Total Synthesis of Enigmazole A from *Cinachyrella enigmatica*. Bidirectional Bond Constructions with an Ambient 2,4-Disubstituted Oxazole Synthon

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Abstract: The first total synthesis of the cytotoxic marine macrolide enigmazole A has been completed in 22 steps (longest linear sequence). The sensitive, densely functionalized 2,4-disubstituted oxazole fragment was constructed using an efficient Negishi-type coupling of an oxazol-2-ylzinc reagent formed directly from the parent ethyl 2-iodooxazole-4-carboxylate by zinc insertion. Other key steps include a hetero-Diels−Alder cycloaddition to form the central embedded pyran ring, a Wittig reaction to unite Eastern and Western hemispheres, and a ring size-selective Keck macrolactonization.

Introduction

Enigmazole A (**1**, Figure 1) and related congeners **2** and **3** are members of a family of cytotoxic macrolides isolated from the sponge *Cinachyrella enigmatica* that includes compounds that selectively target aberrant c-Kit signaling.[1−3] This appears to be a very rare phenotypic effect, seen before in only 32 natural product extracts of a panel of 134 631 extracts that were screened in a differential response assay with wild-type and c-Kit mutant cells. c-Kit is a type-III transmembrane protein−tyrosine kinase[4] that is important for control of gametogenesis, hematopoiesis, mast cell development and function, and melanogenesis[5] but also implicated in several gain-of-function mutations in humans that confer constitutive, ligand-independent kinase activity. The latter has implications for cancer patients with a specific c-Kit genotype that undergo treatment with Gleevec (Novartis Pharmaceuticals Corp.; common name: imatinib mesylate) for gastrointestinal stromal cell tumors (GISTs).[6] Enigmazole A (**1**) exhibits potent in vitro cytotoxicity toward IC-2 mast cells (IC$_{50}$ 0.37 μg/mL).[1]

The structure of **1** consists of an 18-membered macrolide ring decorated with a densely functionalized 2,4-disubstituted oxazole

enigmazole A **1**: R^1 = H, R^2 = H
2: R^1 = Me, R^2 = H
3: R^1 = Me, R^2 = OH
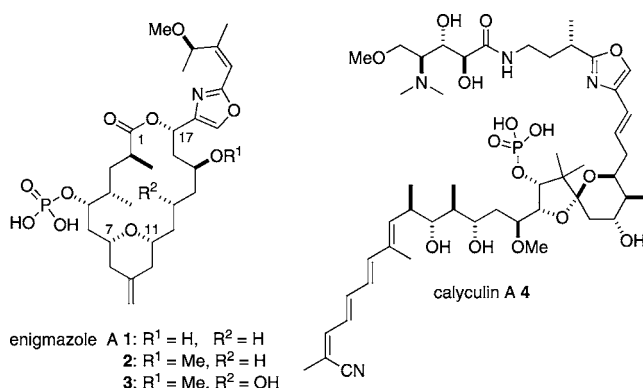
Figure 1. Structure of the cytotoxic macrolide enigmazole A (**1**).

appended at C17 and a phosphate ester at C5, a rare feature found in only a few polyketide natural products, including calyculin A.[7] Calyculin A (**4**) is a potent phosphatase inhibitor that has been the subject of several total syntheses.[8] We report here the first total synthesis of enigmazole A (**1**) which deploys bidirectional C−C bond construction around a preformed 2,4-disubstituted oxazole unit. This strategy exploits both electrophilic and (latent) nucleophilic reactivity of a versatile oxazole synthon, ethyl 2-aminooxazole-4-carboxylate (**11**), which is readily available in one step from urea and ethyl bromopyruvate.[9]
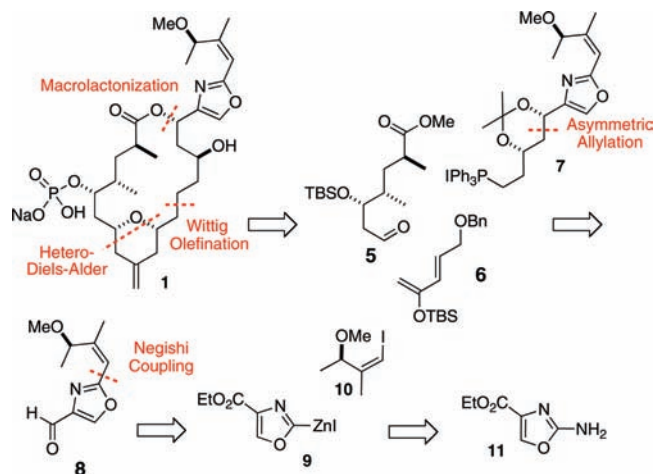
† Department of Chemistry and Biochemistry.
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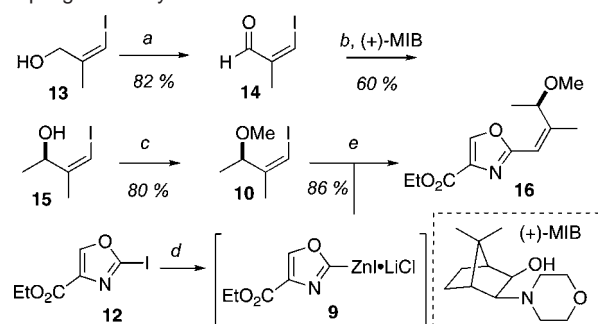
Scheme 1. Retrosynthetic Analysis of Enigmazole A (**1**)

Scheme 2. Formation of Oxazol-2-ylzinc Reagent **9** and Negishi Coupling with Vinyl Iodide **10**[a]

[a] Reagents and conditions: (a) MnO$_2$, CH$_2$Cl$_2$, rt, 1 h, 82%; (b) (+)-MIB, Me$_2$Zn, hexanes, 0 °C → rt, overnight, 60%; (c) (i) NaH, THF, imidazole (cat.), 0 °C → rt, 2 h, then (ii) MeI, 1.5 h, 80%; (d) Zn, LiCl, THF, rt, 10 min; (e) Pd(PPh$_3$)$_4$, rt, 1 h, 86%.

Synthetic Plan

Antithetic analysis (Scheme 1) shows major disconnections at the macrolide ester bond and C12−C13 bond leading to the "Eastern" fragment **7** that could be united with the remainder of the molecule by Wittig olefination. The central embedded pyran ring was envisioned to arise in turn from a diastereoselective hetero-Diels−Alder (HDA) cycloaddition between aldehyde **5** and diene **6**. We were cognizant that the major challenges would lie in construction of the Eastern fragment bearing the oxazole. Commonly, methods for construction of 2,4-disubstituted oxazoles are reliant upon *de novo* assembly of the oxazole ring from serine-derived fragments by cyclodehydration−oxidation.[10] We sought to introduce the oxazole ring of **1** at an early stage by "grafting" of C2 and C4 substituents to a preformed oxazole synthon, represented by oxazol-2-ylzinc reagent **9**, in anticipation of C20−C21 bond formation through Negishi coupling with **10**.[11]

The use of metalated oxazoles, in particular 2-oxazole zincates, is underdeveloped in natural product synthesis.[12] Simple oxazol-2-ylzinc reagents have been prepared previously

by transmetalation of 2-lithiooxazole with ZnCl$_2$; however, the strongly basic conditions required for C2 deprotonation are mutually exclusive with the preparation of oxazole zincates bearing reactive substituents such as carboxylic acid esters.[13] The 2-aminooxazole carboxylate ester **11** embodies ambident reactivity that can be revealed in stages: the *electrophilicity* of the carboxylate at C4 and latent *nucleophilicity* at C2 that can be unmasked through diazonium salt formation, conversion to the iodide **12**, and direct metalation with Zn^0 to give the oxazol-2-yl zincate **9**. While the corresponding ethyl 2-bromooxazole-4-carboxylate has been used in Pd-promoted Stille coupling of oxazoles,[14] our preliminary surveys showed the latter were poor substrates for Zn insertion. Iodooxazole **12** (Scheme 2), a new oxazole synthon, was conveniently prepared on a multigram scale by condensation of urea and ethyl bromopyruvate to provide **11**, followed by diazotization and iodide displacement (see Supporting Information). Iodide **12** was then smoothly transformed into the oxazol-2-yl zincate **9** under Knochel conditions (Zn, LiCl, THF, 10 min).[15] Solutions of **9** in THF were appreciably stable; a stock solution of **9** (0.5 M) stored in the dark under N$_2$ at 4 °C lost less than 23% of its titer over 1 month.[16]

Synthesis of the Eastern Hemisphere

Synthesis of the key intermediate **7** began with preparation of vinyl iodide **10**. Oxidation of allylic alcohol **13**[17] gave the geometrically unstable aldehyde **14**, which was immediately

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Scheme 3. Synthesis of Eastern Hemisphere Phosphonium Salt 7[a]
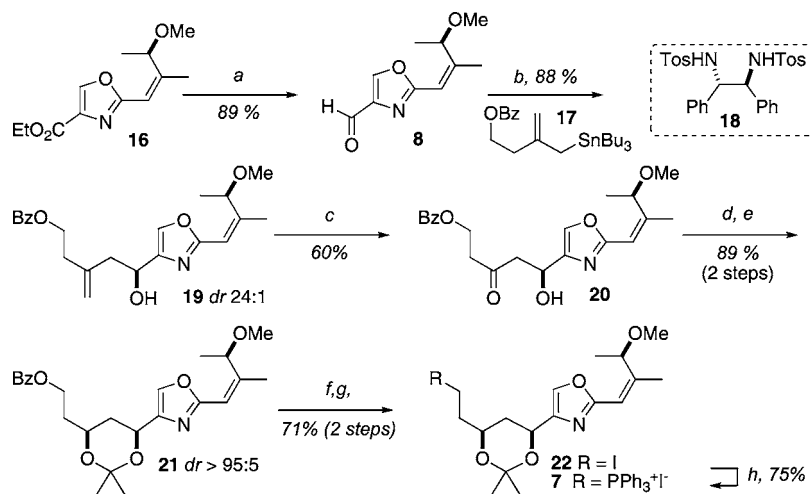
[a] Reagents and conditions: (a) DIBAL, CH$_2$Cl$_2$, toluene, −90 °C, 2 h, 89%; (b) N,N′-((1S,2S)-1,2-diphenylethane-1,2-diyl)bis(toluenesulfonamide) (18), BBr$_3$, CH$_2$Cl$_2$, 0 °C → rt, 1 h, then 17, 0 °C → rt, 15.5 h, then 8, −78 °C, 1.5 h, 88%, dr 24:1; (c) (i) OsO$_4$, K$_3$Fe(CN)$_6$, K$_2$CO$_3$, NaHCO$_3$, DABCO, t-BuOH/H$_2$O, rt, 2.5 h, then (ii) NaIO$_4$, THF/H$_2$O, 0 °C → rt, 30 min, 60%; (d) Et$_2$BOMe, NaBH$_4$, THF, MeOH, −78 °C, 4 h; (e) 2,2-dimethoxypropane, CSA, rt, 1 h, 89% (two steps); (f) DIBAL, CH$_2$Cl$_2$, toluene, −78 → −10 °C, 2 h, 80%; (g) PPh$_3$, imidazole, I$_2$, THF, 0 °C, 1 h, 89%; (h) PPh$_3$, Li$_2$CO$_3$, MeCN, toluene, microwave, 130 °C, 30 min, 75%.

treated with Me$_2$Zn in the presence of (+)-MIB[18] to give secondary alcohol 15 in good yield and high enantiomeric excess (60%, 93% ee from Mosher's ester analysis;[19] see Supporting Information), with retention of olefin geometry. Methylation of the newly formed alcohol under standard conditions provided 10. Treatment of 9 with vinyl iodide 10 in the presence of Pd(0) resulted in smooth Negishi cross-coupling to give 16 in 86% overall yield (based on 10 as the limiting reagent). To the best of our knowledge, this represents the first preparation and utilization of an oxazol-2-ylzinc reagent by direct Zn^0 insertion; in our hands, multigram quantities of 16 could be prepared in three steps from the known aminoxazole 11.

Treatment of 16 with DIBAL at low temperature (−90 °C) gave the corresponding aldehyde 8 in good yield (Scheme 3). Williams and co-workers have previously demonstrated[20] the utility of Corey's C_2-symmetric catalyst[21] 18 in allylations of oxazole-4-carboxaldehydes en route to phorboxazole A. In our hands, reaction of 8 with 17 in the presence of 18 gave 19 with excellent diastereoselectivity (dr 24:1), as determined by ^{1}H NMR integration of the corresponding Mosher's ester.[19]

Oxidative cleavage of the vinylidene double bond (OsO$_4$, K$_3$[Fe(CN)$_6$], then NaIO$_4$) gave ketone 20, which was subsequently reduced under Narasaka's conditions[22] to give the syn-1,3-diol (dr > 95:5) and immediately protected as the acetonide 21.[23,24] Reductive removal of the benzoate protecting group and sequential elaboration of the resulting alcohol through the

terminal iodide 22 to phosphonium salt 7 proceeded without incident (Scheme 3).[25,26]

Synthesis of the Western Hemisphere

Synthesis of aldehyde 5 commenced with dehydration of 23 (prepared by resolution of the racemic acid as the phenethylamine salt)[27] to give the cyclic anhydride 24 (quantitative), which was subjected to methanolysis in the presence of pyridine to give 25 without epimerization (87%) (Scheme 4).[28] Reduction of 25 using conditions described by Lautens and co-workers gave alcohol 26[28,29] (82%), which was oxidized to the corresponding aldehyde under Swern conditions (85%).[30]

Several methods for allylation of 27 were surveyed. Substrate-directed allylations with a range of standard Lewis acid catalysts gave poor ratios of 29a:29b, indicating that 27 lacks significant intrinsic diastereofacial bias. Hence we turned our attention to reagent-controlled alternatives (Table 1). The recently reported asymmetric Barbier-type allylation developed by Singaram and co-workers[31] conveniently gave 29a:29b in good yield (Table 1, entries 1 and 2; 81% and 83%, respectively) with operational simplicity but only modest diastereoselectivity (dr 3.9:1). Further, it was found the diastereomers were difficult to separate. Chiral Brown allylborane addition[32] gave the desired product

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Scheme 4. Synthesis of Western Hemisphere Aldehyde 5[a]
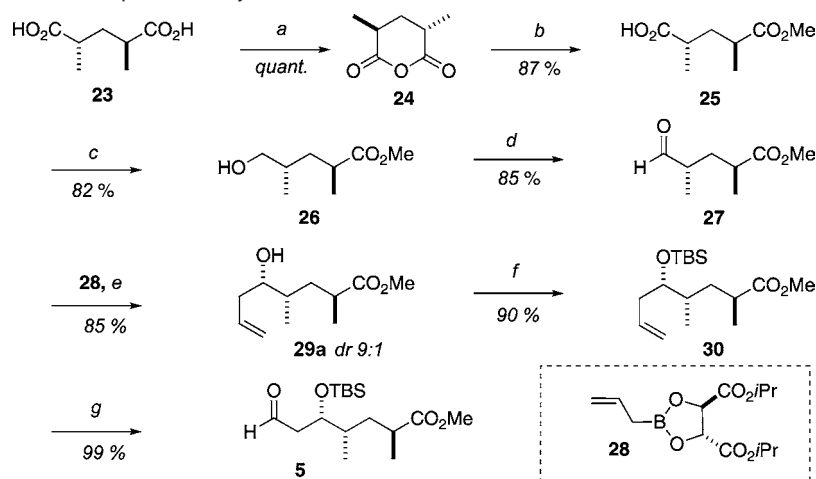
[a] Reagents and conditions: (a) AcCl, 50 °C, 30 min, quantitative; (b) MeOH, pyridine, CH_2Cl_2, 3 h, 87%; (c) $BH_3 \cdot DMS$, $B(OMe)_3$, THF, 0 °C → rt, 3 h, 82%; (d) $Cl(CO)_2Cl$, DMSO, CH_2Cl_2, −78 °C, 30 min, then 26, −78 °C, 30 min, then Et_3N, −78 → 0 °C, 2 h, 85%; (e) 28, 4 Å MS, toluene, −78 °C, 2 h, 85%; (f) TBSCl, imidazole, DMF, 17 h, 90%; (g) O_3, CH_2Cl_2, −78 °C, then PPh_3, CH_2Cl_2, −78 °C → rt, 1 h, then rt, 30 min, 99%.

Table 1. Optimization of Allylation of Aldehyde 27[a]

	allyl donor	additive	solvent	temp, °C	t, h	yield, % (29a:29b)
1	32	33	THF	−78	1.5	81 (3.9:1)
2	32	33	THF	−95	1.5	83 (3.9:1)
3	31	N/A	Et₂O	−95	0.5	29 (≥10:1)
4	28	4 Å MS	toluene	−78	2	85 (9:1)

[a] See Supporting Information for experimental details.

with high diastereoselectivity (≥10:1); however, isolation from byproducts proved troublesome (entry 3). Roush allylation conditions[33] gave optimal yields and dr for high throughput of material, providing 29a in good yield (85%) and dr (9:1). Protection of the newly formed alcohol as its TBS ether (90%) followed by ozonolysis (99%) gave the key aldehyde 5 in 46% overall yield from 23.

Fragment Coupling and Macrolactonization

Unification of "Eastern" and "Western" hemispheres of enigmazole A began with HDA cycloaddition between aldehyde 5 and diene 6 (Scheme 5). All attempts to induce a reagent-controlled HDA reaction (Jacobsen's chiral Cr(salen) catalyst[34]) failed to give product. It was found that treating a mixture of 5 and 6 with catalytic $BF_3 \cdot OEt_2$ led to a highly diastereoselective *substrate*-controlled HDA reaction. Optimization of the reaction (see Supporting Information) included *in situ*, one-pot conversion to dimethylketal 34b ($CH(OCH_3)_3$, MeOH, and CSA, 81%

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yield) to give a separable mixture of three of the four possible diastereomers (34a−c; dr 1.0:4.2:0.25); the stereochemistry of the diastereomers was assigned by NOE analysis and Mosher's ester analysis.[35]

Hydrogenolysis of 34b, followed by Swern oxidation of product 35, gave aldehyde 36 that was immediately subjected to Wittig reaction with the ylide derived from 7. Selective hydrogenation of the C12−C13 olefin of Wittig product 37 in the presence of the more substituted C21−C22 double bond (Wilkinson's catalyst, H_2) proceeded slowly but with excellent regioselectivity to give 38.[36,37]

Saponification of methyl ester 38 and acid-promoted liberation of the C15, C17-diol 39 set the stage for macrolide formation. Unfortunately, application of standard macrolactonization conditions to 39 (Yamaguchi[38] or Yonemitsu's variant[39] or Shiina's

(35) The relative configuration of 34b were assigned from observation of NOEs between the axial ¹H NMR signals of H7 and H11. The absolute configuration of 34b was assigned from a parallel analysis of the analogue S9b and its diastereomers, obtained under the same conditions: liberation of the corresponding ketone S10 (*p*-TSA, H_2O− CH_2Cl_2) followed by reduction (LiAlH(*t*-OBu)₃, THF) gave equatorial alcohol S11, Mosher's analysis of which confirmed the (7*R*,9*S*,11*R*) configuration; see Supporting Information. The relative configuration of the *anti*-isomers 34a and 34c were assigned by similar NOE and *J* analyses (arbitrary absolute configurations); however, the fourth expected *syn* diastereomer could not be detected (HPLC).
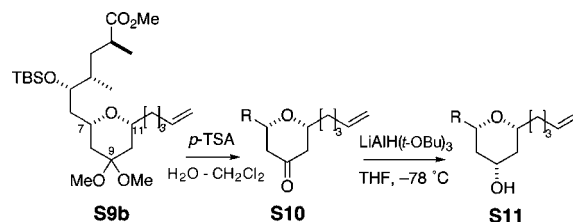
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Scheme 5. Unification of Eastern and Western Hemispheres and Attempted Macrolactonization[a]

34a : 34b : 34c = 1.0 : 4.2 : 0.25

34b R[1] = CH$_2$OBn
35 R[1] = CH$_2$OH
36 R[1] = CH=O
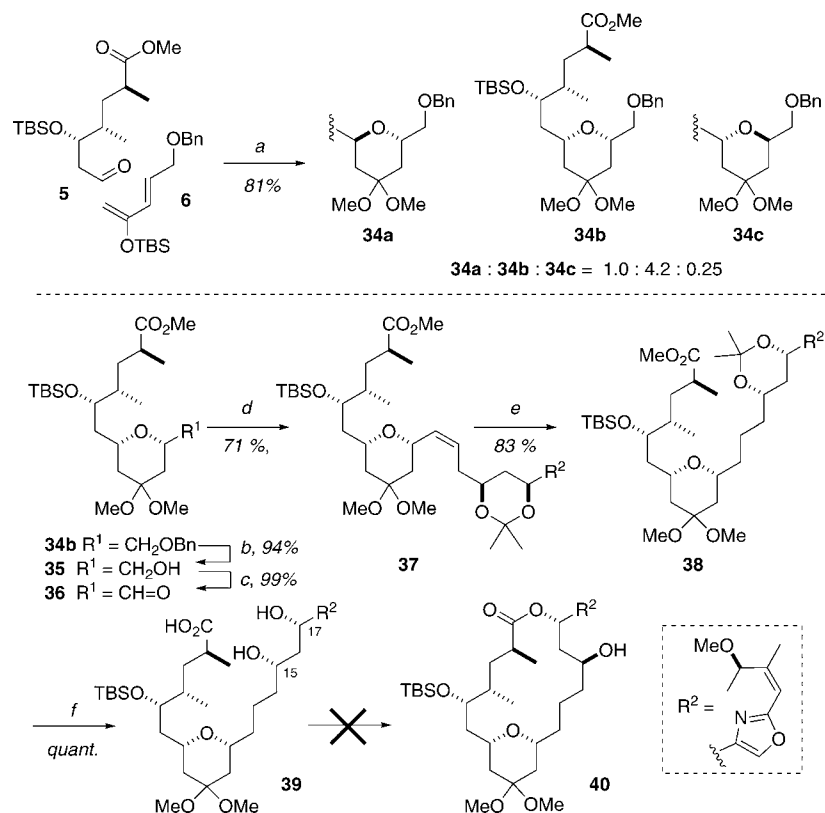
[a] Reagents and conditions: (a) BF$_3$·OEt$_2$ (0.2 equiv), CH$_2$Cl$_2$, −78 °C, 40 min, then CH(OCH$_3$)$_3$, MeOH, CSA, −78 °C → rt, 1 h, 81%; (b) H$_2$, Pd/C, EtOAc, 3 h, 94%; (c) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, − 78 °C, 10 min, then **35**, −78 °C, 30 min, then Et$_3$N, −78 °C, 30 min, then 0 °C, 30 min, 99%; (d) (i) LiHMDS, **7**, THF, −78 °C, 30 min, then 0 °C, 30 min, then (ii) **36**, −78 °C, 75 min, then 0 °C, 45 min, 71%; (e) (PPh$_3$)$_3$RhCl, H$_2$, THF/t-BuOH (1:1), 50 °C, 6 h, 83%; (f) (i) LiOH, MeOH/H$_2$O, 80 °C, 1 h, then (ii) CSA, MeOH, rt, 1 h, quant.

method[40]) gave only complex, intractable mixtures. Ring closure was achieved only by using Mukaiyama or Keck conditions, but to our disappointment the predominant product was the undesired 16-membered macrolide **40b**, formed by attack of the C15 hydroxyl upon the activated carboxylate ester, rather than the 18-membered ring lactone **40a**.[41,42] All attempts to optimize the Keck macrolactonization of **39** were unsuccessful (Table 2). Under standard prescribed conditions (reflux, (CH$_2$)$_2$Cl$_2$), the smaller-ring macrolide **40b** was obtained exclusively (entry 1), while at lower temperature no product was formed (entry 2). Variation of the solvent gave little improvement. Replacement of (CH$_2$)$_2$Cl$_2$ with toluene gave only slightly better yield (**40a:b** 1:3, 30% yield, entry 4), while use of CHCl$_3$ led predominantly to the desired macrolide **40a**; however, difficulties in purification led to an unsatisfactory yield (entry 5). Switching to DCC/PPTS/pyridine (entry 7)[43] gave **40b** exclusively in reasonable yield, and similar results were obtained using EDC·HCl/DMAP (entry 8).[44]

These results suggested strongly that ring closure of **39** was both kinetically and thermodynamically biased toward the

unwanted smaller ring size.[45] Paterson observed the opposite problem in the syntheses of aplyronine and scytophicin—formation of an undesired *kinetic* macrolactonization product—which could be corrected by inducing 1,3-acyl migration in the unwanted product [Ti(Oi-Pr)$_4$] to set the desired macrolide ring size.[46] In our case, treatment of the C9-keto derivative of **40b** with Ti(Oi-Pr)$_4$ returned only the 16-membered macrolide.

We reasoned that if the trajectory of attack of the C15-OH group to the activated carboxylate ester intermediate was more favorable than that of the C17-OH, and the product more stable, then alteration of the bond geometry in the vicinity of C15 and C17 may impose an energetically more favorable reaction trajectory and/or product stability by altering the conformation in the precursor. Consequently, the order of hydrogenation—macrolactonization was reversed. Deprotection of **37** (Scheme 6) gave the corresponding dihydroxy acid with the Z-C12−C13 olefin intact, and we were gratified to find that Keck macro-

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(43) Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407–7408.

(44) Hanessian, S.; Ma, J.; Wang, W. *J. Am. Chem. Soc.* **2001**, *123*, 10200–10206.
(45) Evidence that **40b** is the kinetic *and* thermodynamic product of macrolactonization arises from our observation that the dihydro-**41** (*vide infra* and ref 46) undergoes an anomalous reaction upon attempted Wittig olefination. The Wittig reagent was sufficiently basic to cleave the acetate ester, presumably liberating an alkoxide, which undergoes spontaneous ring contraction (1,3-acyl migration) to the smaller macrolide ring. Since the alkoxide obtained from base-promoted deacetylation of dihydro-**41** and the alkoxide of **40b**—an intermediate of 1,3-acyl migration that would equilibrate **40a,b**—are identical, it is likely that **40b** is both the kinetic and thermodynamic product of macrolactonization.
(46) (a) Paterson, I.; Watson, C.; Yeung, K.-S.; Ward, R. A.; Wallace, P. A. *Tetrahedron* **1998**, *54*, 11955–11970. (b) Paterson, I.; Woodrow, M. D.; Cowden, C. J. *Tetrahedron Lett.* **1998**, *39*, 6041–6044.

Table 2. Attempted Keck Macrolactonization of Dihydroxy Acid **39**

	solvent	conditions[a]	temp, °C	addition time, h	yield, % (**40a**:**40b**)
1	Cl(CH$_2$)$_2$Cl	A	83	16	47 (0:100)[b]
2	Cl(CH$_2$)$_2$Cl	A	60	16	0[c]
3	THF	A	66	16	0[c]
4	toluene	A	110	16	31 (1:3)
5	CHCl$_3$	A	61	16	28 (1:3.7)[d]
6	CHCl$_3$	A	61	2	0[c]
7	CHCl$_3$	B	61	16	50 (0:100)
8	CHCl$_3$	C	61	16	30 (~1:10)
9	CH$_2$Cl$_2$	A	40	16	0[c]

[a] Conditions A: slow addition (syringe pump) of **39** to a refluxing solution of DCC (25 equiv), DMAP (22 equiv), and DMAP·HCl (24 equiv) in the indicated solvent ($c = 0.3$ mM). Conditions B: slow addition of **39** to a refluxing solution of DCC (20 equiv), pyridine (100 equiv), and PPTS (20 equiv) in the indicated solvent ($c = 0.3$ mM). Conditions C: slow addition of **39** to a refluxing solution of EDC·HCl (5 equiv) and DMAP (5 equiv) in the indicated solvent ($c = 0.3$ mM). [b] Reaction conducted on C9 keto derivative. [c] Neither **40a** or **40b** was observed in crude NMR. [d] Extensive side-product formation, requiring HPLC purification.

Scheme 6. Successful Keck Macrolactonization and Completion of the Synthesis[a]
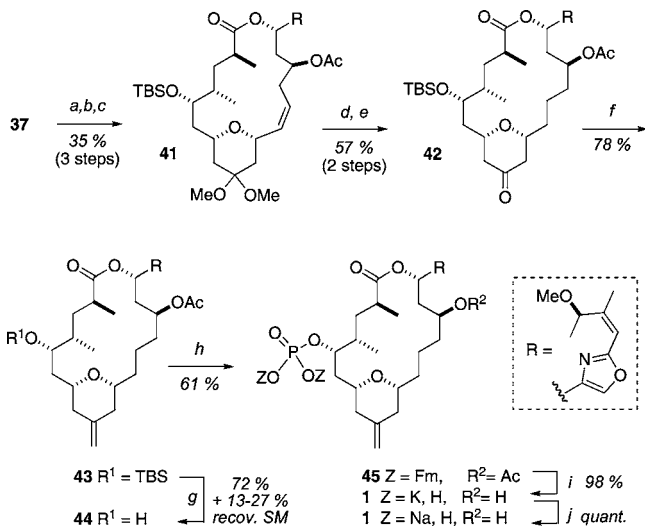
[a] Reagents and conditions: (a) LiOH, MeOH/H$_2$O, 80 °C, 1 h; (b) CSA, MeOH, rt, 1 h; (c) (i) DCC, DMAP, DMAP·HCl, CHCl$_3$, reflux, 15.5 h, then (ii) AcOH, MeOH, concentration, 35% (three steps, after HPLC); (d) (PPh$_3$)$_3$RhCl, H$_2$, THF/*t*-BuOH (1:1), 50 °C, 5 h, 70%; (e) CSA, acetone, rt, 4.5 h, 82%; (f) (i) Zn, Br$_2$CH$_2$, TiCl$_4$, THF, −78 → 0 °C, 2 d, then (ii) **42**, CH$_2$Cl$_2$, 0 °C → rt, 30 min, 78%; (g) 48% HF/MeCN/H$_2$O (5:86:9), rt, 2 d, 72% mean yield (based on recovered **43**) + 13−27% recovered **43**; (h) (i) *i*-Pr$_2$NP(OFm)$_2$, 1*H*-tetrazole, MeCN/CH$_2$Cl$_2$, rt, 40 min, then (ii) 30% H$_2$O$_2$, 0 °C, 10 min, 61%; (i) K$_2$CO$_3$, MeOH, H$_2$O, rt, 25 h, 98%; (j) RP HPLC, Phenomenex Luna 5 μm C$_{18}$, 28 → 53% MeCN in 100 mM NaClO$_4$, 0.75 mL/min. Fm = 9-fluorenylmethyl.

lactonization of this precursor now furnished the desired 18-membered macrolide **41** cleanly and exclusively (35% yield over three steps after HPLC). Quenching the reaction mixture, containing overequivalents of DCC, with excess AcOH also conveniently

protected the C15 hydroxyl as the acetate ester **41** in preparation for final elaboration to the desired natural product.

Completion of the Synthesis

Compound **41** was selectively hydrogenated as before using Wilkinson's catalyst followed by acetal hydrolysis to provide ketone **42** (Scheme 6). Standard Wittig olefination of **42** (Ph$_3$PCH$_2$, THF, 0 °C) gave poor conversions;[47] however, the nonbasic Lombardo's reagent[48] (Zn, TiCl$_4$, CH$_2$Br$_2$) led to smooth olefination of ketone **42** to **43** (78%).

Compound **43** proved unexpectedly resistant to desilylation (no reaction with TBAF). The best conditions (HF/MeCN/H$_2$O, 2 days) gave the desired alcohol in 72% average yield.[49] The phosphate was introduced to the C5 secondary hydroxyl group of **44** as a protected phosphoramidite (*i*-Pr$_2$NP(OFm)$_2$) to give the fully protected natural product **45** in 61% yield.[50] Treatment of **45** with K$_2$CO$_3$ in MeOH/H$_2$O smoothly cleaved the C15 acetate and both 9-fluorenylmethyl groups of the phosphate ester, providing enigmazole A (**1**) as the K$^+$ salt in near-quantitative yield. Ion exchange of the product[51] gave the Na$^+$ salt of **1**, identical in all respects to the natural product (^{1}H, ^{13}C, and ^{31}P

(47) The Wittig reagent was sufficiently basic to induce cleavage of the C15 acetate and subsequent 1,3-acyl migration of the 18- to 16-membered macrolide (39%), leaving only 46% of the desired **43**. Lowering the temperature to −40 °C suppressed this side reaction but did not improve the yield of **43**.

(48) Lombardo, L. *Org. Synth.* **1987**, *65*, 81−85.

(49) Based on recovered starting material (59% average isolated yield, 13−27% recovered starting material).

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(51) HPLC (Phenomenex Luna 5 μm C$_{18}$, 28−53% CH$_3$CN in 100 mM NaClO$_4$, 0.75 mL/min), followed by desalting over a C$_{18}$ cartridge.
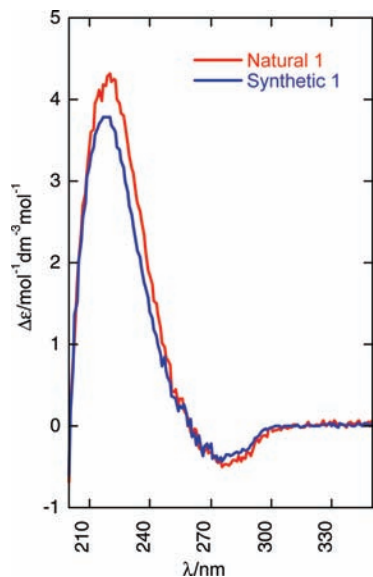
Figure 2. CD spectra (MeOH, 25 °C) of natural and synthetic enigmazole A (**1**).

NMR, UV, HPLC retention time). Finally, CD spectra of natural and synthetic **1** were superimposable (Figure 2).

Conclusions

In summary, we have completed the first total synthesis of enigmazole A (**1**) in 22 steps and 0.41% overall yield from the known aldehyde **14**. Our approach to the key oxazole-containing side chain employs an efficient Negishi coupling with the oxazol-2-ylzinc reagent **9**, prepared from an ambient 2,4-disubstituted oxazole synthon **11** by conversion to iodooxazole **12** and direct Zn^0 insertion under Knochel conditions.[15] Other key features of the synthesis include substrate-directed hetero-Diels−Alder cycloaddition to form the embedded 2,6-*syn* pyran ring, a Wittig coupling to unite key fragments **7** and **36**, and a strategic, selective, conformationally directed Keck macrolactonization of an advanced 1,3-dihydroxy carboxylic acid intermediate to the desired 18-membered macrolide.

Supporting Information Available: Experimental procedures, optimization of the synthesis of **34b** (Scheme S2), full characterization and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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