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180° Unidirectional Bond Rotation in a Biaryl Lactone Artificial Molecular Motor Prototype

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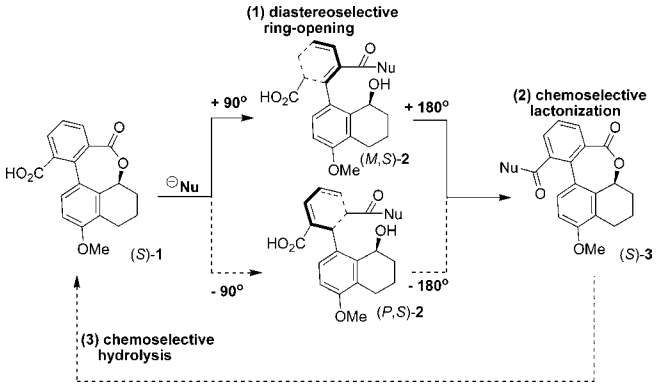
ABSTRACT



A bifunctional biaryl lactone has been synthesized that should be capable of iterative unidirectional aryl–aryl bond rotation via: (1) a diastereoselective lactone ring opening, (*S*)-1 to (*P*,*S*)-2 or (*M*,*S*)-2; (2) a chemoselective lactonization, (*P*,*S*)-2 or (*M*,*S*)-2 to (*S*)-3; and (3) a chemoselective hydrolysis, (*S*)-3 to (*S*)-1. Preliminary results of a racemic sample have indicated unidirectional 180° rotation with very high directional selectivity per individual artificial molecular motor molecule through the first two steps of this sequence.

Synthetic molecular machines[1] imitate the mechanical movements of biological molecular machines[2] as well as everyday large-scale machines and machine parts. The most basic requirement of a totally synthetic *rotary* molecular motor is an iterative directed bond rotation via a controllable energetic input.[3] There must be a net rotation in one direction vs the other for the system to be useful as a molecular motor. To date, three general synthetic designs have been determined to achieve iterative 360° net directed bond rotation: (1) photochemical cis/trans isomerizations and thermal helix inversions, rotating once about strained double bonds in four steps;[4] (2) enantioselective reduction of a biaryl lactone and chemoselective relactonization requiring a total of 10 synthetic steps, rotating once about the aryl−aryl bond;[5] and (3) photochemical alkene isomerizations and multiple chemical transformations, rotating once about two fused ring systems in catenanes.[6] There has been one synthetic system

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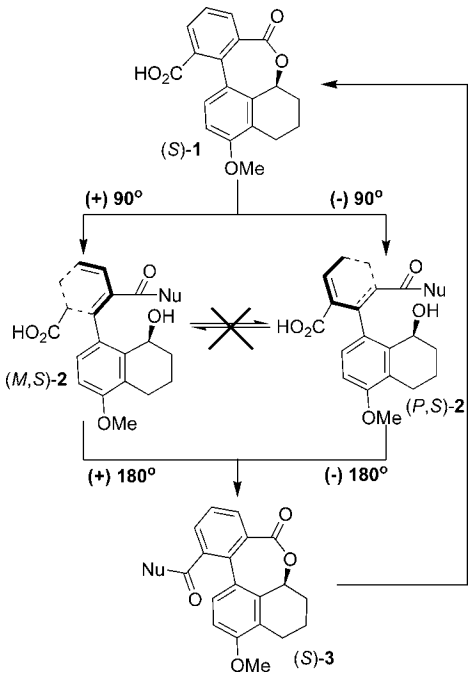
that has achieved 120° net directed bond rotation using purely chemical transformations, rotating about a single bond in a triptycene.[7] We have reported an achiral biaryl lactone system capable of 180° directed bond rotation in two steps about an aryl−aryl bond using two different chiral nucleophilic lactone cleavages and relactonizations.[8]

In this paper, we report an original design of a totally synthetic *rotary* molecular motor based on a chiral biaryl lactone structure. The design and synthesis of a similar monofunctional system has been reported.[9] However, direct characterization of the rotation in that system was not possible due to rapid equilibration of diastereomeric intermediates, scrambling information about the direction of bond rotation. Herein, we report the synthesis of the proposed bifunctional motor and preliminary results of an experimentally determined 180° directed bond rotation about the aryl−aryl bond. Under the appropriate reaction conditions, this system should be capable of a 360° unidirectional bond rotation in six steps, which would be the most efficient purely chemically driven motor system to date.

Tri-ortho-substituted chiral biaryl lactone (*S*)-**1** should undergo diastereoselective ring cleavage via nucleophilic attack at the lactone to afford either (*M*,*S*)-**2** or (*P*,*S*)-**2** in excess, resulting in a 90° directed aryl−aryl bond rotation (Scheme 1). Unless one of the ortho substituents is small,

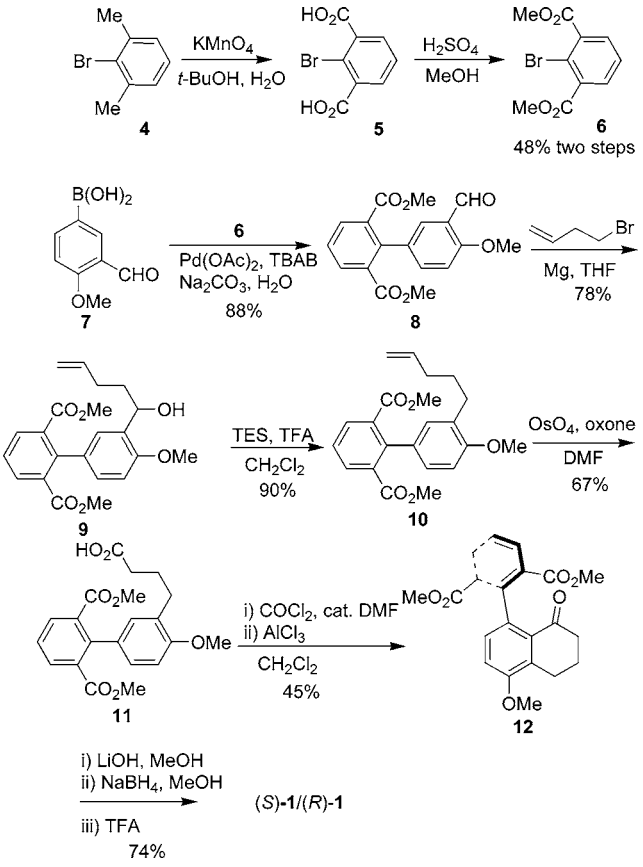
Scheme 1. Proposed Iterative Directed Aryl−Aryl Bond Rotation



tri-ortho-substituted biaryls are stable atropisomers that do not interconvert,[10] and thus the intermediates (*M*,*S*)-**2** and (*P*,*S*)-**2** should be amenable to characterization by simple analysis of diastereomer ratios. The absolute direction of the initial 90° rotation can be controlled completely through the chirality of (*S*)-**1** and the kinetics of the atroposelective lactone ring opening. Through chemoselective carboxylic acid activation, relactonization should occur to afford (*S*)-**3**. This would result in another $^1/_4$ turn about the aryl−aryl bond from (*M*,*S*)-**2** or (*P*,*S*)-**2** to (*S*)-**3** resulting in a 180° unidirectional rotation relative to (*S*)-**1**. The directionality of this step is completely dependent on the orthogonal reactivity of the carboxyl moiety relative to the opposing C═O(Nu) functionality in the lactonization process. Therefore, regardless of the initial atropisomer formed in excess, (*M*,*S*)-**2** or (*P*,*S*)-**2**, unidirectional rotation at the relactonization step is inherent. To achieve iterative directed bond rotation, lactone (*S*)-**1** must be reformed by selective cleavage of the C═O(Nu) moiety on (*S*)-**3** in the presence of the lactone moiety.[11]

Racemic lactone **1** was synthesized in 11 steps in a 6.6% overall yield (Scheme 2). Xylene **4** was oxidized and esterified to afford dimethyl ester **6**. This was then reacted under Leadbeater Suzuki coupling conditions[12] with boronic

Scheme 2. Racemic Synthesis of Proposed Motor **1**



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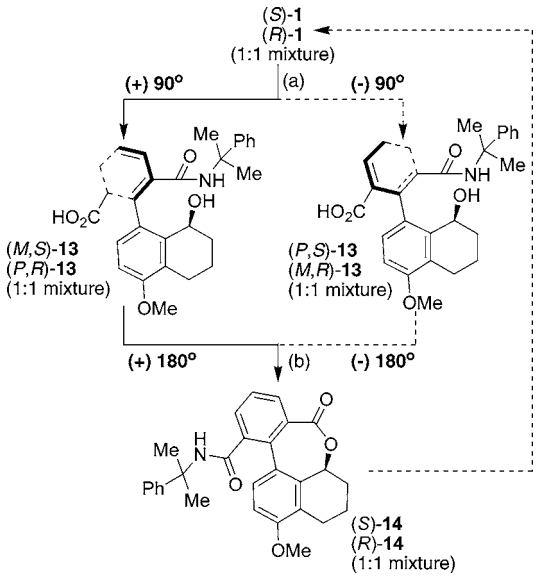
acid **7** resulting in biaryl **8**. Grignard addition of 4-bromo-1-butene to the aldehyde moiety was followed by a triethylsilane reduction of the resulting benzyl alcohol functionality to afford **10**. An oxidative alkene cleavage with catalytic OsO_4 and excess oxone[13] afforded **11** which then underwent an intramolecular Friedel−Crafts acylation sequence resulting in tetralone **12**. The ester functionalities were then hydrolyzed. The tetralone was reduced with $NaBH_4$, and two functionalities were lactonized in the presence of neat trifluoroacetic acid to afford the proposed biaryl lactone motor (*S*)-**1**/(*R*)-**1** as a racemic mixture.

Attempts to reduce the sterically hindered tetralone moiety on **12** to afford enantiomerically enriched samples of (*S*)-**1** or (*R*)-**1** using conventional chiral reducing agents were unsuccessful. However, proof of concept of unidirectional bond rotation is inherent as characterization of the racemic mixture vs an enantiomerically pure sample would be equivalent via NMR spectroscopy.[14]

Racemic motor (*S*)-**1**/(*R*)-**1** was subjected to lactone cleavage under Weinreb conditions[15] in the presence of cumylamine and $AlMe_3$ to afford the ring-opened amide (*M*,*S*)-**13**/(*P*,*R*)-**13** with very high diastereoselectivity (Scheme 3). Following this, a portion of the crude mixture was

Scheme 3. 180° Directed Aryl−Aryl Bond Rotation[a]

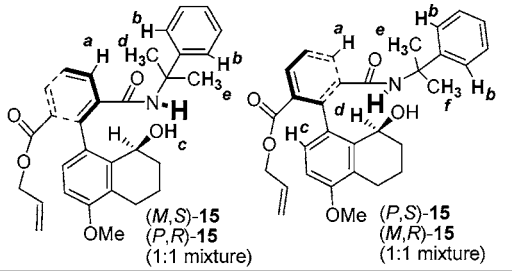


[a] Conditions used: (a) $PhC(CH_3)_2NH_2$, $AlMe_3$, CH_2Cl_2, reflux; (b) DCC, DMAP, DMAP·HCl, $CHCl_3$, reflux.

immediately lactonized under Keck conditions[16] to afford biaryl lactone (*S*)-**14**/(*R*)-**14**, thus achieving 180° aryl−aryl bond rotation with very high rotational selectivity.

Because of the poor solubility and difficulty purifying the intermediates (*M*,*S*)-**13**/(*P*,*R*)-**13** following ring cleavage of (*S*)-**1**/(*R*)-**1**, a portion of the crude mixture was directly derivatized to the more soluble allyl ester (*M*,*S*)-**15**/(*P*,*R*)-**15**. NMR analysis of the purified products and side products in the allyl ester formation indicated only one racemic component, (*M*,*S*)-**15**/(*P*,*R*)-**15**, and thus very high rotational selectivity for the lactone cleavage step.[17]

To confirm the relative axial stereochemistry of the ring-opened intermediates (*M*,*S*)-**13**/(*P*,*R*)-**13**, a sample of (*M*,*S*)-**15**/(*P*,*R*)-**15** was studied by qualitative transient ^{1}H NOESY-1D. The irradiated amide hydrogen exhibited no NOE interactions with the benzyl hydrogen *ipso* to the hydroxyl on the lower ring but did have NOE interactions with the hydroxyl hydrogen (Figure 1). To obtain a sample with the



diastereomer	amide chemical shift (ppm)	nOe chemical shift (ppm)	nOe assignment
(*M*,*S*)-**15**/(*P*,*R*)-**15**	7.48	7.94	ArH, ***a***
		7.08	ArH, ***b***
		2.16	OH, ***c***
		1.42	CH_3, ***d***
		1.36	CH_3, ***e***
(*P*,*S*)-**15**/(*M*,*R*)-**15**	5.53	8.02	ArH, ***a***
		7.10	ArH, ***b***
		6.91	ArH, ***c***
		4.63	BnH, ***d***
		1.49	CH_3, ***e***
		1.33	CH_3, ***f***

Figure 1. Transient ^{1}H NOESY-1D data for amide N−H protons.

opposite axial chirality, lactone (*S*)-**14**/(*R*)-**14** was hydrolyzed to afford (*P*,*S*)-**13**/(*M*,*R*)-**13** and was directly converted to allyl ester (*P*,*S*)-**15**/(*M*,*R*)-**15** and studied by qualitative transient ^{1}H NOESY-1D. The irradiated amide hydrogen on

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(11) The motor should also rotate unidirectionally following the same sequence of reactions (Scheme 1) starting with enantiomer (*R*)-**1**, in the opposite direction about the aryl−aryl bond.

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(14) Racemic **1** can be used to study directed bond rotation by NMR spectroscopy because each enantiomer of **1** can undergo a diastereoselective directed bond rotation process (see Scheme 1), with each enantiomer rotating in the opposite direction. Each step in the directed bond rotation for each enantiomer will be observed as the same diastereoselective reaction by NMR spectroscopy.

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(17) One can assume on the basis of the detection limits of NMR spectroscopy that the diastereoselectivity is 90−100%. The loss of the other diastereomer in the derivatization process could be possible but very unlikely on the basis of NMR analysis of crude **13**, indicating a single diastereomer. Given that the overall yield of the two-step ring opening and allyl derivatization process was 72%, the rotational selectivity is *at minimum* 72% even if one diastereomer was not derivatized.

(*P*,*S*)-**15**/(*M*,*R*)-**15** was determined to have NOE interactions with the benzyl hydrogen *ipso* to the hydroxyl moiety but had no NOE interactions with the alcohol hydrogen (Figure 1).

Thus, we have determined that the first step in the unidirectional aryl−aryl rotation in (*S*)-**1** or (*R*)-**1** results in (*M*,*S*)-**13** or (*P*,*R*)-**13**, respectively, with very high diastereoselectivity. Because of this and the inherent directed bond rotation in the relactonization step ((*M*,*S*)-**13** or (*P*,*R*)-**13** to (*S*)-**14** or (*R*)-**14**), (*S*)-**1** and (*R*)-**1** are both potentially excellent chemically driven synthetic molecular motors.

The high atroposelectivity of the ring-opening reactions is due to an axial preorganization (*M*/*P*) of the *ortho*-carboxyl moiety in (*S*)-**1**/(*R*)-**1** behind the plane of the tetrahydronapthol ring and the lactone moiety protruding in front of the ring, as determined by the X-ray crystal structure (Figure 2). The cleavage of the lactone ring (*S*)-**1** or (*R*)-**1**

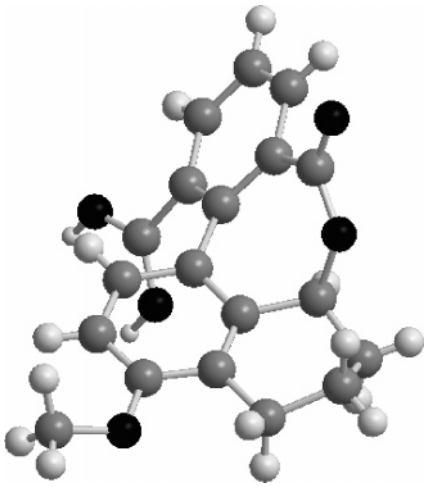

Figure 2. Molecular structure of motor **1**. The Chem 3D structure of (*S*)-**1** (in a racemic mixture) using coordinates obtained by X-ray crystallography. The Chem 3D structure is shown to clearly illustrate the lowest-energy conformation with *M* axial chirality.

with *M* or *P* axial chirality results in an atropisomer that preserves this axial stereochemistry (*M*,*S*)-**13** or (*P*,*R*)-**13**, respectively. Nucleophilic addition most likely occurs at the unhindered exo face of the carbonyl. However, facial selectivity in this system is inconsequential as the tetrahedral intermediate can easily obtain a geometry to eliminate to afford the atropisomer consistent with the preorganized *M* or *P* axial configuration.

To achieve iterative bond rotations, we made several attempts to hydrolyze the cumylamide moiety of (*S*)-**14**/(*R*)-**14** chemoselectively. Both TFA and BF_3 have been reported to cleave the dimethylbenzyl group on secondary cumylamides to afford primary amides.[18] It has also been reported that primary amides can be hydrolyzed in the presence of esters with $CuCl_2$ and glyoxal.[19] However, when (*S*)-**14**/(*R*)-**14** was subjected to either TFA or BF_3 using either stoichiometric amounts or a large excess, no reaction occurred. Thus, experimental conditions have not yet been discovered to achieve an iterative directed bond rotation process in this system.

In conclusion, preliminary results have shown that that biaryl lactone (*S*)-**1**/(*R*)-**1** is capable of unidirectional rotation about the aryl−aryl bond. Lactone (*S*)-**1**/(*R*)-**1** was determined to achieve 180° unidirectional rotation in two steps: (1) (*S*)-**1**/(*R*)-**1** → (*M*,*S*)-**13**/(*P*,*R*)-**13** and (2) (*M*,*S*)-**13**/(*P*,*R*)-**13** → (*S*)-**14**/(*R*)-**14** with very high directional selectivity. The amide functionality in (*S*)-**14**/(*R*)-**14** was unable to be selectively hydrolyzed. Current investigations of other amide nucleophiles that are designed to be selectively cleavable in the presence of a lactone are underway. An alternate synthesis of (*S*)-**1** or (*R*)-**1** to achieve an enantiomerically pure sample is also in progress. This synthetic motor system requires the sequential exposure to different conditions to achieve rotation which, using the current conditions described, would make it difficult to achieve continuous rotation in one solution. Nevertheless, this system is now only one of four known *purely chemically driven* molecular motor designs that has been experimentally determined to achieve directed bond rotation.

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Supporting Information Available: Experimental procedures and characterization data for all synthetic steps, including ^{1}H and ^{13}C NMR spectra. ^{1}H NOESY-1D spectra for (*M*,*S*)-**15**/(*P*,*R*)-**15** and (*P*,*S*)-**15**/(*M*,*R*)-**15** are provided. X-ray crystallographic data (cif file) for **1** is also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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