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Synthesis of Substituted Tetralins and Benzosuberans via BF_3·OEt_2-Mediated Formal (4 + 2) and (5 + 2) Stereocontrolled Cycloaddition of 4-Alkenols with Veratrol

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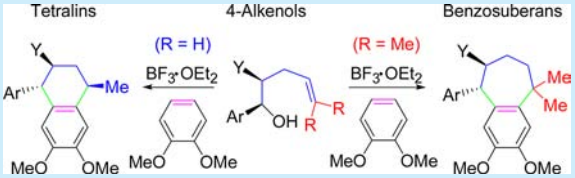
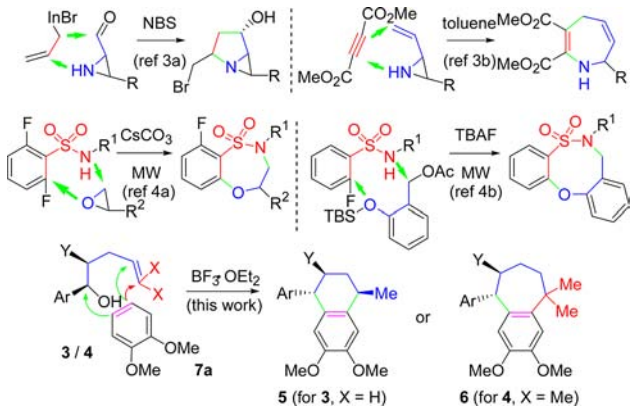
Supporting Information

ABSTRACT: BF_3·OEt_2-mediated one-pot formal (4 + 2) and (5 + 2) stereocontrolled cycloaddition of 4-alkenols **3** and **4** with veratrol affords the respective substituted tetralins **5** and benzosuberans **6** in good yields. The cascade protocol combines a facile double Friedel–Crafts benzannulation of 4-alkenols **3** and **4** (having two electrophilic sites) and veratrol (**7a**) (having two nucleophilic sites). A plausible mechanism was studied and proposed.



One-pot domino cycloaddition reactions have attracted significant attention in the field of synthetic organic chemistry due to their successful utilization for the formation of unique molecules.[1] The development of a new single-step route for simultaneous bond formation or ring construction is an important challenge because it allows for the rapid buildup of molecular complexity from relatively simple substrates.[2] Cascade transformations of masked ambiphilic synthons are particularly promising because they exhibit donor–acceptor dipolarophilic reactivities.[3−5] The most successful strategy to build an ambiphilic pairing strategy is to take advantage of the tandem protocol that was established by Yudin[3] and Hanson[4] (see Scheme 1).

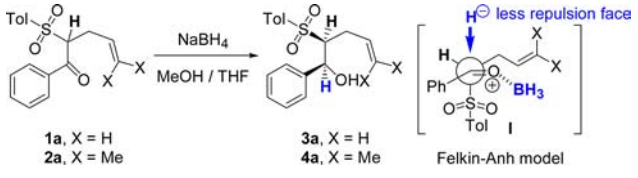
Scheme 1. Masked Ambiphilic Domino Cycloadditions



Our interest in the utilization of cascade protocols for $Bi(OTf)_3$-mediated synthesis of diverse tetralin scaffolds[6a] has led us to explore protocols wherein dipolarophilic 4-alkynols are combined with a veratrol. As part of our efforts in the chemistry of β-ketosulfones,[6] we streamlined the BF_3·OEt_2-mediated one-pot stereocontrolled synthesis of 1-aryltetralins and 1-arylbenzosuberans via the formal (4 + 2) and (5 + 2) cycloaddition. Tetralin is a highly privileged core structure found in numerous valuable biologically active molecules[7] and natural products.[8] Various alternative routes have been developed for the synthesis of functionalized 1-aryltetralins, including Lewis-acid-mediated Friedel–Crafts alkylation/acylation of dihydronaphthalene with arenes,[9] Diels–Alder cycloaddition of an in situ generated *o*-quinodimethane intermediate with a dienophile,[10] Pd-catalyzed C(sp^3)–H activation of a tetralin with an aryl iodide,[11] fluoride-promoted protodeboronation of a homologated boronic ester,[12] and electrocyclization of an (*E*,*E*)-dibenzylidenesuccinate.[13] Benzosuberan (i.e., benzocycloheptene) is an attractive bicyclic building block used in the pharmaceutical sciences.[14] It has been synthesized by various methods,[15,16] such as the [4 + 3] coupling reaction of zirconacyclopentadiene with 2-iodobenzyl chloride,[15b] ring expansion of six-membered rings,[15c] and intramolecular annulations.[15d,e]

Initially, α-allyl or α-prenyl β-ketosulfones **1a** and **2a** were chosen as model starting materials to examine the $NaBH_4$-mediated stereoselective reduction reaction (see Scheme 2). Applying the Felkin–Anh model,[17] the steric hindrance of a sulfonyl substituent should inhibit the carbonyl addition of hydride such that the hydride should attack the carbonyl face of less repulsion to form two sulfonyl 4-alkenols **3a** (92% yield) and

Scheme 2. Reduction of 1a and 2a



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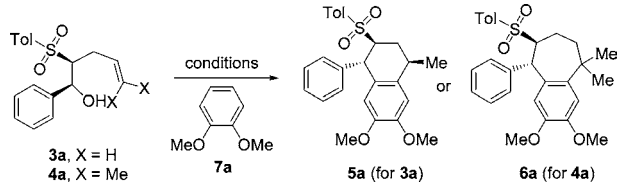
4a (90% yield) via the possible intermediate **I** (see the Supporting Information).

Subsequently, one-pot domino Friedel–Crafts (4 + 2) and (5 + 2) benzannulation reactions were examined where sulfonyl 4-alkenols **3a** and **4a** (four- or five-carbon synthons, respectively) were reacted with veratrol (**7a**) (a two-carbon synthon) to afford the desired stereocontrolled tetralin **5a** and benzosuberan **6a**, respectively. As shown in Table 1, entry 1, using 2.0 equiv of BF_3·

Table 1. Reaction Conditions[a]



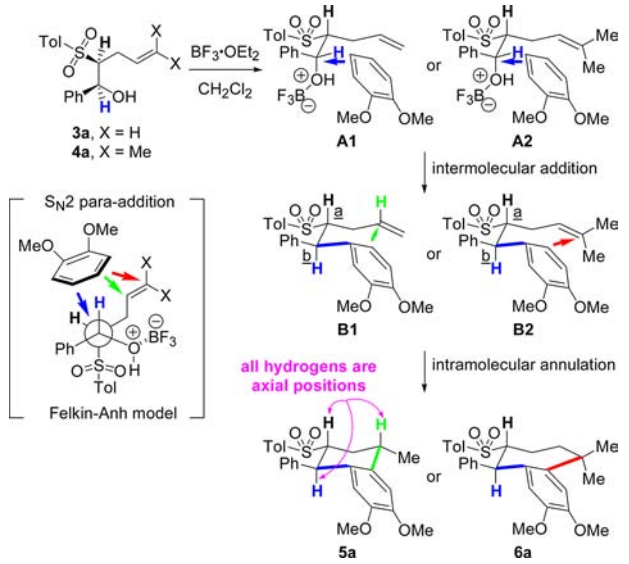
entry	Lewis acid (equiv), solvent (mL)	yield (%)[b] 5a/6a
1	BF_3·OEt_2 (2.0), CH_2Cl_2 (5)	90/82
2	BF_3·OEt_2 (2.0), $MeNO_2$ (5)	42 (72)[c]/50 (65)[c]
3	BF_3·OEt_2 (2.0), $(CH_2Cl)_2$ (5)	70 (82)[c]/67 (78)[c]
4	BF_3·OEt_2 (4.0), CH_2Cl_2 (5)	72 (83)[c]/66 (80)[c]
5	TFA (2.0), CH_2Cl_2 (5)	30/21[d]
6	PPA (2.0), CH_2Cl_2 (5)	28/32[d]
7	$AlCl_3$ (2.0), CH_2Cl_2 (5)	22/24[d]
8	$TiCl_4$ (2.0), CH_2Cl_2 (5)	28/15[d]
9	$ZnCl_2$ (2.0), CH_2Cl_2 (5)	–/–[e]
10	$CuCl_2$ (2.0), CH_2Cl_2 (5)	–/–[e]
11	$FeCl_3$ (2.0), CH_2Cl_2 (5)	28/22[d]

[a]Reactions were run on a 0.2 mmol scale with **3a** or **4a**, **7a** (1.5 equiv), 20 h, 25 °C. [b]Isolated yields. [c]40 h. [d]Major unknown products were obtained. [e]No reactions.

OEt_2 and CH_2Cl_2 as solvent at 25 °C for 20 h provided high yields of **5a** (90%) and **6a** (82%). Changing the solvent from CH_2Cl_2 to $MeNO_2$ or $(CH_2Cl)_2$) gave rise to sluggish conversions to the desired products (entries 2 and 3). When 4.0 equiv of BF_3·OEt_2 was used (entry 4), the isolated yields of **5a** and **6a** decreased to 72 and 56%, respectively. When 2.0 equiv of a Bronsted acid (e.g., TFA or PPA) was used in place of BF_3·OEt_2, an unknown mixture was isolated as the majority product (entries 5 and 6). Among the Lewis acids screened (entries 7–11), the use of $ZnCl_2$ and $CuCl_2$ resulted in recovery of starting materials **3a** and **4a** (entries 9 and 10). Other catalysts that were screened gave rise to poor yields of **5a** and **6a**, along with the formation of complex mixtures. No significant yield changes occurred under metal complex-promoted reaction conditions. Based on the above results, we envisioned that BF_3·OEt_2 should be an optimal catalyst for generating **5a** and **6a** via one-pot domino cycloaddition.

A possible reaction mechanism for the formation of **5a** and **6a** is proposed (Scheme 3). Mechanistically, the sequence initiates with the formation of intermediate **A1** (or **A2**) by BF_3·OEt_2 complexation of the hydroxyl motif of **3a** (or **4a**). Participation of **7a** leads to intermediate **B1** (or **B2**) via the methoxy-group-promoted intermolecular S_N2 *para*-addition (see blue arrow). The stereochemistry of the α- and β-carbon is well-established based on the Felkin–Anh model.[17] Following another methoxy-group-promoted intramolecular annulation of **B1** (see green arrow), **5a** is obtained by the stereocontrolled addition of an in situ generated secondary carbocation via a six-membered chair

Scheme 3. Possible Mechanism



conformation under thermodynamic conditions. All substituents (i.e., tosyl, phenyl, and methyl groups) of **5a** are oriented in equatorial positions. In the other pathway, after an intramolecular annulation of **B2** (see red arrow), the seven-membered ring-containing **6a** is obtained via the more stable tertiary carbocation.

To the best of our knowledge, there is no literature on BF_3·OEt_2-mediated one-pot domino Friedel–Crafts (4 + 2) and (5 + 2) benzannulations of β-hydroxysulfones bearing an α-allyl or α-prenyl substituent with oxygenated benzenes. Having determined the optimized conditions (i.e., Table 1, entry 1), we further explored the substrate scope of the reaction; the results are shown in Table 2. For Ar (aryl) and Y (sulfonyl or phenyl) substituents of **3** (X = H) and **4** (X = Me) and oxygenated benzenes **7**, both electron-withdrawing and electron-donating groups provided the desired products **5a–v** (80–92% yields, entries 1–22) and **6a–i** (76–85% yields, entries 24–32), respectively, in moderate to good yields. Changing the substituents on **3** or 4-alkenols **4** (Ar = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-PhC_6H_4, 2-naphthalene; Y = $TolSO_2$, $PhSO_2$, $MeSO_2$, 3-$MeC_6H_4SO_2$, 4-*n*$BuC_6H_4SO_2$, Ph) or the oxygenated benzenes **7** (RO = MeO, CH_2O_2, *n*BuO) did not affect the outcome of the one-pot procedure, and no obvious yield changes were observed for the generation of **5a–v** or **6a–i**. By the involvement of an unsymmetrical arene **7e**, a mixture of **5w** and **5x** was obtained in a ratio of 2:1 in 75% yield (entry 23). No significant regiocontrol was observed. The structures of **5g**, **5p**, **5s–u**, **6a,b**, and **6i** were determined by single-crystal X-ray crystallography.[18]

The effect of removing the oxygenated benzenes **7** on the cyclization was investigated via the BF_3·OEt_2-mediated reactions of **3b** and **3p–r**, as shown in Table 3, entries 1–4. Reaction of **3p–r**, which contain electron-withdrawing groups (Ar = 4-$CF_3C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$), afforded 3-sulfonyl tetrahydrofurans **8a–c** in 90–95% yields. However, when an electron-donating group (**3b**, Ar = 4-$MeOC_6H_4$) was used, none of the desired product (i.e., **8d**) was isolated. In entries 5–11, the BF_3·OEt_2-mediated reaction of **4a** and **4d,e**, each containing an electron-neutral group (Ar = Ph, 4-PhC_6H_4, 2-naphthalene), and **4h–k**, each containing an electron-withdrawing group (Ar = 4-FC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-$CF_3C_6H_4$), provided 3-

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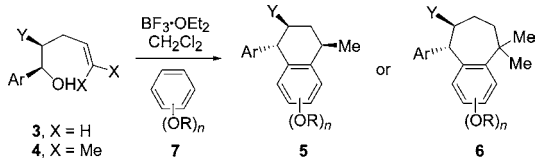
Table 2. Synthesis of 5 and 6[a]



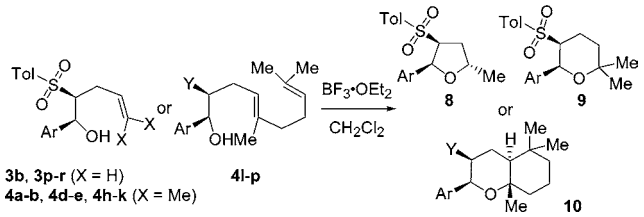
entry	3/4 Ar, Y; 7 $(RO)_n$	yield (%)[b] 5/6
1	**3a**, Ph, $TolSO_2$; **7a**, 1,2-$(MeO)_2$	**5a**, 90
2	**3b**, 4-$MeOC_6H_4$, $TolSO_2$; **7a**, 1,2-$(MeO)_2$	**5b**, 92
3	**3c**, 4-FC_6H_4, $TolSO_2$; **7a**, 1,2-$(MeO)_2$	**5c**, 89
4	**3d**, 4-MeC_6H_4, $TolSO_2$; **7a**, 1,2-$(MeO)_2$	**5d**, 88
5	**3e**, Ph, $MeSO_2$; **7a**, 1,2-$(MeO)_2$	**5e**, 82
6	**3f**, 2-naphthalene, $TolSO_2$; **7a**, 1,2-$(MeO)_2$	**5f**, 83
7	**3g**, 4-PhC_6H_4, $TolSO_2$; **7a**, 1,2-$(MeO)_2$	**5g**, 86
8	**3h**, 4-$MeOC_6H_4$, $PhSO_2$; **7a**, 1,2-$(MeO)_2$	**5h**, 86
9	**3i**, 4-FC_6H_4, $PhSO_2$; **7a**, 1,2-$(MeO)_2$	**5i**, 87
10	**3j**, 4-MeC_6H_4, $MeSO_2$; **7a**, 1,2-$(MeO)_2$	**5j**, 84
11	**3k**, 4-PhC_6H_4, $PhSO_2$; **7a**, 1,2-$(MeO)_2$	**5k**, 89
12	**3l**, Ph, $PhSO_2$; **7a**, 1,2-$(MeO)_2$	**5l**, 82
13	**3m**, Ph, 3-$MeC_6H_4SO_2$; **7a**, 1,2-$(MeO)_2$	**5m**, 86
14	**3n**, Ph, 4-$FC_6H_4SO_2$; **7a**, 1,2-$(MeO)_2$	**5n**, 80
15	**3o**, Ph, 4-*n*-$BuC_6H_4SO_2$; **7a**, 1,2-$(MeO)_2$	**5o**, 86
16	**3a**, Ph, $TolSO_2$; **7b**, 1,2-CH_2O_2	**5p**, 86
17	**3m**, Ph, 3-$MeC_6H_4SO_2$; **7b**, 1,2-CH_2O_2	**5q**, 87
18	**3o**, Ph, 4-*n*-$BuC_6H_4SO_2$; **7b**, 1,2-CH_2O_2	**5r**, 89
19	**3s**, Ph, Ph; **7a**, 1,2-$(MeO)_2$	**5s**, 80
20	**3t**, 4-FC_6H_4, Ph; **7a**, 1,2-$(MeO)_2$	**5t**, 84
21	**3a**, Ph, $TolSO_2$; **7c**, 1,3-$(MeO)_2$	**5u**, 84
22	**3a**, Ph, $TolSO_2$; **7d**, 1,2,3-$(MeO)_3$	**5v**, 80
23	**3a**, Ph, $TolSO_2$; **7e**, 1-(*n*BuO)-2-(MeO)	**5w**/**5x**, 75
24	**4a**, Ph, $TolSO_2$; **7a**, 1,2-$(MeO)_2$	**6a**, 82
25	**4b**, 4-$MeOC_6H_4$, $TolSO_2$; **7a**, 1,2-$(MeO)_2$	**6b**, 82
26	**4c**, 4-MeC_6H_4, $TolSO_2$; **7a**, 1,2-$(MeO)_2$	**6c**, 80
27	**4d**, 4-PhC_6H_4, $TolSO_2$; **7a**, 1,2-$(MeO)_2$	**6d**, 82
28	**4e**, 2-naphthalene, $TolSO_2$; **7a**, 1,2-$(MeO)_2$	**6e**, 78
29	**4f**, 4-$MeOC_6H_4$, $PhSO_2$; **7a**, 1,2-$(MeO)_2$	**6f**, 76
30	**4g**, 4-$MeOC_6H_4$, $MeSO_2$; **7a**, 1,2-$(MeO)_2$	**6g**, 80
31	**4h**, 4-$MeOC_6H_4$, $TolSO_2$; **7b**, 1,2-CH_2O_2	**6h**, 85
32	**4i**, 4-$MeOC_6H_4$, $TolSO_2$; **7f**, 1,2-(*n*-BuO)$_2$	**6i**, 85

[a]Reactions were run on a 0.2 mmol scale with **3** or **4**, **7** (1.5 equiv), $BF_3{\cdot}OEt_2$ (2.0 equiv), CH_2Cl_2 (5 mL), 25 °C, 20 h. [b]Isolated yields.

sulfonyl tetrahydropyrans **9a–f** in 82–90% yields. Under the above conditions, treatment of **4b** (Ar = 4-$MeOC_6H_4$) still produced a complex mixture, and none of the desired product, **9g**, was isolated. According to these observations, we envisioned that intramolecular hydroalkoxylation of alkenols **3** or **4** with an electron-withdrawing group, mediated by $BF_3{\cdot}OEt_2$, could lead to substituted cyclic ether **8** or **9** in good yields. Cyclic ethers are important structural motifs in synthetic organic chemistry due to their occurrence in natural products and biologically active molecules.[19] Based on similar conditions, bicyclic **10a** (76%) and **10b** (80%), with a *trans*-orientation of the ring junction, were isolated as sole isomers, but no formation of **10c–e** was observed. The structures of **8a,b**, **9a**, and **10a,b** were determined by single-crystal X-ray crystallography.[18]

In summary, we have developed a $BF_3{\cdot}OEt_2$-mediated one-pot formal (4 + 2) and (5 + 2) stereocontrolled cycloaddition of 4-alkenols **3** and **4** with oxygenated benzenes **7** to generate sulfonyl tetralins **5** and benzosuberans **6**, respectively. Additionally, we

Table 3. Synthesis of 8, 9, and 10[a]



entry	3/4, Ar, X/Y	yield (%)[b] 8/9/10
1	**3p**, 4-$CF_3C_6H_4$, H	**8a**, 90
2	**3q**, 3-$NO_2C_6H_4$, H	**8b**, 92
3	**3r**, 4-$NO_2C_6H_4$, H	**8c**, 95
4	**3b**, 4-$MeOC_6H_4$, H	**8d**, –[c]
5	**4a**, Ph, Me	**9a**, 90
6	**4h**, 4-FC_6H_4, Me	**9b**, 92
7	**4i**, 3-$NO_2C_6H_4$, Me	**9c**, 90
8	**4j**, 4-$NO_2C_6H_4$, Me	**9d**, 94
9	**4k**, 4-$CF_3C_6H_4$, Me	**9e**, 90
10	**4d**, 4-PhC_6H_4, Me	**9f**, 82
11	**4b**, 4-$MeOC_6H_4$, Me	**9g**, –[c]
12	**4l**, Ph, $TolSO_2$	**10a**, 76
13	**4n**, 4-FC_6H_4, $TolSO_2$	**10b**, 80
14	**4m**, 2-naphthalene, $TolSO_2$	**10c**, –[c]
15	**4o**, 4-$MeOC_6H_4$, $TolSO_2$	**10d**, –[c]
16	**4p**, 4-$MeOC_6H_4$, $MeSO_2$	**10e**, –[c]

[a]Reactions were run on a 0.2 mmol scale with **3** or **4**, **7** (1.5 equiv), $BF_3{\cdot}OEt_2$ (1.0 equiv for **8** or **9**; 2.0 equiv for **10**), CH_2Cl_2 (5 mL), 25 °C, 20 h. [b]Isolated yields. [c]Complex mixture.

found that reaction of **3** and **4** in the absence of **7** afforded tetrahydrofurans **8** and tetrahydropyrans **9** and **10**. **3** and **4** were also synthesized in good yields via $NaBH_4$-mediated stereoselective reduction. A plausible mechanism has been proposed for these cyclization reactions. The structures of the key products were confirmed by X-ray crystallography. Further investigations regarding the synthetic application of *β*-ketosulfones will be conducted and published 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.5b03696.

X-ray analysis data of **5g** (CIF)
X-ray analysis data of **5p** (CIF)
X-ray analysis data of **5s** (CIF)
X-ray analysis data of **5t** (CIF)
X-ray analysis data of **5u** (CIF)
X-ray analysis data of **6a** (CIF)
X-ray analysis data of **6i** (CIF)
X-ray analysis data of **8a** (CIF)
X-ray analysis data of **8b** (CIF)
X-ray analysis data of **9a** (CIF)
X-ray analysis data of **10a** (CIF)
X-ray analysis data of **10b** (CIF)
Detailed experimental procedures and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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