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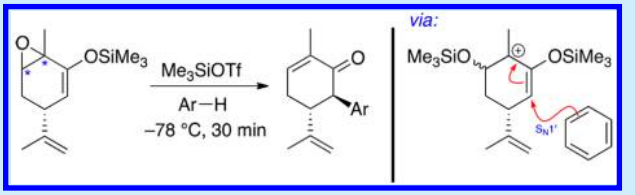
Lewis-Acid-Mediated Union of Epoxy-Carvone Diastereomers with Anisole Derivatives: Mechanistic Insight and Application to the Synthesis of Non-natural CBD Analogues

Sophia J. Bailey,[†] Rishi R. Sapkota,[†] Alexandra E. Golliher,[†] Barry Dungan,[‡] Marat Talipov,[†] F. Omar Holguin,[‡] and William A. Maio*[,†]

[†]Department of Chemistry and Biochemistry and [‡]Department of Plant and Environmental Sciences, New Mexico State University, Las Cruces, New Mexico 88003, United States

Supporting Information

ABSTRACT: The use of trimethylsilyl trifluoromethanesulfonate as a mild means to unite epoxy-carvone silyl ethers with anisole derivatives to yield products that are structurally similar to the CBD scaffold is reported. Importantly, unlike related methods, this process can utilize both epoxy-carvone diastereomers and does not require the use of air/moisture-sensitive organometallic reagents. Several examples of aryl nucleophiles as well as mechanistic insight based on in silico computational analysis are presented.



Recently, (−)-cannabidiol [CBD, (−)-**1**] (Figure 1) has emerged as a potent treatment option for the management

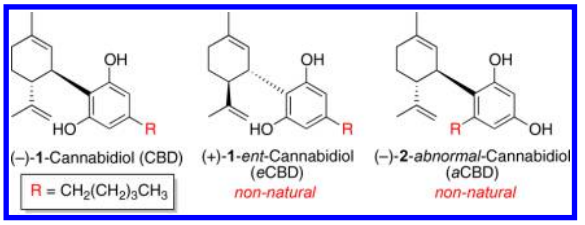
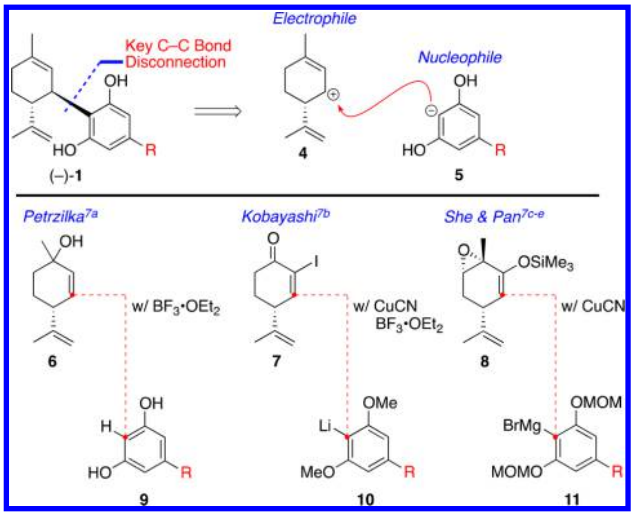


Figure 1. Cannabidiol enantiomers and its known regioisomer.

of Alzheimer's disease (AD) and related neurological disorders.[1] Although its mode of action currently remains unclear, there is strong evidence that (−)-**1** can protect against oxidative stress in neural cells and reduce neuroinflammation, the effects of which can cause the buildup of neurotoxic substances over time and lead to neurodegeneration.[2] There is also emerging data that link nonsteroidal anti-inflammatory drug use with a reduced risk of AD, presumably due to the ability to inhibit cyclooxygenase, which is the enzyme responsible for converting prostaglandin H2 into inflammatory mediators that are important factors in AD pathogenesis.[3] While it is believed that CBD instead interacts with the endocannabinoid system in some way, data suggest that (−)-**1** exhibits a low affinity for the cannabinoid receptors CB_1 and CB_2.[4] Surprisingly, its non-natural synthetic enantiomer *e*CBD [(+)-**1**] and related congeners are known to have a high affinity for these same membrane receptors and may prove valuable as lead structures in the discovery of more potent derivatives.[4]

We became interested in this area, in part, due to our interest in natural product enantiomers[5] and regioisomers [(−)-**2**] but also to address a growing need to source purified CBD as many literature studies have suffered from a reliance on extracts with inconsistent amounts of neuroactive agent.[6] At the onset of our synthetic work, we envisioned a flexible strategy that would allow us to generate both enantiomers of CBD from inexpensive, commercially available starting materials. From a retrosynthetic perspective, we believed that the most convergent method would arise from the union of an electrophilic western hemisphere (**4**) with a nucleophile generated from the eastern aryl ring portion (**5**) (Scheme 1). Representative work utilizing

Scheme 1. Retrosynthetic Analysis and Some Representative Examples



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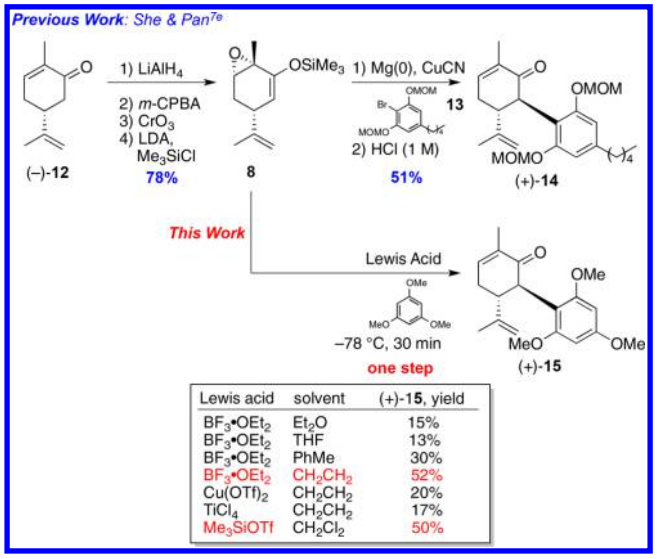
this disconnection has involved either the Lewis-acid-mediated addition of olivetol **9** to allyl alcohol **6**[7a] or the combination of organometallic reagents with electrophiles such as **7**[7b] or **8**.[7c] After considering previous strategies, we believed the best approach would involve a modification to the work of Pan and She who exploited the Marino mixed organocuprate method[8] to add aryl nucleophiles to silyl enol ether **8** as a means to access both (+)-machaeriol D[7d] and (−)-Δ^8-*trans*-tetrahydrocannabinol[7c] employing both (+)- and (−)-carvone [(−)-**12**].

A main drawback of their work, however, is the requirement of generating a moisture-sensitive nucleophile from **13** via magnesium−halogen exchange followed by addition of the in situ-generated Grignard reagent to a suspension of copper(I) cyanide.[7c] As initially disclosed by Marino,[8] it is believed that this reaction occurs via an S_N2' mechanism; subsequent β-hydroxy elimination is effected in a second synthetic operation using 1 M HCl to generate α-aryl carvone (+)-**14** in 51% isolated yield from **8** [or 40% from (−)-**12**] (Scheme 2).[7e] Of note, based on the established literature precedent, for a productive S_N2' addition to occur, the nucleophile must approach *anti* to the face of the epoxide.[8b] To generate this epoxide from carvone, it is first necessary to stereoselectively reduce the ketone in (−)-**12** to an alcohol so that epoxidation can occur in a substrate-directed fashion before oxidation and silyl ether formation [(−)-**12** to **8**] (four steps, 78% yield).[7c,9]

Scheme 2. Previous Work and Optimization Studies

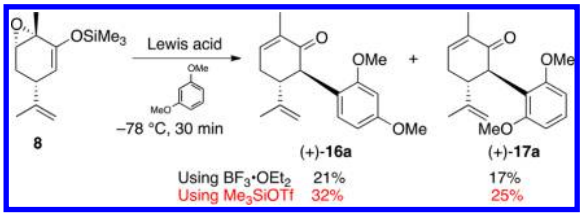


Lewis acid	solvent	(+)-15, yield
BF_3•OEt_2	Et_2O	15%
BF_3•OEt_2	THF	13%
BF_3•OEt_2	PhMe	30%
BF_3•OEt_2	CH_2CH_2	52%
$Cu(OTf)_2$	CH_2CH_2	20%
$TiCl_4$	CH_2CH_2	17%
Me_3SiOTf	CH_2Cl_2	50%

Based on previous studies in our laboratory,[10] we believed that it might also be possible to access related α-arylated products under Lewis acidic conditions; however, a search of the literature did not reveal any previous reports documenting the addition of nucleophiles to cyclohexadiene monoepoxides bearing a C3 siloxy group in this fashion.[11] When a solution of **8** and 1,3,5-trimethoxybenzene in ether was treated with a single equivalent of BF_3·OEt_2 at −78 °C, the desired α-arylated carvone product [(+)-**15**] (Scheme 2) could be accessed directly, without the need for an additional β-elimination step. Whereas the isolated yield for this adduct was extremely low (15%), we were encouraged by this result and initiated a solvent/Lewis acid screen. We found that when using either BF_3·OEt_2 or Me_3SiOTf in CH_2Cl_2, yields could be improved to 52 and 50%, respectively (Scheme 2 table, red), which is comparable to the direct nucleophilic addition method used by She and Pan (51% over two steps, using olivetol-derived **13**).[7c] To our surprise, ethereal solvents and both titanium and copper Lewis acids provided good, but somewhat lower, yields when compared to those of either BF_3·OEt_2 or Me_3SiOTf in CH_2Cl_2. Increasing the reaction time to 1 h or separately employing 2 equiv of Lewis acid did not improve yields, and allowing the reaction to run at higher temperature (0 °C and rt) resulted in decreased product formation. Importantly, nucleophilic addition occurred without the need to employ air- and moisture-sensitive organometallic reagents and gave the C5−C6 *trans* product exclusively, as evidenced by ^{1}H NMR spectroscopy. Several unidentified byproducts (accounting for the mass balance) were also isolated and spectroscopically determined to arise from the degradation of **8** not having incorporated the aryl group.

Once suitable conditions had been established, our attention turned to a screen of several different nucleophiles with 1,3-dimethoxybenzene being the first (Scheme 3). Based on the well-known nucleophilic preferences for substituted aromatics with electron-donating groups (i.e., *ortho*/*para* directing),[12] we anticipated that there might be two distinct modes of addition. Not surprisingly, when a solution of **8** and dimethoxybenzene was treated with BF_3·OEt_2, both possible α-addition products were isolated after aqueous workup and silica gel chromatography [(+)-**16a** and (+)-**17a**] (Scheme 3), with the major product resulting from a preference for addition at C(4) of the aryl ring and not at C(2), which lies between the two methoxy substituents.[13] Similar results were realized when using Me_3SiOTf as Lewis acid, although the yields of the two regioisomers were somewhat higher than that of BF_3·OEt_2. As a result, all subsequent reactions were screened solely using Me_3SiOTf.

Scheme 3. Regiochemical Outcome with Dimethoxybenzene



It was at this stage that we began questioning the mechanism of our Lewis-acid-mediated reaction (vide infra). Previously, when addition occurred using the Marino mixed organocuprate method, it was necessary to synthesize **8** so that the epoxide leaving group could be orientated *anti* to the incoming nucleophile (Scheme 2).[8b] However, based on knowledge from the literature,[14] we believed it was reasonable to assume that, under Lewis acidic conditions, the epoxide in **8** may first open to a reveal a 3° allylic carbocation, which is then trapped by the incoming aryl nucleophile via an S_N1' process (**19**) (Scheme 4). If this mechanism is operative, it should be possible to access the same products **16** and **17** using diastereomer **18** (Scheme 4),[15] where the approach of the nucleophile would be *syn* to the epoxide. If viable, α-addition products of this type could be achieved in two fewer steps from carvone and three fewer steps when compared to the Marino method.[8] After **18** was synthesized and subjected to our Lewis-acid-mediated reaction conditions, (+)-**15** was isolated in good overall yield from (−)-**3** (Scheme 4), which helped to confirm our hypothesis that an S_N1' mechanism may be operative.

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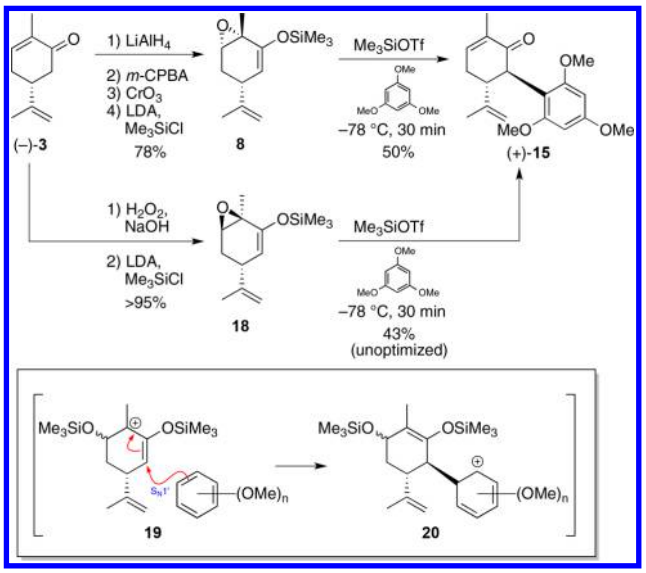
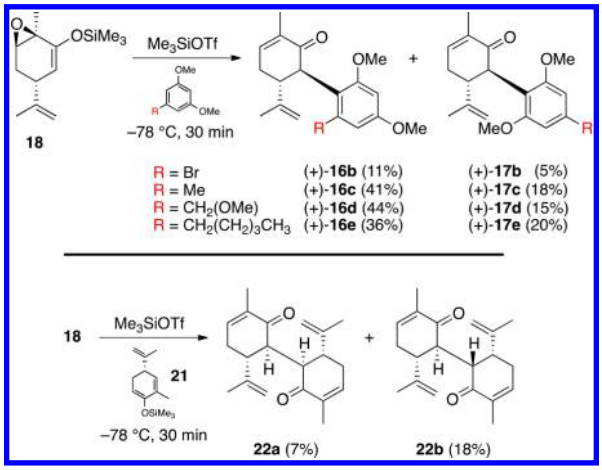
Scheme 4. Modified Three-Step Protocol and Proposed Transition State



To further prove the S_N1' mechanism, we initiated in silico computational studies using the trimethylsilyl-ate complexes of both **8** and **18** (**A** and **A′**, respectively) (Figure 2) as starting points with which to relate subsequent intermediates.[16] We found that epoxide opening to reveal a 3° carbocation is facile, requiring only a 0.9 kJ/mol increase in energy for **A** and a 1.5 kJ/mol increase for **A′**. Once formed, these two reactive intermediates, **B** and **B′**, differing only in stereochemistry at the 2° trimethylsiloxy center, are essentially equi-energetic (−42.7 and −43.6 kJ/mol) relative to **A** and **A′**. They go on to react with the π-system of dimethoxybenzene via transition states that are only slightly higher overall than those of the starting ate complexes, leading to intermediates **C** and **C′** (+4.2 and +14.7 kJ/mol, respectively). We believe that the increase in energy for **B′** relative to that for **B** is due, in part, to nucleophilic addition on the same face as the 2° trimethylsiloxy substituent. Importantly, our analysis also revealed that the lowest energy transition state for either pathway is accessed when the nucleophile approaches *anti* to the isopropylidene moiety. In fact, studies trying to model either the transition state or the *syn*-addition product itself did not yield promising results. Based on these data, we conclude that the S_N2' pathway, viable only for epoxide **8** based on orbital symmetry considerations, is not operative due to the extremely low barrier for epoxide ring opening with Lewis acid present (0.9 kJ/mol). To substantiate this claim, when the S_N2' pathway is modeled in silico, epoxide opening to form a 3° carbocation occurs before the π-system in dimethoxybenzene can approach within 3.5 Å of intermediate **A**.

To demonstrate the generality of this novel three-step protocol for the synthesis of α-addition adducts, we sought to screen several substituted methoxy aromatics (Scheme 5).

Scheme 5. Nucleophile Screen



Although we did not observe any product from the addition of anisole (not shown) to epoxide **18**, both abnormal (**16b**−**16e**) and normal (**17b**−**17e**) addition products could be achieved in good to moderate yields when using monosubstituted dimethoxybenzene derivatives. Noteworthy is the use of dimethylolivetol, which allowed access to (+)-**16e** and (+)-**17e** in moderate overall yield (56% combined) from (−)-carvone.[17] Significantly, compound (+)-**17e** should serve as a key intermediate in the synthesis of CBD, after oxidation state adjustment and protecting group removal,[18] and whereas we do

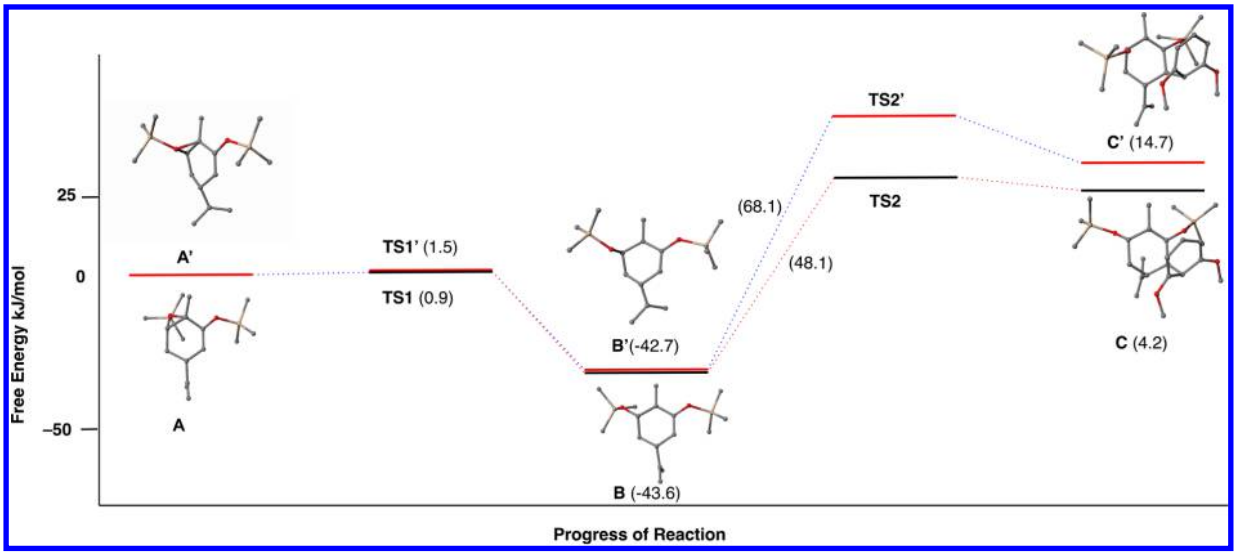


Figure 2. Free energy profile diagram for the S_N1' pathway.

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not demonstrate it in this current paper, it is prudent to assume that by using this method employing (+)-carvone as starting material, it would be possible to generate the enantiomer series of products **16** and **17**. As a final note, we have also explored the α-addition of nonaromatic nucleophiles and have successfully united carvone-derived silyl ether **21** with **18**, yielding dimers **22a** and **22b** (unoptimized yields).[19]

In conclusion, we have shown that it is possible to generate α-addition products from the reaction of epoxy-carvone silyl ethers with anisole derivatives in the presence of trimethylsilyl trifluoromethanesulfonate. These products can be accessed in useful yields and in three synthetic operations from (−)-carvone. In silico data analysis suggests that an S_N1' mechanism is operative. Additional investigations exploiting nonaromatic nucleophiles and biological evaluation of these novel CBD derivatives are currently ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01909.

Detailed experimental procedures, compound characterization, computational details, and ^{1}H and ^{13}C NMR scans (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wmaio@nmsu.edu.

ORCID

Marat Talipov: 0000-0002-7559-9666
William A. Maio: 0000-0001-8561-2273

Notes

The authors declare no competing financial interest.

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(16) Electronic structure calculations were performed using a DFT approach, in which the geometry structures of interest were optimized at the M06-L/def2-SV(P)+PCM(CH_2Cl_2) level of theory. Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297−3305.

(17) We also explored the use of nonprotected olivetol as nucleophile. Although we did observe the desired α-addition adduct, the yields for this process are extremely low. We are currently investigating alternative reaction conditions that may help improve this yield.

(18) As an example, a similar oxidation state adjustment strategy was employed by She and Pan during their synthesis of Δ^8-*trans*-THC. In our case, alkene rearrangement would also be necessary. See ref 7c for details.

(19) For a method using copper catalysis to affect the homodimerization of carvone, see: Do, H.-Q.; Tran-Vu, H.; Daugulis, O. *Organometallics* **2012**, *31*, 7816−7818.

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