translation (±5 Å) and rotation (±180°) as well as intramolecular torsional changes (±180°) for the 24 bonds highlighted in Figure 4a. The pentyl side-chains were ignored since their conformation is not defined by the experimental data. van der Waals clashes were penalized at distances of less than 2 Å for intermolecular clashes and 1 Å for intramolecular clashes for non-hydrogen atoms. The eight NOE constraints illustrated in Figure 4a were imposed by applying a penalty if the inter-proton separation exceeded 6 Å. The search converged to a value of $R_{expt}/R_{\Delta\delta}$ of 11 in about 6000 generations for a population of 1000 (R_{expt} is the root mean square (rms) of the experimentally observed CIS values, and $R_{\Delta\delta}$ is the rms difference between the calculated and experimental values).

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[11] Crystal data for $C_{142}H_{132}N_{16}O_4Zn_2$, $M_r = 2257.38$, crystallizes from chloroform as purple blocks, crystal dimensions $0.18 \times 0.16 \times 0.07$ mm. Triclinic, space group $P\bar{1}$ (C_i^1, no. 2), $a = 11.676(7)$, $b = 16.849(10)$, $c = 17.478(11)$ Å, $\alpha = 116.307(12)$, $\beta = 100.205(14)$, $\gamma = 95.904(13)°$, $U = 2969(3)$ Å^3, $Z = 1$, $\rho_{calcd} = 1.263$ Mg m^3, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $\mu(Mo_{K\alpha}) = 0.468$ mm^{-1}, $F(000) = 1188$. Data collected were measured on a Bruker Smart CCD area detector with Oxford Cryosystems low-temperature system. Cell parameters were refined from the setting angles of 78 reflections (range $1.34 < \theta < 28.47°$). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-157703. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk

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Synthetic seco Forms of (−)-Diazonamide A**

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Diazonamide A (**1**, Scheme 1) is a uniquely structured peptide metabolite whose potential pharmacological value and low natural abundance[1] have fueled an interest in its preparation—a pursuit that continues to gain momentum.[2] Our studies[3] in this area have centered upon a ring-contracting glycol rearrangement that stereoselectively assembles a central diazonamide C10 triarylacetaldehyde. Elaborations on this core provide intermediate **2**, wherein D/E biaryl synthesis was to occur through oxidation; the event timed late to obviate consideration of fixed axial chirality maintained in the eastern region of **1**.[2c,h] Notably, both aerobic and anaerobic oxidations of **2** generate biaryl ether **3** rather than the target D/E biaryl compound.[4] This fact was not directly recognized and experiments attempting to transform **3** into **1** would come to highlight additional limitations of the design; particularly in its provisions for oxidation state adjustment at C11 and peripheral halogenations. These

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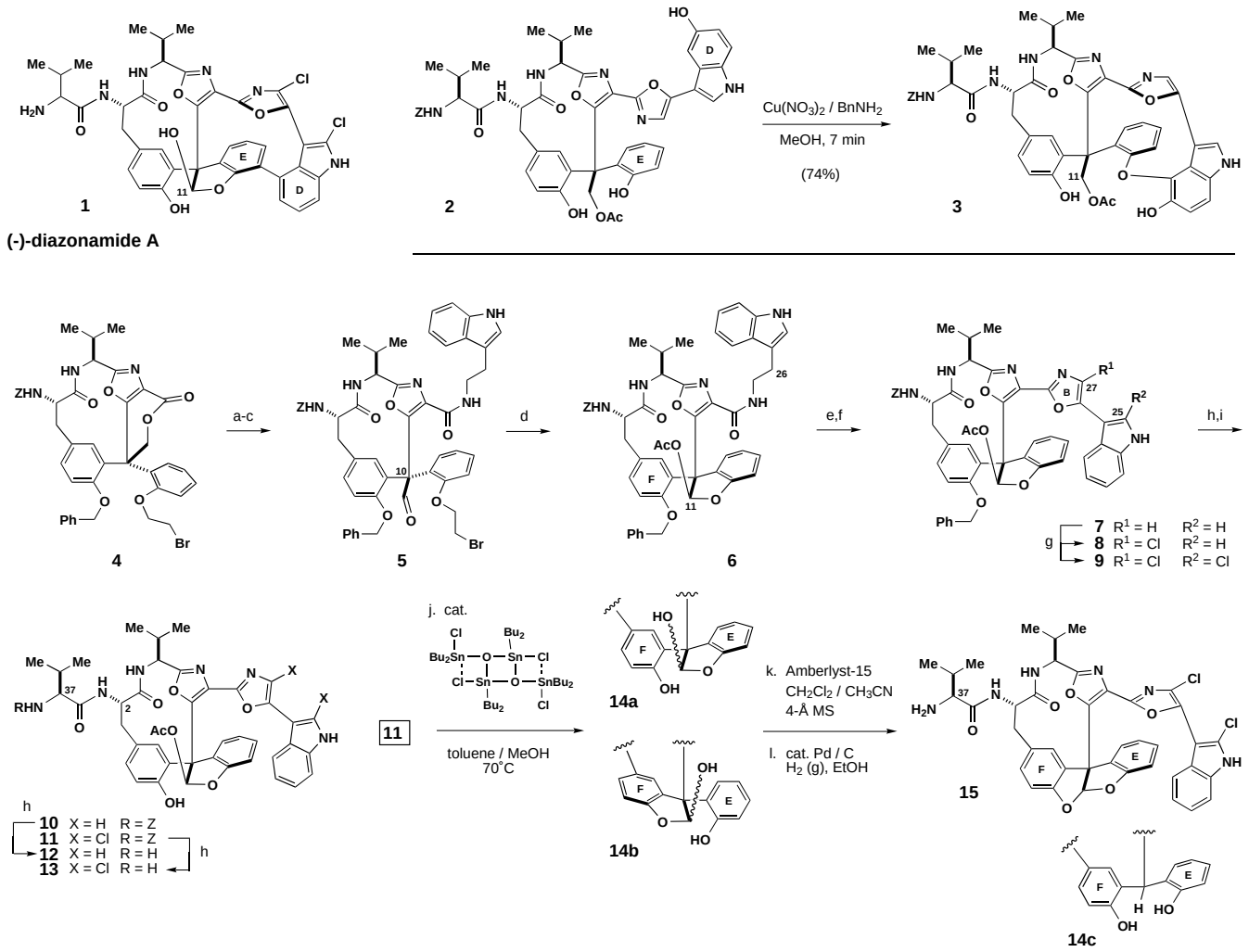

Scheme 1. Reaction conditions: a) LiOH, THF/H_2O; b) Dess–Martin periodinane, CH_2Cl_2; c) tryptamine hydrochloride, HATU, $(i\text{Pr})_2\text{NEt}$, DMF, $-30\,^\circ\text{C}$ (60% from **4**); d) Rieke zinc (excess), THF, $0\,^\circ\text{C}$; Ac_2O quench (74%); e) DDQ, THF/H_2O (82%); f) $(Cl_3C)_2$, Ph_3P, Et_3N, THF (77%); g) NCS (2.1 equiv), CCl_4/THF, $35\,^\circ\text{C}$, 14 h (85%); h) Pd black, 1 atm H_2(g), MeOH; i) Z-L-Val-OH, TBTU, $(i\text{Pr})_2\text{NEt}$, DMF. HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBTU = 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate.

aspects of the problem prompted a model study that culminates in the synthesis of structure **15**. Polycycle **15** is a desiccated, two-electron reduction product of **1** which is biologically active and luminescent upon photoexcitation.

Valerolactone **4** (Scheme 1) is a common precursor of advanced synthetic intermediates. The central features of the sequence used to prepare this compound have been published.[3a] Hydrolysis of its lactone ring, periodinane oxidation of the resultant neopentyl carbinol, and incorporation of tryptamine by amidation affords triarylacetaldehyde **5**. Aldehydes of this type are susceptible to deformylation (generating a corresponding C10 triarylmethane) under various conditions, and progress requires a tailored protection/deprotection scheme. Protection is achieved by subjecting **5** to active-zinc reduction[5] to initiate ethylene extrusion, and the metallohemiacetal putatively formed in situ is intercepted with Ac_2O. α-Acetoxybenzofuran **6** is thus conveniently generated as a single diastereomer (likely *S*-configured at C11)[6] in 74% yield. Four-electron oxidation at the indole benzylic position (C26) of **6**, and dehydration of the resultant β-keto amide,[2k] closes the B-ring to afford **7**. Halogenation of the 3-oxazoylindole segment in this context is controlled and facile. *N*-chlorosuccinimide (NCS) halogenates **7** at positions C27 and C25, in that order. Monochloride **8** can be isolated or **7** can be converted directly into bischloride **9**.[7] Re-exposing **8** to NCS provides **9** although, beginning with **7** or **8**, reagent stoichiometry must be metered to avoid production of a trichlorinated indolenine contaminant.[8]

Chlorine substituents do not interfere with the hydrogenolytic removal of protecting groups. For example, **11** is efficiently produced from **9** by heterogeneous hydrogenolysis followed by condensing the amine liberated at C2 with Z-L-Val-OH (Z = benzyloxycarbonyl). Bis(des-chloro) congener **10** is similarly prepared. Difficulty arises only when attempting to unmask the hemiacetal at C11. Alkaline hydrolysis induces deformylative degradation, the 2-chloroindole ring is intolerant of aqueous acid, and anhydrous acid treatment leads (inefficiently) to a C11 diphenyl acetal (see below). In our hands, transesterification with methanol catalyzed by an Otera stannoxane is uniquely successful.[9] Under these

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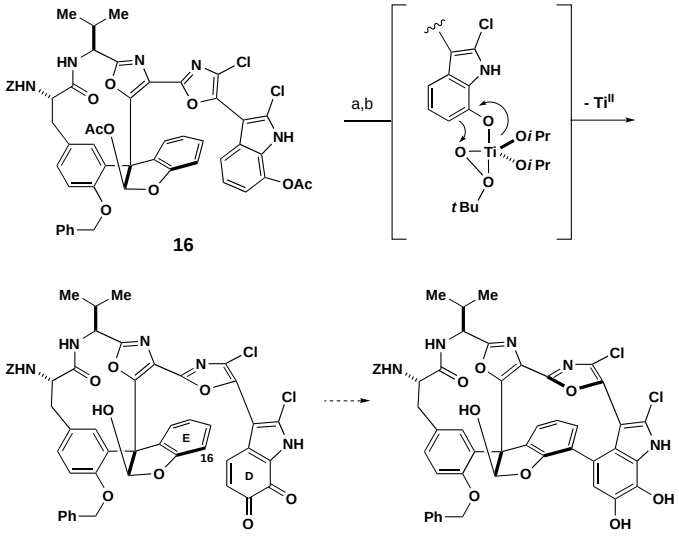
conditions **11** converts into a free hemiacetal in near quantitative yield. The ^{1}H NMR spectra of the product show the signals are broadened and temperature-dependent in hydroxylic solvents, but sharp at RT in [D_8]THF. However, the precise structure and configuration of this species (for example, **14a** versus **14b**) has not been assigned; a task complicated by increasing contamination on handling.[10] Fortunately, dehydrating the molecule with acidic resin gives a stable diphenyl acetal whose hydrogenolysis provides structure **15**.

The pathway to **15** represents an intact model for late-stage diazonamide functional group manipulations. In addition, this compound and its phenolic hemiacetal congeners have provided an initial look into diazonamide structure/activity relationships. Compounds **13** and **15** inhibit the growth of cultured human malignant melanoma SK-MEL-5 in a time and dose-dependent manner ($GI_{50} = 7$ and 9 μM, respectively).[11] However, while data indicates that **1** may target the mitotic machinery in mammalian cells,[1d,e] we find no evidence for **12**–**15** acting similarly. For example, flow cytometry studies show that cultures of human colorectal carcinoma HCT-116 incubated with **13** ($GI_{50} = 22$ μM) do not accumulate as a tetraploid population. Moreover, immunofluorescence microscopy fails to detect any effects on cytosolic tubulin architecture or an impairment of mitotic cell division (data not shown). This last experiment images a fluorescent antibody that recognizes an epitope on α-tubulin. Notably, compounds **12**–**15** themselves emit a blue luminescence upon ultraviolet photoexcitation (Figure 1B).[12] We have been able to directly visualize the uptake and localization of **13** in living cultures of human ovarian adenocarcinoma OVCAR-3. In comparison to an over-exposed negative control (Figure 1C), OVCAR-3 cells incubated with **13** (100 μM, 37 °C), washed, and imaged[13] show a bright perinuclear fluorescence which concentrates in vesicular patterns over several hours (Figure 1D). Luminescent **13** is clearly membrane permeant and appears not to associate with cytoskeletal elements. Interpretation of the results would be premature, since we lack a positive control (namely, **1**) and **13** is about 10^3-fold less toxic towards OVCAR-3 than is **1**.[1d] However, in all likelihood, the cellular toxicity manifested by these topographically altered forms of diazonamide is through mechanisms unrelated to that of the natural product. To address the latter, we are using experience gained in preparing **13**–**15** to re-approach synthetic diazonamides along new pathways. For example, in an effort to shift reliance away from one-electron oxidation methods to a reversible, heterolytic process for synthesis of the D/E biaryl bond, we have recently prepared 7-hydroxytryptamine conjugate **16** (Scheme 2).



Scheme 2. Reaction conditions: a) 20 mol% $[Bu_2Sn(O)Cl]_2$, toluene/MeOH 70 °C (91%); b) $(i\text{PrO})_4\text{Ti}$ (2 equiv), 3-Å molecular sieve, CH_2Cl_2, −10 °C; tBuOOH (5 equiv), −10° → 0 °C; aq $(COOH)_2$ (65% at ≈70% conversion).

Catalyzed deacetylation of this material followed by a novel, regioselective α-hydroxylation of the resultant 7-hydroxyindole[14] provides the blood-red indoloquinone **17**. One might envision that acid activation of **17** will engage the indoloquinone with the E-ring phenol in a reversible Michael addition—a C–C-bonded product of which is a prototropic form of indolocatechol **18**. This idea is laden with challenge,[15] yet it finds compelling analogy in the putative biogenesis of the tryptophan tryptophylquinone prosthetic cofactor of methylamine dehydrogenase.[16]

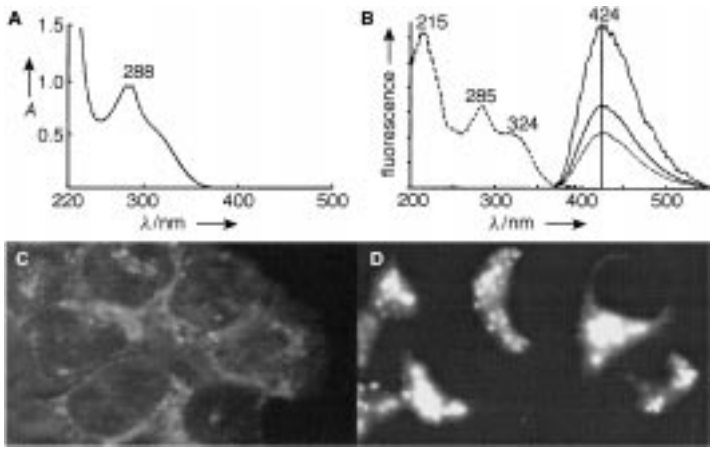


Figure 1. A) UV/Vis spectrum of **13** (64 μM in MeOH), $\varepsilon =$ 1790 L mol^{-1} cm^{-1} at 324 nm. B) Normalized fluorescence excitation (dashed) and emission (solid) spectra of **13** (2.8 μM in MeOH). C) Digital fluorescence micrograph (63×) of untreated OVCAR-3 cells (5.8 s exposure). D) Digital fluorescence micrograph (100×) of OVCAR-3 cells (1.7 s exposure) pre-incubated with **13** (100 μM, 12 h, 37 °C).

Experimental Section

15: Amberlyst-15 resin (ca. 85 mg) and 4-Å molecular sieves (ca. 75 mg) were added to a solution of crude **14** (7.6 mg, 8.2 μmol) in anhydrous CH_3CN (200 μL) and CH_2Cl_2 (1.5 mL). The mixture was warmed to 32 °C and stirred for 14 h. Filtration (EtOAc transfer), concentration, and purification by flash chromatography (SiO_2, EtOAc/benzene 3/7) afforded a cream film (7.1 mg, 84%; $R_f = 0.42$ (EtOAc/benzene 4/6); electrospray-MS (ES-MS): calcd for $C_{48}H_{42}Cl_2N_6O_8$ $[M+H]^+$: 901.25, found: 901.20; calcd for $C_{48}H_{42}Cl_2N_6O_8$ $[M-H]^-$: 899.23, found: 899.16). This residue (7.8 μmol) was dissolved in absolute ethanol (0.9 mL) and 10% Pd/C (2 mg) added. The mixture was placed under balloon-pressure H_2 and stirred vigorously for 1 h. Filtration through celite and concentration provided material which was purified by preparative thin-layer chroma-

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tography (SiO_2, MeOH/CH_2Cl_2 1/9) to afford **15** (3.7 mg, 62%). $R_f = 0.14$ (MeOH/CH_2Cl_2 1/9); $[\alpha]_D^{25} = -219.1^\circ$ ($c = 0.14$, MeOH); IR (film): $\tilde{\nu} =$ 3278, 3062, 2962, 2928, 2873, 1652, 1492, 1462, 1342, 1248, 1066, 954, 904, 746 cm^{-1}; ^1H NMR (400 MHz, [D$_8$]THF, 25 °C): $\delta = 7.88-7.84$ (m, 2H), 7.49–7.46 (m, 1H), 7.40 (d, $J = 1.8$ Hz, 1H), 7.35–7.32 (m, 2H), 7.27–7.00 (m, 6H), 6.85 (d, $J = 8.2$ Hz, 1H), 6.79 (td, $J = 7.5$, 0.9 Hz, 1H), 6.71 (d, $J =$ 8.1 Hz, 1H), 4.95 (dd, $J = 7.3$, 1.3 Hz, 1H), 4.37–4.31 (m, 1H), 3.25 (t, $J =$ 12.0 Hz, 1H), 3.03 (d, $J = 4.4$ Hz, 1H), 2.69 (dd, $J = 12.4$, 3.4 Hz, 1H), 2.21–2.16 (m, 2H), 2.02–2.00 (m, 2H), 1.09 (d, $J = 6.8$ Hz, 3H), 0.98 (d, $J =$ 6.8 Hz, 3H), 0.94 (d, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 7.0$ Hz, 3H); ES-MS: calcd for $C_{40}H_{36}Cl_2N_6O_6$ $[M+H]^+$: 767.22, found: 767.34; calcd for $C_{40}H_{36}Cl_2N_6O_6$ $[M-H]^-$: 765.20, found: 765.30; HR-MS (FAB) calcd for $C_{40}H_{36}Cl_2N_6O_6$ $[M+Li]$: 773.2233, found: 773.2248.

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[4] The phenolic oxidation of **2** shown in Scheme 1 is the most efficient identified. Ether **3** is also produced on treatment with di-μ-hydroxo-bis[(*N*,*N*,*N*′,*N*′-tetramethyl-ethylenediamine)copper(II)] chloride (TCI America) under an O_2 atmosphere and with various peroxidase isoforms in buffered media. Other oxidants examined (for example, Fe^{III}, V^{V}, Pb^{IV}, Tl^{III}) provide dimers and/or intractibles. Among the possible two-electron oxidation products of **2**, two are regioisomeric (single atropisomers) D/E biaryls (namely, *ortho*–*ortho* and/or *ortho*–*para* coupling). Neither has been convincingly detected in an oxidation of **2**.

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[6] Models of a macrolactam conformer paralleling that observed in the X-ray structure of a relative (ref. [3a]) indicate destabilizing non-bonded interactions between the benzyl ether of the F-ring and the C11 acetoxy substituent in (11*R*)-**6**.

[7] Chlorination of **7** causes a downfield shift of C25-H which, in the ^1H NMR spectrum (400 MHz, $CDCl_3$) of **8**, remains coupled ($\delta = 7.66$, $J = 2.8$ Hz) to an exchangeable (D_2O) signal at $\delta = 8.41$ (indole NH). The chlorine content of **8** and **9** was ascertained by mass spectrometry.

[8] Similar observations have been made in a model study by Magnus and McIver (ref. [2j]).

[9] For an early synthetic application of related methodology, see: S. L. Schreiber, H. V. Meyers, *J. Am. Chem. Soc.* **1988**, *110*, 5198–5200.

[10] Passage of **14** through silica generates trace (5–10%) by-products tentatively assigned as C10 epimers of **14c** (by mass spectrometry). This problem is magnified with hydrogenolyzed samples of crude **14**. By reducing the benzyl carbamate of **14** net deformylation is avoided only under conditions of transfer hydrogenation in neutral phosphate buffer containing excess Mg^{2+} ions. The crude product cannot be purified or adequately characterized.

[11] Crude samples of **14** also perform in this assay ($GI_{50} \approx 5$ μM). No significant difference in potency is observed in the *epi*-C37 series (derived from D-valine).

[12] Compound **13** has a fluorescence quantum yield (QY) of 0.45, as estimated by emission at 350–550 nm relative to an equal optical density of 1-aminoanthracene (QY = 0.61) in MeOH. Nonchlorinated congener **12** is more intensely luminescent (λ_{max}^{ex} 348 nm, λ_{max}^{em} 438 nm, $\varepsilon = 7960\ L\,mol^{-1}\,cm^{-1}$ at 348 nm, QY = 0.62) but less active against OVCAR-3.

[13] Fluorescence micrographs were obtained on a Zeiss Axiovert 100M microscope using the OpenLab Imaging System and a Chroma Tech filter set optimized for 4′,6-diamidino-2-phenylindole, dihydrochloride (DAPI) imaging (λ_{max}^{ex} 359 nm, λ_{max}^{em} 461 nm).

[14] For a seminal demonstration of ML_n (M = Ti, Zr, V)/alkyl hydroperoxide oxidations of phenols and naphthols, see: K. Krohn, H. Rieger, K. Khanbabaee, *Chem. Ber.* **1989**, *122*, 2323–2330.

[15] Preliminary results for treatment of **17** with lanthanide triflates are encouraging. We are now working through issues of product autooxidation, handling, and stability of both **17** and "**18**", as well as conclusive structural assignments. Details will be provided in a forthcoming full article.

[16] W. S. McIntire, D. E. Wemmer, A. Chistoserdov, M. E. Lidstrom, *Science* **1991**, *252*, 817–823.

Ring-Opening Polymerization of 1-Methylene-2-phenylcyclopropane Catalyzed by a Pd Complex To Afford Regioregulated Polymers**

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Palladium(II) complexes with N-donor ligands have recently attracted significant interest as a result of their utility as alkene polymerization catalysis.[1] Strained cyclic olefins such as cyclopropenes and norbornadiene also undergo addition polymerization catalyzed by palladium(II) complexes.[2] On the other hand, much less effort has been devoted to applying Pd catalysis to polymer synthesis that involves ring opening of the monomer. Herein we report a ring-opening polymerization of 1-methylene-2-phenylcyclopropane that is catalyzed by a Pd complex to give a polymer with a highly

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