of the southern sector **7a** for our first-generation synthesis of nominal chagosensine had relied on robust chemistries, including Sharpless asymmetric epoxidation and dihydroxylation, Still-Gennari and Stork-Zhao olefinations, as well as yet

Scheme 5[a]



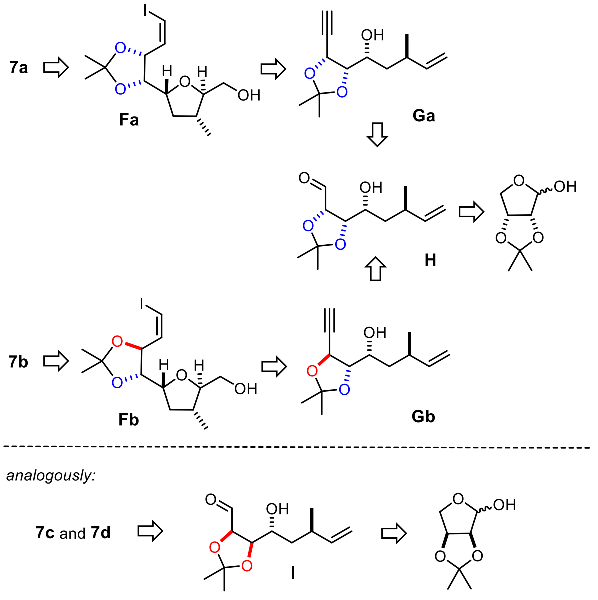
[a] Reagents and conditions: (a) $Sn(OTf)_2$, $nBu_2Sn(OAc)_2$, **25**, **26**, CH_2Cl_2, −78 °C, 55% (8 mmol scale), 66% (3.6 mmol scale), dr ≥20:1; (b) MOMCl, TBAI (1 mol %), $(iPr)_2NEt$, CH_2Cl_2, 0 °C → RT, 81%; (c) Et_3SiH, Pd/C (2 × 10 mol %), CH_2Cl_2, then acetone; (d) $MgBr_2{\cdot}(OEt_2)$, CH_2Cl_2, −30 °C then allyl tributyltin, −78 °C, dr ≥20:1, 49% (two steps, ca. 80% conversion); (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 84%; (f) DDQ, CH_2Cl_2/phosphate buffer (4:1), 0 °C 83%; (g) O_2 (1 atm), $Co(nmp)_2$ (10 mol %), *t*BuOOH (10 mol %), *i*PrOH, 55 °C, rr ≥ 20:1, dr ≥20:1, 69% (pure isomer); (h) [$SO_3{\cdot}$pyridine], $(iPr)_2NEt$, DMSO, CH_2Cl_2, −25 °C → −10 °C; (i) trimethylsilylacetylene (5.8 equiv), $Zn(OTf)_2$ (5.5 equiv), (−)-*N*-methylephedrine (6.1 equiv), $(iPr)_2NEt$ (6.2 equiv), toluene, dr = 19:1, 89% (pure diastereomer, over two steps); (j) K_2CO_3, MeOH, 84%; (k) $(Bu_3Sn)_2$, $[(tBuNC)_2PdCl_2]$ (10 mol %), THF, 75%.

another oxidative Mukaiyama cyclization reaction for the formation of the tetrahydrofuran ring.[1] The resulting building block **7a** deliberately carried a fluoride-labile ester to match the C15-OTBS group of the northern segments in anticipation for macrolactonization of these two sites, and the acetonide was chosen to streamline the final deprotection.

Even though it should be possible to prepare all four targeted diastereomeric segments **7a**−**7d** (Figure 1) in similarly protected format by adaptation of this route, we opted to explore an entirely new approach. This decision was taken because the original sequence had been linear rather than convergent and has also had close literature precedent;[13,39] moreover, the separation of the unwanted diastereomer from the Sharpless dihydroxylation had proven tedious on scale.[1] The revised blueprint centered on compounds of type **G** (Scheme 6): provided such an enyne succumbs to chemoselective oxidative cyclization at the alkene site, the stoichiometric Stork-Zhao olefination chemistry[47] previously used might be replaced altogether by a more convenient and atom-economical radical hydroindation/iodination of the alkyne unit (**G** → **F**).[48,49]

The projected formation of the tetrahydrofuran ring, however, bore considerable risk, not least because the compatibility of a terminal alkyne with the cobalt-catalyzed oxidative cyclization had never been proven before and actually seemed questionable;[36−39] only a single case from our own laboratory was known at the outset in which an *internal* alkyne did survive.[13] As the application of the Mukaiyama oxidative cyclization to the northern segment (**17** → **18**) had suggested

Scheme 6. Conceived Diverted Approach to the Southern Segments



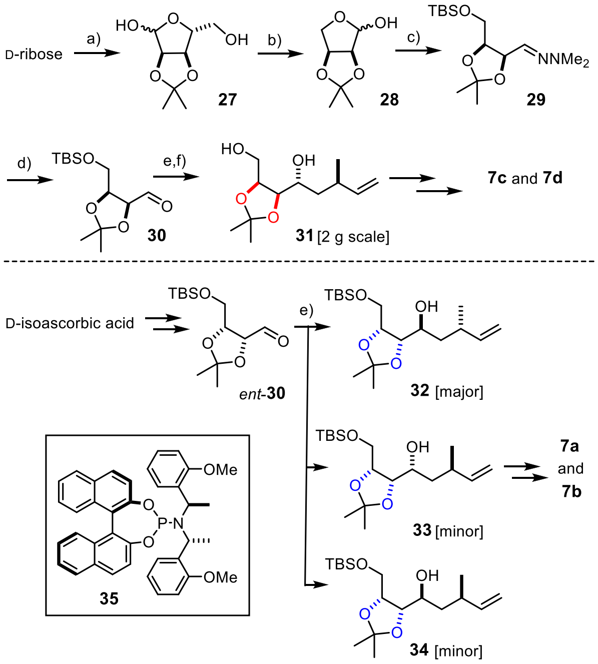
that binding of the π-bond to the cobalt center is decisive, one might expect that an unhindered triple bond in a substrate of type **G**—for its higher electron density—will outcompete the terminal alkene. Moreover, the projected case would certainly not allow any kinetic selectivity to be harnessed because of the equidistance between the hydroxy group in **G** and the two different unsaturations, each of which could cyclize in a favorable 5-*exo* manner.

These daunting issues notwithstanding, the overall route seemed attractive, as the required enynes **G** should be readily accessible from aldehydes **H** or **I** by homologation, which can be performed with or without epimerization. Such splitting minimizes the synthetic exertion, since only one pair of precursors has to be prepared to ultimately access all four required southern building blocks.

Direct Homocrotylation. In contrast to literature reports on the direct homocrotylation of hemiacetals,[50] the nickel-catalyzed addition of isoprene to **28** met with failure; gratifyingly though, the derived open-chain aldehyde **30**[51] reacted smoothly when Et_3B (rather than $ZnEt_2$)[52] was used as the promotor for this "Tamaru homo-crotylation reaction" (Scheme 7).[53] A number of chiral ligands were screened, but none of them allowed noticeable catalyst control to be exerted; rather, the inherent substrate bias favoring a "Felkin-Ahn" addition mode prevailed. In case of the D-ribose-derived aldehyde **30**, this stereochemical course leads to the desired product **31**. The best results were obtained when the reaction mixture was supplemented with phosphoramidite ligand **35**,[54] which seems to synergize and renders the reaction clean. Under these conditions, diol **31** was isolated in up to 60% yield on (multi)gram scale; **31** was then elaborated into two of the four targeted southern building blocks (**7c**,**7d**) as described below.

For the mismatched case, however, substrate control is detrimental. In fact, *ent*-**30** afforded a product mixture comprising compound **32** as the major component and its epimer **34**, both of which are formed via Felkin-Ahn-type transition states; the Cram-chelate adduct **33** needed for the preparation of the targeted fragments **7a**,**7b** was also generated

Scheme 7[a]



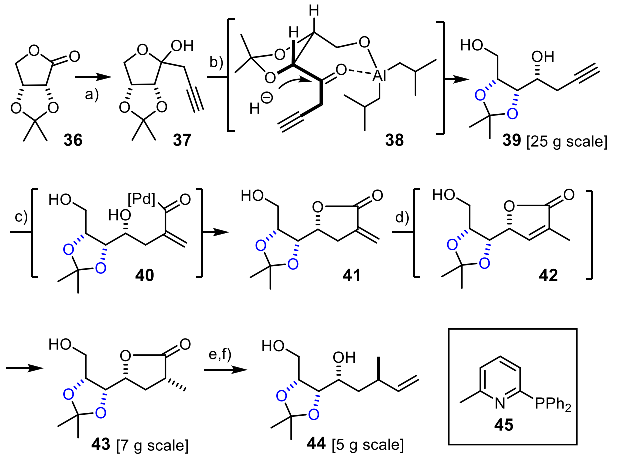
[a]Reagents and conditions: (a) acetone, H_2SO_4 cat, 78%; (b) (i) $NaBH_4$, MeOH, 4 °C → RT; (ii) $NaIO_4$, 83%; (c) (i) NH_2NMe_2, EtOH, reflux; (ii) TBSCl, imidazole, CH_2Cl_2, 0 °C → RT, 90% (over both steps); (d) O_3, Sudan red III, CH_2Cl_2, −78 °C, then Me_2S, 69%; (e) $Ni(cod)_2$ (5 mol %), **35** (5 mol %), isoprene, Et_3B, toluene, dr = 5:2, 60% (**31**); analogously: **32** (30%) + **33** (15%) + **34** (15%); (f) TBAF, THF, 0 °C, 96%.

but in a yield that was much too low for the required material throughput. We were hence forced to develop an alternative entry into the missing building blocks.

The α-Methylene-γ-lactone Route. In conceptual terms, the inherent substrate bias might be used to advantage by switching from a carbanion to hydride as the incoming nucleophile in the stereodetermining step. To this end, D-isoascorbic acid was converted into lactone **36** on scale by following a literature procedure (Scheme 8).[55] Subsequent reaction with allenylmagnesium bromide[56] furnished the propargyl derivative **37** almost quantitatively, provided that the temperature was strictly controlled during the addition of the Grignard reagent as well as the aqueous quench.

Since the *tert*-lactol unit renders compound **37** rather unstable and its terminal alkyne proved isomerization-prone to the corresponding allene, the material was subjected to reduction without delay. After some optimization it was found that addition of a solution of freshly prepared **37** in THF to a solution of Dibal-H (2 equiv) in the same solvent at −78 °C resulted in the exquisitely selective (dr $\geq$19:1) and essentially quantitative formation of the desired alcohol **39**. As an additional bonus, we noticed that this product can be crystallized directly from the crude mixture, which made the upscaling facile (25 g, single largest batch). The stereostructure of **39** was confirmed by X-ray crystallography (see the Supporting Information). The auspicious outcome is best explained by a chelate transition state **38**, which forces the incoming hydride to attack from the top face. This critical array is evidently favored in THF as the solvent, most likely because coordination of the ether to the Al-center enhances the basicity of Dibal−H and hence accelerates deprotonation of the substrate; if this step is (too) slow, a much less selective nucleophilic attack onto the nonchelated ketone will occur, which seems to be the case when the reaction is performed in toluene.

Scheme 8[a]



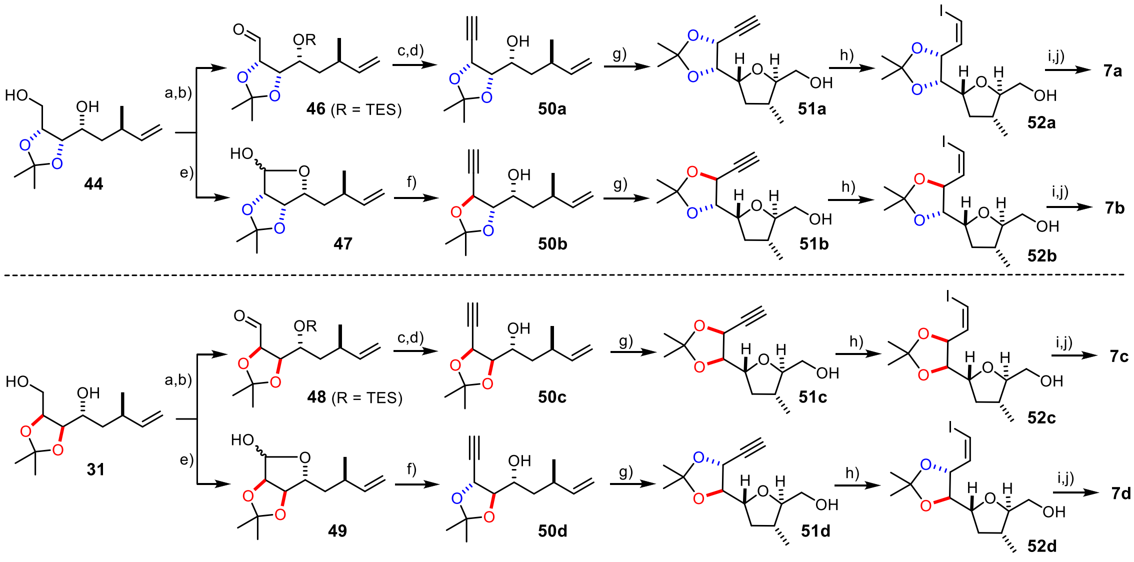
[a]Reagents and conditions: (a) allenylmagnesium bromide, THF, −78 °C; (b) Dibal-H, THF, −78 °C → RT, 80% (over both steps), dr = 19:1; (c) $Pd(OAc)_2$ (0.1 mol %), **45** (3 mol %), pTsOH·H_2O (2 mol %), BHT (10 mol %), NMP, CO (60 bar), 45 °C; (d) (i) Pd/C (10% *w/w*), EtOAc, H_2 (1 atm); (ii) filtration through silica (see Text), then Pd/C (10% *w/w*), EtOAc, H_2 (1 atm), dr = 19:1, 92% (over both steps); (e) Dibal-H, CH_2Cl_2, −78 °C; (f) $Ph_3P{=}CH_2$, toluene, −78 °C → RT; 91% (over two steps).

With quantities of pure **39** at hand, the stage was set for the palladium-catalyzed regioselective alkoxycarbonylation of the alkyne at the internal position.[57−59] The envisaged case has the charm that the putative acylpalladium intermediate **40** should get trapped by the neighboring −OH group to deliver product **41** directly. Such lactone formation allows the catalytic cycle to be closed without need for an exogenous nucleophile.[60] Although this type of transformation is well-known, it has not found any applications in natural product synthesis, even though the resulting α-methylene-γ-lactones are ubiquitous in nature and often show promising bioactivities.[61]

At the outset of our study, however, we found the reaction to be erratic, in that the yields were highly variable; related to the problem was competing polymerization of the product and/or uncontrolled precipitation of the catalyst. Therefore, a careful optimization was performed, which resulted in the development of a robust protocol. Key to success is (i) the use of highly pure substrate (any allene contaminant seems to poison the catalyst); (ii) use of *N*-methyl-2-pyrrolidone (NMP) as the solvent; (iii) recourse to ligand **45** in combination with pTsOH as the optimal promotor; (iv) a ligand-to-acid ratio that avoids acidic conditions and hence precludes acid-catalyzed polyester formation; (v) addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT, 10 mol %) to prevent radical polymerization of the methacrylate substructure from occurring; (vi) a low palladium loading ($\leq$0.1 mol %). The last aspect is a considerable advantage on scale but comes at the price of rigorous exclusion of oxygen to avoid premature catalyst deactivation.

For the sensitivity of the resulting product **41**, the crude material was just filtered through a pad of Florisil before it was subjected to catalytic hydrogenation over Pd/C, which was expected to be highly diastereoselective.[62] Since some NMP

Scheme 9[a]



[a] Reagents and conditions: (a) TESCl, DMAP (20 mol %), pyridine, quant; (b) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C → −35 °C; then $(iPr)_2NEt$, −78 °C → RT, 81% (**46**, dr = 12.5:1), 77% (**48**, dr = 3.8:1); (c) MeOH, KHMDS, THF 0 °C → −78 °C, Bestmann-Ohira reagent $[MeC(O)C(N_2)P(O)(OMe)_2]$, −78 °C → −50 °C; (d) TBAF·$3H_2O$, THF, 0 °C → RT, 81% over two steps (**50a**); 38% over two steps (**50c**); (e) IBX, DMSO, quant; (f) Bestmann-Ohira reagent $[MeC(O)C(N_2)P(O)(OMe)_2]$, K_2CO_3, MeOH, reflux, 25% over two steps (**50b**), 28% over two steps (**50d**); (g) O_2 (1 atm), $Co(nmp)_2$ (10 mol %), *t*BuOOH (10 mol %), *i*PrOH, 55 °C, dr ≥20:1, 64% (**51a**), 66% (**51b**), 63% (**51c**), 58% (**51d**); (h) $InCl_3$, Dibal-H, Et_3B (20 mol %), then I_2, THF, −78 °C or −40 °C (see text), *Z*/*E* ≥ 20:1, 67% (**52a**), 92% (**52b**), 79% (**52c**), 88% (**52d**); (i) TEMPO (30 mol %), BAIB, aqueous MeCN; (j) 2-(trimethylsilyl)ethanol, EDCI, DMAP (20 mol %), 2-(trimethylsilyl)ethanol, CH_2Cl_2, 0 °C → RT, 62% (**7a**), 74% (**7b**), 69% (**7c**), 56% (**7d**) (over two steps each)

was carried over in this way, which poisons the supported catalyst surface and/or desorb Pd nanoparticles by ligation, the reduction was best performed by first running the reaction for ∼1 h under H_2 atmosphere; the resulting mixture was passed through silica, and the collected material (which mostly consisted of the double bond isomer **42**)[63] was resubjected to a second round of hydrogenation. This sequence of catalytic carbonylation/reduction proved well-reproducible on scale, furnishing product **43** as a single isomer in 92% yield over two steps (7 g, single largest batch).

The lactol formed on treatment of **43** with Dibal-H in CH_2Cl_2 at low temperature is highly water-soluble. To remedy the issue, an unconventional workup was developed, which may be useful in a different context too. To this end, the reaction was quenched with a stoichiometric amount of MeOH (or *t*BuOH) at −78 °C to destroy any residual reactive aluminum species, followed by addition of stoichiometric water to hydrolyze the aluminum alkoxides. Silica was then introduced, and the slurry was stirred at ambient temperature for 1 h before it was filtered. The filtrate was concentrated, and the resulting product was subjected to Wittig olefination in toluene at low temperature to avoid epimerization.[64] Compound **44**, which had been beyond the reach of the Ni-catalyzed homocrotylation, was thus obtained in high overall yield and with excellent purity (5 g, single largest batch).

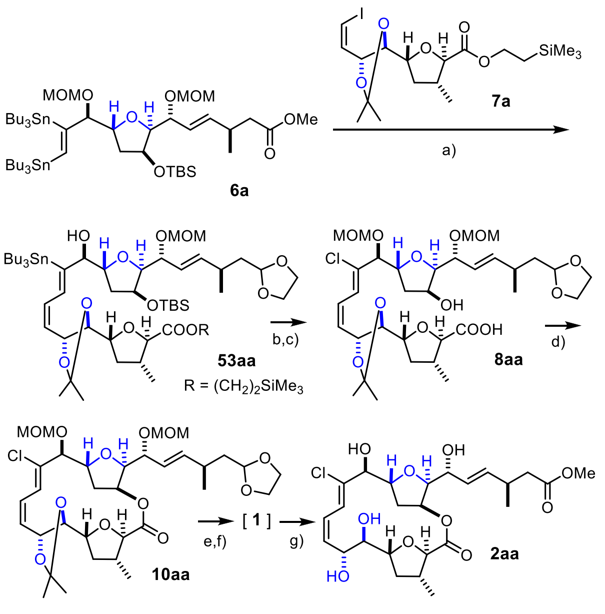
The Southern Fragments: Completion of the Diverted Approach. As discussed above, the "diverted" approach to the four required southern fragments foresaw a homologation with or without epimerization. To this end, diol **44** was triethylsilyl (TES)-protected, and the resulting product was subjected to Swern oxidation.[65] Aldehyde **46** was then added at low temperature to a solution of the Bestmann-Ohira reagent[66] that had been preactivated with MeOK in THF at −78 °C (Scheme 9).[67] Cleavage of the remaining silyl ether furnished enyne **50a** in readiness for oxidative ring closure. Isomer **50c** was prepared analogously from **31**. For homologation with concomitant epimerization,[68] **44** (or **31**) was first oxidized to the corresponding lactol **47** (or **49**), which was then reacted with the Bestmann-Ohira reagent and K_2CO_3 under equilibrating protic conditions in refluxing MeOH to give **50b** (or **50d**). For the brevity of this sequence, the low yield of this last step was deemed acceptable, and the reaction was not optimized any further.

Rather, our focus shifted to the critically important cobalt-catalyzed oxidative cyclization of these compounds to the required 2,5-*trans*-configured tetrahydrofuran derivatives.[36−39] In view of the uncertainties concerning this transformation mentioned above, we were pleased with the nearly perfect chemoselectivity manifest in the formation of **51a**−**51d**: only the double bond of the enyne substrates **50** participated in a 5-*exo-trig* cyclization, regardless of the equidistance between the −OH group and the unhindered terminal alkyne.[69] This exquisite profile comes on top of the impeccable diastereoselectivity for the *trans*-isomer (dr ≥20:1), a virtue that had already surfaced during the preparation of the northern sector (see above) as well as in many other examples documented in the literature.[13,36−40] One can therefore rightfully claim that the oxidative Mukaiyama cyclization is a premier methodology when it comes to making such cyclic ethers.

Equally gratifying was the outcome of the subsequent hydroindation/iodination reaction.[48,49] To this end, $InCl_3$ was treated with Dibal-H to form $[HInCl_2]$ in situ, which adds to the terminal alkyne of **51** in the presence of Et_3B/O_2 as radical initiator to give the corresponding (*Z*)-configured iodoalkene upon quench with I_2. The stereoselectivities were exquisite, and the yields were good to excellent in all cases investigated herein, but the reaction rate was found to be substrate-dependent. Specifically, compounds **51a** and **51d** reacted swiftly at −78 °C, whereas the temperature had to be raised to −40 °C in case of the isomeric substrates **51b** and **51c**. This aspect deserves further study, since no obvious reasons present themselves to explain this differential reactivity. Compounds **52a**−**52d** were then transformed into the appropriately protected southern building blocks **7a**−**7d** by oxidation/esterification under standard conditions.

The Macrocyclic "Library" and End-Game. With two northern and four diastereomeric southern sectors in hand, the preparation of all eight envisaged "chagosensine-type" isomers was a matter of "parallel" synthesis. Full optimization of the individual steps was not intended at this stage; rather, it was hoped that the sequence originally developed in this laboratory in pursuit of this challenging target would be sufficiently robust to bring all targeted macrocyclic chagosensine precursors into reach without amendment of the reaction conditions.[1] This proved indeed to be the case (Scheme 10): critically important was the fact that the challenging site-selective Stille coupling of the polyfunctionalized 1,2-distannane derivatives **6** with the elaborate (*Z*)-iodoalkene derivatives **7** worked in yields of 32−70% for all combinations under our standard conditions (($(tBu_3P)_2Pd$ (15−20 mol %), $[Ph_2PO_2][NBu_4]$, LiCl, NMP, 60 °C).[70−72] The subsequent tin/chloride exchange with retention of the double-bond geometry was invariably high yielding (69−98%).[22−24] It is perhaps unsurprising that the biggest scatter in terms of yields was observed in the macrolactonization step of the *seco*-acids **8** under forcing Yamaguchi conditions (11−72%):[25,73] it is at this point that the different stereochemical arrays translate into largely different ring strain, which obviously affects the ease of cyclization. In the least favorable cases, competing cyclodimerization of the *seco*-acid to the corresponding lactide was observed (see the Supporting Information). This aspect notwithstanding, all targeted lactones of type **10** were secured, the constitution of which was rigorously confirmed at this stage by extensive spectroscopic and spectrometric analyses (see the Supporting Information).

Scheme 10. Preparation of the Chagosensine-type Macrolactones Exemplified for the Stable Diastereomer 2aa[a]



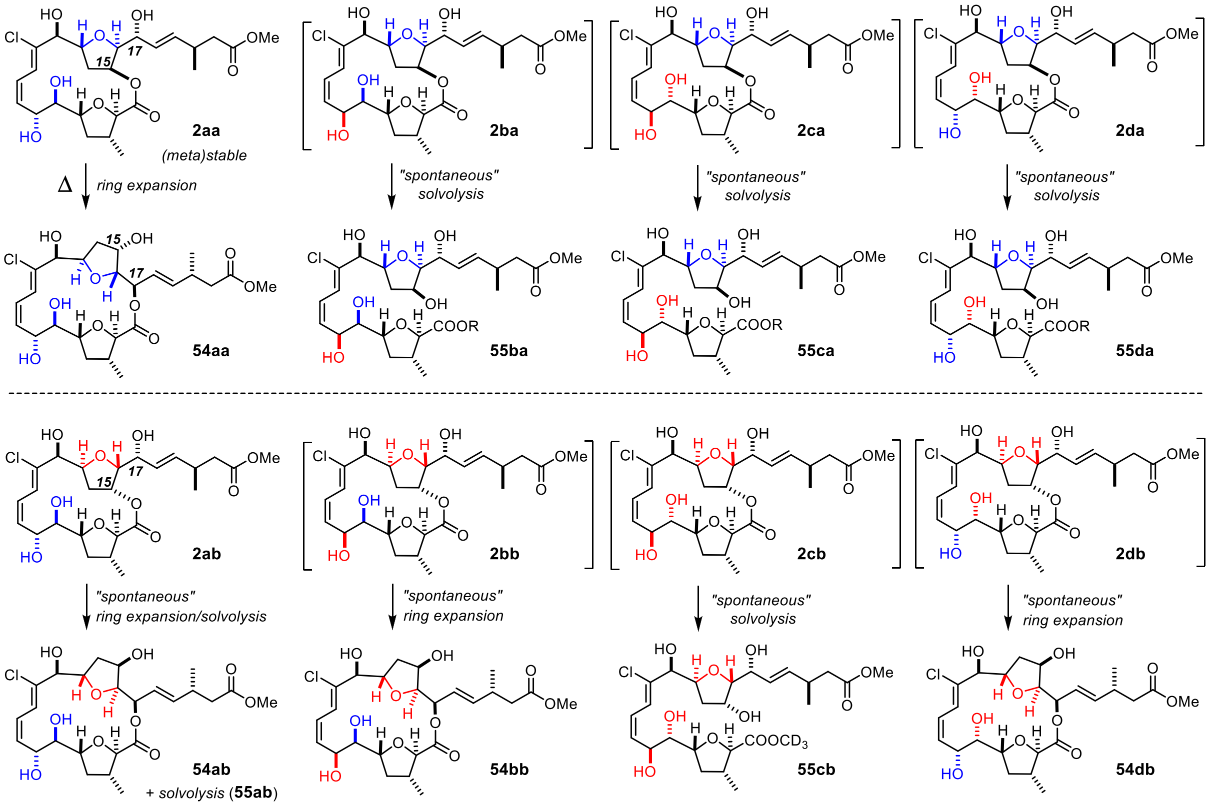
[a]Reagents and conditions: (a) **7a** (slow addition), $(tBu_3P)_2Pd$ (15 mol %), $[Ph_2PO_2][NBu_4]$, LiCl, NMP, 60 °C, 50%; (b) $CuCl_2$, 2,6-lutidine, THF, 78%; (b) MOMCl, TBAI, $(iPr)_2NEt$, 1,2-dichloroethane, 50 °C, 92%; (c) TBAF·$3H_2O$, THF, 0 °C → RT, quant; (d) 2,4,6-trichlorobenzoyl chloride, $(iPr)_2NEt$, THF, then DMAP, toluene, reflux, 40% (**10aa**) + ca. 6% (epimer) + 13% (lactide); (e) Me_2BBr, CH_2Cl_2, −78 °C; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/$tBuOH$/H_2O (4:4:1), 0 °C; (g) CH_2N_2, CH_2Cl_2, 20% (over three steps).

All that remained at this juncture was the global deprotection of these compounds with excess Me_2BBr[28−30] followed by Pinnick-oxidation of the unmasked aldehydes to the corresponding acids.[74,75] On the basis of our experience with the first isomer (see the Introduction), we were prepared to convert these acids immediately into the corresponding methyl esters **2** on treatment with diazomethane (see Scheme 10).[1]

Despite this precaution, we were confronted with the acute instability of all but the initial isomer **2aa**. Only this product—which corresponds to the originally proposed structure of chagosensine—was stable in $[D_4]$-MeOH/$[D_5]$-pyridine (1:1; this solvent mixture had been used in the isolation paper) to allow for full characterization by NMR spectroscopy, but the data were far from matching those reported in the literature (see the Introduction).[1] *All other isomeric lactones of type* **2** *react with the medium used to analyze the supposed natural product* (Scheme 11).[76] They underwent solvolysis with formation of the corresponding (deuterated) methyl esters **55** during the time it takes to record high-resolution NMR spectra (600 MHz). In addition, the derivatives comprising an inverted northern THF ring (**2ab**, **2bb**, **2cb**, **2db**) were prone to competing translactonization with the C17−OH group in the side chain, resulting in the formation of the ring-expanded 18-membered lactones **54**; no such behavior was mentioned in the isolation paper.[2] Three of the expanded isomers were sufficiently stable to be isolated and fully characterized; the structure assignment is hence unambiguous. Moreover, when metastable **2aa** was heated in toluene for several days, it also succumbed to ring expansion to give **54aa**. These results show that the stereostructure of the northern THF impacts on the ease of translactonization, but the bias to undergo this reaction is inherent to the entire series, likely because of the high ring strain of the core.

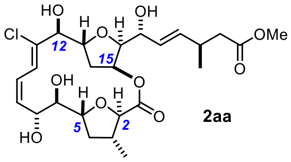
Comparison of the Analytical Data. This innate instability in the medium used to characterize the natural product implies that "chagosensine" cannot be any of the eight diastereomeric macrolides prepared during this synthesis campaign. NMR spectroscopy confirms this conclusion: even though lactone opening and/or translactonization occurred during the time it took to record full NMR data sets, the initially targeted yet unstable 16-membered lactones were transiently observed. In the cases of **2ba**, **2bb**, **2cb**, and **2da** we were been able to extract their data from the very complex spectra of the mixtures. Comparison with the published data of chagosensine methyl ester[2] showed beyond any doubt that none of them are matching (see the Supporting Information). In cases in which ring expansion was occurring, the data of the resulting 18-membered lactones **54** were also compared with those of the natural product but once again were found to deviate considerably. The same is true for the data of the (deutero) methyl esters **55** formed by solvolysis.

Scheme 11. Final Product Library



The overall conclusion is hence clear—and disillusioning. Even though this situation may make a discussion of further details unnecessary, a few observations are so striking that they demand explicit mentioning:

(i) The graphic in the original publication depicting relevant NOESY data does not show any correlation between the northern and the southern sectors of chagosensine,[2] which is at odds with a compound that is supposed to be a strained 16-membered lactone. Such indicative contacts are prominently featured in the spectra of all synthetic samples, both in protected and unprotected format. We wonder if their absence in the isolation paper is nothing but a lapse or whether the problem is more profound in that the sectors of chagosensine might not be united in the way proposed in the isolation paper.



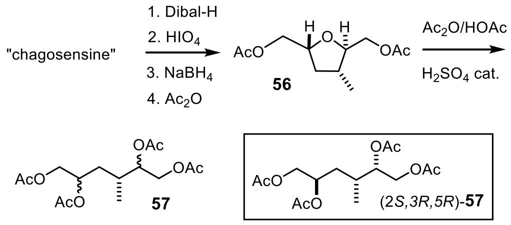
2aa

(ii) Several conspicuous NMR shifts reinforce the doubt: H15 of chagosensine is reported to resonate at $\delta_H = 5.08$ ppm,[2] whereas the corresponding protons of all synthetic samples experience a much more pronounced acylation shift ($5.39 \leq \delta_H \leq 5.55$ ppm). The same is true for related natural products such as haterumalide NA, NC, and isolaulimalide (see Scheme 1, $\delta_H = 5.29$, 5.27, and 5.44 ppm, respectively).[6−10] For this consistent difference, it is questionable if chagosensine actually contains a lactone ring.

(iii) Yet another systematic deviation concerns the southern THF ring. Specifically, the ^{13}C NMR signals of C2 and C5 of all synthetic samples are strongly deshielded relative to the corresponding sites in chagosensine, with shift differences of no less than $\Delta\delta_{C2}$ 4.6−6.3 ppm and $\Delta\delta_{C5}$ 8.1−9.3 ppm. Discrepancies of such magnitude render the presence of this supposedly *trans*-disubstituted cyclic ether in the natural product improbable.

(iv) Related to this issue is an incertitude about the degradation study undertaken by the isolation team to establish the stereostructure of the presumed southern THF ring (Scheme 12).[2] Excision from the natural product by oxidative degradation followed by ring fission of the resulting fragment **56** with Ac_2O/HOAc and catalytic H_2SO_4 is supposed to furnish four diastereomeric tetraacetates **57**.

Scheme 12. Reassessment of the Degradation Study



The corresponding scheme in the isolation paper does indeed show wiggled bonds, but the experimental part lists only the ^{1}H NMR data of a single diastereomer isolated in no less than 48.5% yield.[2] All reported shift and *J*-values correspond exactly (up to two digits after the comma) to those previously reported for (*S*,*R*,*R*)-**57**, although the pertinent reference is missing.[77] Such perfect concordance is certainly possible; interestingly, this prior study had also reported the data of (*R*,*R*,*R*)-**57**, which are distinctly different. If this compound (and probably two additional isomers) had been formed in the degradation study, it (they) should not have gone unrecognized.

(v) Yet another puzzling data point concerns the allylic alcohol C12 adjacent to the chlorodiene. This C atom purportedly resonates at $\delta_C = 61.3$ ppm in chagosensine[2] but is massively deshielded in all synthetic samples, with $\Delta\delta$ of up to 18.2 ppm (!) in isomer **2aa** (δ_C = 79.5 ppm). The ring-expanded lactones **54** as well as a number of other products containing a similar motif—be they simple or structurally complex (Figure 2)[9c,23,24]—show equally deshielded signals, regardless of the NMR solvent used. Therefore, it is possible if not even likely that chagosensine does not contain this particular substructure.

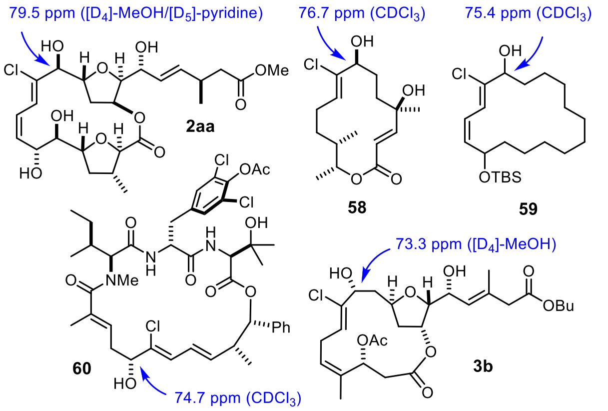


Figure 2. Reference compounds that make it unlikely that the signal reported for chagosensine (δ_C = 61.3 ppm) shows the presence of an allylic alcohol adjacent to a chlorodiene (alkene).

(vi) Even the presence of the salient (*Z*,*Z*)-configured 1,3-chlorodiene entity altogether is questionable, which supposedly renders chagosensine unique. The literature reports an absorption maximum of the natural product of λ_{max} = 230 nm (MeOH),[2] whereas all synthetic samples show $\lambda_{max} \geq 244$ nm (MeOH/H_2O or MeCN/H_2O).[78] One might argue that our reference compounds are macrolides in which the 1,3-chlorodiene unit could be twisted out of coplanarity, whereas the issues addressed above cast doubts if the natural product really contains the proposed macrolactone ring. Even if it does not, such a bathochromic shift corresponding to an excitation energy difference of at least 0.25 eV is almost certainly too big to be explained by conformational differences; for example, acyclic 7-chloroocta-4,6-dienoic acid ester also absorbs at λ_{max} = 244 nm (solvent not specified).[79] Curiously, it was this particular compound that had been cited in the isolation paper to support the structure assignment—but without mentioning the actual data or discussing the obvious discrepancy.[2]

(vii) For compound **2aa**, which is nominal chagosensine methyl ester, we obtained high-resolution mass data for $[M + Na]^+$ (m/z = 553.1809) corresponding to m/z = 553.1811 calculated for $C_{25}H_{35}{}^{35}ClO_{10}$ + Na. The isolation team reported high-resolution fast atom bombardment mass spectrometry (HR-FABMS) for what they call chagosensine methyl ester ($C_{25}H_{35}{}^{35}ClO_{10}$ + H, $[M^+ + H]^+$):[2] their experimental result (m/z = 531.2313) is compared to a theoretical value of m/z = 531.2308, but this reference point turns out to be wrong: the correct mass for the proposed composition is m/z = 531.1992. An inadvertency is unlikely, since the same mistake is documented for chagosensine itself:[2] for a compound with the presumed composition $[C_{24}H_{33}{}^{35}ClO_{10} + H]^+$ ($[M + H]^+$) the authors measured m/z = 517.2153 matching their calculated m/z = 517.2151, but the correct theoretical mass is m/z = 517.1835. The differences are significant but unexplained: The recorded m/z would better fit to a compound of the formula $C_{25}H_{38}{}^{35}ClO_9$ (m/z = 517.2199) with a degree of unsaturation of only six rather than eight as in nominal chagosensine.

CONCLUSIONS

For the many inconsistencies, inaccuracies, and potential mistakes, we firmly believe that chagosensine has little to do with the structure proposed by the isolation team.[2] We certainly appreciate the difficulties in elucidating the structure of natural products of this level of complexity, especially when isolated from the (marine) source organism in tiny amounts, but even this argument is somehow invalid, since an appreciable 24 mg of chagosensine had been available at the outset.[2]

Mis-assigned natural products are by no means rare, an experience that our group also had to make on several occasions in the past.[80,81] In view of the degree and dimension of the present case, it is regrettable that neither an authentic sample nor copies of the original spectra have been made available upon request; no Supporting Information has been deposited with the original publication either.[2] As any reassessment is therefore precluded, it is idle to speculate about why and where the structure elucidation exercise went wrong.[82]

From the more holistic viewpoint, the endeavor outlined above—comprising well over 100 synthetic transformations—can certainly be taken as a cautionary tale for natural product chemistry at large, which is criticized as hyperbolic anyway in certain academic, industrial, and political environs. To reduce the story to this sole conclusion, however, would miss out on other lessons: the enigmatic chagosensine case shows that virtually any inspiring target—even if incorrect—instigates methodological and strategic innovation that only complex settings are able to incubate. Along comes a moral about standards in data documentation (and perhaps peer review). Finally, it reiterates that structure elucidation remains error-prone even in the age of advanced spectroscopy. Humankind has benefitted enormously from natural products;[83] it would be ignorant to deny the bigger picture on the basis of probably legitimate yet, in the end, sporadic discontent.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c01700.

Experimental section including reassessment and comparison of published data, characterization data (PDF)

NMR spectra of new compounds (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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