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Concise Total Synthesis of Enigmazole A

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Abstract: *An efficient entry into the phosphorylated marine macrolide enigmazole A is described. Enigmazole A interferes with c-Kit signaling by an as yet unknown mode of action and is therefore a potential lead in the quest for novel anticancer agents. Key to success is a gold-catalyzed cascade comprising a [3,3]-sigmatropic rearrangement of a propargyl acetate along the periphery of a macrocyclic scaffold, followed by a transannular hydroalkoxylation of the resulting transient allenyl acetate. This transformation mandated the use of a chiral gold catalyst to ensure a matching double-asymmetric setting. Other noteworthy steps are the preparation of the oxazole building block by a palladium-catalyzed C–H activation, as well as the smooth ring-closing alkyne metathesis of a diyne substrate bearing a propargylic leaving group, which has only little precedent.*

Enigmazole A (**1**) and two unnamed congeners (**2** and **3**) were isolated from a sponge of the genus *Cinachyrella enigmata* collected off the Papua New Guinean coast line (Scheme 1).[1] These compounds are not only the first phosphorylated macrolides of marine origin but were reported to elicit an exceptionally rare phenotypic response in that they interfere with c-Kit signaling. The c-Kit receptor is an evolutionary highly conserved transmembrane glycoprotein with tyrosine kinase activity, which regulates, inter alia, the proliferation, differentiation, growth, and survival of hematopoietic cells.[2] The encoding proto-oncogene serves as an important tumor marker, as mutations resulting in aberrant c-Kit signaling have been implicated in the development, migration, and recurrence of various cancers, most notably acute myelogenous leukemia and gastrointestinal stromal tumors.[2] The clinical relevance of this causal nexus is underlined by the success of kinase inhibitors such as Imatinib (Gleevec), an approved drug for the treatment of exactly these tumors, which hits c-Kit as one of its molecular targets.[3]

Interestingly, the available data suggest that the enigmazoles do not act as kinase inhibitors but rather interfere with a different, as yet unknown step of the c-Kit signaling cascades.[1] Equally noteworthy is the fact that **1**–**3** were reported not to distinguish between cells with wild-type or mutant c-Kit, whereas several minor side fractions of the crude sponge extract showed high selectivity for malignant cells expressing mutant c-Kit. The recorded spectral data suggest that the active components are siblings of **1**–**3**.[1] Therefore a diverted total synthesis exercise[4] centered on the enigmazole core holds considerable promise: It might help identify the minimum pharmacophore and the structural determinants responsible for the desired selectivity, while affinity- or fluorescence-tagged derivatives could enable the identification of the actual biological target. To this end, it is necessary to establish a concise entry into this class of exceedingly rare macrolides, an entry which is sufficiently robust to allow a meaningful material throughput, yet flexible enough to accommodate late-stage digressions towards hybrid analogues.

An elegant total synthesis of enigmazole A (**1**) as the parent compound of this series has already been reported, by Molinski and co-workers, back-to-back with the isolation paper.[5,6] Their approach hinged upon a selective macrolactonization of an almost fully decorated *seco*-acid which had to be conformationally biased for cyclization by a supplementary unsaturation in the frame. We saw the opportunity to develop a fundamentally different route which envisaged the concomitant formation of the signature tetrahydropyran ring and the C5–C7 oxygenation pattern in the final stages of the synthesis, only after the macrocycle had been closed (Scheme 1). This task might be accomplished by a gold-catalyzed reaction cascade[7,8] commencing with a [3,3]-sigmatropic rearrangement of a propargylic acetate of type **C**.[9] The resulting allenyl acetate **B** is expected to engage with the same catalyst, and an ensuing transannular hydroalkoxylation should lead to the formation of the compound **A**, featuring a *cis*-disubstituted tetrahydropyran ring and a properly placed enol acetate as a handle for the installation of the phosphate at C5.[10,11] Obviously, the proper phasing of the two events is critical since any premature intervention of the C11–OH group across the macrocyclic ring would be detrimental. However, a simple feasibility study encouraged us to pursue this route.[12] If successful, the projected sequence provides opportunities for late-stage modification of the region carrying the distinctive phosphate ester, once the project enters into the phase of diverted total synthesis. From the purely chemical vantage point, it would help illustrate the prowess of π-acid catalysis, which remains surprisingly underrepresented in total synthesis compared with the overall activity in this topical field of research.[13,14]

An oxazole of type **H** had already been used by the group of Molinski,[5] but our route to this building block represents a convenient short cut (Scheme 2). Specifically, a copper-mediated *anti*-carbometalation[15] of the commercial propargyl alcohol **4** terminated by an iodine quench and subsequent O-methylation furnished compound **5**, which participated in direct coupling with the commercial oxazole-4-carboxylate **6** by palladium-catalyzed C–H activation.[16] This reaction obviates the need to prefunctionalize the heterocycle and furnished gram amounts of **7** in a well reproducible yield of 74%. The aldehyde **8**, formed by Dibal-H reduction of **7**,

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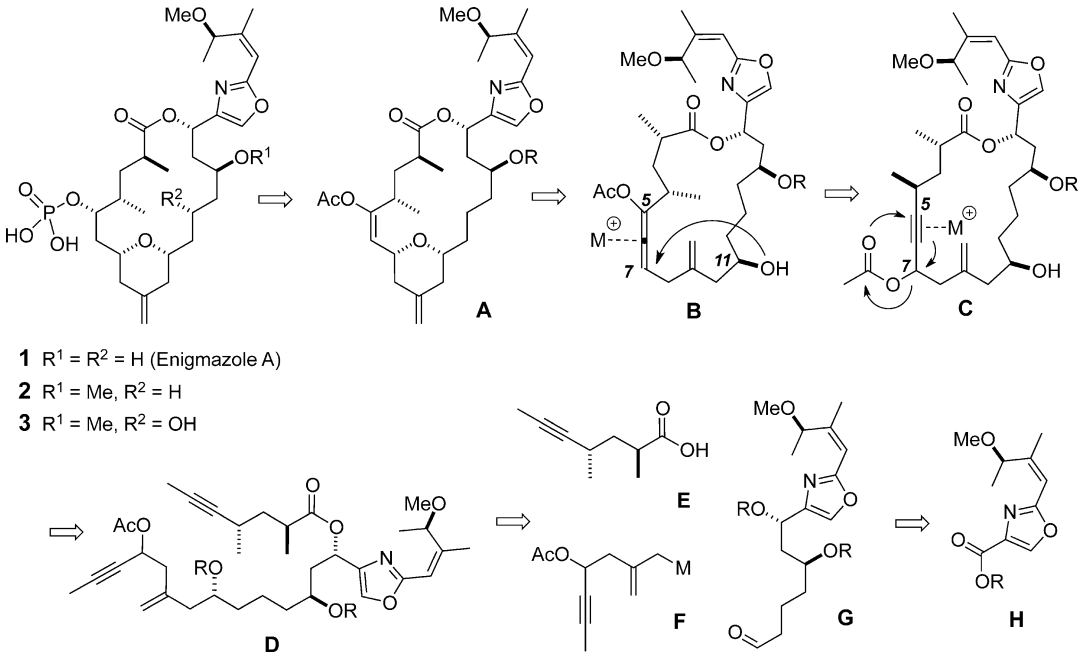


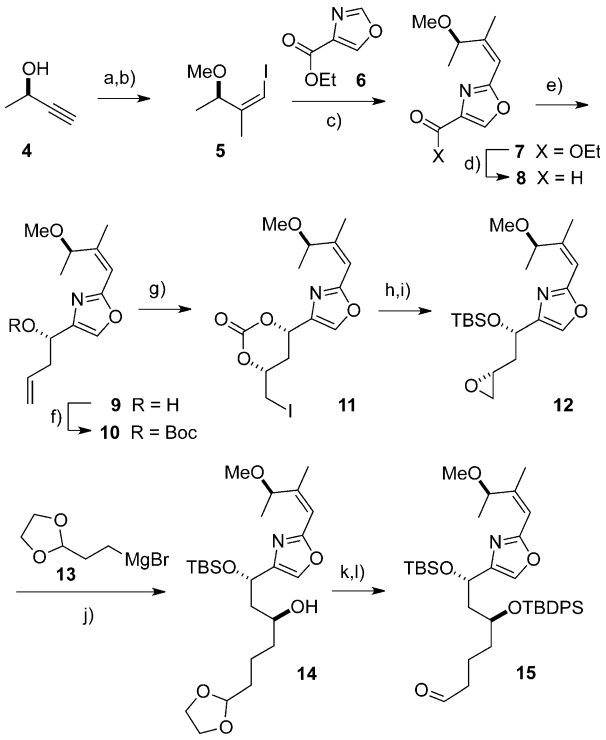
Scheme 1. Structures of **1**–**3** and retrosynthetic analysis of enigmazole A; R = generic protecting group.

participated exceedingly well in an asymmetric Keck allylation to give the alcohol **9** with high optical purity.[17] Other procedures were less productive. Attachment of a Boc-group then allowed the chiral information to be relayed to a terminal epoxide. To this end, the double bond in **10** was activated with IBr and the resulting product **11** was treated with K_2CO_3 in MeOH to cleave the cyclic carbamate and close the oxirane ring.[18,19] A copper-catalyzed opening of the epoxide in **12** with the functionalized Grignard reagent **13,**[20] in concert with routine protecting group management, led to **15** which was endowed with the necessary orthogonal silyl ethers.

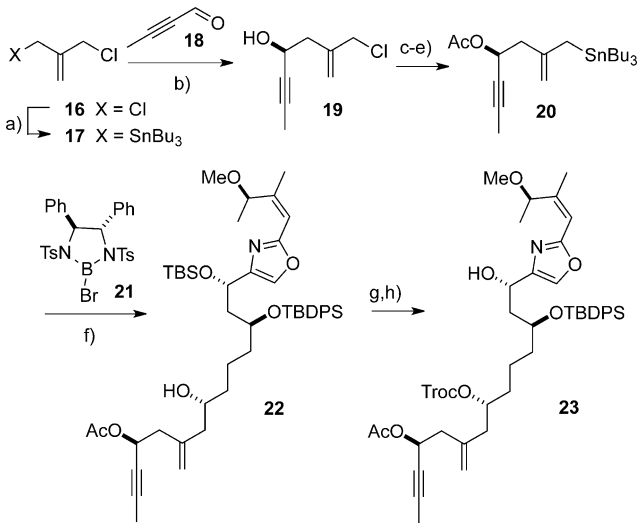
When the reaction of **15** with the functionalized allyltin reagent **20** was promoted with Corey's chiral bromoborane **21**,[21] the corresponding homoallyl alcohol **22** was obtained with high diastereoselectivity (d.r. > 10:1) and yield (Scheme 3). This outcome is rewarding in view of the delicate character of **20**, which bears an elimination-prone propargyl acetate motif. At the same time, it is instrumental for the projected transannular cycloetherification cascade in which the newly set stereocenter at C11 has to play a key role. In contrast to the ease of formation of **22**, the seemingly routine protection as the corresponding PMB ether failed to afford workable yields under a variety of reaction conditions. Gratifyingly, though, a Troc group was better behaved and equally orthogonal to the silyl ethers as evident from the selective TBS-cleavage with formation of the compound **23**.[22]

With good amounts of **23** in hand, the assembly and elaboration of the macrocyclic frame of enigmazole A was tackled. To this end, **23** was esterified with the acid **30**, which was prepared in a few straightforward steps, as shown in Scheme 4, using Myers auxiliary to control the enolate alkylation step.[23] The resulting ester **31** was subjected to a ring-closing alkyne metathesis (RCAM),[24] which furnished the desired cycloalkyne **32** in 79% yield on a 1.2 gram scale (single largest batch) at ambient temperature. In assessing this result, one has to consider that propargylic ester derivatives are inherently challenging substrates for RCAM and the number of successful applications is limited:[25] All alkyne metathesis catalysts are Schrock alkylidynes comprising an early-transition-metal center in its highest possible oxidation state.[26] Unless sufficiently tempered by an appropriate ancillary ligand set, their intrinsic Lewis acidity endangers substituents at the propargylic position as illustrated by the generic structure **I** (see insert in Scheme 4). Even if the propargyl alcohol remains intact, the presence of the leaving group opens yet another possible decomposition pathway in that the emerging alkylidyne of type **J**, which is nucleophilic at the carbon atom, might extrude the adjacent nucleofuge. The molybdenum ate-complex **38**, however, has the right balance: it exhibits high metathesis activity but leaves even sensitive functionality untouched.[27] The price to pay in this particular application was the fairly high loading of **38** (31 mol%) necessary for a full, fast, and clean conversion of the diyne **31**, which is endowed with many different donor sites.

An ultrasound-accelerated Troc cleavage with zinc dust furnished the alcohol **33** as an adequate substrate for the critical π-acid-catalyzed reaction cascade. Yet, this compound did not react when exposed to an assortment of catalysts of the type LAuX (L = Ph_3P, XPhos, NHC; X = SbF_6, NTf_2, OTs) in either CH_2Cl_2 or related solvents. This reluctance came as a surprise since $Ph_3PAuNTf_2$ had proven remarkably effective in our earlier, though admittedly rudimentary, model study.[12] We conceived that the most likely explanation[28] for this striking difference is the fact that the possible π-complexes[29] formed upon initial coordination of the catalyst to the alkyne in **33** are diastereomeric. If only one



Scheme 2. a) 1. MeMgBr, CuI, toluene, −78 °C→RT; 2. I_2, THF, −40 °C→RT, 74%; b) MeI, NaH, imidazole (10 mol%), THF, −40 °C→RT, 64%; c) $Pd(OAc)_2$ (5 mol%), 2-(dicyclohexylphosphino)-biphenyl (10 mol%), Cs_2CO_3, 1,4-dioxane, 110 °C, 74%; d) Dibal-H, CH_2Cl_2, −90 °C, 80%; e) allyltributyltin, $Ti(OiPr)_4$ (10 mol%), (*S*)-Binol (10 mol%), 4 Å M.S., CH_2Cl_2, −20 °C, 98% (d.r. > 95:5); f) $(Boc)_2O$, DMAP, MeCN, 92%; g) IBr, toluene, −90 °C, 54–73%;[19] h) K_2CO_3, MeOH, 79% (d.r. > 95:5); i) TBSCl, imidazole, DMAP (10 mol%), THF, 98%; j) **13**, CuI (20 mol%), THF, −78 °C→−40 °C, 92%; k) TBDPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 88%; l) TMSOTf, 2,4,6-trimethylpyridine, CH_2Cl_2, 97%; Boc = *tert*-butyloxycarbonyl, Dibal-H = diisopropylaluminum hydride, DMAP = 4-dimethylaminopyridine, M.S. = molecular sieves, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.



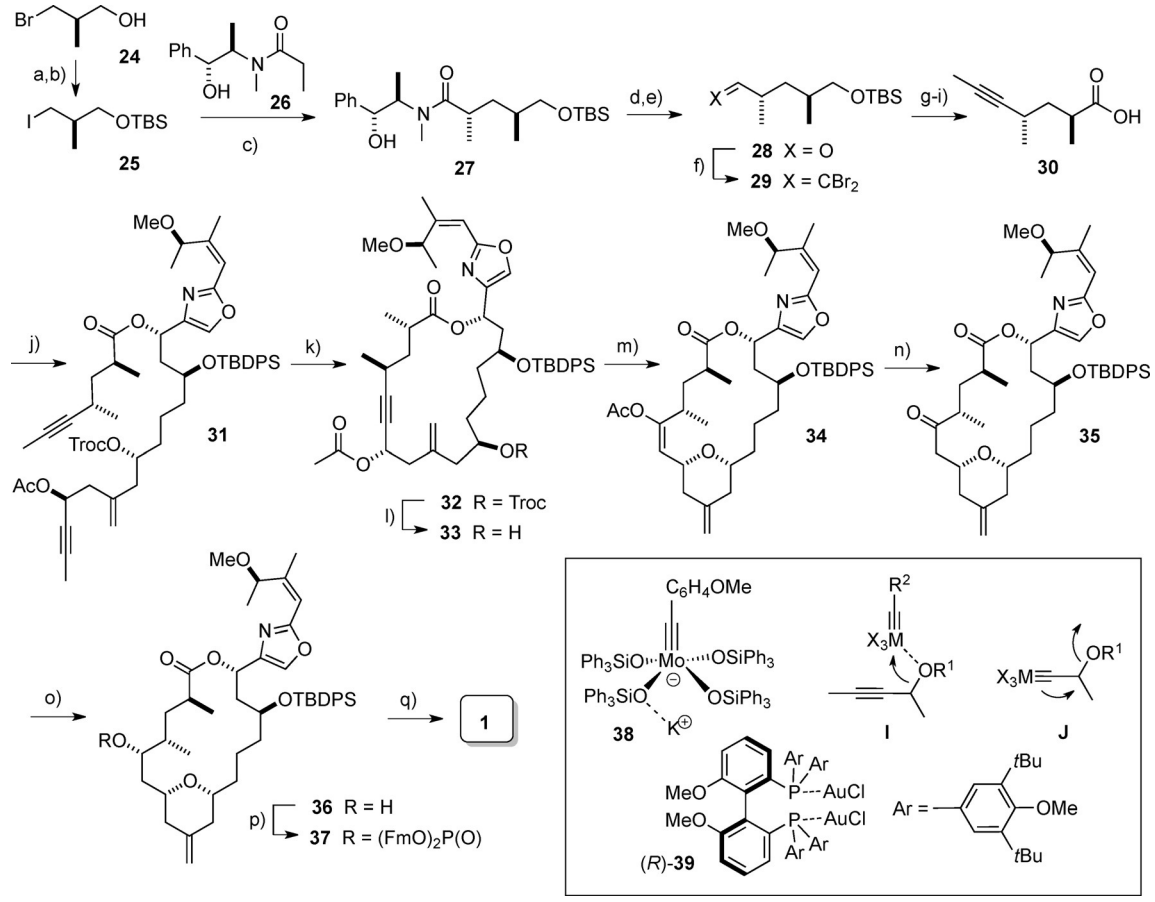
Scheme 3. a) LDA, Bu_3SnH, THF/pentane, 0 °C, then **16**, pentane, −78 °C, 49%; b) **18**, $Ti(OiPr)_4$ (10 mol%), (*S*)-Binol (10 mol%), 4 Å M.S., CH_2Cl_2, −20 °C, 84%, (≥95% *ee*); c) Ac_2O, Et_3N, DMAP (10 mol%), CH_2Cl_2, 93%; d) NaI, acetone, 70 °C, 88%; e) $Bu_3SnSnBu_3$, $[Pd_2(dba)_3]$ (2×1.7 mol%), THF, 55 °C, 73%; f) **15**, **21**, CH_2Cl_2, −78 °C, 95% (d.r. > 10:1); g) TrocCl, DMAP (10 mol%), pyridine, CH_2Cl_2, 0 °C→RT, quant.; h) camphorsulfonic acid (20 mol%), CH_2Cl_2/MeOH (3:1), 0 °C→RT, 61% (98% based on recovered starting material). dba = dibenzylideneacetone, LDA = lithium diisopropylamide, Troc = trichloroethyloxycarbonyl, Ts = 4-toluenesulfonyl.

of them is disposed for a [3,3]-sigmatropic rearrangement on conformational grounds, but does not readily form for steric and/or electronic reasons, no conversion will ensue.[30]

Based on this rationale, we started to screen chiral gold complexes with the hope of finding a matching substrate/catalyst pair.[31,32] In fact, the cationic species derived from the dinuclear Biphep complex (*R*)-**39** and 2 $AgSbF_6$[33] was not only able to overcome the inertia of the substrate but provided the desired enol acetate **34** in a well reproducible yield of no less than 91%. This excellent outcome met our expectation that the gold catalyzed [3,3]-sigmatropic rearrangement should be faster than the attack of the C11−OH group onto the resulting allenyl acetate of type **B** across the macrocyclic perimeter (Scheme 5). Moreover, the ether bond formation occurred exclusively at the site distal to the AcO substituent such that a six-membered rather than eight-membered ring is closed. The *cis* stereochemistry at the ring junctions, as rigorously confirmed by NMR spectroscopy, is indicative of the pseudo-chairlike transition state **K** for the transannular event. Methanolysis of the acetate in **34** released the desired ketone **35** in readiness for the completion of the total synthesis.[34]

While this result ultimately paved the way to the target, it remained to be seen whether the success was in fact rooted in the match between substrate and catalyst (Scheme 5). One may take the outcome of the reaction of **33** with the enantiomeric gold precatalyst (*S*)-**39** as a first indication: Although the desired product **34** was obtained, the reaction was erratic, thus giving yields in the range of 50–70%. Appreciable amounts (20–30%) of a by-product were formed in all runs; we confidently ascribe to it the structure **40** based on a detailed NMR investigation (see the Supporting Information), even though the stereochemistry of the bridging cyclopropane ring could not be unambiguously elucidated. Evidently, it is the *exo*-methylene group at C9 rather than the C11−OH which acts as a competing nucleophile, thus attacking the activated triple bond prior to allene formation. This sequence triggers a prototype cycloisomerization which has ample precedent in π-acid catalysis.[7,8,35]

An even stronger case is made by the completely different reactivity observed with 7-*epi*-**33** (Scheme 5), which was deliberately prepared to test our mechanistic hypothesis by reacting **15** with the stannane *ent*-**20** and thereafter following the route outlined above. While 7-*epi*-**33** was simply decomposed on treatment with (*S*)-**39**, the use of (*R*)-**39** furnished the benzene derivative **41** as the major product (together with ca. 10–20% of **34**). Its formation can be rationalized by assuming an attack of the *exo*-methylene group after the transient allenyl acetate **B** (or 5-*epi*-**B**) has formed, thus giving rise to an intermediate of type **O** which aromatizes by loss of HOAc.[36]

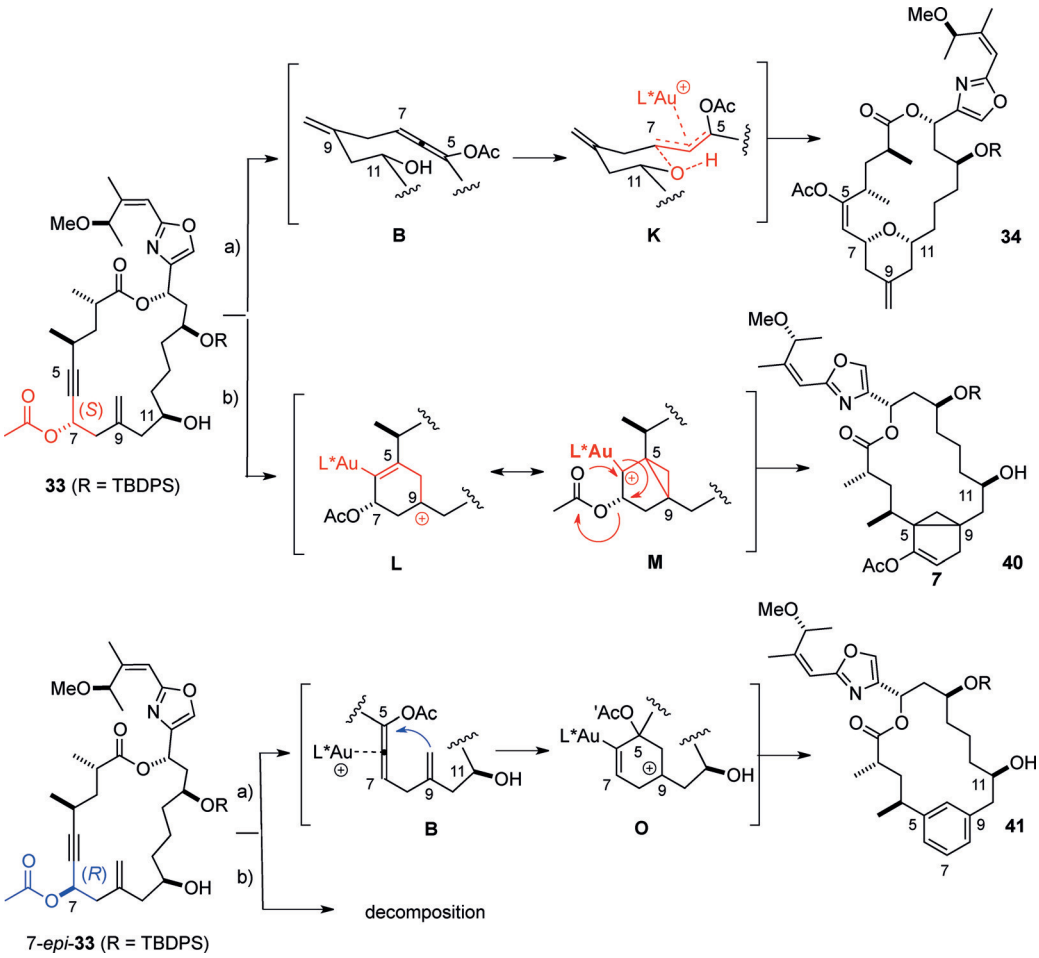


Scheme 4. a) NaI, acetone, reflux; b) TBSCl, imidazole, CH_2Cl_2, 0 °C, 85 % (over both steps); c) LDA, LiCl, THF, −78 °C→RT, 98 % (d.r. = 96:4); d) LDA, then $BH_3{\cdot}NH_3$, THF, 0 °C→RT, 89 %; e) TPAP (5 mol %), NMO, 4 Å M.S., CH_2Cl_2, 88 %; f) CBr_4, PPh_3, Zn, CH_2Cl_2, 74 %; g) *n*BuLi, then MeI, −78 °C→RT, 97 %; h) TBAF, THF, 96 %; i) TPAP (10 mol %), NMO·H_2O, MeCN, 92 %; j) 2,4,6-trichlorobenzoyl chloride, Et_3N, then **23**, DMAP, toluene, 0 °C, quant.; k) **38** (31 mol %), 4 Å M.S., 5 Å M.S., toluene, 79 %; l) Zn, HOAc, ultrasonication, 93 %; m) (*R*)-**39** (17 mol %), $AgSbF_6$ (34 mol %), CH_2Cl_2, 91 %; n) K_2CO_3, MeOH, 95 %; o) $NaBH_4$, MeOH, −40 °C, 61 % (+33 % of 5-*epi*-**36**); p) (i) $(FmO)_2PN{i}Pr_2$, tetrazole, MeCN; (ii) aq. H_2O_2, 0 °C, quant.; q) TBAF, HOAc, THF, 40 °C, 82 %. FmO = 9-fluorenylmethyloxy, NMO = *N*-methylmorpholino-*N*-oxide, TBAF = tetra-*n*-butylammonium fluoride, TPAP = tetra-*n*-propylammonium perruthenate.

Collectively, these greatly different outcomes demonstrate the critical role of proper stereochemical pairing between substrate and catalyst. This finding must be seen in the context of previous literature reports which showed that gold-catalyzed [3,3]-sigmatropic rearrangements of propargylic esters are reversible and the resulting allenyl derivates subject to rapid racemization.[37,38] If this were true for **33** and 7-*epi*-**33**, the configuration of the acetate-carrying C7 center should not matter. It remains to be seen whether the conflicting observations described herein are rooted in the peculiarities of the chosen catalyst or in the constraints of the particular substrate. At the *meta* level, however, this example bears witness to the notion that target-oriented synthesis often dissects scope and limitations of a given transformation more rigorously than collections of model compounds and hence remains an eminent driver for method development.

With the late-stage transannular cascade successfully reduced to practice, the conquest of enigmazole A (**1**) was only a few steps away (Scheme 4). Reduction of the ketone **35** with excess $NaBH_4$ gave the desired alcohol **36** in good yield, together with the readily separable 5-*epi*-**36** as a first candidate for library synthesis. The attachment of the FmO-protected phosphate was straightforward,[39] whereas the global deprotection of **37** required optimization. In the end, it was accomplished in a single operation using excess TBAF/HOAc buffer at a slightly elevated temperature to cleave the FmO substituents as well as the remaining silyl ether. The spectral data of synthetic enigmazole A (**1**), which was isolated as the free acid as well as in salt form, matched those reported in the literature (for details see the Supporting Information).[1,5]

Overall, the total synthesis of enigmazole A (**1**) described above is robust, concise and convergent, and provides a platform for structural modifications. First forays are currently being pursued. Although the step count is similar to that of the only previous synthesis of this promising target (23 versus 24 steps for the longest linear route),[5] the new entry is considerably more productive (up to 3.3 % versus 0.41 %) and conceptually different. It illustrates the power of transannular functionalization,[11,40] a concept that gains momentum to the extent that macrocycle formation becomes increasingly more facile, not least with the help of ever more mature (alkyne)



Scheme 5. a) (*R*)-**39** (17 mol%), $AgSbF_6$ (34 mol%), CH_2Cl_2, from **33**: 91% (**34**), from 7-*epi*-**33**: [ca. 50% (**41**) + 10–20% (**34**)]; b) (*S*)-**39** (10 mol%), $AgSbF_6$ (20 mol%), CH_2Cl_2, from **33**: [50–70% (**34**) + 20–30% (**40**)], from 7-*epi*-**33**: decomposition. L* = chiral ligand.

metathesis catalysts. Furthermore, this project was initially conceived to showcase our growing confidence in π-acid catalysis, which still has a long way to go in terms of applications to elaborate and highly precious substrates.[13] Though ultimately successful, the still rather empirical flavor of this topical field became apparent. This conclusion, drawn from a total synthesis project, invigorates our parallel efforts to contribute to a deeper mechanistic understanding of noble-metal catalysis in general.[41]

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Keywords: alkynes · gold · metathesis · natural products · transannular reactions

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