Alkaloid Synthesis

International Edition: DOI: 10.1002/anie.201505604
German Edition: DOI: 10.1002/ange.201505604

Synthesis of *ent*-Ketorfanol via a C–H Alkenylation/Torquoselective 6π Electrocyclization Cascade

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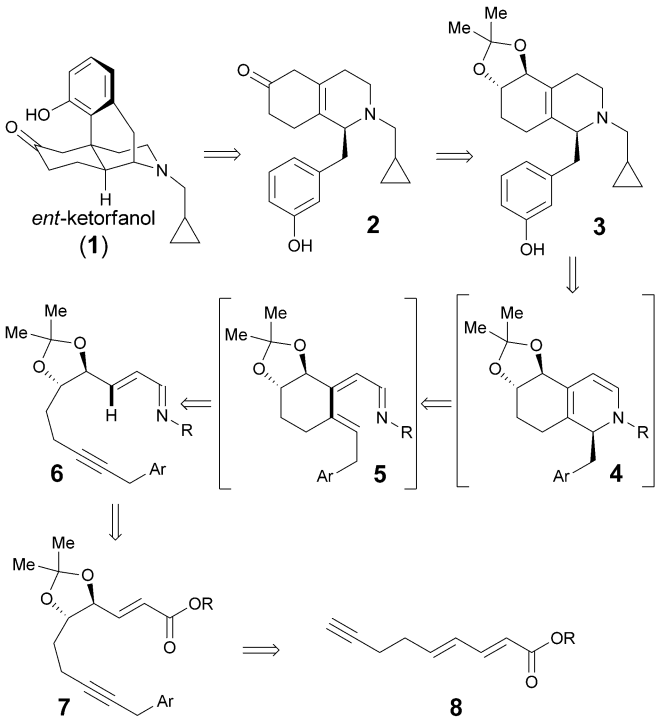
Abstract: *The asymmetric synthesis of ent-ketorfanol from simple and commercially available precursors is reported. A Rh^I-catalyzed intramolecular C–H alkenylation/torquoselective 6π electrocyclization cascade provides a fused bicyclic 1,2-dihydropyridine as a key intermediate. Computational studies were performed to understand the high torquoselectivity of the key 6π electrocyclization. The computational results demonstrate that a conformational effect is responsible for the observed selectivity. The ketone functionality and final ring are introduced in a single step by a redox-neutral acid-catalyzed rearrangement of a vicinal diol to give the requisite carbonyl, followed by intramolecular Friedel–Crafts alkylation.*

Oxycodone[1] and related semisynthetic opioid ligands are effective and pervasively used medications for the management of pain. However, these compounds have significant liabilities that include dependency, tolerance, which results in increasing doses being required to maintain efficacy, and the serious side effects of higher doses, such as respiratory failure. The recently reported high-resolution structures of a number of opioid receptor ligands in complex with several receptor subtypes provide an exceptional opportunity for the structure-based design of new opioid ligands with reduced drawbacks.[2] However, access to different structural variants is constrained by reported synthetic routes to the approved semisynthetic opioid ligands, which rely on morphine, thebaine, and other morphinoid natural products as heavily functionalized starting materials.[3,4]

Our recently developed Rh-catalyzed C–H functionalization/6π electrocyclization cascade[5] should enable direct and rapid entry to this important class of alkaloids from readily available achiral precursors. Herein, we demonstrate this approach with the asymmetric synthesis of *ent*-ketorfanol (**1**), the nonregulated enantiomer of the semisynthetic opioid drug ketorfanol (Scheme 1). *ent*-Ketorfanol should be accessible through acid-catalyzed intramolecular Friedel–Crafts cyclization of intermediate **2**.[6] This intermediate could potentially be obtained in situ from **3** under the acidic reaction conditions via a speculative redox-neutral process[7] proceeding through ionization of the allylic oxygen functionality followed by a hydrogen shift (see below). Fused bicyclic tetrahydropyridine **3** would then be obtained through reduction of dihydropyridine **4** under mildly acidic reductive amination conditions. In the key step, bicyclic intermediate **4** should be accessible via an intramolecular Rh-catalyzed syn C–H bond addition to the alkyne, followed by electrocyclization, which should hopefully proceed with high torquoselectivity owing to remote asymmetric induction provided by the isopropylidine protected diol.[8–10] The precursor for this cascade reaction, imine **6**, should be readily accessible from ester **7** through straightforward functional-group transformations. Ester **7** should be obtainable by regioselective Sharpless asymmetric dihydroxylation,[11] isopropylidene protection, and alkyne benzylation of the achiral dienoate **8**.



Scheme 1. Retrosynthetic analysis of *ent*-Ketorfanol.

The synthesis commenced with Swern oxidation of 4-pentyn-1-ol (**9**) and subsequent Horner–Wadsworth–Emmons reaction (Scheme 2) to furnish dienoate **10** (60% yield, 2 steps). A highly regio- and enantioselective Sharpless

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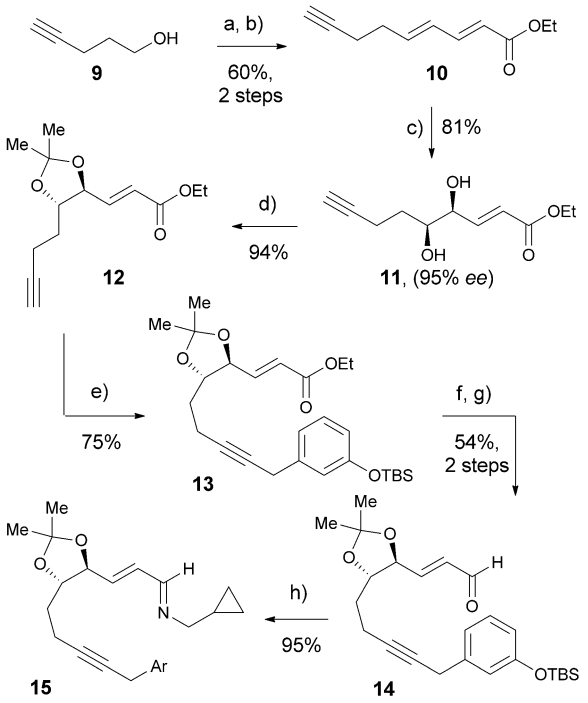
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201505604.

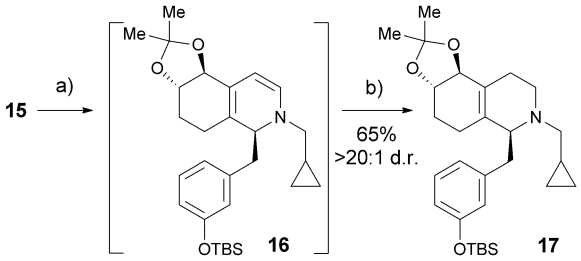


Scheme 2. Synthesis of imine **15**. Reagents and conditions: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; b) *n*BuLi, *i*Pr_2NH, (*E*)-ethyl-4-(diethoxyphosphoryl)but-2-enoate, −78→0 °C; c) AD-mix-α, $MeSO_2NH_2$, *t*BuOH, H_2O, 0 °C; d) 2,2-dimethoxypropane, *p*TsOH (10 mol%), CH_2Cl_2, 0 °C; e) 3-TBSOPhCH_2Cl, $PdCl_2(CH_3CN)_2$ (5 mol%), XPhos (15 mol%), Cs_2CO_3, THF, 65 °C; f) DIBAL, CH_2Cl_2, −78 °C; g) Dess–Martin periodinane, pyridine, CH_2Cl_2, 0 °C; h) cyclopropylmethyl amine, toluene, 3 Å MS. DMSO = dimethyl sulfoxide, TsOH = 4-toluenesulfonic acid, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran, DIBAL = diisobutylaluminium.

asymmetric dihydroxylation was performed on the olefin distal to the ester (81% yield, 95% *ee*).[11] Diol **11** was immediately protected using 2,2-dimethoxypropane and *p*TsOH to furnish acetonide **12** in 94% yield. X-ray structural analysis of **11** was also carried out to confirm that its absolute configuration was consistent with that predicted for AD-mix-α.[12]

Alkyne **12** was next benzylated by Cu^I-mediated coupling to give a moderate yield of product **13** (50–70%).[13] However, this process was plagued by long reaction times (4 days), the need for stoichiometric Cu^I, and difficulty in obtaining pure material. Ultimately, the efficient Pd-catalyzed method developed by Buchwald and co-workers[14] enabled the coupling of benzyl chloride and terminal alkyne **12** in 75% yield (Scheme 2). DIBAL reduction and Dess–Martin periodinane oxidation afforded α,β-unsaturated aldehyde **14** (54% yield, 2 steps). Condensation with cyclopropylmethyl amine gave our key imine substrate **15** in 95% yield.

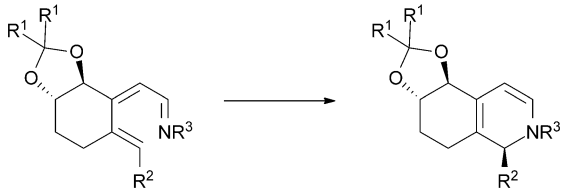
With α,β-unsaturated imine **15** in hand, we attempted the crucial tandem Rh^I-catalyzed intramolecular alkenylation/6π electrocyclization (Scheme 3).[5] Notably, while previously reported examples of diastereoselective electrocyclizations of azatrienes rely on stereogenic centers directly attached to the two atoms involved in ring closure,[8–10] azatriene **5** incorporates vicinal diol stereocenters that are distant from the stereocenter to be formed. Exposure of imine **15** to 2.5 mol% of $[\{RhCl(coe)_2\}_2]$ and 5 mol% of the electron-rich ligand 4-(diethylphosphino)-*N*,*N*-dimethylaniline at 65 °C led to highly selective formation of dihydropyridine **16** in excellent yield (84% by ^1H NMR analysis). While this tandem reaction was found not to be overly sensitive to concentration, reaction temperature is important, with higher temperatures resulting in lower yields and the formation of isomeric byproducts. Intermediate **16** was reduced without isolation by using $NaHB(OAc)_3$ and AcOH to provide tetrahydropyridine **17** in 65% overall yield and greater than 20:1 d.r., thereby confirming the high torquoselectivity of the reaction.



Scheme 3. The Rh^I-catalyzed C–H insertion reaction. Reagents and conditions: a) $[\{RhCl(coe)_2\}_2]$ (2.5 mol%), 4-(diethylphosphino)-*N*,*N*-dimethylaniline (5 mol%), toluene, 65 °C; b) $NaHB(OAc)_3$, AcOH, EtOH, 0→23 °C.

To determine the origins of the torquoselectivity observed in the Rh^I-catalyzed cascade sequence, computional studies of the key aza-electrocyclization were conducted using the ωB97x-D density functional with the 6-31 + G(d,p) basis set. Table 1 illustrates the truncated substrates modeled computationally as well as the kinetic diastereoselectivities of ring closures of these compounds. The sense and level of the torquoselectivities computed are consistent with the experimental results. The discussion of the stereoinduction (see below) emphasizes the results of our computational studies on **E**, the 1-azatriene that most closely resembles the experimental substrate **5**.

Table 1: 1-Aza-3,5-trienes modeled computationally, computed activation free energy differences, and computed torquoselectivities.



Compound	R^1	R^2	R^3	$G^{\ddagger}$ [kcal mol^{-1}]	Torquoselectivity[a]
A	H	H	H	3.1	187:1
B	H	Me	H	3.3	262:1
C	Me	Me	H	3.6	435:1
D	H	Me	Me	3.1	187:1
E	Me	Me	Me	3.2	221:1

[a] Free energies and torquoselectivities determined assuming a standard state of 1 atm and 298.15 K.

The torquoselectivity of the electrocyclization is controlled by the transition-state conformational preferences of the six-membered ring appended to the 1-azatriene. In the favored transition structure **c-tsE**, the six-membered ring adopts a distorted chair-like arrangement, whereas this ring is forced into a twist boat arrangement in **tb-tsE**, thereby destabilizing this transition structure by 3.2 kcal mol^{-1}. Arguments first proposed to rationalize electrophilic additions to cyclohexenes and their corresponding oxides[15] can be extended to rationalize these conformational differences. The favored mode of disrotation forces C5 of the triene moiety to pyramidalize "downwards" (as shown in Figure 1),

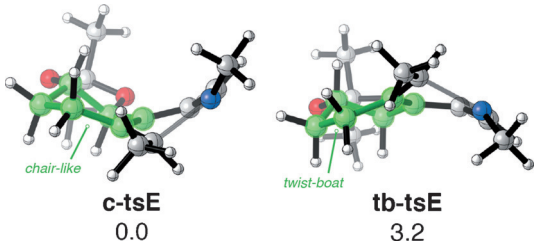


Figure 1. ωB97x-D/6-31 + G(d,p)-optimized transition structures and their relative free energies (in kcal mol^{-1}).

thus allowing the six-membered ring to adopt a chair-like conformation; pyramidalization of this carbon in the opposite direction is responsible for the twist-boat arrangement found in **tb-tsE**. This effect is likely general and could be exploited to perform diastereoselective electrocyclizations of similar chiral cyclic trienes.[16]

Figure 2 depicts the free energy surface of both modes of disrotatory electrocyclization as well as the reactant conformers of **E**. The global minimum conformer of **E** is **c-E1**, which features a chair-like six-membered ring and an s-*trans* arrangement of the azatriene moiety. **tb-E1** has a relative energy of 4.1 kcal mol^{-1} and leads to the disfavored transition structure. The helical arrangement of the azatriene in this structure forces the fused ring to adopt the less stable twist-boat conformation, thus demonstrating that the geometry required to form **tb-tsE** is inherently strained. The reactive conformers **c-E2** and **tb-E2** also differ in energy by approximately 4 kcal mol^{-1}, suggesting that the magnitude of this conformational effect is similar in the ground and transition states.

With the concise asymmetric synthesis of intermediate **17** accomplished, the stage was set for completing the synthesis of *ent*-ketorfanol (**1**). The remaining tasks included cleavage of the silyl ether and ketal protecting groups, intramolecular Friedel–Crafts alkylation, and transformation of the diol into the desired ketone moiety. All of these steps could theoretically be accomplished under acidic conditions. We therefore attempted to carry out this sequence in a single step by subjecting **17** to phosphoric acid at elevated temperature, which resulted in a 2:1 inseparable mixture of **18** and *ent*-ketorfanol (**1**), favoring **18** in a combined 69% yield (Scheme 4). Under these strongly acidic conditions, rapid cleavage of the ketal and silyl protecting group occurs along

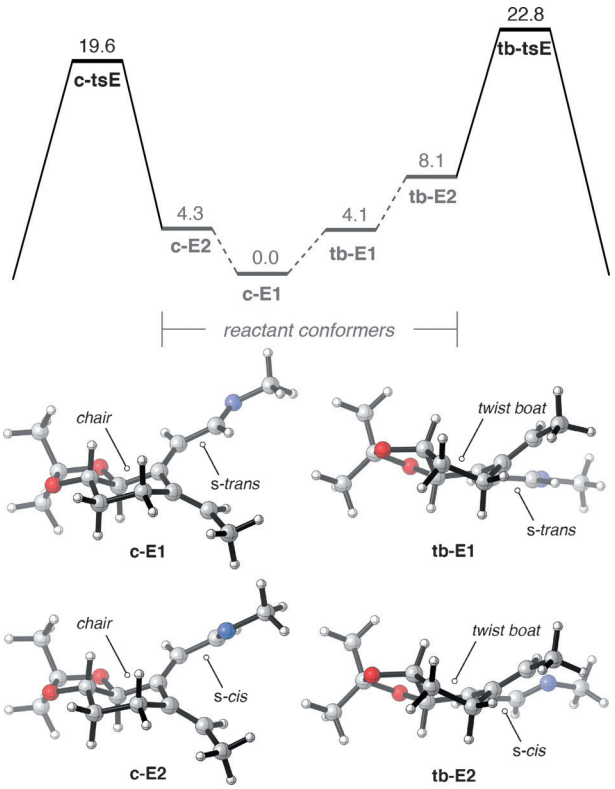
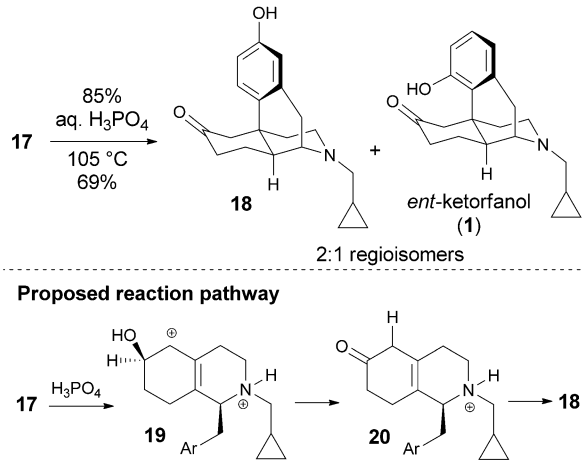


Figure 2. Free-energy diagram of the electrocyclization of 1-aza-3,5-triene **E** and the computed structures of the reactant conformers of **E**. Free energies (in kcal mol^{-1}) and structures were determined using ωB97x-D/6-31 + G(d,p).



Scheme 4. Intramolecular Friedel–Crafts alkylation with concomitant redox-neutral diol-to-ketone interconversion.

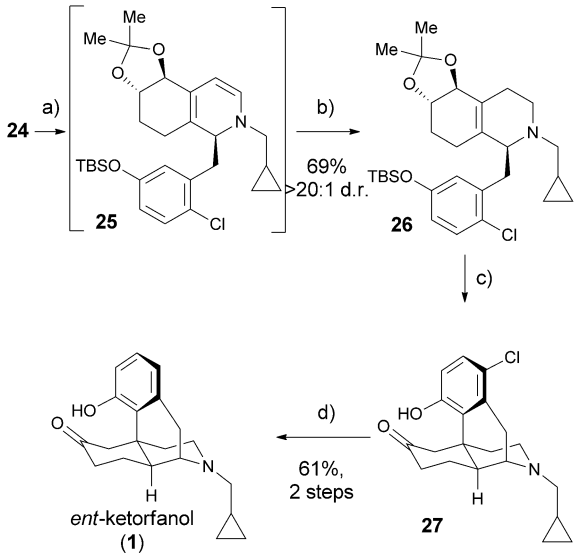
with ionization to give the stabilized 2°/3° allylic carbocation **19**, which upon hydrogen migration affords ketone **20**. This ketone intermediate accumulates as determined by NMR reaction monitoring. Subsequent intramolecular Friedel–Crafts alkylation of **20** then provides regioisomers **18** and **1**.

The poor regioselectivity of the Friedel–Crafts reaction was not unexpected but did pose a significant challenge. An effective solution to this problem would be to block the

position *para* to the hydroxy group on the aromatic ring. However, a silicon blocking group would likely not survive the strongly acidic conditions necessary for the Friedel–Crafts cyclization and a bromine blocking group would likely be incompatible with the C–H functionalization conditions owing to competitive C–Br insertion.[17] We therefore targeted a substrate with a chloride *para* to the hydroxy group (Scheme 5). Benzyl chloride **21** was readily coupled with terminal alkyne **12** according to our previously described alkynylation conditions. Transformation of the α,β-unsaturated ester **22** into the required imine **24** then proceeded without incident.

We were now ready to subject imine **24** to our Rh^I-catalyzed C–H functionalization conditions (Scheme 6). At 55 °C within 3 h, dihydropyridine **25** was produced in excellent yield as a single diastereomer (> 95:5 d.r.). Subsequent reduction with $NaHB(OAc)_3$ provided tetrahydropyridine **26** in 69 % yield of isolated product. Although the deactivating nature of the chloride substitution in **26** necessitated a higher temperature for the phosphoric acid mediated Friedel–Crafts alkylation compared to the des-chloro compound, cyclization to give **27** proceeded with excellent levels of regio- and diastereocontrol. Hydrodehalogenation of the aryl chloride in **27** with H_2 in the presence of Pd/C and $NaHCO_3$ cleanly afforded *ent*-ketorfanol (**1**). The structure and absolute configuration were rigorously established by X-ray crystallography.[12]

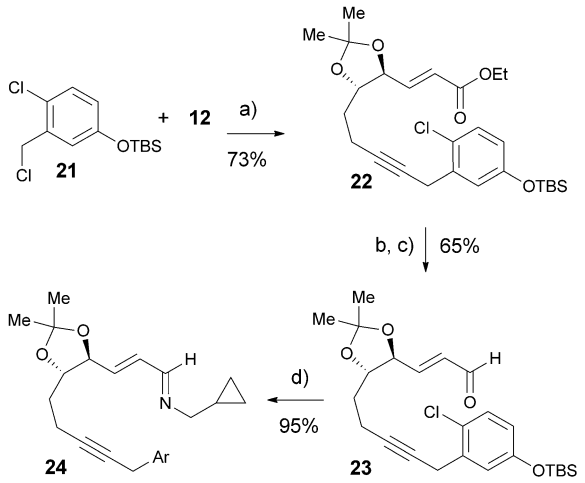
The asymmetric total synthesis of *ent*-ketorfanol was accomplished in 11 steps and 9 % overall yield from commercially available achiral starting materials. In contrast, the only published routes to ketorfanol proceed through multistep degradations of morphine or naltrexone.[3] The Rh^I-catalyzed alkenylation/6π electrocyclization cascade rapidly furnishes a bicyclic 1,2-dihydropyridine that serves as a key intermediate in the synthesis. The electrocyclization is highly torquoselective and thus enables the use of a Sharpless asymmetric dihydroxylation to readily produce either enantiomer of



Scheme 6. Synthesis of *ent*-ketorfanol (**1**). Reagents and conditions: a) $[\{RhCl(coe)_2\}_2]$ (5 mol %), 4-(diethylphosphino)-*N*,*N*-dimethylaniline (10 mol %), toluene, 55 °C; b) $NaHB(OAc)_3$, AcOH, EtOH, 0→23 °C; c) 85 % phosphoric acid, 125 °C; d) H_2, Pd/C, $NaHCO_3$, EtOH.

ketorfanol. The acid-catalyzed tandem pinacol rearrangement/Friedel–Crafts alkylation not only provides the multicyclic drug framework but also converts the diol that served as the stereocontrolling element to the requisite ketone moiety in an efficient redox-neutral process.

In previous reports, we have demonstrated the versatility of our Rh^I-catalyzed C–H functionalization, electrocyclization, and reduction sequence for the regio- and stereoselective incorporation of diverse substituents into tetrahydropyridines.[5c–h] For this reason, the synthetic route reported herein should enable the straightforward preparation of a variety of ketorfanol analogues and thus provide an avenue for improving drug properties.



Scheme 5. Synthesis of imine **24**. Reagents and conditions: a) $PdCl_2(CH_3CN)_2$ (5 mol %), XPhos (15 mol %), Cs_2CO_3, THF, 65 °C; b) DIBAL, THF, −78 °C; c) Dess–Martin periodinane, pyridine, CH_2Cl_2, 0 °C; d) cyclopropylmethyl amine, toluene, 3 Å MS.

Acknowledgements

This work was supported by NIH Grant GM069559 (to J.A.E.). E.M.P. also acknowledges support from an NRSA postdoctoral fellowship (F32GM090661), and S.D. is grateful to the Swiss National Science Foundation for a postdoctoral fellowship (PBZHP2-130-966). We gratefully acknowledge Dr. Michael Takase for solving the crystal structure of **1**·HCl. We also acknowledge the financial support of the NIH (GM-36700 and CHE-1351104 to K.N.H.) A.P. thanks the Chemical-Biology Interface Training Program for its support (T32 GM 008496). A.P acknowledges the University of California, Los Angeles for financial support. Density functional theory computations were performed using the Extreme Science and Engineering Discovery Environment (XSEDE)'s Gordon supercomputer (OCI-1053575) at the San Diego Supercomputing Center.

Keywords: alkaloids · asymmetric synthesis · C–H activation · heterocycles · torquoselectivity

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 12044–12048
Angew. Chem. **2015**, *127*, 12212–12216

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[12] Synthetic details, characterization, and molecular structures obtained by X-ray structural analysis of compounds are described in the Supporting Information. CCDC 1404582 (**11**) and 1404583 (**1**·HCl) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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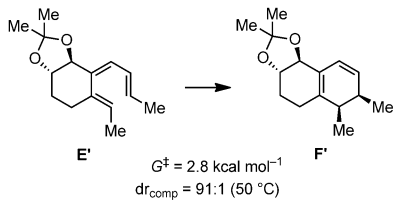
[16] Computations of the electrocyclic reaction of carbatriene analogue of **E** predict a similar level of torquoselectivity.



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Received: June 17, 2015
Published online: August 17, 2015