ORGANIC LETTERS

2009
Vol. 11, No. 1
189−192

Convergent Formal Syntheses of (±)-Brussonol and (±)-Abrotanone via an Intramolecular Marson-Type Cyclization

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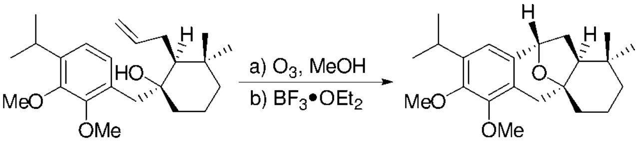
Received October 14, 2008

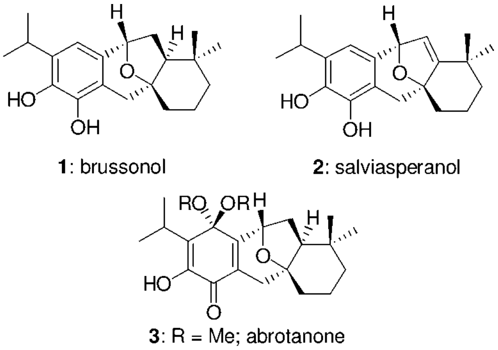
ABSTRACT



The formal convergent syntheses of both (±)-brussonol and (±)-abrotanone are reported. The key step involved the diastereoselective capture of an in situ generated oxocarbenium cation via an intramolecular Friedel−Crafts/Marson-type cyclization.

Virtually every culture has utilized biologically relevant extracts from plants and animals for specific medicinal indications ranging from anti-inflammation to hepatitis.[1] Currently, plants continue to provide biologically active compounds as well as synthetically challenging targets. Along this line, the icetexane diterpenoids are representative of these types of medicinally relevant and architecturally intriguing compounds.[2] Members within this family of natural products, as depicted in Scheme 1, include brussonol (**1**), salviasperanol (**2**), and abrotanone (**3**). Isolated from the root cultures of *Salvia broussoneti*, brussonol (**1**) was reported by Fraga and co-workers in 2005 and was shown to be cytotoxic toward insect and mammalian cell lines.[3] In addition to the initial biological investigation of **1**, it has recently been shown that **1** was found to exhibit moderate cytotoxicity against the P388 murine leukemia cell line with an IC_{50} value of 1.9 μg/mL.[4]

Scheme 1. Icetexane Natural Products



Due to the novel and intriguing structures, coupled with the limited biological profiles of such icetexane natural products, brussonol (**1**) and abrotanone (**3**) are attractive targets for chemical synthesis. Recently, Sarpong and co-workers achieved the first total syntheses of (±)-brussonol

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(1) Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022.

(2) Esquivel, B.; Flores, M.; Hernandez-Ortega, S.; Toscano, R. A.; Ramamoorthy, T. P. *Phytochemistry* **1995**, *39*, 139.

(3) Fraga, B. M.; Diaz, C. E.; Guadano, A.; Gonzalez-Coloma, A. *J. Agric. Food Chem.* **2005**, *53*, 5200.

(4) Aoyagi, Y.; Takahashi, Y.; Fukaya, H.; Takeya, K.; Aiyama, R.; Matsuzaki, T.; Hashimoto, S.; Kurihara, T. *Chem. Pharm. Bull.* **2006**, *54*, 1602.

10.1021/ol802375g CCC: $40.75

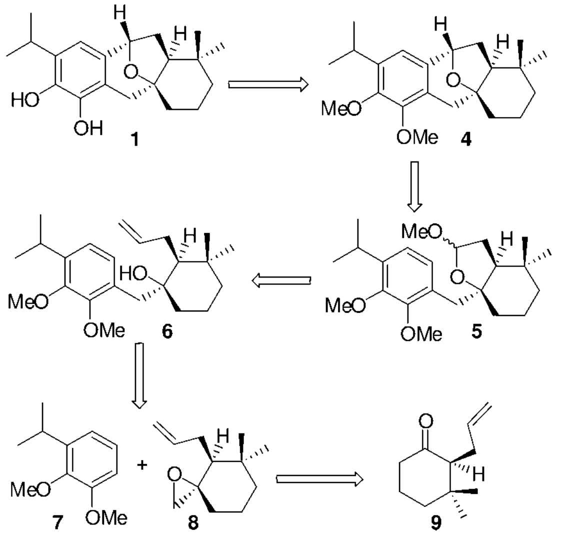
and (±)-abrotanone by utilizing an innovative Ga(III)-catalyzed cycloisomerization strategy.[5] This work led to the structural revisions of abrotanone and abrotandiol; the latter was found to be identical to brussonol (**1**). Subsequently, Majetich identified and reported conditions that lead to the production of (−)-brussonol starting from (+)-demethyl-salvicanol.[6]

We became attracted to the synthesis of **1** due to our long-standing interest in constructing highly substituted *β-C*-glycoside moieties via oxocarbenium cation intermediates and the limited knowledge of its biological profile.[7] Our previous synthesis of bruguierol C featured a diastereoselective capture of an in situ generated oxocarbenium ion via an intramolecular Marson-type Friedel−Crafts cyclization as the key step that readily delivered the natural product.[8] We were hopeful that a similar strategy would allow for the formal syntheses of both (±)-brussonol and (±)-abrotanone in a very rapid and efficient manner utilizing inexpensive staring materials and reagents.

Our synthetic plan, if realized, would not only be a prime example of a step-economical synthesis but its convergency would ensure that it could be amenable to the practical synthesis of analogues in the search of more potent cytotoxic therapeutic leads. Herein, we wish to report the formal syntheses of both (±)-brussonol and (±)-abrotanone via an intramolecular Friedel−Crafts/Marson-type cyclization.[9,10]

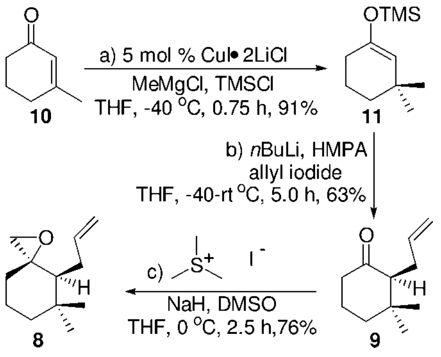
As delineated in Scheme 2, our initial approach was based on the successful union of epoxide **8** and isopropylveratrol **7** via an *ortho*-directed metalation reaction.[11] Synthons **8** and **7** should be both readily obtained starting from commercially available 3-methyl-2-cyclohexen-1-one **10** and veratrol **12**. Once this coupling was completed, it could be envisioned that acetal **5** would arise in a single step from an oxidation of the terminal alkene moiety of **6** via the aldehyde intermediate in the presence of MeOH. Similar to bruguierol C, oxocarbenium formation under Lewis acidic conditions followed by an intramolecular Friedel−Crafts capture of the oxocarbenium cation intermediate should provide **4**, thus constituting a formal synthesis of (±)-brussonol. Subsequent cleavage of the methoxy phenyl ethers should provide **1** and an ensuing oxidation under Sarpong's conditions should ultimately afford **3**.[6]

Scheme 2. First-Generation Retrosynthetic Analysis of **1**



With our initial retrosynthetic plan in mind, focus was placed on the synthesis of the required coupling fragments, **7** and **8**. As shown in Scheme 3, the preparation of epoxide **8** commenced with a classical Kharasch-type reaction with the α,*β*-unsaturated ketone **10**.[12] Under the conditions described by Reetz,[13] copper-catalyzed (5 mol % of CuI•2LiCl) conjugate addition of MeMgCl to ketone **10** in the presence of TMSCl provided silyl enol ether **11** in 91% yield which was used without further purification.

Scheme 3. Synthesis of Epoxide **8**



Subsequent treatment of **11** with *n*-BuLi in the presence of HMPA followed by electrophilic quench of the corresponding lithium enolate with allyl iodide provided a mixture of ketone **9** and the *O*-alkyated allylic ether, which was then transformed into the desired product **9** by means of a Claisen rearrangement at elevated temperature in an overall yield of 63% from enol ether **11**. An ensuing Corey−Chaykovsky epoxidation[14] of **9** with the standard reagents (trimethylsulfonium iodide and the Na salt of the DMSO anion) delivered the desired coupling partner **8** with an overall yield of 44% over three steps from **10**. Much to our delight, nucleophilic addition of the corresponding trimethyl sulfonium anion to ketone **9** led to

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(5) Simmons, E. M.; Yen, J. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 2705.

(6) Majetich, G.; Zou, G. *Org. Lett.* **2008**, *10*, 81.

(7) (a) Jennings, M. P.; Clemens, R. T. *Tetrahedron Lett.* **2005**, *46*, 2021. (b) Ding, F.; Jennings, M. P. *Org. Lett.* **2005**, *7*, 2321. (c) Clemens, R. T.; Jennings, M. P. *Chem. Commun.* **2006**, 2720. (d) Sawant, K. B.; Jennings, M. P. *J. Org. Chem.* **2006**, *71*, 7911. (e) Sawant, K. B.; Ding, F.; Jennings, M. P. *Tetrahedron Lett.* **2006**, *47*, 939. (f) Sawant, K. B.; Ding, F.; Jennings, M. P. *Tetrahedron Lett.* **2007**, *48*, 5177. (g) Ding, F.; Jennings, M. P. *J. Org. Chem.* **2008**, *73*, 5965.

(8) Solorio, D. M.; Jennings, M. P. *J. Org. Chem.* **2007**, *72*, 6621.

(9) Marson, C. M.; Campbell, J.; Hursthouse, M. B.; Abdul Mailk, K. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1122.

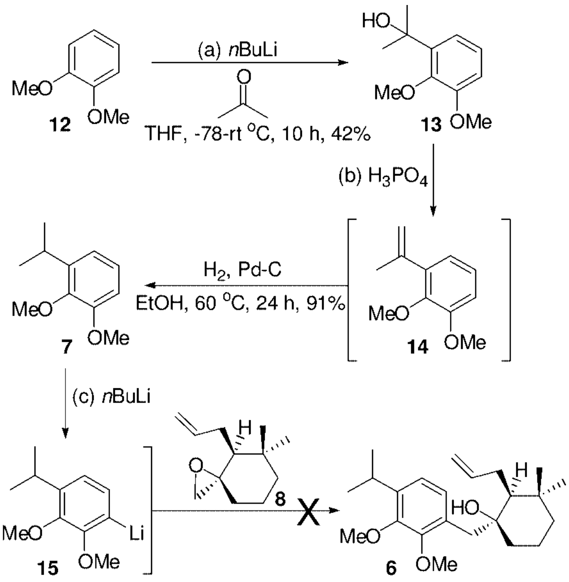
(10) (a) Fan, J.-F.; Wu, Y.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1189. (b) Wu, Y.; Li, Y.; Wu, Y.-L. *Helv. Chim. Acta* **2001**, *84*, 163.

(11) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

exclusive formation of the desired epoxide as a single diastereomer.

With epoxide **8** in hand, we next turned our attention to the completion of 3-isopropylveratrol (**7**) using a short and practical two-step sequence as first reported by Majetich and is depicted in Scheme 4.[15] Thus, treatment of **12** with 1.05 equiv of *n*-BuLi at −78 °C afforded the intermediate *ortho*-metalated anion which was subsequently trapped with acetone to provide the tertiary benzyl alcohol **13** in 42% yield. An ensuing acid promoted dehydration and hydrogenation under atmospheric pressure using 10% Pd/C delivered **7** conveniently in a one-flask operation, presumably through intermediate **14**, in an overall yield of 91% from **13**. It is worth noting that we modified the original Majetich procedure to circumvent the usage of a high-pressure one-pot dehydration/hydrogenation protocol from **13** to **7**.

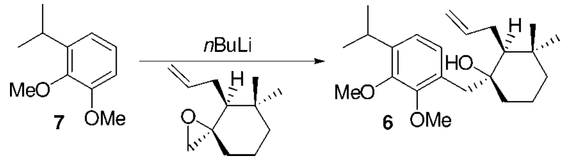
Scheme 4. Attempted Coupling of **7** and **8** via Directed Lithiation



With our two fragments, **7** and **8**, in hand we were ready to explore conditions which would lead to the formation of the highly desired tertiary alcohol **6**. Unfortunately, as highlighted in Table 1, all attempts failed to provide the coupled product **6** in workable yields and purity. Attempted *ortho*-lithiation of **7** under a variety of conditions, solvents, and additives was quite successful (vide infra); however, quenching of the lithiated arene with epoxide **8** generally led to little or no desired product **6**.

With the failure of the initial synthetic blueprint to **4**, we reformulated our synthetic plan. As depicted in Scheme 5, our end-game strategy remained identical to that of our first-generation retrosynthetic analysis. The major difference between the two strategies lies in the formation of tertiary alcohol **6**.

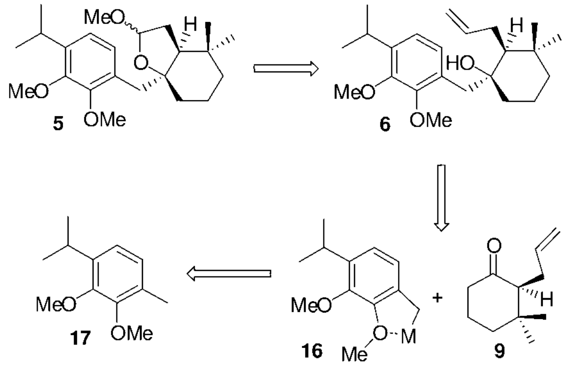
Table 1. Attempted *ortho*-Lithiation of **7** Followed by Electrophilic Quench with Epoxide **8**



no.	solvent	T (°C)	time (h)	additive	yield (%)
1	THF	−78 to rt	12	none	trace
2	THF	−78 to rt	24	HMPA	~10[a]
3	THF	−78 to rt	24	TMEDA	~15[a]
4	THF	−78 to rt	24	BF_3·OEt_2	trace
5	Et_2O	−78 to rt	12	none	trace
6	Et_2O	−78 to rt	48	HMPA	~10[a]
7	Et_2O	−78 to rt	48	TMEDA	~10[a]
8	Et_2O	−78 to rt	48	BF_3·OEt_2	trace
9	Et_2O	−78 to rt	48	BF_3·OEt_2[b]	trace

[a] The quoted yields are a mixture of products (which includes **6**) that coelute from a silicia gel column. [b] reaction ran also with TMEDA as a second additive.

Scheme 5. Second-Generation Retrosynthetic Analysis of **5**



In the second-generation approach, we envisaged that a chemoselective directed benzylic lithiation of the methyl moiety of **17** should provide the stabilized organometallic reagent followed by electrophilic quench of our previously synthesized ketone **9** should afford the elusive tertiary alcohol **6**. In turn, **17** could be readily obtained from the previously prepared isopropylveratrol **7** via a directed aromatic lithiation/ alkylation protocol.

Armed with our revised strategy, we focused our attention to the formation of **6** via the proposed coupling of **17** and **9**. Thus, a second *ortho*-directed metalation followed by electrophilic quench with iodomethane provided **17** in a 83% yield. Once again, the stage was set for the attempted coupling of fragments **17** and **9**. Gratifyingly, fragment union was achieved by a chemoselective directed benzylic lithiation of **17** in Et_2O and in the presence of TMEDA at −78 °C, which presumably generated the stabilized five-membered chelate intermedi-

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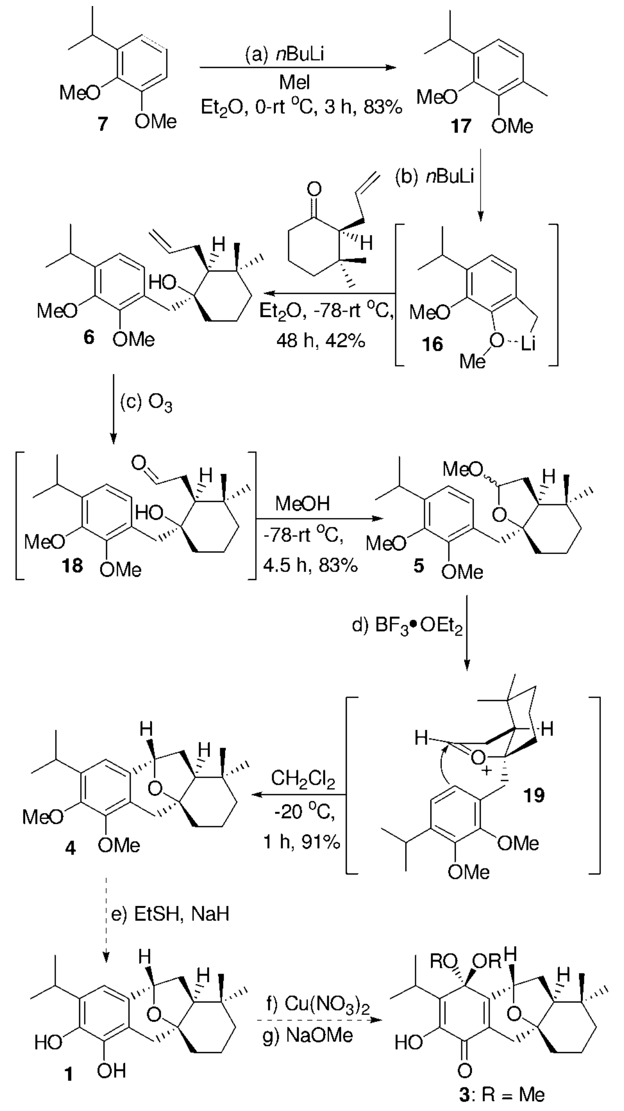
(12) Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308.
(13) Reetz, M. T.; Kindler, A. *J. Organomet. Chem.* **1995**, *502*, C5.
(14) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.



Scheme 6. Completion of **5** via a Marson Cyclization

ate **16**, followed by electrophilic quench with ketone **9** to furnish **6** in 42% yield.

Much to our delight, the nucleophilic addition of the lithiated intermediate **16** to **9** provided **6** as a single diastereomer via selective axial attack. With our fragments successfully coupled, we next turned our attention to the rapid completion of **4**. Thus, terminal olefin oxidation of **6** via ozonolysis in MeOH presumably formed intermediate aldehyde **18**, followed by creation of the methoxy oxonium cation which subsequently cyclized to deliver the methoxy ketal **5** in 89% yield. Much to our delight, final treatment of **5** with 2 equiv of BF_3•OEt_2 at −20 °C for 1 h provided the cyclized product **4** in 91% yield apparently via the proposed intermediate **19**. The spectral data (^{1}H NMR, 600 MHz; ^{13}C NMR, 125 MHz) and HRMS data of synthetic **4** were in complete agreement with those previously reported.[6] Finally, **4** could be converted to (±)-brussonol (**1**) by cleavage of the two methoxy ethers by means of treatment of **4** with the thiolate anion in DMF.[6] In addition, it has been reported by Sarpong that **1** can be readily converted into (±)-abrotanone (**3**) via a copper-mediated oxidation sequence in a solution of NaOMe−MeOH.[6]

In conclusion, we have completed a highly practical and convergent formal synthesis of both (±)-brussonol and (±)-abrotanone (in seven steps, longest linear sequence, from veratrol for brussonol and nine steps for abrotanone) by featuring a diasteroselective capture of an in situ generated oxocarbenium ion via an intramolecular Friedel−Crafts/Marson-type cyclization.

Acknowledgment. Support for this project was provided by the University of Alabama.

Supporting Information Available: Full experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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