

isomer in 81 % yield. Protection as the ethoxyethyl (EE) ether followed by desilylation and oxidation of the resulting alcohol with TPAP/NMO provided ketone **37**. Exposure of **37** to EtSH in the presence of $\text{Zn}(\text{OTf})_2$ gave mixed thioketal **38**. Finally, radical reduction^[18] of **38** furnished the target GHIJKLM ring system **2** in 56 % overall yield from **36**. The configuration of **2** was unambiguously determined by NOE experiments.

In conclusion, we have developed a highly convergent synthetic route to the GHIJKLM ring system **2** of ciguatoxin. The present synthesis demonstrates the general applicability of a strategy based on *B*-alkyl Suzuki coupling to the convergent synthesis of a polyether system. Progress toward the completion of the total synthesis of ciguatoxins is underway.

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Turning On Cell Migration with Electroactive Substrates**

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Herein we describe an electroactive substrate that was designed to turn on the migration of mammalian cells. The migration of cells is important in many developmental and disease processes that are temporally regulated.^[1] Mechanistic studies of cell migration—which depend on specific interactions of cell-surface receptors with ligands of the extracellular matrix^[2]—are complicated by the large number of ligands present in the matrix and the changes in ligand activity over

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time. Studies of cell migration would benefit from model substrates that both define completely the ligand–receptor interactions between substrate and cell and that allow those interactions to be regulated in time. We now report a class of dynamic substrates that can selectively “turn on” ligands under electrical control and induce the migration and proliferation of cells. We use this substrate to demonstrate a new screening assay for the discovery of promigratory and antimigratory compounds.

The dynamic substrate is based on a self-assembled monolayer (SAM) that presents hydroquinone groups on a background of penta(ethylene glycol) groups.^[3, 4] We have shown that the hydroquinone group undergoes oxidation when an electrical potential is applied to the underlying gold film to give the corresponding quinone, which then undergoes a selective and efficient Diels–Alder reaction with cyclopentadiene to afford a covalent adduct.^[5] When the diene is tethered to a ligand, the Diels–Alder reaction results in the immobilization of the ligand on the monolayer.^[6] This strategy therefore provides an electrochemical route to turn on the presentation of immobilized ligands. The penta(ethylene glycol) groups, which comprise the major component of the monolayer, are critical to this design because they prevent the nonspecific adsorption of proteins to the monolayer and

ensure that the interaction of cells with the substrate is mediated by the immobilized ligands alone.^[7]

To create a surface that could be electrically switched from a state that prevented cell attachment (an inert monolayer) to a state that promoted cell attachment, we prepared a monolayer presenting hydroquinone and penta(ethylene glycol) groups in a ratio of 1:99. This monolayer was completely inert to the attachment of cells. Application of an electrical potential of 500 mV (versus Ag/AgCl reference^[8]) for 10 seconds resulted in the oxidation of hydroquinone to quinone, which then reacted with a conjugate of cyclopentadiene and the peptide Gly-Arg-Gly-Asp-Ser-NH₂ (i.e. RGD-Cp) to install the peptide at the surface (Figure 1). This RGD peptide, found in the central cell-binding domain of fibronectin, mediates cell adhesion by binding to cellular integrin receptors.^[9] In previous work, we showed that monolayers presenting this peptide mixed with oligo(ethylene glycol) groups supported the integrin-mediated attachment and spreading of cells.^[10] Swiss 3T3 fibroblasts also attached and spread efficiently on dynamic substrates on which peptide was immobilized.^[11] Immunofluorescence microscopy showed that the adherent cells assembled focal adhesions and actin stress filaments (data not shown). Further, adherent cells could be released from the substrate when soluble Gly-Arg-

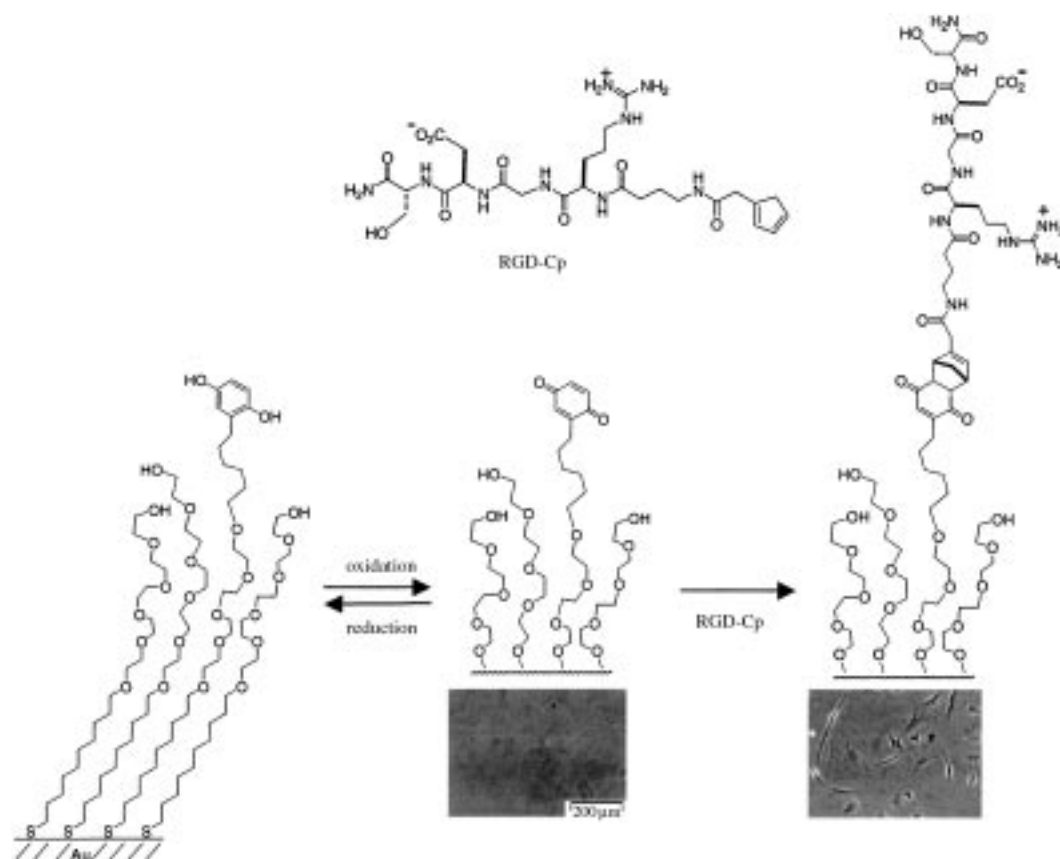


Figure 1. Strategy for the design of a substrate that can be electrically switched to turn on cell adhesion. A monolayer presenting a mixture of hydroquinone groups and penta(ethylene glycol) groups (left) is converted into a monolayer presenting the corresponding quinone groups (center) by application of a potential to the underlying gold. Both monolayers are inert to the attachment of cells (bottom left optical micrograph). Addition of a conjugate of cyclopentadiene and the peptide Gly-Arg-Gly-Asp-Ser-NH₂ to the monolayer presenting the quinone group results in the Diels–Alder-mediated immobilization of peptide (right). 3T3 Fibroblasts attach and spread on the resulting surface. Monolayers presenting the hydroquinone group are unaffected by the treatment with RGD-Cp and remain inert to cell attachment.

Gly-Asp-Ser-NH₂ (GRGDS) was added to the medium,^[10] confirming that adhesion to the monolayer was mediated entirely by the immobilized peptide ligands and that the surface was otherwise inert to nonspecific adsorption and matrix remodeling. We also found that monolayers presenting only penta(ethylene glycol) groups remained inert to cell attachment after an identical electrochemical and chemical treatment, showing that cell adhesion resulted from the Diels–Alder mediated immobilization of peptide.

We next demonstrate that the conditions required to turn on the immobilization of ligands are compatible with cell culture, and that this active substrate could turn on the migration and growth of cells *in situ*. We patterned a monolayer of hexadecanethiolate into circular regions (220 μm in diameter) and derivatized the remaining bare regions of gold with a mixed monolayer presenting hydroquinone and penta(ethylene glycol) groups (Figure 2).^[12, 13] Immersion of the patterned substrate in a solution of fibronectin resulted in adsorption of protein only to the

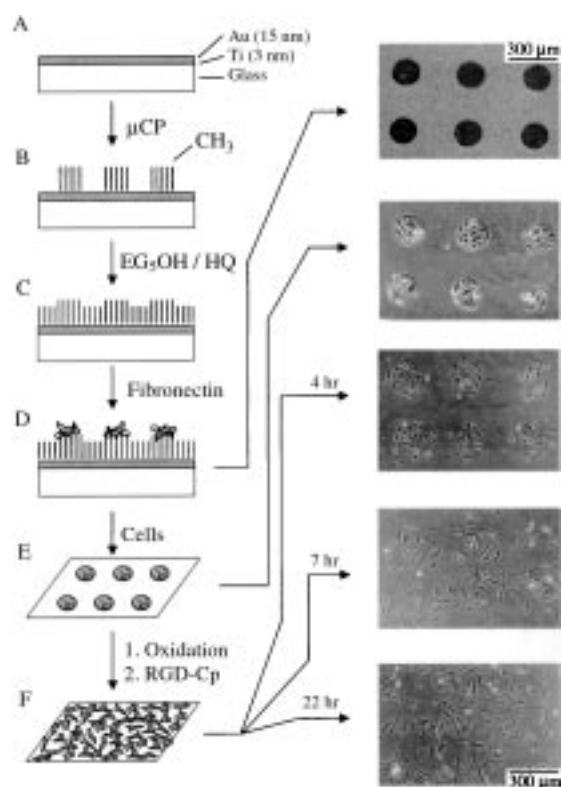


Figure 2. Example of turning on the migration and growth of cells with an electroactive substrate. A) Substrates were prepared by evaporating titanium (3 nm) and then gold (15 nm) onto glass coverslips. B) Micro-contact printing was used to pattern hexadecanethiolate into circles. C) A second monolayer was assembled on the remaining regions of gold by immersing the substrate into a solution of hydroquinone-terminated alkanethiol (HQ) and penta(ethylene glycol)-terminated alkanethiol (EG₅OH). D) The substrate was then immersed in a solution of fibronectin in PBS for four hours. A scanning electron micrograph shows that protein adsorbed only to the methyl-terminated regions of the monolayer. E) 3T3 Fibroblasts attached only to the circular regions presenting fibronectin, and when cultured in serum-containing media divided to fill these regions entirely. The surrounding inert monolayer strictly confined the cells to the circular regions. F) Electrochemical oxidation of the monolayer in the presence of serum-free media containing RGD-Cp (2 mM) led to the immobilization of the peptide and migration of cells from the circular regions.

circular regions. Swiss 3T3 fibroblasts attached only to these regions of the monolayer and proliferated to fill them completely. Cells remained confined to the circular regions for several days when cultured in serum-containing media. The inert regions of the substrate were turned on by applying an electrical potential of 500 mV (10 seconds) to the gold substrate in the presence of serum-free culture medium containing RGD-Cp (2 mM).^[14] The immobilization of RGD-Cp was essentially complete after two hours, at which time substrates were transferred to culture-media containing serum and maintained at 37 °C. Cells immediately began to migrate from the circular patterns onto the regions that were previously inert. After 7 hours most cells had moved completely off the pattern, and by 22 hours, the cells were evenly distributed on the substrate and the original pattern was no longer evident. After two days in culture, the cells had proliferated to give a near confluent layer across the entire substrate.^[15] Control experiments showed that oxidation of the substrate and addition of RGD-Cp were both required to induce cell migration from the patterned regions.

These substrates provide new opportunities for mechanistic studies of cell migration and for identifying molecules that affect migration in a novel screening assay. In the screening experiment, patterned cells are treated with candidate molecules at a specified concentration and for a designated period of time (Figure 3). The inert regions of the substrate

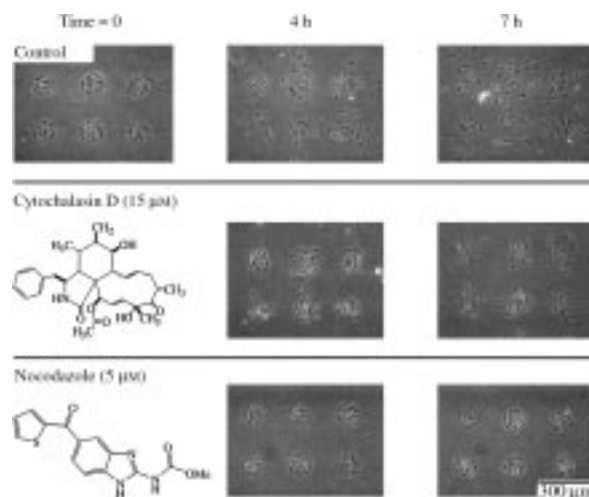


Figure 3. Example of a screening assay for compounds that influence cell migration. Top) 3T3 Fibroblasts patterned to a substrate. Upon electrochemical treatment and immobilization of RGD (described in Figure 2) the cells migrate to the pattern. Middle) Cells treated with Cytochalasin D migrate more slowly than cells on control substrates. Bottom) Cells treated with Nocodazole do not migrate from the pattern.

are then turned on by immobilization of RGD-Cp and cell migration is monitored. In three parallel experiments, cells were treated with either no compound, cytochalasin D, or nocodazole. Both compounds disrupt remodeling of the cytoskeleton and interfere with the migration process. Figure 3 shows the striking effects of the two drugs on migration. Nocodazole completely prevented migration of cells from the patterned regions, while cytochalasin D significantly retarded migration. When the medium was exchanged to remove the

compounds, cells resumed migration and proliferated to give a confluent layer, indicating the drugs were not cytotoxic over the time course of this assay.

This example establishes that the dynamic substrates are compatible with experiments to modulate cell behavior in situ and in real time. Our results suggest that this method will be broadly useful in assays for screening libraries of drug candidates that have antimigratory effects, and that can block metastasis in cancer.^[16] These substrates also offer immediate opportunities for mechanistic studies of cell migration including investigations of the dependence of cell migration on the density and affinity of immobilized ligands. Finally, these active surfaces can be combined with microelectrode arrays to modulate the presentation of ligands on select regions of the substrate and to even immobilize multiple ligands on the substrate.

The most important feature of this method is that these substrates are defined at the molecular scale and therefore provide complete control over ligand–receptor interactions between cell and substrate. The use of physical organic and synthetic chemistry was critical to the design and preparation of this dynamic substrate. This molecular approach is significant because it can be applied to the design of dynamic substrates having other functions, including those that selectively release immobilized ligands and that reversibly modulate the activities of ligands.^[17] Most importantly, the chemical approach described here provides unprecedented control in developing tailored substrates for modulating cell behavior, and will have an impact on programs in bioorganic chemistry, cell biology, and materials science.

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- [12] Patterned substrates containing islands coated with fibronectin were prepared using microcontact printing.^[13] Hexadecanethiol [HS(CH₂)₁₅CH₃] was printed onto gold-coated substrates with a poly(dimethylsiloxane) stamp containing the pattern in relief. The substrate was then immersed immediately in an ethanolic solution containing the quinone alkanethiol conjugate and (1-mercapto-undec-11-yl)penta(ethylene glycol) (10 μM in quinone, 1 mM in total thiol), which modified the remaining bare regions of gold with monolayer. The substrates were immersed in a solution of fibronectin (100 μg mL⁻¹ in phosphate-buffered saline) for four hours, to modify only the stamped regions with an adsorbed layer of protein.
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Asymmetric Induction by Helical Hydrocarbons: [6]- and [5]Helicenes**

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Enantiomerically enriched organic compounds that have been used as chiral catalysts and ligands in asymmetric synthesis possess a heteroatom(s) such as oxygen, nitrogen, sulfur, and phosphorus in addition to carbon and hydrogen atom(s).^[1] To the best of our knowledge, no chiral hydrocarbon has ever been used successfully as a chiral ligand or catalyst in asymmetric synthesis. On the other hand, [6]- and

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