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Synthesis and characterization of a functionalized chiral biaryl capable of exhibiting unidirectional bond rotation

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Abstract—A class of chiral biaryl molecules that have been designed to undergo unidirectional rotation about the aryl–aryl bond may show promise for future application in the area of synthetic molecular motors. These asymmetric molecules should be capable of channeling chemical energy into repeated 360° rotation in one direction. Herein we report the synthesis and characterization of one such biaryl molecule (**1**).

Chemists have been very interested in designing molecules that mimic the mechanical behavior of everyday large scale machines. Synthetic molecular motors, in which controlled unidirectional molecular motion can be converted into useful work, are envisioned to be the central components of future nanoscale machines[1] and may be useful for materials application. The primary challenge thus far in synthetic molecular motor research has been in the design and synthesis of molecular systems capable of controlled unidirectional motion. Feringa and co-workers[2–4] have synthesized a class of chiral molecules that achieve unidirectional bond rotation via light-driven isomerization about sterically crowded carbon–carbon double bonds. Kelly and co-workers[5,6] have synthesized a triptycyl/helicene-based phosgene-driven system that can achieve 120° unidirectional bond rotation around the single bond connecting the triptycene to the helicene. We have designed a class of biaryl molecules that should utilize diastereoselective reactions to undergo repeated unidirectional 360° rotation about the aryl–aryl bond.

Lactone **1** could be used as the starting material for a series of three processes that would lead to directed bond rotation about the aryl–aryl bond (Fig. 1).[7] Directed bond rotation is defined here as energy-driven rotation about a bond in a single direction. There must be a net rotation in one direction versus the other in order for the system to be useful as a molecular motor. Exclusive unidirectional rotation is therefore ideal, but not required. The three processes contributing to directed bond rotation are (1) ring opening of **1**, (2) thermal isomerization of diastereomers **2a*S*** and **2a*R***, and (3) cyclization of diastereomers **2a*S*** and **2a*R*** to form **1** again. First, addition at lactone **1** can occur at either diastereoface of the carbonyl yielding either diastereomer **2a*S*** (with *S* axial chirality) or **2a*R*** (with *R* axial chirality). Any reaction that generates two diastereomers will generate one in excess, therefore, ring opening of

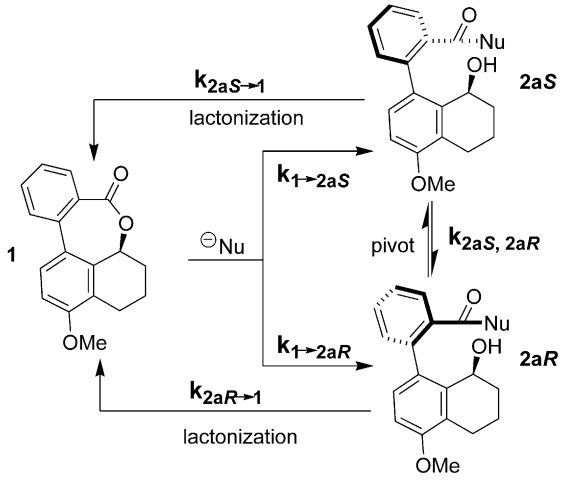

Figure 1.

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1 will generate either **2a*S*** or **2a*R*** in excess ($k_{\mathbf{1}\rightarrow\mathbf{2a}S} \neq k_{\mathbf{1}\rightarrow\mathbf{2a}R}$). Second, thermal isomerization of **2a*S*** and **2a*R*** should occur by a back-and-forth 'windshield wiper' type of rotation about the aryl–aryl bond with the C(=O)Nu group passing over aryl hydrogen instead of the sterically bulky cyclohexenol ring. Third, intramolecular lactonization of either diastereomer results in the reformation of lactone **1**. Diastereomers inherently cannot react at exactly the same rate ($k_{\mathbf{2a}S\rightarrow\mathbf{1}} \neq k_{\mathbf{2a}R\rightarrow\mathbf{1}}$), so either **2a*S*** or **2a*R*** will exhibit faster cyclization. Three examples are given analyzing the effects these contributing factors would have on the efficiency of the directed bond rotation.

Both ring-opening and ring-closing reactions are highly diastereoselective: A high efficiency of directed bond rotation would result if ring opening of **1** is highly diastereoselective to form mainly **2a*S***, thermal isomerization of **2a*S*** and **2a*R*** is fast relative to the other processes, and cyclization of **2a*R*** is faster than the cyclization of **2a*S***. Similarly, a high efficiency of directed bond rotation (in the opposite direction) would result if the opposite diastereoselectivity in ring-opening and closing was exhibited. *Result*: *excellent motors with very efficient directed bond rotation.*

Only ring opening is highly diastereoselective: A moderate efficiency of directed bond rotation would result if ring opening of **1** is highly diastereoselective to form mainly **2a*S***, thermal isomerization of **2a*S*** and **2a*R*** is fast relative to the other processes, and cyclization of **2a*R*** and **2a*S*** proceed at comparable rates. Similarly, a moderate efficiency of directed bond rotation (in the opposite direction) would result if the opposite diastereoselectivity in the ring opening was exhibited. *Result*: *good motors with moderately efficient directed bond rotation*.

Only ring closing is highly diastereoselective: A moderate efficiency of directed bond rotation would result if ring opening of **1** is not significantly diastereoselective, thermal isomerization of **2a*S*** and **2a*R*** is fast relative to the other processes, and cyclization of **2a*R*** is much faster than **2a*S***. Similarly, a moderate efficiency of directed bond rotation (in the opposite direction) would result if the opposite diastereoselectivity in the ring closing was exhibited. *Result*: *good motors with moderately efficient directed bond rotation*.

The discussion above describes how systems such as the one shown in Figures 1 and 2 could be designed to create molecular motors. There is good reason to believe that specific features that have been designed into the structure of lactone **1** should result in an excellent molecular motor system, with highly diastereoselective ring opening and ring closing. The AM1 minimized models in Figure 2 illustrate these key features. Nucleophilic additions to carbonyl groups are known to proceed at the Burgi–Dunitz angle:[8] 105° ± 5° relative to the plane of the carbonyl. Therefore, attack by a nucleophile on lactone **1** should proceed via the unhindered *exo* face. After going through an sp^3 hybridized intermediate, the subsequent bond breaking should result in a 90° bond rotation direction to afford the ring opened **2a*S*** in excess. Larger

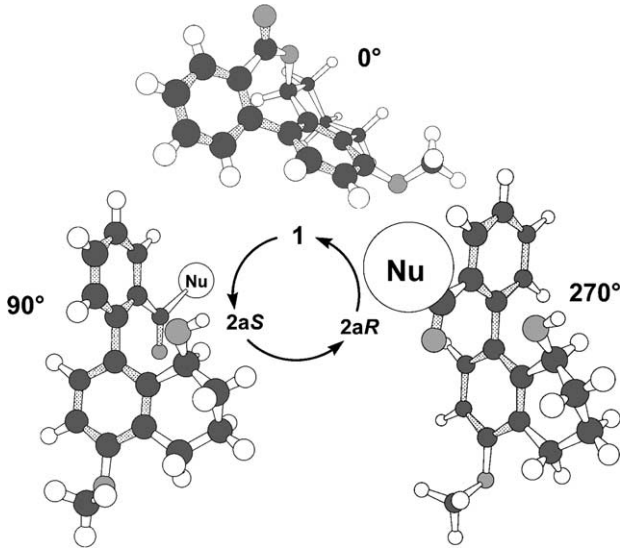
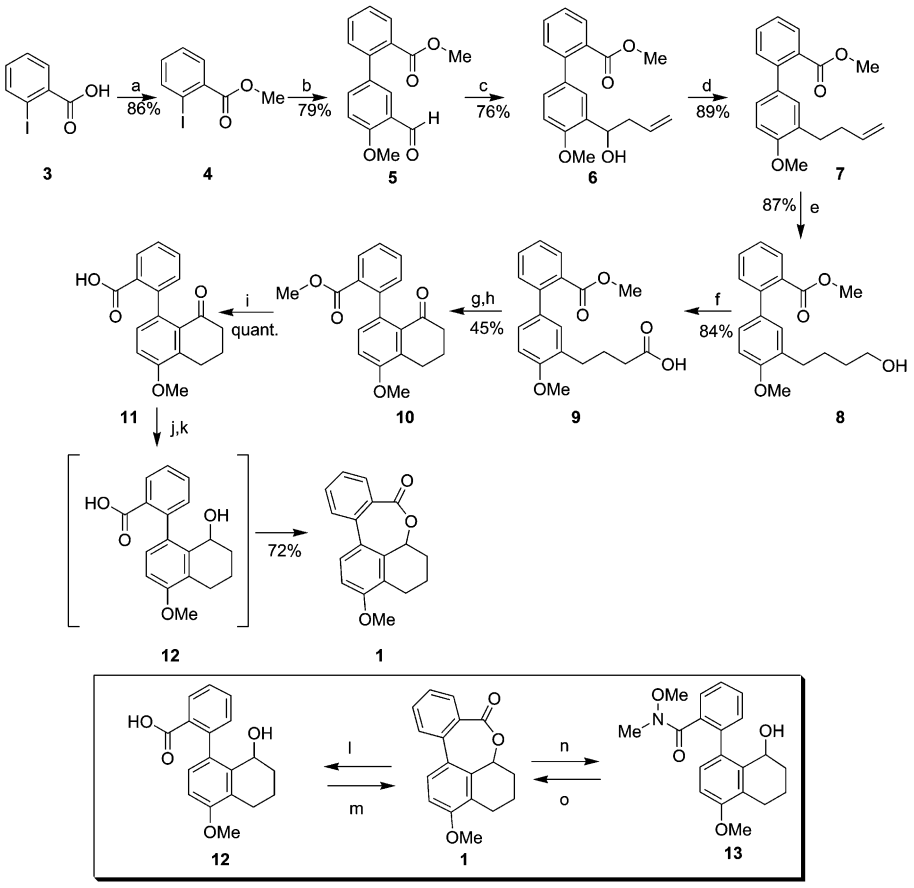


Figure 2.

nucleophiles should enhance the selectivity of the ring opening. Thermal isomerization of **2a*S*** and **2a*R*** should be fast relative to the other processes. Cyclization of **2a*R*** should be faster than cyclization of **2a*S*** due to a proximity effect: in **2a*R*** the hydroxyl and the carbonyl are close to each other and they can easily get within bonding distance, with the proper Burgi–Dunitz angle for nucleophilic attack on the carbonyl. In contrast, **2a*S*** cannot easily cyclize because the hydroxyl and carbonyl are not close to each other and the proper geometry for cyclization is difficult to attain. Thus, this three step system of **1**→**2a*S***→**2a*R***→**1** would result in a net 360° unidirectional rotation about the aryl–aryl bond.

The synthesis of racemic **1** was achieved in 11 steps (Scheme 1).[9] Aryl iodide **4**, prepared via Fischer esterification of **3**, was successfully coupled in 10 min under high temperature Suzuki conditions[10] to afford **5**. An indium mediated allylation reaction[11] was employed, resulting in high yields of **6**. Triethyl silane reduction of **6**, hydroboration–oxidation of **7**, and Jones reagent oxidation of alcohol **8** were used in succession to afford **9**. The acid chloride of **9** was formed with oxalyl chloride followed by a standard $AlCl_3$ induced Friedel–Crafts acylation to form biaryl tetralone **10** followed by ester hydrolysis to **11**. Sodium borohydride reduction of **11** resulted in high yields of **1** after a 5% HCl quench. The carboxylic acid ring opened **12** was not detected or isolated under these conditions as determined by TLC, ^{1}H NMR and mass spectrometry.

In order to study the aryl–aryl bond rotation, the lactone **1** must be effectively opened and closed (Figs. 1 and 2) and the resulting kinetic products (**2a*S*** and **2a*R***) must be isolated before equilibration. Ring-opened **12** has proven to be difficult to isolate after LiOH hydrolysis of **1** because of its propensity to re-lactonize back to **1** under acidic work-up conditions. However, ^{1}H NMR of **12**[9] (isolated after a careful mild oxalic acid quench) has indicated that axial diastereomers are not observed at room temperature. This is the result of fast



Scheme 1. Reagents and conditions: (a) MeOH, H_2SO_4, reflux; (b) 3-formyl-4-methoxyphenyl-boronic acid, tetrabutylammonium bromide, Na_2CO_3, $Pd(OAc)_2$, H_2O, 150 °C; (c) allyl bromide, In, DMF, then 5% HCl; (d) triethylsilane, TFA, CH_2Cl_2; (e) 1 M BH_3–THF, then H_2O_2, NaOH, THF; (f) CrO_3, H_2SO_4, acetone; (g) oxalyl chloride, cat. DMF, CH_2Cl_2, 0 °C; (h) $AlCl_3$, CH_2Cl_2, reflux; (i) LiOH, THF/H_2O (2:1), reflux, then 5% HCl; (j) $NaBH_4$, 5% NaOH in H_2O; (k) 5% HCl; (l) LiOH, THF/H_2O (2:1), reflux, then oxalic acid; (m) 5% HCl; (n) N-O-dimethylhydroxylamine hydrochloride, 2.0 M isopropylmagnesium chloride in THF, then 5% HCl; (o) trifluoroacetic acid, neat.

isomerization between **12a*S*** and **12a*R*** on the NMR time scale, with undetermined equilibrium. In order to observe a stable ring-opened compound, lactone **1** was completely converted to the Weinreb amide **13**[9] in 30 min with Me(MeO)NMgCl. The ^1H NMR studies of **13** showed two axial diastereomers at room temperature due to the bulkier amide group. These diastereomers are present in unequal amounts ($K_{eq} = 1.6$ in DMSO at room temperature). Coalescence of the diastereomers was observed via ^1H NMR at approximately 85 °C in DMSO and the barrier to 'windshield wiper' rotation was estimated to be approximately 17 kcal/mol. The Weinreb amide **13** was readily lactonized back to **1** in the presence of neat trifluoroacetic acid, with a complete reaction occurring in 45 min.

Because of the fast equilibrium occurring between **12a*S*** and **12a*R*** and **13a*S*** and **13a*R***, the kinetic products of ring opening cannot be isolated and the initial direction of rotation upon ring opening is currently undeterminable. The rate of diastereomer isomerization could be slowed down by introducing more steric hindrance to bond rotation by using bulkier nucleophiles or by replacing the *ortho* C–H on the lower ring with a larger group. The discovery that **1** can be opened with LiOH or Me(MeO)NMgCl and closed with 5% HCl or TFA activation (instead of a more typical activation with DCC and DMAP) greatly simplifies the system. One pot iterative bond rotations may be possible by cycling of basic (nucleophilic) conditions to ring open and acidic conditions to lactonize. Current efforts toward obtaining the best possible conditions for selective opening and closing of the chiral lactone **1** are being explored.

Acknowledgements

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