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Development of a Bio-Inspired Acyl-Anion Equivalent Macrocyclization and Synthesis of a *trans*-Resorcylide Precursor

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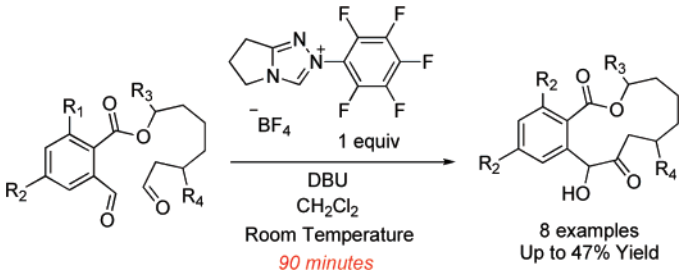
Received April 2, 2007

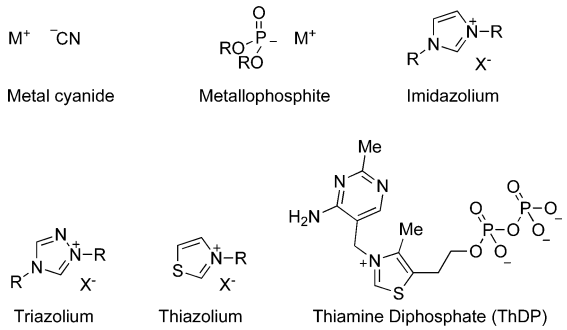


Studies on the macrocyclization of α,ω-dialdehydes have revealed a strong dependence on ring size with respect to the ultimate efficiency of the reaction. Strong catalyst dependence was observed, as thiazolium salts led to no detectable product formation, whereas electron-deficient triazolium salts served as precatalysts for the cyclization. Surprisingly, the *N*-pentafluorophenyl triazolium variant led to cyclization at room temperature within a short 90-min reaction time. These findings were applied to a range of substrates, including the synthesis of a key intermediate in a rapid synthesis of *trans*-resorcylide.

Introduction

The ability to access "umpolung" reactivity through the use of catalysts has resulted in a resurgence of interest in chemistry that proceeds through formal acyl-anion equivalents. With a rich foundation in the classical mechanistic work of Breslow,[1] synthetic catalysts that mimic the chemistry of the cofactor thiamine diphosphate have led to the introduction of a range of new synthetic transformations. Furthermore, striking examples of asymmetric catalysis based on chiral heterozolium ylids (Chart 1) have also been documented,[2] establishing the basis for a thriving and fast-moving subdiscipline in the area of asymmetric catalysis. Highlights in the area have included remarkable demonstrations of asymmetric Benzoin chemistry,[3] Stetter cyclizations,[4] syntheses through formal homoenolate,[5] cyclizations through formal Diels−Alder reactions,[6] nucleophilic acylation,[7] and an impressive array of heterozolium-based redox processes.[8]

CHART 1. Umpolung Catalysts



Within the subset of reactions based on benzoin reactions, the cyclization of dialdehydes is particularly intriguing. Our own interest in this area was stimulated by the existence of natural

(1) Breslow, R. *J. Am. Chem. Soc.* **1958**, *60*, 699−702.

(2) (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534−541. (b) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506−7510. (c) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326−1328. (d) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988−3000. (e) Enders, D.; Balensiefer, T.; Niemeier, O.; Christmann, M. In *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007; pp 331−335.

(3) (a) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743−1745. (b) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463−1467. (c) Hachisu, Y.; Bode, J. W.; Suzuki, K.; *J. Am. Chem. Soc.* **2003**, *125*, 8432−8433. (d) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K.; *Angew. Chem., Int. Ed.* **2006**, *45*, 3492−3494. (e) Linghu, X.; Bausch, C. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2006**, *127*, 1833−1840.

10.1021/jo070676d CCC: $37.00
Published on Web 06/19/2007

SCHEME 1. Synthesis of Acyloin Standards

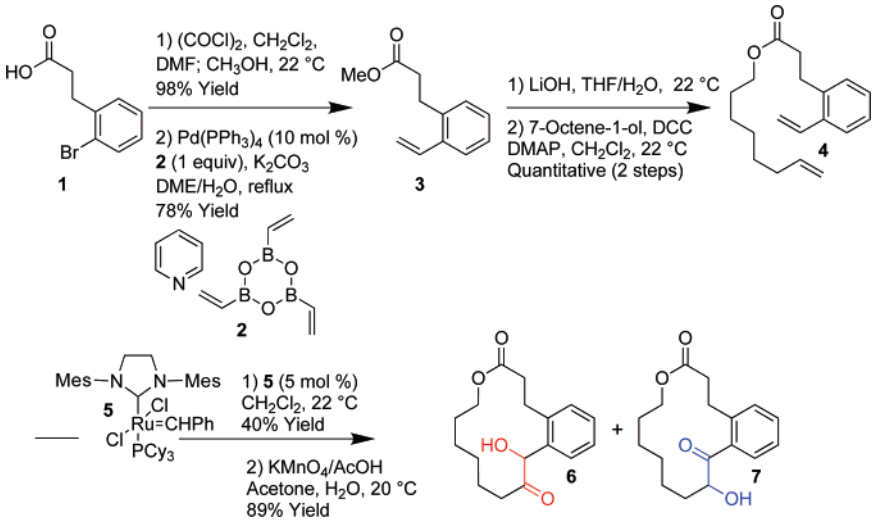
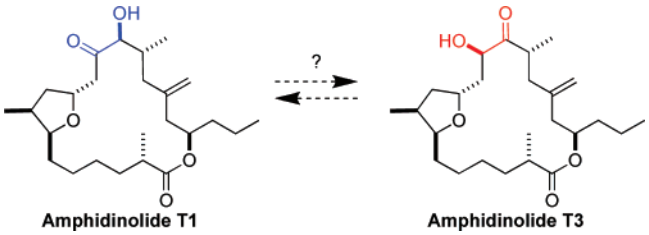


CHART 2. Naturally Occurring Regioisomeric Acyloins



products containing the "acyloin" substructure (i.e., an α-hydroxyketone). Among these, examples such as amphidinolide T1 and T3 include representatives that constitute either of two regioisomers (Chart 2). Could the existence of either regioisomer in nature stem from (a) acid- or base-mediated interconversion via an enediol structure or (b) retrocyclization−cyclization under kinetic control via thiamine diphosphate-catalyzed retro-acyloin/acyloin formation via an intermediate dialdehyde? Such a mechanism would require an as-of-yet unreported macrocyclizations of dialdehydes via the acyloin mechanism. Moreover, could acyloin-containing natural products undergo catalyst-dependent reorganization upon exposure to synthetic catalysts (or enzymes)? We examined model studies to see the likelihood of the above mechanistic pathways. In a sense, since the catalytic apparatus for acyloin chemistry is present in the milieu of biosynthesis (and manifested in thiamine diphosphate-dependent enzymes), we embarked upon the study of a potential biosynthetically significant reaction.

Results and Discussion

Our studies began with the synthesis of macrocycles **6** and **7** with the hypothesis that interconversion would proceed to a thermodynamically favored benzylic ketone (**7**). The synthesis of key macrolide regioisomers was accomplished in six straightforward synthetic steps from commercially available 3-(2-bromophenyl)-propionic acid (**1**, Scheme 1). The vinyl group was installed with a Suzuki reaction,[9] and saponification of the methyl ester and esterification with 7-octene-1-ol afforded diene **4**. Ring-closing metathesis followed by ketohydroxylation with acidic $KMnO_4$ afforded a 1:1 mixture of separable acyloins **6** and **7**.[10]

In our initial attempts to observe a catalyst-mediated interconversion between regioisomers, we subjected both regioisomers to a solution of either 1,2,2,6,6-pentamethylpiperidine (PEMP) or thiazolium salt **8** and PEMP in a 1:1 mixture of methanol/methylene chloride. Heating a solution of thiazolium salt **8** and regioisomer **7** in a sealed tube at 60 °C for 16 h allowed for 57% interconversion to regioisomer **6**, whereas heating PEMP and **7** allowed for 30% interconversion (Figure 1). Most surprisingly, we observed that the benzylic ketone appeared to be the less stable isomer in this interconversion, contrary to our hypothesis.

Since we observed interconversion in the control reaction, as well as in the reaction containing a thiazolium catalyst, we

(4) (a) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899−1902. (b) Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298−10299. (c) Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195−197. (d) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314−2315. (e) Matsumoto, Y.; Tomioka, K. *Tetrahedron Lett.* **2006**, *47*, 5843−5846.

(5) (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370−14371. (b) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205−6208. (c) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131−3134. (d) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736−8737. (e) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507−509.

(6) (a) He, M.; Struble, J. R.; Bode, J. *J. Am. Chem. Soc.* **2006**, *128*, 8418−8420. (b) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088−15089.

(7) (a) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654−1655. For examples of alkylation of *umploung* nucleophiles, see: (b) Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 1472−1473. (c) He, J.; Zheng, J.; Liu, J.; She, X.; Pan, X. *Org. Lett.* **2006**, *8*, 4637−4640. For examples of acylation/transesterification, see: (d) Movassaghi, M.; Schmidt, M. *Org. Lett.* **2005**, *7*, 2453−2456. (e) Thompson, J. E.; Rix, K.; Smith, A. D. *Org. Lett.* **2006**, *8*, 3785−3788. For examples of azirididine opening, see: (f) Liu, Y.-K.; Li, R.; Yue, L.; Li, B.-J.; Chen, Y.-C.; Wu, Y.; Ding, L.-S. *Org. Lett.* **2006**, *8*, 1521−1544. (g) Sun, X.; Ye, S.; Wu, J. *Eur. J. Org. Chem.* **2006**, 4787−4790. (h) Wu, J.; Sun, X.; Ye, S.; Sun, W. *Tetrahedron Lett.* **2006**, 4813−4816.

(8) (a) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126−8127. (b) Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518−9519. (c) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406−16407. (d) Zeitler, K. *Org. Lett.* **2006**, *8*, 637−640. (e) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905−908. (f) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4558−4559.

(9) Kerins, F.; O'Shea, D. F. *J. Org. Chem.* **2002**, *67*, 4968−4971.

(10) (a) For a streamlined strategy, see: Scholte, A. A.; An, M. H.; Snapper, M. L. *Org. Lett.* **2006**, *8*, 4759−4762. (b) Scholl, S.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. For recent reviews, see: (c) Fuerstner, A. *Angew. Chem. Int Ed.* **2000**, *39*, 312. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

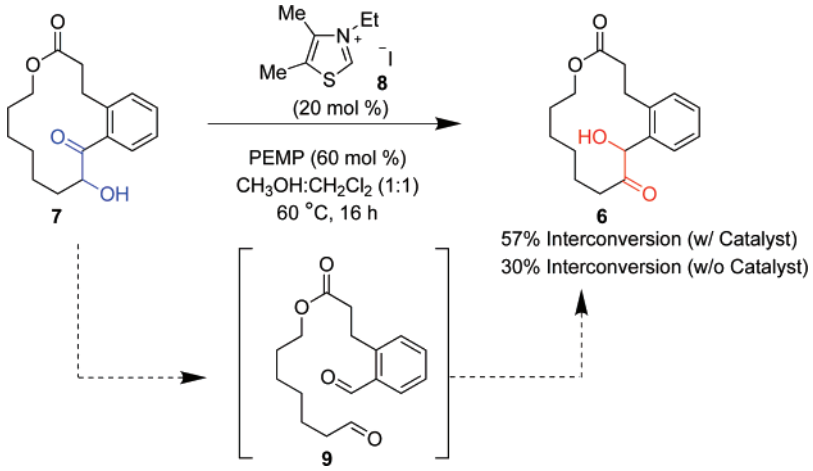
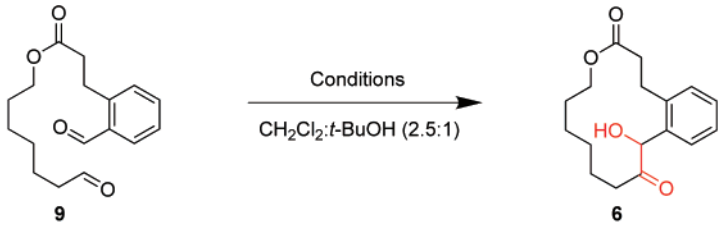
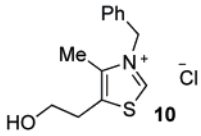
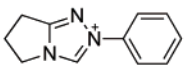


FIGURE 1. Interconversion of macrocyclic acyloins.

TABLE 1. Initial Development of a Macrocyclization Reaction



entry	catalyst (100 mol %)	base	conc. (M)	time (h)	temp (°C)	yield (%)
1		DBU	0.01	24	22	No Reaction
2		DBU	0.01	24	Reflux	No Reaction
3		DBU	0.01	24	22	Trace
4		DBU	0.01	24	Reflux	21
5		K^+t-BuO$^-$	0.01	24	Reflux	16
6[a]		LiHMDS	0.01	24	56	9
7		DBU	0.0025	36	Reflux	30

[a] Reaction was performed in toluene.

could not discount the possibility of interconversion through an enediol mechanism. However, we did observe trace aldehyde in the crude ^{1}H NMR of the reaction mixture. The presence of an aldehyde could be the result of our proposed retro-benzoin reaction (Figure 1) or the product of a base-mediated acyloin rearrangement.[11] Intrigued by the former possibility, we wanted to validate the possibility that our proposed dialdehyde intermediate (**9**) could indeed be cyclized to macrolide **6**.

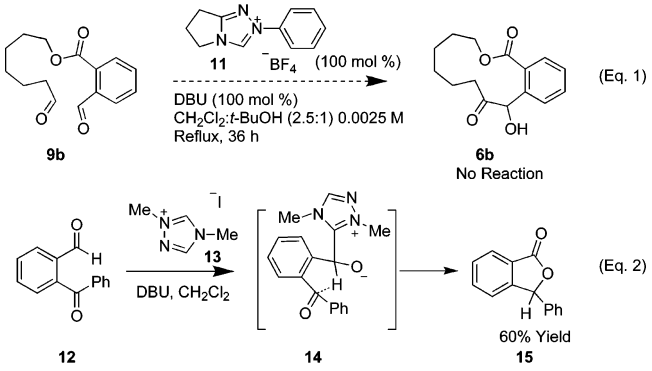
The development of an *N*-heterocyclic carbene (NHC)-mediated macrocyclization began with the examination of different solvent systems, using DBU to deprotonate the precatalyst salt. When reactions were performed in toluene or tetrahydrofuran, no products were observed. In a mixture of methylene chloride and *tert*-butanol,[12] we observed macrolide **6** by thin layer chromatography when using triazolium catalyst **11** (Table 1, entry 3). Encouraged by this empirical observation, we suspected that, as with many macrocyclization reactions, an increase in the reaction temperature might lead to a more efficient reaction. Heating a 2.5:1 mixture of methylene chloride/*tert*-butanol to reflux for 20 h allowed for macrolide **6** to be isolated in 21% yield as the sole regioisomer (entry 4). With potassium *tert*-butoxide, triazolium salt **11** provided 16% yield (entry 5), whereas lithium hexamethyldisilazide at 56 °C in toluene afforded a 9% yield of **6** (entry 6). Diluting a 2.5:1 mixture of methylene chloride/*tert*-butanol from 0.01 to 0.0025 M and utilizing DBU provided **6** in 30% yield after a 36 h reaction time (entry 7).

Different ring systems affected the cyclization. When the location of the ester was moved, as in benzoate **9b**, no desired product was observable under our macrocyclization conditions (eq 1). Independent synthesis of **6b** ensured that this compound was stable toward isolation. We suspected that the proximity of the aldehyde and the benzoate could induce a triazolium-mediated Cannizzaro reduction of the benzoate. Recent and fascinating studies in the literature have documented similar behavior that

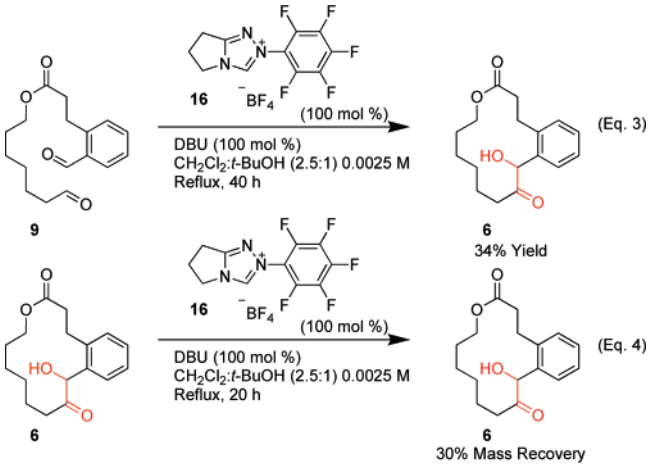
(11) Gelin, S.; Gelin, R. *J. Org. Chem.* **1979**, *44*, 808−810.

(12) Using *tert*-butanol as a solvent has proven successful for the development of intramolecular ketone Benzoin reactions; see: (a) Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432−8433. (b) Enders, D.; Niemeier, O. *Synlett* **2004**, 2111−2114.

supports the possibility of an intramolecular reduction (eq 2).[8f] We speculated that the incorporation of an electron-withdrawing group on the triazolium salt would lower the basicity of the NHC and serve to bypass this nonproductive pathway.



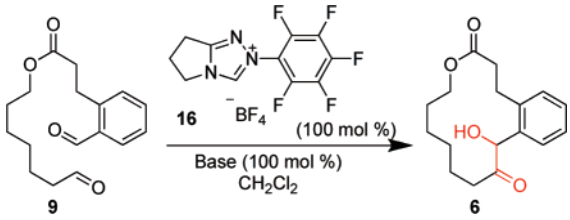
When precatalyst **16**[13] was allowed to react at reflux for 40 h in a 2.5:1 mixture of methylene chloride/*tert*-butanol, our desired product was produced in 34% yield (eq 3). Given our previous results in acyloin equilibration, we moved to examine if the product formed would be stable to the reaction conditions under which it was formed. By resubjecting macrolide **6** to a refluxing solution of triazolium and DBU for 20 h in a 2.5:1 mixture of methylene chloride/*tert*-butanol, **6** was recovered in 30% yield (eq 4). We postulated that the refluxing temperatures might contribute to product degradation and that pentafluorophenyl triazolium precatalyst **16** would allow for cyclization at lower temperatures.



Surprisingly, at 22 °C pentafluorophenyl triazolium catalyst **16** cyclized dialdehyde **9** *in only 17 min*, providing **6** in 39% yield (Table 2, entry 1). At 0 °C, **6** was isolated in 31% yield after 25 min (entry 2). Further lowering the temperature to −10 °C allowed for 33% yield in 30 min (entry 3). At −15 °C, a 21% yield was obtained after 90 min (entry 4). Concentration played a key role in the efficiency of the reaction (entries 1, 5, and 6). Use of *tert*-butyl magnesium bromide as our base completely decomposed the starting material, potassium hexamethyldisilazide provided only recovered starting material, and PEMP produced the desired product in 26% yield (entries 7−9).

(13) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725−5728.

TABLE 2. Influence of Concentration and Base



entry	base	time (min)	temp (°C)	conc (μM)	yield (%)
1	DBU	17	22	250	39
2	DBU	25	0	250	31
3	DBU	30	−10	250	33
4	DBU	90	−15	250	21
5	DBU	45	22	100	42[a]
6	DBU	90	22	50	48[a]
7	*t*-BuMgBr	30	0	250	decomposition
8	KHMDS	30	0	250	starting material
9	PEMP	30	0	250	26

[a] Conversion by ^{1}H NMR based on internal bromoform standard.

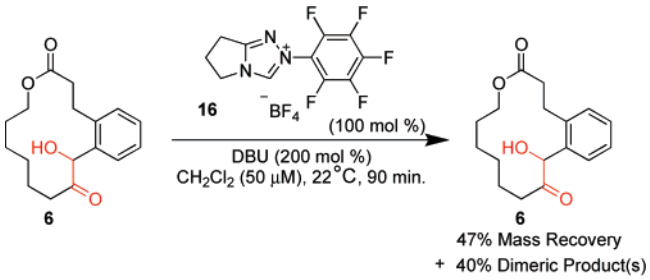


FIGURE 2. Product stability.

Mass Balance and Product Stability Studies. By using the more reactive pentafluorophenyl triazolium salt, we were able to execute the macrocyclization at ambient temperature. Our previous experiments demonstrated that the product of the reaction is slowly decomposed upon extended exposure to the reaction conditions; therefore, under milder conditions, we were hopeful that this undesirable pathway would be prevented. By resubjecting macrolide **6** to a 50 μM solution of pentafluorophenyl triazolium precatalyst **16** and DBU for 90 min, we were able to reisolate only 47% of our starting macrolide along with 40% of a material that has mass spectrum signals indicating one or more dimeric products (Figure 2).

Thin layer chromatography of the macrocyclization reaction shows clean conversion from dialdehyde **9** to macrolide **6** along with baseline material. Although DBU·HBF$_4$ and triazolium NHC are expected to reside on the baseline, flushing the silica gel column with increasingly polar solvents allows for the isolation of a complex mixture of at least six products, which, by mass spectrometry analysis, indicates possible variable dimeric materials. ^{1}H NMR analysis of the isolable baseline compounds indicates the presence of the aliphatic chain as well as aromatic functionality present in the starting material. Because of the complexity, no definite assignments of the baseline mixture could be made, but the two experiments show that the products are being consumed by the reaction conditions under which they are formed and that it is likely this is occurring by dimerization processes (cross-benzoin, aldol, aldol-dehydration, Cannizzaro reduction, acyloin rearrangement, etc.). Nonetheless, we are pleased to document facile macrocyclization under NHC conditions. These experiments have established this approach

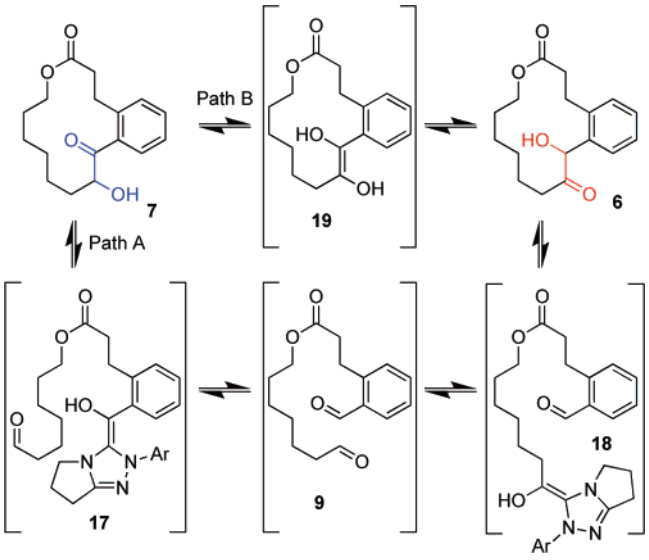
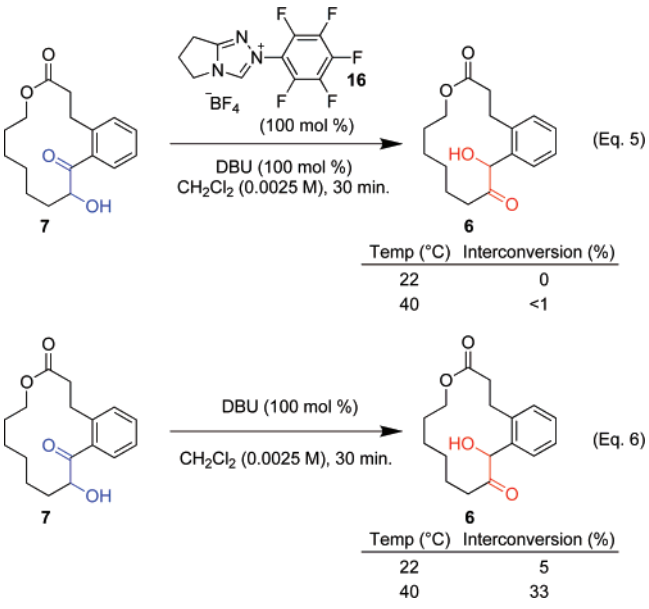


FIGURE 3. Possible mechanisms for the interconversion of **7** to **6**. (Enamine double bond geometries for **17** and **18** are not known. An arbitrary configuration is drawn for clarity.)

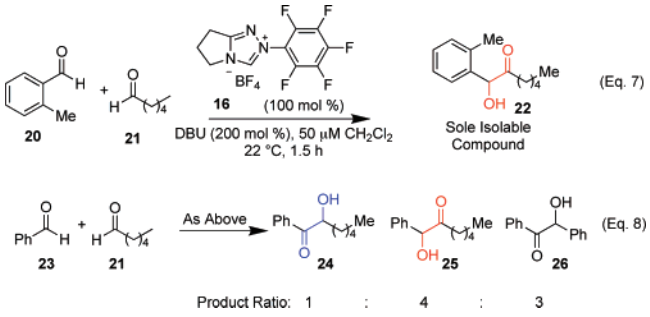
as a potential disconnection in chemical synthesis and a possible process in biosynthesis.

Interconversion and Selectivity Studies. The exclusive regioselectivity in the macrocyclization led us to question whether the selectivity was dictated by thermodynamic or kinetic control and the possible underlying factors that influence the selectivity. As with our preliminary studies, we hypothesized two possible scenarios for the interconversion: first, NHC-mediated retro-benzoin reaction, followed by catalyst dissociation and thermodynamically controlled macrocyclization (Figure 3, Path A) and second, enolization to enediol (**19**) followed by protonation (Path B).

Subjection of **7** to a mixture of triazolium salt **16** and DBU in methylene chloride at room temperature for 30 min allowed for the recovery of **7**. Under otherwise identical conditions, heating to reflux for 30 min allowed for trace conversion to **6** (<1%) as determined by ^{1}H NMR (eq 5). When **7** was allowed to react with *only* DBU for 30 min, 5% interconversion was observed. Heating the reaction containing only DBU to reflux did, however, allow for 33% interconversion of **7** to **6** in 30 min (eq 6). Since the macrocyclization reaction is performed at ambient temperature, the lack of interconversion under the reaction conditions led us to conclude that **6** is the kinetic product. Additionally, on the basis of the slow interconversion with DBU, presumably via the enediol (**19**), we found that **6** is also more stable than **7**.



The experimental observations reported above indicate that the productive acyl-anion formation occurs at the aliphatic aldehyde, not the aromatic aldehyde. We decided to design an experiment in which we could examine two possible contributing factors: the conformational constraints for the macrocyclization and the steric hindrance of the ortho-substituted benzaldehyde. Reaction of hexanal and *ortho*-tolualdehyde under the macrocyclization conditions afforded **22** as the only isolable compound after silica gel chromatography (eq 7). The cross-coupling of benzaldehyde and hexanal shows that, in the absence of an ortho substituent, a mixture of **24**/**25**/**26** in a 1:4:3 ratio is isolated (eq 8). These results indicate that sterics *may* preclude triazolium catalyst **16** from generation of the acyl-anion at the ortho-substituted benzaldehyde. We cannot exclude the possibility that the conformational constraints are also an additive effect, especially considering the data that suggest that **6** is more stable than **7**.



α-Phenylketone Stereoelectronic Effect. Our interconversion studies supported that regioisomer **6** is more stable than **7** and that the steric effect of the ortho substituent is, to some degree, responsible for the product distribution. Nevertheless, we were still curious why the benzylic carbonyl (**7**) was less favored. Independent synthesis demonstrated the benzylic carbonyl (**7**) is isolable, indicating that there is not a conformational restriction preventing the formation of **7**. We speculated that benzylic ketone **7** may contain an inherent entropic penalty resulting from conjugation that would not be present in benzylic alcohol **6**. A less obvious possibility was the potential existence of a subtle stereoelectronic effect that may be stabilizing **6**.

α-Phenylcarbonyl compounds are believed to possess a stabilizing interaction wherein the π face of the carbonyl and the π face of the aryl ring are orthogonally aligned (**I**, Figure 4).[14−17] This interaction can be observed by UV−vis spectroscopy by the presence of a band at 290 nm which displays an unusually high extinction coefficient ($\epsilon \geq 100$). Kumler and co-workers have studied numerous α-phenylcarbonyl compounds, and they have suggested that this particular stereoelectronic effect is on the order of magnitude of 3−5 kcal.[15] Cookson and co-workers later proposed that the π-orbitals of the carbonyl and the π-system were directed approximately toward each other.[16] This interaction is not observable with 2-phenylcyclohexanone (**27**), indicating that the interaction is

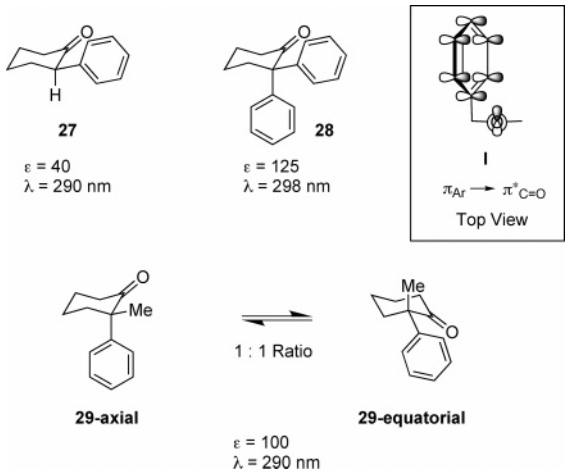


FIGURE 4. Examples of an α-phenylketone stereoelectronic effect.

not strong enough to overcome the equatorial preference of a phenyl group. However, when a phenyl group is fixed in the axial position, as in 2,2-diphenylcyclohexanone (**28**), the appropriate geometry is readily achieved.[16] A particularly noteworthy example is the high extinction coefficient observed with 2-methyl-2-phenylcyclohexanone (**29**).[17] The phenyl group would be predicted to preferentially adopt an equatorial geometry; however, an almost 1:1 mixture of the axial vs equatorial phenyl is observed.

Analysis of our 12-membered macrocycle **6d** by single-crystal X-ray analysis provides an alluring depiction of this α-phenylcarbonyl stereoelectronic effect (Figure 5). Macrolide **6d** disposes the plane of the carbonyl and the face of the aryl ring in an orthogonal arrangement in agreement with Cookson et al.'s proposal. Additionally, X-ray analysis indicates that the acyloin is involved in a hydrogen-bonding arrangement. The hydrogen bond may lower the carbonyl LUMO and serve to enhance the α-phenylcarbonyl stereoelectronic effect. This analysis suggests that an intriguing α-phenylcarbonyl stereoelectronic effect could be at the heart of our observed macrocyclization regiochemistry.

Macrocyclization Substrate Scope. An examination of the scope of this macrocyclization provided valuable data on the current limits of this methodology. The 14-membered ring (**6**) served as the starting point for this analysis. As shown in Table 3, entry 1, reducing the concentration to 50 μM allowed for the product to be isolated in 43% yield in only 90 min. The yield of the macrocyclization reaction decreased as the ring size decreased, presumably as a result of greater ring strain (entries

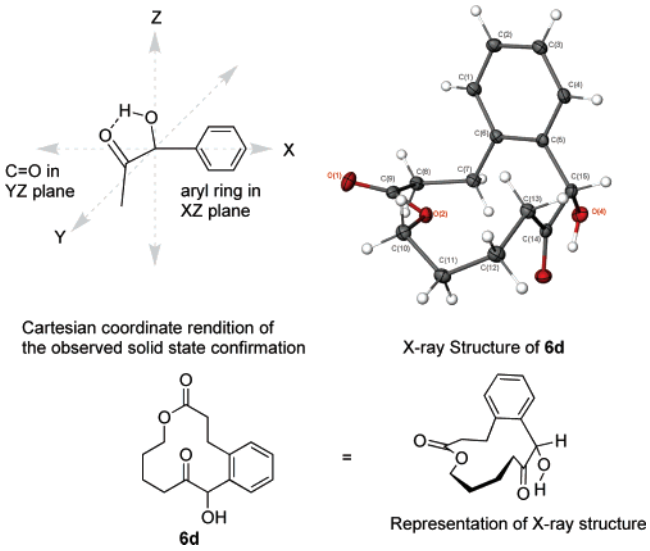


FIGURE 5. X-ray analysis of an α-phenylketone stereoelectronic effect.

1−4). Remote stereocenters (entries 5 and 6) helped the cyclization, affording **6f** and **6g** in 42 and 47% yield, respectively. Of particular interest was the cyclization of compound **9b**. During our initial examination with catalyst **11**, carboxybenzaldehyde derivative **9b** afforded no conversion to our desired product. We reasoned that the more basic carbene may promote an intramolecular Cannizzaro reduction and that reducing the basicity of the carbene by employing pentafluorophenyl triazolium salt **16** would minimize this pathway. Indeed, the solution to our hypothesis allowed for **9b** to be cyclized under the macrocyclization conditions to afford macrolide **6b** (entry 7). This exciting result ultimately served as the springboard toward applying this methodology in a synthesis of the natural product *trans*-resorcylide.

Synthesis of *trans*-Resorcylide. *trans*-Resorcylide is a 12-membered macrocycle belonging to a family of naturally occurring benzoic acid-derived macrolide plant growth inhibitors isolated from the species *Penicillium* sp.[18] This family of natural products[19] has received attention from the laboratories of Danishefsky,[20] De Brabander,[21] Fürstner,[22] Porco,[23] Snider,[24] Tsuji,[25] as well as Couladouros,[26] who recently completed the first total synthesis of both *cis*- and *trans*-resorcylide. Our acyloin synthetic disconnection affords a direct opportunity to test the possibility of using in situ acyl-anion equivalents as a

(14) (a) Marsocci, S. F.; MacKenzie, S. *J. Am. Chem. Soc.* **1959**, *81*, 4513−4516. (b) Labhart, H.; Wagnier, G. *Helv. Chim. Acta* **1959**, *42*, 2219−2227. (c) MacKenzie, S.; Marsocci, S. F.; Lampe, H. C. *J. Org. Chem.* **1965**, *30*, 3328−3332. (d) Gencarelli, R.; Abajian, H.; Irving, P.; MacKenzie, S. *J. Org. Chem.* **1970**, *35*, 2673−2677. (e) Scanlan, M. E.; MacKenzie, S. *J. Org. Chem.* **1972**, *37*, 1579−1583. (f) Hagishita, S.; Kuriyama, K. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1937−1941. (g) Schippers, P. H.; van der Ploeg, J. P. M.; Dekkers, H. P. J. M. *J. Am. Chem. Soc.* **1983**, *105*, 84−89.

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(17) (a) Colard, P.; Elphimoff-Felkin, I.; Verrier, M. *Bull. Soc. Chim. Fr.* **1961**, 516−520. (b) Elphimoff-Felkin, I.; Verrier, M. *Bull. Soc. Chim. Fr.* **1967**, 1047−1052.

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(20) (a) Yoshino, T.; Ng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 14185−14191. (b) Yang, Z.-Q.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 9602−9603. (c) Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903−10908.

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(22) (a) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005−7008. (b) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990−7995. (c) Fürstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731−3734. (d) Fürstner, A.; Dierkes, T.; Theil, O. R.; Blanda, G. *Chem.−Eur. J.* **2001**, *7*, 5286−5298.

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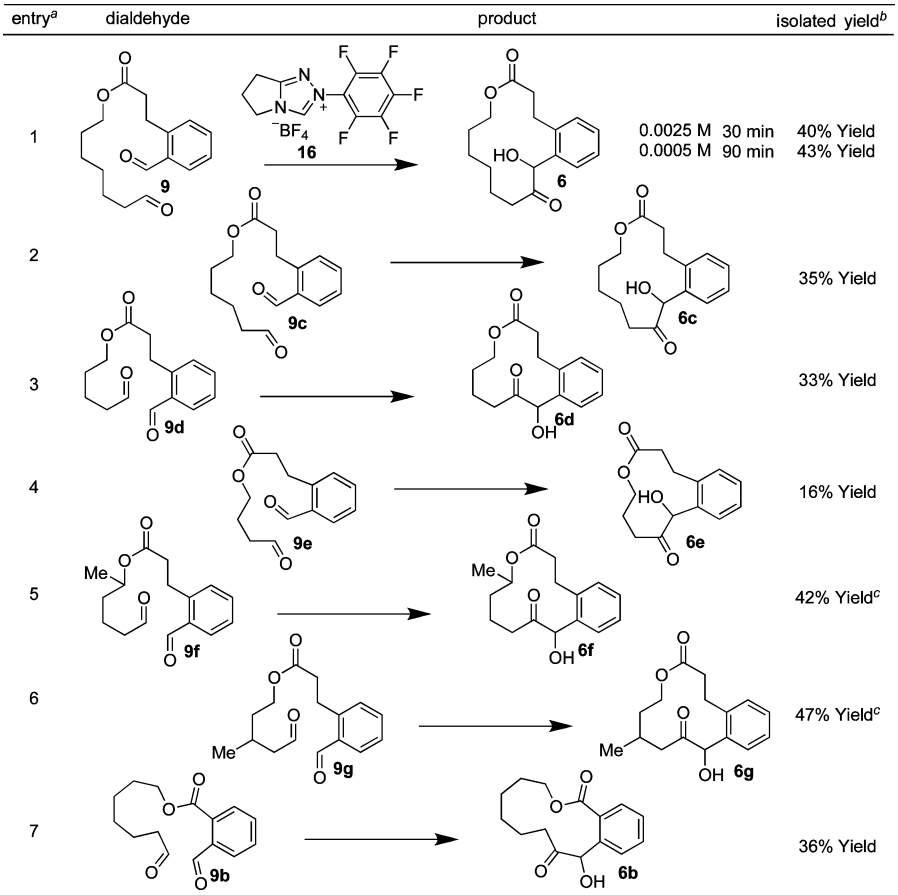
(25) Takahashi, T.; Minami, I.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 2651−2654.

TABLE 3. Substrate Scope



[a] Reactions were conducted at a concentration of 50 μM in CH_2Cl_2 under an argon atmosphere at 22 °C for 90 min and employed 1 equiv of **16** and 2 equiv of DBU. [b] Yield refers to the mass isolated after silica gel chromatography. [c] Diastereomeric mixtures were deoxygenated for characterization.

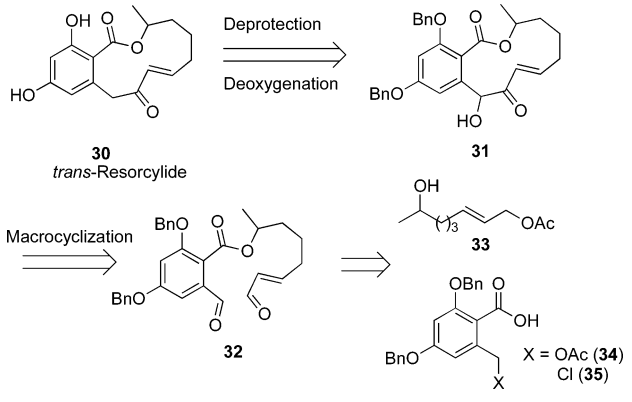


FIGURE 6. Retrosynthetic analysis of *trans*-resorcylide.

novel method for macrocyclization in natural product synthesis, as depicted in Figure 6.

Synthesis of Dialdehyde 32. The synthesis of benzoic acid **34** was accomplished as described by Couladouros and coworkers.[26,27] Alcohol **33** was synthesized from commercially available alcohol **37** by acylation with acetic anhydride (Ac_2O), followed by Wacker oxidation and $NaBH_4$ reduction as described by Tsuji and Mandai.[28] Coupling of the congested *o*,*o*-disubstituted chlorobenzoic acid **35** to secondary alcohol **33** was accomplished by a Mitsunobu protocol to provide chloroacetate **38** in 60% yield (Scheme 2).[26] After experimenting with several modifications of the Kornblum oxidation,[29] we found that by allowing **38** to react with silver(I) tosylate, followed by the addition of 10 equiv of tri-*n*-propylamine (BP = 156 °C) and heating to 110 °C in dimethylsulfoxide for 2 h we could isolate aldehyde **39** in 44% yield. However, subjecting **39** to several hydrolysis conditions hydrolyzed the benzoate within 30 min.

Suspecting that the electron-withdrawing benzaldehyde was activating the benzoate (vinylogous glyoxylate) toward hydrolysis, we speculated that changing the order of steps would allow access to the desired dialdehyde (Scheme 3). Hydrolyzing chloroacetate **38** with K_2CO_3 at 0 °C for 2 h (81% yield) followed by isolation and immediate oxidation with Dess−Martin periodinane (DMP) provided α,β-unsaturated aldehyde **42** in 83% yield. Kornblum oxidation with silver(I) tosylate followed by the addition of 10 equiv of tri-*n*-propylamine and heating to 110 °C in dimethylsulfoxide for 2 h allowed for the isolation of dialdehyde **32** in 16% yield. The Kornblum procedure produced an extremely complex mixture of com-

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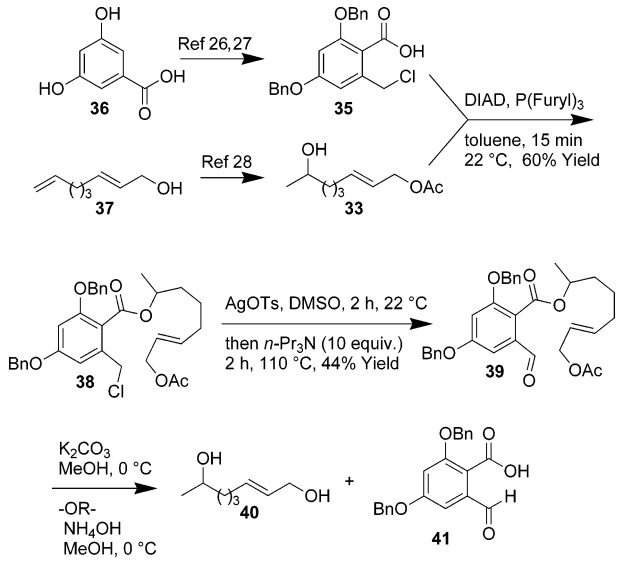
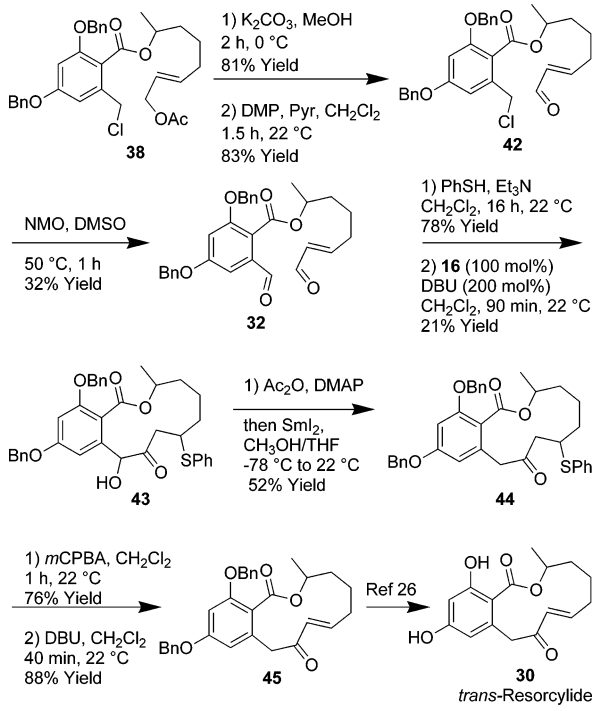
SCHEME 2. Synthesis of *trans*-Resorcylide



SCHEME 3. Synthesis of *trans*-Resorcylide Precursor



pounds, which made isolation of pure dialdehyde exceedingly difficult. Thus, substituting the Kornblum oxidation with a modification known as the Ganem oxidation[30] (i.e., a tertiary amine-*N*-oxide is the oxidant) provided an operationally more appealing protocol. Oxidation of benzylic chloride **32** with 5 equiv of *N*-methylmorpholine-*N*-oxide in a solution of dimethylsulfoxide at 50 °C for 1 h allowed for the smooth isolation of dialdehyde **32** in 32% yield.

The α,*β*-unsaturated aldehyde was first converted to the *β*-thioether to prevent homoenolate formation.[5] Subjection of α,*β*-unsaturated aldehyde **32** to benzenethiol with catalytic triethylamine afforded the *β*-thioether in 78% yield. This compound was poised for the crucial macrocyclization, and our optimized conditions for macrocyclization afforded **43** as an inconsequential mixture of diastereomers in 21% yield. Acylation of the acyloin followed by immediate deoxygenation with SmI_2 provided **44** in 51% yield.[31] Sulfide **44** was oxidized with *meta*-chloroperoxybenzoic acid (*m*-CPBA) to the sulfone (76% yield), which was immediately eliminated with DBU to afford *trans*-dibenzylresorcylide (**45**) in 88% yield. Compound **45** was converted to *trans*-resorcylide by Couladouros et al.,[26] and thus, the present route constitutes a formal synthesis of *trans*-resorcylide.

Conclusions

In summary, stimulated by ruminations about biosynthetic possibilities for natural products containing the acyloin substructure, we have explored the utility of *N*-heterocyclic carbene catalysts for the macrocyclization of α,*ω*-dienes. In the process, we have discovered a remarkably fast cyclization protocol for several large rings, including one of relevance to the synthesis of *trans*-resorcylide. While reaction yields are modest in many cases, it appears that this drawback may be due to product stability, rather than inherent limitations associated with the catalytic cyclization strategy. Moreover, we find that there are striking issues of macrocycle structure that dictate thermodynamic stability of products and kinetic facility of ring formation of various regioisomers. The plausibility of thiamine diphosphate participation in the biosynthesis of acyloin-containing natural products remains to be determined. Yet, it appears that speculation about biosynthesis, in terms of both biosynthesis pathways and the potential role of various enzymes and cofactors, remains a fruitful avenue for the conception of intriguing new synthetic chemistry and for the discovery of unanticipated chemical behavior.

Experimental Section

General Procedure for Macrocyclization. Preparation of Acyloin 6. To a 1-L Schlenk flask was added methylene chloride (500 mL) directly from a Seca Solvent System under an atmosphere of argon. Dialdehyde **9** (80.9 mg, 0.279 mmol) in CH_2Cl_2 (30 mL) was added by cannula, followed by the addition of DBU (0.083 mL, 0.558 mmol). Then, a vigorously stirred suspension of pentafluorophenyl triazolium salt **16** (101 mg, 0.279 mmol) in CH_2Cl_2 (25 mL) was added by cannula over 10 min. The reaction was stirred at 22 °C for 90 min, at which time the reaction turned from a colorless solution to a resilient yellow solution. At 90 min, the contents of the reaction vessel were filtered through a plug of silica gel (100 cm^3) followed by eluting the plug with 400 mL of EtOAc. The filtrate was concentrated under reduced pressure to yield crude **6**, which was purified by silica gel chromatography (12% EtOAc/hexane, 35.1 mg, 43% yield). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.32−7.22 (m, 4H), 5.32 (d, $J = 3.6$ Hz, 1H), 4.07 (m, 1H), 3.95 (m, 1H), 3.35 (m, 1H), 3.00−2.77 (m, 3H), 2.52 (m, 1H), 2.27 (dt, $J = 16.0$ Hz, $J = 2.3$ Hz, 1H), 1.62 (p, $J = 6.9$ Hz, 1H), 1.49−1.40 (m, 2H), 1.33 (m, 1H), 1.23−1.12 (m, 2H), 1.05−0.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 209.9, 172.3, 138.5, 135.1, 129.6, 128.9, 127.3, 126.6, 78.9, 64.7, 36.2, 32.9, 26.5, 26.3, 25.9, 23.7, 22.1; IR (film, cm^{-1}): 3454, 2934, 2862, 1726; TLC R_f 0.29 (25% EtOAc/hexane); HRMS [$C_{17}H_{22}O_4$ + Na] requires *m*/*z* 313.1416. Found 313.1411 (ESI).

Preparation of Acyloin 6c. Acyloin **6c** was prepared in a manner analogous to that described for acyloin **6**, employing dialdehyde **9c** (62.7 mg, 0.227 mmol), pentafluorophenyl triazolium salt **16**

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(31) Molander, G.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135−1138.

(82.4 mg, 0.227 mmol), DBU (68 μL, 0.454 mmol), and CH_2Cl_2 (454 mL), which afforded acyloin **6c**, which was purified by silica gel chromatography (12% EtOAc/hexane, 21.9 mg, 35% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36−7.30 (m, 2H), 7.23 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 6.3 Hz, 1H), 5.27 (d, J = 2.6 Hz, 1H), 4.23 (d, J = 3.2 Hz, 1H), 4.12 (m, 1H), 3.79 (dt, J = 9.1 Hz, J = 2.2 Hz, 1H), 3.25 (m, 1H), 2.95 (m, 1H), 2.89−2.82 (m, 2H), 2.58 (m, 1H), 2.22 (m, 1H), 1.54−1.47 (m, 2H), 1.45−1.37 (m, 2H), 1.33−1.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 210.8, 171.8, 138.0, 135.8, 130.0, 129.0, 127.0, 126.7, 79.2, 64.3, 36.4, 32.6, 26.0, 25.5, 24.7, 22.5; IR (film, cm^{-1}): 3453, 2952, 2925, 2854, 1730, 1717, 1256; TLC R_f 0.20 (25% EtOAc/hexane); HRMS [$C_{16}H_{20}O_4$ + Na] requires m/z 299.1259. Found 299.1262 (ESI).

Preparation of Acyloin 6d. Acyloin **6d** was prepared in a manner analogous to that described for acyloin **6**, employing dialdehyde **9d** (65.5 mg, 0.250 mmol), pentafluorophenyl triazolium salt **16** (91 mg, 0.250 mmol), DBU (75 μL, 0.50 mmol), and CH_2Cl_2 (500 mL), which afforded acyloin **6d**, which was purified by silica gel chromatography (12% EtOAc/hexane, 21.5 mg, 33% yield). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.37 (d, J = 7.8 Hz, 1H), 7.31−7.26 (m, 2H), 7.20 (t, J = 7.3 Hz, 1H), 5.76 (d, J = 3.8 Hz, 1H), 5.17 (d, J = 3.5 Hz, 1H), 3.87 (m, 1H), 3.79 (m, 1H), 2.99 (m, 1H), 2.83−2.77 (m, 2H), 2.72 (m, 1H), 2.46 (m, 1H), 2.30 (m, 1H), 1.73 (m, 1H), 1.63−1.49 (m, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 209.5, 171.3, 138.7, 138.1, 128.4, 127.9, 125.9, 64.6, 35.8, 34.5, 25.3, 25.1, 20.6; IR (film, cm^{-1}): 3455, 2961, 2923, 2852, 1724, 1257; TLC R_f 0.53 (50% EtOAc/hexane); HRMS [$C_{15}H_{18}O_4$+] requires m/z 262.1205. Found 262.1202 (EI). X-ray: crystal obtained by slow evaporation from EtOAc/hexane.

Preparation of Acyloin 6e. Acyloin **6e** was prepared in a manner analogous to that described for acyloin **6**, employing dialdehyde **9e** (62.8 mg, 0.253 mmol), pentafluorophenyl triazolium salt **16** (91.8 mg, 0.253 mmol), and DBU (76 μL, 0.506 mmol) in CH_2Cl_2 (506 mL), which afforded acyloin **6e**, which was purified by silica gel chromatography (12% EtOAc/hexane, 10.0 mg, 16% yield). ^{1}H NMR (DMSO-d_6, 400 MHz, T = 55 °C): δ 7.47 (d, J = 7.6 Hz, 1H), 7.32−7.20 (m, 3H), 5.49 (bs, 1H), 5.16 (d, J = 3.3 Hz, 1H), 3.73 (dt, J = 10.9 Hz, J = 4.6 Hz, 1H), 3.46 (td, J = 10.4 Hz, J = 3.6 Hz, 1H), 2.96 (m, 1H), 2.75−2.62 (m, 3H), 2.33−2.12 (m, 3H), 1.69 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 208.0, 170.8, 137.6, 128.8, 128.0, 126.0, 63.7, 34.4, 25.0, 21.2; IR (film, cm^{-1}): 3451, 2957, 2920, 2852, 1733, 1715, 1252; TLC R_f 0.17 (25% EtOAc/hexane); HRMS [$C_{14}H_{16}O_4$ + Na] requires m/z 271.0946. Found 271.0951 (ESI).

Preparation of Acyloin 6f and Deoxy-6f. Acyloin **6f** was prepared in a manner analogous to that described for acyloin **6**, employing dialdehyde **9f** (69.4 mg, 0.251 mmol), pentafluorotriazolium salt **16** (91.0 mg, 0.251 mmol), DBU (75 μL, 0.502 mmol), and CH_2Cl_2 (502 mL), which afforded acyloin **6f** as a mixture of diastereomers, which was purified by silica gel chromatography (12% EtOAc/hexane, 29.4 mg, 42% yield). To a stirred solution of acyloin **6f** (19.9 mg, 0.071 mmol) and DMAP (13.5 mg, 0.107 mmol) in CH_2Cl_2 (0.50 mL) was added acetic anhydride (10 μL, 0.107 mmol) in one portion. The reaction mixture was stirred at 22 °C for 1 h, followed by filtering the crude reaction mixture through a short plug of silica gel and eluting with 50% EtOAc/hexane. The filtrate was concentrated under reduced pressure and dissolved in 9:1 THF/CH_3OH (211 μL) and added over 5 min to a −78 °C solution of freshly prepared SmI_2 (1.78 mL, 0.178 mmol, 0.1 M). The resulting blue solution was stirred at −78 °C for 10 min and then allowed to warm to 22 °C. The reaction mixture was quenched by addition of 10 mL of saturated K_2CO_3, extracted with diethyl ether (3 × 10 mL), dried over $MgSO_4$, and concentrated to afford **deoxy-6f**, which was purified by silica gel chromatography (10% EtOAc/hexane, 14.3 mg, 77% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 6.9 Hz, 1H), 7.19 (t, J = 7.2 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 4.74 (m, 1H), 3.89 (d, J = 16.4 Hz, 1H), 3.50 (d, J = 16.4 Hz, 1H), 3.04 (m, 1H), 2.87−2.73 (m, 3H), 2.36 (m, 1H), 2.25 (m, 1H), 1.83−1.75 (m, 2H), 1.46 (m, 2H), 1.13 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 209.5, 171.6, 138.2, 133.4, 131.2, 128.4, 127.8, 126.7, 72.3, 48.8, 39.1, 35.6, 32.2, 26.1, 20.4, 20.1; IR (film, cm^{-1}): 2974, 2929, 2852, 1724, 1716, 1255; TLC R_f 0.45 (25% EtOAc/hexane); HRMS [$C_{16}H_{21}O_3$ + H] requires m/z 261.1491. Found 261.1496 (ESI).

Preparation of Acyloin 6g and Deoxy-6g. Acyloin **6g** was prepared in a manner analogous to that described for acyloin **6**, employing dialdehyde **9g** (83.6 mg, 0.303 mmol), pentafluorophenyl triazolium salt **16** (110 mg, 0.303 mmol), DBU (90 μL, 0.606 mmol), and CH_2Cl_2 (605 mL), which afforded acyloin **6g** as a mixture of diastereomers, which was purified by silica gel chromatography (12% EtOAc/hexane, 39.4 mg, 47% yield). Acyloin **6g** (32.4 mg, 0.117 mmol) was deoxygenated in a manner analogous to that described for compound **deoxy-6f**, employing DMAP (21 mg, 0.176 mmol), CH_2Cl_2 (1.7 mL), and acetic anhydride (17 μL, 0.176 mmol) followed by 9:1 THF/CH_3OH (351 μL) and SmI_2 (2.3 mL, 0.234 mmol, 0.1 M), which afforded **deoxy-6g**, which was purified by silica gel chromatography (10% EtOAc/hexane, 15.6 mg, 52% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.22−7.19 (m, 2H), 7.15−7.10 (m, 2H), 3.94 (m, 1H), 3.85 (m, 1H), 3.67 (d, J = 16.1 Hz, 1H), 3.58 (d, J = 16.1 Hz, 1H), 2.90 (m, 1H), 2.83−2.70 (m, 3H), 2.32 (dd, J = 10.1 Hz, J = 8.2 Hz, 1H), 2.18−2.11 (m, 2H), 1.88 (m, 1H), 1.42 (m, 1H), 0.84 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 208.1, 171.7, 138.4, 133.4, 131.7, 128.2, 127.7, 126.6, 63.0, 48.9, 47.0, 35.3, 33.3, 26.5, 25.5, 21.3; IR (film, cm^{-1}): 2926, 2896, 1720, 1707, 1269; TLC R_f 0.40 (25% EtOAc/hexane); HRMS [$C_{16}H_{21}O_3$ + H] requires m/z 261.1491. Found 261.1495 (ESI).

Preparation of Acyloin 6b. Acyloin **6b** was prepared in a manner analogous to that described for acyloin **6**, employing dialdehyde **9b** (39.1 mg, 0.150 mmol), pentafluorotriazolium salt **16** (54.0 mg, 0.150 mmol), and DBU (45 μL, 0.30 mmol) in CH_2Cl_2 (300 mL), which afforded acyloin **6b**, which was purified by silica gel chromatography (12% EtOAc/hexane, 14.1 mg, 36% yield). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.78 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.40 (t, J = 7.4 Hz, 1H), 6.49 (bd, J = 4.5 Hz, 1H), 5.83 (bs, 1H), 4.39 (m, 1H), 4.12 (m, 1H), 4.12 (m, 1H), 2.84 (m, 1H), 2.47 (m, 1H), 1.79−1.73 (m, 2H), 1.68−1.55 (m, 2H), 1.49−1.30 (m, 4H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 209.1, 167.6, 139.3, 131.3, 130.1, 129.7, 127.4, 127.0, 74.5, 65.2, 37.1, 25.4, 25.0, 23.4, 21.1; IR (film, cm^{-1}): 3447, 2940, 1713, 1283; TLC R_f 0.30 (5% acetone/toluene); HRMS [$C_{15}H_{18}O_4$ + Na] requires m/z 285.1103. Found 285.1088 (ESI).

Synthesis of *trans*-Resorcylide.

Preparation of Dialdehyde 32. To a stirred solution of **42** (429 mg, 0.846 mmol) in DMSO (1.69 mL) under an atmosphere of argon was added *N*-methylmorpholine-*N*-oxide (497 mg, 4.23 mmol) and heated to 50 °C for 1 h. The reaction mixture was cooled to 22 °C and partitioned with 1:1 H_2O/brine (200 mL), extracted with EtOAc (4 × 50 mL), and dried over Na_2SO_4. The solution was then concentrated and purified by silica gel chromatography (10% EtOAc/hexane) to afford dialdehyde **32** as a clear oil (133 mg, 32% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.96 (s, 1H), 9.43 (d, J = 7.9 Hz, 1H), 7.42−7.32 (m, 10H), 7.06 (d, J = 2.2 Hz, 1H), 6.83 (d, J = 2.2 Hz, 1H), 6.68 (dt, J = 15.6 Hz, J = 6.8 Hz, 1H), 6.05 (dd, J = 15.6 Hz, J = 7.8 Hz, 1H), 5.23 (m, 1H), 5.11 (s, 2H), 5.07 (d, J = 2.3 Hz, 2H), 2.27−2.21 (m, 2H), 1.71−1.63 (m, 1H), 1.60−1.48 (m, 3H), 1.29 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.9, 189.8, 166.0, 160.7, 158.0, 157.2, 135.8, 135.7, 135.3, 133.1, 128.8, 128.6, 128.4, 128.3, 127.5, 127.4, 119.0, 106.7, 106.4, 72.1, 71.0, 70.6, 35.3, 32.3, 23.6, 19.9; IR (film, cm^{-1}): 2927, 2852, 2737, 1725, 1718, 1684, 1600, 1577; TLC R_f 0.26 (25% EtOAc/hexane); HRMS [$C_{30}H_{30}O_6$ + H] requires m/z 487.2121. Found 487.2134 (ESI).

Preparation of Resorcylide Acyloin 43. To a stirred solution of dialdehyde **32** (104 mg, 0.215 mmol) in CH_2Cl_2 (2.2 mL) under an atmosphere of argon was added benzenethiol (0.0242 mL, 0.236 mmol) and Et_3N (0.0015 mL, 0.0107 mmol). The reaction was stirred at 22 °C for 14 h, concentrated under reduced pressure, and quickly purified by silica gel chromatography (12% EtOAc/hexane) to afford β-thioether **32a** as a clear oil (100 mg, 78% yield), which was immediately used for the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.97 (d, J = 0.8 Hz, 1H), 9.69 (m, 1H), 7.42−7.25 (m, 15H), 7.06 (d, J = 2.2 Hz, 1H), 6.81 (d, J = 2.2 Hz, 1H), 5.20 (m, 1H), 5.11−5.08 (m, 4H), 3.44 (m, 1H), 2.54 (m, 2H), 1.67−1.46 (m, 6H), 1.29−1.27 (m, 3H); TLC R_f 0.31 (25% EtOAc/hexane).

A Schlenk flask containing a stirred solution of β-thioether **32a** (100 mg, 0.167 mmol) and pentafluorophenyl triazolium salt **16** (61.0 mg, 0.167 mmol) in CH_2Cl_2 (35 mL) was cannulated to a Schlenk flask containing CH_2Cl_2 (300 mL). Then, DBU (0.050 mL, 0.334 mmol) was added by syringe, and the reaction turned from a colorless solution to a resilient yellow solution. At 90 min, the now bright red reaction mixture was filtered through a plug of silica gel (100 cm^{-1}) followed by eluting the plug with 300 mL of EtOAc. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography (12% EtOAc/hexane) to afford resorcylide acyloin **43** (21.1 mg, 21% yield as an approximately 4:1 mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42−7.20 (m, 15H), 6.51−6.47 (m, 2H), 5.60 (d, J = 4.4 Hz, 0.8H), 5.32 (d, J = 11.1 Hz, 0.2H), 5.26 (m, 0.2H), 5.06 (m, 0.8H), 4.97−4.87 (m, 4H), 4.65 (d, J = 11.1 Hz, 0.2H), 4.09 (d, J = 4.4 Hz, 0.8H), 3.73 (m, 0.2H), 3.53 (dd, J = 10.5 Hz, J = 8.1 Hz, 0.2H), 3.20 (m, 0.8H), 2.90 (dd, J = 9.8 Hz, J = 3.6 Hz, 0.8H), 2.59 (d, J = 18.6 Hz, 0.2H), 2.13 (t, J = 12.5 Hz, 0.8H), 1.80−1.37 (m, 6H), 1.07 (d, J = 6.3 Hz, 2.4H), 0.91 (d, J = 6.3 Hz, 0.6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 212.2, 207.0, 204.2, 171.0, 170.4, 167.3, 167.0, 166.0, 161.6, 160.9, 159.1, 158.7, 157.5, 148.2, 142.9, 138.5, 136.0, 136.0, 135.9, 135.8, 135.5, 135.3, 135.1, 134.6, 134.0, 132.5, 131.7, 131.1, 129.0, 129.0, 128.9, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5, 127.3, 126.7, 126.7, 117.0, 113.5, 110.5, 106.0, 103.5, 102.3, 100.9, 100.7, 99.6, 82.8, 82.2, 73.1, 72.1, 71.5, 71.1, 70.9, 70.7, 70.6, 70.3, 70.3, 67.7, 60.3, 44.6, 44.3, 43.5, 43.1, 42.8, 40.9, 38.7, 36.6, 34.8, 34.7, 34.3, 33.5, 33.1, 24.6, 23.4, 22.8, 22.0, 21.0, 20.5, 19.4, 19.3, 14.1; IR (film, cm^{-1}): 3449, 2932, 1770, 1717, 1603; TLC R_f 0.39 (25% EtOAc/hexane); HRMS [$C_{36}H_{36}O_6S$ + H] requires m/z 597.2311. Found 597.2334 (ESI).

Preparation of Sulfide 44. Deoxygenation of resorcylide acyloin **43** was performed in a manner analogous to that described for acyloin **6f**, employing resorcylide acyloin **43** (20.0 mg, 0.034 mmol). The reaction mixture was quenched by addition of 10 mL of saturated $NaHCO_3$, extracted with diethyl ether (3 × 10 mL), dried over Na_2SO_4, and concentrated to afford sulfide **44** after purification by silica gel chromatography (5% EtOAc/hexane, 10.2 mg, 52% yield as an approximately 1.8:1 mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44−7.22 (m, 15H), 6.54 (d, J = 2.1 Hz, 1H), 6.38 (d, J = 2.1 Hz, 0.65H), 6.35 (d, J = 2.1, 0.35H), 5.25 (m, 0.65H), 5.17 (m, 0.35H), 5.04−4.99 (m, 4H), 4.14 (d, J = 18.0 Hz, 0.35H), 4.07 (d, J = 17.0 Hz, 0.65H), 3.89 (m, 0.35H), 3.75 (m, 0.65H), 3.55 (d, J = 17.1 Hz, 0.65H), 3.52 (d, J = 18.0 Hz, 0.35H), 2.85 (dd, J = 10.7 Hz, J = 5.0 Hz, 0.35H), 2.76 (dd, J = 9.5 Hz, J = 5.3 Hz, 0.65H), 2.64 (dd, J = 13.3 Hz, J = 2.3 Hz, 0.35H), 2.51 (dd, J = 9.9 Hz, J = 4.9 Hz, 0.35H), 1.93−1.24 (m, 6H), 1.17−1.14 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.4, 205.2, 168.0, 167.3, 160.5, 160.3, 157.8, 156.9, 136.4, 136.4, 136.3, 134.9, 133.9, 133.9, 133.2, 132.3, 130.7, 129.0, 128.6, 128.4, 128.3, 128.1, 128.1, 127.9, 127.8, 127.5, 127.5, 127.3, 127.3, 127.2, 126.7, 118.4, 117.8, 109.2, 109.1, 100.0, 99.6, 72.1, 71.3, 70.7, 70.4, 70.2, 48.8, 47.9, 47.1, 47.1, 43.2, 41.8, 36.6, 34.1, 33.5, 32.3, 31.8, 24.6, 23.3, 22.6, 20.7, 19.9, 19.4; IR (film, cm^{-1}): 2931, 1717, 1603; TLC R_f 0.52 (25% EtOAc/hexane); HRMS [$C_{36}H_{36}O_5S$ + H] requires m/z 581.2362. Found 581.2365 (ESI).

Preparation of *trans*-Dibenzylresorcylide (45). To a stirred solution of sulfide **44** (5.0 mg, 0.0086 mmol) in CH_2Cl_2 (500 mL) was added *m*-CPBA (7.4 mg, 0.043 mmol) in one portion. The reaction was stirred for 1 h at 22 °C, partitioned with saturated $NaHCO_3$ (15 mL), extracted with CH_2Cl_2 (4 × 10 mL), and dried over Na_2SO_4. The organic solution was concentrated under reduced pressure and was purified by silica gel chromatography (10−25% EtOAc/hexane), which afforded sulfone **44a** (4.0 mg, 76% yield as an approximately 1.8:1 mixture of diastereomers), which was immediately carried forward.

To a conical vial containing sulfone **44a** (4.0 mg, 0.0065 mmol) was added a stock solution of toluene (0.650 mL) containing DBU (1.06 μL, 0.0072 mmol) and stirred at 22 °C for 40 min. The reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography (10% EtOAc/hexane) to afford *trans*-dibenzylresorcylide (**45**) as a white foam (2.7 mg, 88% yield) that is in agreement with the literature characterization data.[26]

Data for Sulfone 44a: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (d, J = 7.2 Hz, 2H), 7.69−7.65 (m, 1H), 7.57 (t, J = 7.5 Hz, 2H), 7.44−7.28 (m, 10H), 6.55 (d, J = 2.0 Hz, 0.65H), 6.54 (d, J = 2.0 Hz, 0.35H), 6.37 (d, J = 2.0 Hz, 0.65 Hz), 6.33 (d, J = 2.0 Hz, 0.35H), 5.21−5.10 (m, 1H), 5.07−4.97 (m, 4H), 4.24 (d, J = 18.1 Hz, 0.35H), 4.00 (d, J = 17.8 Hz, 0.65H), 3.85 (d, J = 17.8 Hz, 0.65H), 3.78−3.70 (m, 1H), 3.55 (d, J = 18.3 Hz, 0.35H), 2.97−2.84 (m, 1.35H), 2.73 (dd, J = 13.5 Hz, J = 2.7 Hz, 0.65H), 1.93−1.42 (m, 4H), 1.14−1.10 (m, 3H); TLC R_f 0.28 (33% EtOAc/hexane).

Data for *trans*-Dibenzylresorcylide (45): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44−7.29 (m, 10H), 6.91 (ddd, J = 16.1 Hz, J = 9.6 Hz, J = 5.2 Hz, 1H), 6.66 (d, J = 2.2 Hz, 1H), 6.49 (d, J = 2.2 Hz, 1H), 5.94 (d, J = 16.2 Hz, 1H), 5.15−5.09 (m, 1H), 5.04 (dd, J = 11.4 Hz, J = 2.9 Hz, 1H), 4.98 (dd, J = 11.4 Hz, J = 8.7 Hz, 1H), 4.62 (d, J = 12.2 Hz, 1H), 3.30 (d, J = 12.2 Hz, 1H), 2.35−2.27 (m, 1H), 2.26−2.19 (m, 1H), 1.88−1.79 (m, 2H), 1.77−1.71 (m, 1H), 1.69−1.60 (m, 1H), 1.11 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 199.0, 168.6, 160.5, 157.4, 150.1, 136.3, 136.2, 134.8, 130.8, 128.6, 128.3, 128.1, 128.0, 127.6, 117.9, 107.7, 99.7, 72.2, 70.6, 70.2, 42.8, 34.0, 31.6, 24.6, 20.2; IR (film, cm^{-1}): 3063, 3032, 2973, 2934, 2872, 1708, 1668, 1602, 1581, 1456, 1433, 1379, 1284, 1165, 1062, 740, 697; TLC R_f 0.53 (33% EtOAc/hexane); HRMS [$C_{30}H_{30}O_5$ + Na] requires m/z 493.1991. Found 493.1993 (ESI).

Acknowledgment. This research was supported by the National Science Foundation (CHE-0639069). We thank Professor Glenn Micalizio for helpful discussions, Ms. Stephanie Ng for X-ray assistance, and Dr. Gorka Peris for helpful suggestions in the preparation of this manuscript. S.M.M. thanks the ACS Division of Organic Chemistry for a fellowship sponsored by Abbott Laboratories.

Supporting Information Available: Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for compounds **1a**, **3**, **4**, **4a**, **6**, **7**, **9**−**9g**, **22**, **25**, **38**, **38a**, **39**, and **42**, and X-ray crystallographic data for compound **6d** (CIF). This material is free of charge via the Internet at http://pubs.acs.org.

JO070676D