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Four-Component Benzyne Coupling Reactions: A Concise Total Synthesis of Dehydroaltenuene B

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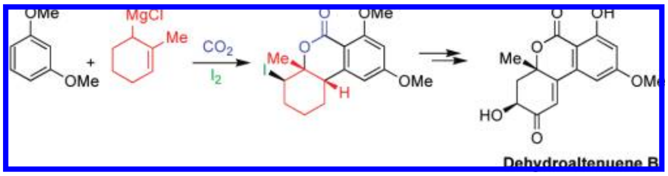
ABSTRACT



A four-component coupling reaction of 3,5-dimethoxybenzyne with 2-methyl-2-cyclohexenylmagnesium chloride, carbon dioxide, and iodine was utilized as a key step in the first total synthesis of dehydroaltenuene B.

One-pot multicomponent reactions have emerged as powerful methods in synthetic organic chemistry.[1] They have proven to provide elegant and rapid entry to access complex structures from simple building blocks. Among various multicomponent reactions, which have been developed, considerable recent attention has been focused on the reactions with arynes.[2] Arynes react with diverse myriad nucleophiles. The sequential three-component reaction of an aryne with a nucleophile and an electrophile provides an attractive synthetic method, especially with the nitrogen-centered nucleophiles and carbanions,[3] for introducing multiple functional groups on aromatic rings. Recently, our group reported the total synthesis of the antifungal (*ent*)-clavilactone, which employed a three-component benzyne coupling strategy as the key step.[4] In an extension of this strategy to elaborate diverse aromatic structures, we now report a four-component reaction of a benzyne intermediate and demonstrate here its utility in the first total synthesis of the antibacterial marine natural product dehydroaltenuene B. Dehydroaltenuenes A and B (**1** and **2**), along with dihydroaltenuenes A and B (**3** and **4**) (Figure 1), were isolated in 2006 by Gloer from cultures of an unidentified freshwater aquatic fungal species from the *Tubeufiaceae* family.[5] The absolute configuration of these new compounds has not been

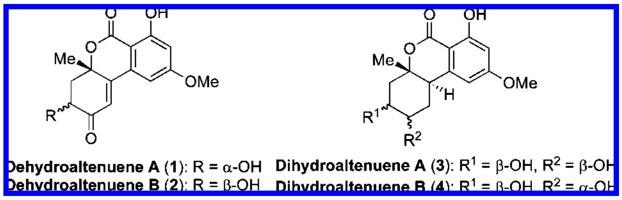


Figure 1. Structures of the altenuenes.

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[1] (a) Zhu, J.; Bienayme, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005. (b) Tietze, L. F.; Brasche, G.; Gericke, K., Eds. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.

[2] (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. For reviews on the use of arynes in organic synthesis, see: (b) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, pp 483−515. (c) Biehl, E. R.; Khanapure, S. P. *Acc. Chem. Res.* **1989**, *22*, 275. (d) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (e) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502.

[3] For recent examples, see: (a) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558. (b) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3935. (c) Uchiyama, M.; Kobayashi, Y.; Furuyama, T.; Nakamura, S.; Kajihara, Y.; Miyoshi, T.; Sakamoto, T.; Kondo, Y.; Morokuma, K. *J. Am. Chem. Soc.* **2008**, *130*, 472. (d) Jayanth, T. T.; Jeganmohan, M.; Cheng, M. J.; Chu, S. Y.; Cheng, C. H. *J. Am. Chem. Soc.* **2006**, *128*, 2232. (e) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112.

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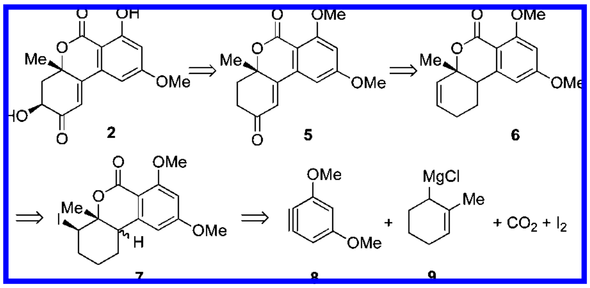
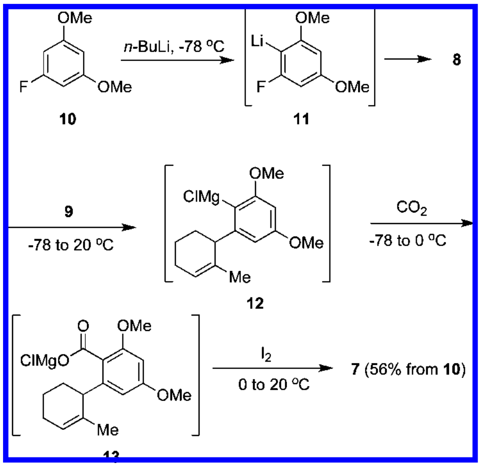
assigned. Interestingly, the difference in the relative stereochemistry of these compounds led to the significant variation in their biological activities. Therefore, a concise total synthesis of this class of natural products would be of considerable interest to assign the absolute configuration and to further define structure−activity relationships. Our retrosynthetic analysis, based on benzyne coupling, is outlined in Scheme 1.

Scheme 1. Retrosynthetic Analysis of Dehydroaltenuene B



Dehydroaltenuene B (**2**) should be obtained from tricyclic lactone **5** using an α-hydroxylation and selective de-*O*-methylation. Lactone **5** should be derived from alkene **6** which should be available from the dehydroiodination of iodide **7**. In turn, we planned to construct iodide **7** in a one-pot operation using a four-component benzyne coupling reaction. Thus, regioselective nucleophilic addition of the unsymmetrical benzyne **8** with the Grignard reagent **9** followed by carboxylation and iodolactonization should provide iodide **7**. The lithiation and elimination of commercially available fluorobenzenes have been successfully used to generate benzynes.[4,6,7] In this work, we have extended the scope of this transformation to 1-fluoro-3,5-dimethoxybenzene (**10**). Reaction of fluoride **10** with *n*-BuLi (1 equiv) gave the *ortho*-fluorolithium **11**,[8] which was allowed to fragment to the benzyne **8**[9] upon warming to room temperature in the presence of the Grignard reagent **9**[10] to regioselectively afford the arylmagnesium chloride **12**.[11] This was trapped with carbon dioxide[12] to give the resulting arylcarboxylate **13**, which, on iodolactonization, provided iodide **7** in 56% yield (Scheme 2). Interestingly, substrate-controlled diastereoselective cyclization[13] was observed, and iodide **7** was obtained as a single diastereoisomer. The relative stereochemistry of the tricyclic product **7** was established by ^{1}H NMR NOESY experiment as shown in Figure 2.

Scheme 2. Four-Component Benzyne Coupling Reaction



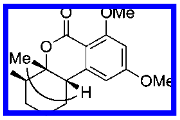


Figure 2. NOESY correlation of lactone **7**.

The observed regioselectivity in the reaction of the unsymmetrical aryne **8** with the Grignard reagent **9** can be explained by the electron-withdrawing inductive effect together with a steric effect,[14] which directs the nucleophilic attack toward the *meta* position of the two methoxy moieties.

Having the key iodide **7** containing the complete carbon skeleton of the target natural product in hand, we focused our attention on oxidation to complete the synthesis of dehydroaltenuene B (Scheme 3).

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(5) Jiao, P.; Gloer, J. B.; Campbell, J.; Shearer, C. A. *J. Nat. Prod.* **2006**, *69*, 612.

(6) (a) Riggs, J. C.; Ramirez, A.; Cremeens, M. E.; Bashore, C. G.; Candler, J.; Wirtz, M. C.; Coe, J. W.; Collum, D. B. *J. Am. Chem. Soc.* **2008**, *130*, 3406. (b) Ramirez, A.; Candler, J.; Bashore, C. G.; Wirtz, M. C.; Coe, J. W.; Collum, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 14700.

(7) (a) Morton, G. E.; Barrett, A. G. M. *J. Org. Chem.* **2005**, *70*, 3525. (b) Morton, G. E.; Barrett, A. G. M. *Org. Lett.* **2006**, *8*, 2859.

(8) Reaction of the *ortho*-fluorolithium **11** with iodine at −78 °C gave the corresponding iodoarene in 83% yield.

(9) For related generation of benzyne from *ortho*-fluorolithium, sodium, and magnesium species, see: (a) Caster, K. C.; Keck, C. G.; Walls, R. D. *J. Org. Chem.* **2001**, *66*, 2932. (b) Fossatelli, M.; Brandsma, L. *Synthesis* **1992**, 756. (c) Gingrich, H. L.; Huang, Q.; Morales, A. L.; Jones, M. *J. Org. Chem.* **1992**, *57*, 3803.

(10) The Grignard reagent **9** was prepared using Rieke-magnesium from the corresponding 2-methyl-2-cyclohexenyl chloride. See also: (a) Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6130. (b) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674.

(11) In preliminary model studies, reaction of 2-cyclohexenylmagnesium chloride with benzyne **8** and quenching with water gave 1-(2-cyclohexenyl)-3,5-dimethoxybenzene in 55% yield.

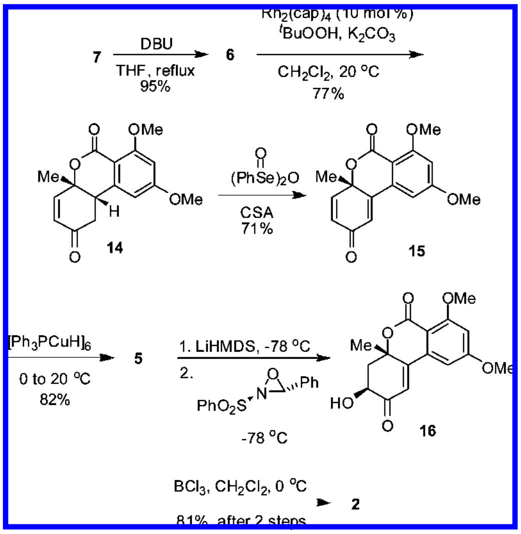
(12) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040.

(13) See, for examples: (a) Garnier, J. M.; Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2007**, 3281. (b) Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273.

(14) Xin, H. Y.; Biehl, E. R. *J. Org. Chem.* **1983**, *48*, 4397. See also ref 12.

(15) (a) Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622. (b) Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 5167.

Scheme 3. Total Synthesis of Dehydroaltenuene B (**2**)



Dehydroiodination of iodide **7** using DBU as base in THF gave the corresponding alkene **6** (95%). Rhodium(II) caprolactam catalyzed allylic oxidation[15,16] of alkene **6** in the presence of ^{t}BuOOH and K_2CO_3 in CH_2Cl_2 afforded α,*β*-unsaturated ketone **14** (77%). Transformation of the α,*β*-unsaturated ketone **14** to the corresponding isomer **5** was performed in two steps, via the dienone **15**. Thus, oxidation of enone **14** using benzeneseleninic anhydride and camphorsulfonic acid in THF[17] gave the dienone **15** (71%). This procedure was superior to enolate phenylselenylation and selenoxide elimination. Reaction of the delicate dienone **15** with Stryker's reagent[18] resulted in the selective conjugate reduction at the less-substituted α,*β*-unsaturated double bond to afford the desired enone **5** in 82% yield. Deprotonation of ketone **5** using LiHMDS followed by the oxidation with Davis' oxaziridine reagent[19] gave the corresponding α-hydroxy-ketone **16**. The *syn*-product **16**, of which the relative stereochemistry was confirmed by the ^{1}H NMR NOESY spectrum of **2**, was obtained as a major product. The *anti*-isomer was also obtained, but only in less than 5%, as observed by ^{1}H NMR. Fortunately, both could be separated by chromatography. The stereochemical outcome for the oxidation of lithium enolate derived from **5** can be explained by the stereoelectronic effect as depicted in Figure 3. Attack of the lithium enolate derived from **5**, represented as A, with an electrophile from the same face as the methyl group (Path a) led to the more favored chair conformation B having both methyl and hydroxyl groups axial. In contrast, attack from the opposite face (Path b) led to the twist boat conformation C, which is apparently less favored. Finally, the *syn*-α-hydroxy ketone **16** was subjected to selective de-*O*-methylation using boron trichloride in dichloromethane[20] to give dehydroaltenuene B (**2**) in 81% yield starting from **5**. Comparison of the spectral data of the synthetic racemic compound **2** with spectral data reported for the natural product confirmed the identity of the synthetic material.

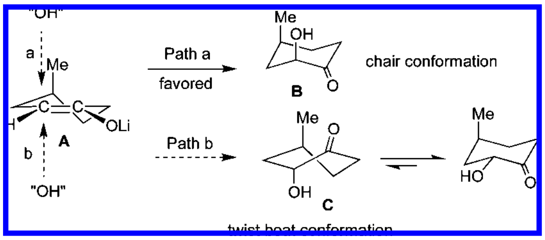


Figure 3. Stereoelectronic control leading to the *syn*-product **16**.

In conclusion, we have developed a concise and convenient four-component benzyne coupling reaction for the conversion of a simple arene into a tricyclic compound **7** in a one-pot operation. We have successfully applied this method to the first total synthesis of antibacterial dehydroaltenuene B (**2**). On the basis of this approach, enantioselective reactions of benzynes with allylmetallic species are currently under investigation including second generation routes to the altenuenes and other target systems.

Acknowledgment. We thank GlaxoSmithKline for the generous endowment (to A.G.M.B.), the Royal Society and the Wolfson Foundation for a Royal Society Wolfson Research Merit Award (to A.G.M.B.), the Engineering and Physical Sciences Research Council (UK) and the Commonwealth Scientific and Industrial Research Organization (Melbourne, Australia) for generous support, and Professor James B. Gloer, University of Iowa, for comparing the ^{1}H and ^{13}C NMR spectral data of our synthetic dehydroaltenuene B with the spectral data of the natural product.

Supporting Information Available: Experimental procedure, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) (±)-*trans*-2-(Phenylsulfonyl)-3-phenyloxaziridine was readily synthesized according to the reported procedure. See: Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth., Coll.* **1993**, *8*, 546.

(20) Mazza, S. M.; Lal, K.; Salomon, R. G. *J. Org. Chem.* **1988**, *53*, 3681.