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An Expeditious Synthesis of Bruguierol A[†]

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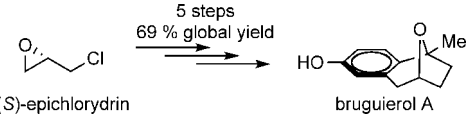
Received September 26, 2008



A very simple strategy for the construction of 2,3-benzofused 8-oxabicyclo[3.2.1]octane derivatives is reported. This new process is based on a platinum-catalyzed tandem intramolecular hydroalkoxylation−hydroarylation reaction of aryl-substituted pentynol derivatives. This reaction has been applied in the key step of the total synthesis of bruguierol A, allowing the synthesis of this natural product in a very straightforward manner.

As part of investigations on mangroves for the search for new natural products, in 2005 Sattler and co-workers isolated and characterized from the stem of *Bruguiera gymmorrhiza* tree a new family of compounds termed bruguierols A−C (Figure 1).[1] The structure of these natural products is characterized by a 2,3-benzofused 8-oxabicyclo[3.2.1]octane core. Additionally, the aromatic ring is substituted with one (bruguierol A) or two hydroxyl groups (bruguierols B and C). Among the three, bruguierol C was shown to exhibit activity against both Gram-positive and Gram-negative bacteria. Thus, the development of a flexible strategy to access these natural products or analogues could be highly interesting in finding new broad spectrum antibiotics. The biological profile combined with the interesting structural features and the potential to exploit methods developed within our group make the bruguierols ideal synthetic targets.[2] Here we describe a new and simple strategy that allows the stereoselective synthesis of bruguierol A, **1**. The method could be easily adapted to the synthesis of the other bruguierols or analogues.

The synthetic plan relied on a late stage tandem intramolecular hydroalkoxylation−hydroarylation reaction of the pentynol

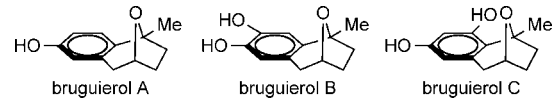
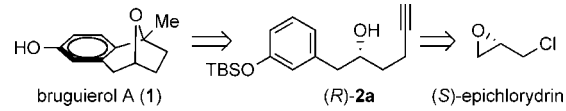


FIGURE 1. Structures of bruguierols A−C.

SCHEME 1. Retrosynthetic Analysis



derivative (*R*)-**2a** to yield the benzofused 8-oxabicyclo[3.2.1]octane skeleton.[3] It was envisaged that the precursor (*R*)-**2a** would be readily synthesized from commercially available (*S*)-epichlorydrin (Scheme 1).

As previously stated, our approach to bruguierol A was guided by the perception that the formation of the oxabicyclo[3.2.1]octane skeleton could be readily achieved by a tandem intramolecular hydroalkoxylation−hydroarylation reaction of the chiral non-racemic alkynol derivative (*R*)-**2a**. This hypothesis was supported by our experience on this kind of reaction performed on hexynol derivatives.[4] However, the extension of this reaction to pentynol derivatives analogous to (*R*)-**2a** had not been evaluated. So, before starting the total synthesis of our target natural product we decided to check the catalytic tandem intramolecular hydroalkoxylation−hydroarylation reaction of pentynol derivatives. It should be noted that although both the hydroalkoxylation and the hydroarylation reactions are known transformations, the development of a method where a single catalyst promotes both reactions in a one-pot process would be highly interesting.

As shown in Scheme 2, the treatment of pentynol derivatives **2** with 5 mol % of $PtCl_4$ in dichloromethane at room temperature readily afforded the tricyclic compounds **3** in high yield and as single diastereoisomers. The reaction was shown to proceed with both secondary and tertiary alcohols **2**. The scope of this reaction is limited by the fact that only alkynols **2** containing electron-rich aromatic rings worked efficiently. In those cases where the starting materials **2** contained simple phenyl groups the hydroarylation reaction did not progress, and we isolated the corresponding enol ethers proceeding from the first hydroalkoxylation reaction of the triple bond. However, this limitation did not affect our plan for the synthesis of bruguierol A as this natural product contains an electron-rich aromatic ring. In fact,

[†] This article is dedicated to Professor José Barluenga.

(1) Han, L.; Huang, X.; Sattler, I.; Moellmann, U.; Fu, H.; Lin, W.; Grabley, S. *Planta Med.* **2005**, *71*, 160.

(2) As far as we know only a total synthesis of the enantiomer of bruguierol A and a total synthesis of bruguierol C have been published. For the synthesis of bruguierol A, see: (a) Ramana, C. V.; Salian, S. R.; Gonnade, R. G. *Eur. J. Org. Chem.* **2007**, 5483. For the synthesis of bruguierol C, see: (b) Solorio, D. M.; Jennings, M. P. *J. Org. Chem.* **2007**, *72*, 6621.

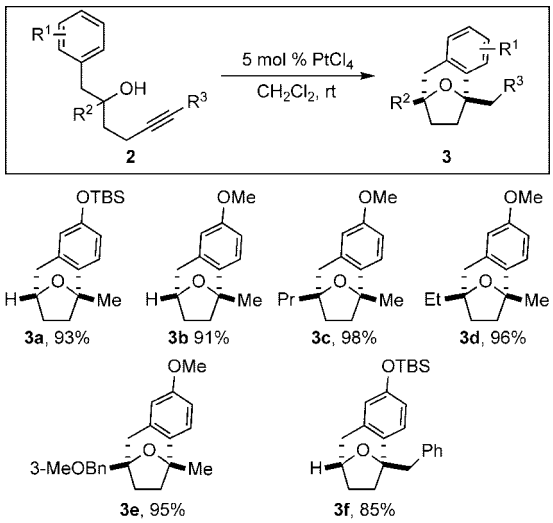
(3) For an excellent paper on the synthesis of 8-oxabicyclo[3.2.1]octane systems, see: Marson, C. M.; Campbell, J.; Hursthouse, M. B.; Malik, K. M. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1122.

(4) Barluenga, J.; Fernández, A.; Satrústegui, A.; Diéguez, A.; Rodríguez, F.; Fañanás, F. J. *Chem. Eur. J.* **2008**, *14*, 4153.

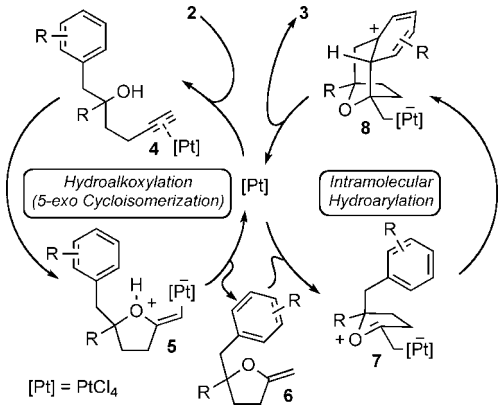
(5) For recent works where platinum complexes have been used as catalysts in hydroalkoxylation reactions of unsaturated carbon−carbon bonds, see: (a) Diéguez-Vázquez, A.; Tzschucke, C. C.; Lam, W. Y.; Ley, S. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 209. (b) Nakamura, I.; Chan, C. S.; Araki, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 309. (c) Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H. *Chem. Eur. J.* **2007**, *13*, 8285. (d) Barluenga, J.; Diéguez, A.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2091. (e) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907. (f) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (g) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (h) Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536. (i) Lucey, D. W.; Atwood, J. D. *Organometallics* **2002**, *21*, 2481.

10.1021/jo8021204 CCC: $40.75
Published on Web 11/21/2008

SCHEME 2. 2,3-Benzofused 8-Oxabicyclo[3.2.1]octane Derivatives 3 by Catalytic Tandem Hydroalkoxylation−Hydroarylation Reaction of Pentynol Derivatives 2



SCHEME 3. Proposed Mechanism for the Formation of 2,3-Benzofused 8-Oxabicyclo[3.2.1]octanes 3 from Alkynols 2

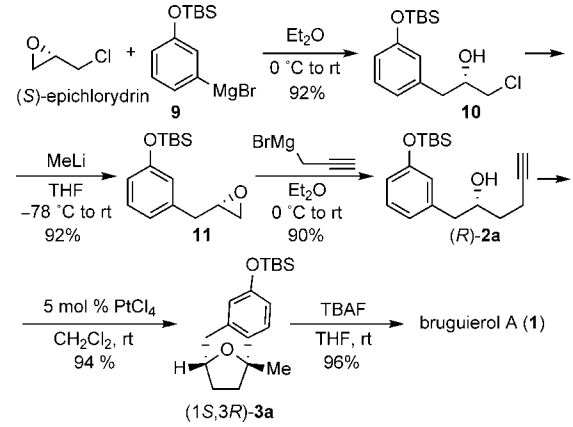


compound **3a**, which is a precursor of racemic bruguierol A, could be easily obtained in 93% yield (Scheme 2).

A mechanism that explains the formation of compounds **3** from pentynol derivatives **2**, supported by our previous studies in the field,[4] is shown in Scheme 3. The reaction is initiated by coordination of the platinum catalyst to the triple bond of the starting alkynol **2** to form intermediate **4**. This coordination favors an intramolecular addition of the hydroxyl group to the internal carbon of the triple bond (5-*exo* addition) to generate **5**. Protodemetalation of the latter affords the enol ether **6** and releases the catalytic species.[5,6] Once enol ether **6** is formed, it enters the second catalytic cycle. Thus, after an initial coordination of the catalyst to the double bond of the enol ether **6**, the oxocarbenium ion intermediate **7** is formed. Further nucleophilic attack of the aryl group affords the intermediate **8** that after a rearomatization and a protodemetalation step leads to the final product **3**, regenerating the catalytic species.

After establishing the feasibility of the catalytic tandem intramolecular hydroalkoxylation−hydroarylation reaction for the synthesis of 2,3-benzofused 8-oxabicyclo[3.2.1]octane systems, we turned our attention to the synthesis of bruguierol A from commercially available (*S*)-epichlorydrin (Scheme 4). The first reaction implies the ring opening of the epoxide by reaction

SCHEME 4. Synthesis of Bruguierol A from (*S*)-Epichlorydrin

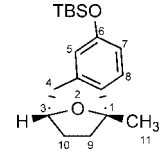


with the Grignard reagent **9** to give the chlorydrin derivative **10** in 92% yield. Further reaction of this alcohol with methyllithium furnishes the new epoxide **11** in 92% yield. The reaction of this epoxide with propargylmagnesium bromide provides the desired pentynol derivative (*R*)-**2a** in 90% yield as a single regioisomer with an enantiomeric ratio of >95:5 as determined by the Mosher method. The pentynol derivative (*R*)-**2a** was subjected to the intramolecular hydroalkoxylation−hydroarylation reaction by using $PtCl_4$ as catalyst in dichloromethane at room temperature. Under these conditions the protected bruguierol A (1*S*,3*R*)-**3a** was obtained in 94% yield. Last, treatment of (1*S*,3*R*)-**3a** with TBAF in THF afforded the natural product bruguierol A in 96% yield. The spectral data and optical rotation of synthetic bruguierol A were in agreement with those of the natural sample.

In conclusion, a very short and efficient total synthesis of bruguierol A has been accomplished from commercially available (*S*)-epichlorydrin (5 steps, ca. 69% overall yield). This synthesis favorably competes with the previous approach in terms of all usual empirical indices.[7] We have also demonstrated the power of the catalytic tandem intramolecular hydroalkoxylation−hydroarylation reaction for the construction of 2,3-benzofused 8-oxabicyclo[3.2.1]octane systems. Clearly, the strategy described here could be readily adapted to the total synthesis of other bruguierols and novel analogues.

Experimental Section

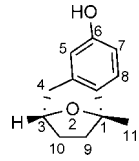
Representative Procedure for the 5-*exo* Hydroalkoxylation−Hydroarylation Reaction: Synthesis of (1*S*,3*R*)-3a.



Alkynol (*R*)-**2a** (1 mmol) was added to an orange solution of $PtCl_4$ (16.7 mg, 0.05 mmol) in dichloromethane (2 mL) at room temperature. The resulting mixture was stirred until complete conversion of the starting alkynol (1 h; monitored by TLC). The solvent was removed at reduced pressure and the residue obtained was purified by flash column chromatography on silica gel (hexane: ethyl acetate 7:1) to yield pure compound (1*S*,3*R*)-**3a** as a colorless oil. R_f 0.55 (hexane:ethyl acetate 5:1). $[\alpha]_D$ −30.1 (c 6 × 10^{-3}, CH_2Cl_2). ^1H (300 MHz, $CDCl_3$) δ 6.98 (d, J = 8.3 Hz, 1H; H_8), 6.58 (dd, J = 8.3, 2.2 Hz, 1H; H_7), 6.53 (d, J = 2.2 Hz, 1H; H_5),

4.68 (ddd, J = 7.1, 5.1, 1.3 Hz, 1H; H_3), 3.29 (dd, J = 16.4, 5.1 Hz, 1H; H_{4a}), 2.43 (d, J = 16.4 Hz, 1H; H_{4b}), 2.30−2.14 (m, 1H; H_{10a}), 1.98 (ddd, J = 11.7, 9.7, 2.7 Hz, 1H; H_{9a}), 1.82 (dd, J = 11.4, 7.1 Hz, 1H; H_{9b}), 1.77−1.59 (m, 1H; H_{10b}), 1.68 (s, 3H), 0.87 (s, 9H; ^{t}Bu-Si), 0.17 (s, 6H; 2 × Me-Si). ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.5, 18.1, 22.8, 25.6, 30.4, 37.5, 42.9, 74.2, 80.2, 117.4, 120.3, 123.6, 133.1, 136.9, 154.1. HRMS calcd for $C_{18}H_{28}O_2Si$ 304.1859, found 304.1857.

Deprotection of (1*S*,3*R*)-3a: Synthesis of Bruguierol A (1).



Bu_4NF (1 mmol) was added to a solution of (1*S*,3*R*)-**3a** (1 mmol) in wet THF (20 mL) at room temperature. The mixture was stirred until complete conversion of the starting material (30 min; monitored by TLC). Water (20 mL) was added, and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed and the crude was purified by flash column chromatography on silica gel (hexane:diethyl ether 1:2) to yield pure compound **1** (Bruguierol A) as a white solid. Mp 129.6−133.1 °C. R_f 0.33 (hexane:ethyl acetate 2:1). $[\alpha]_D$ +14.5 (c 7 × 10^{-3}, $CHCl_3$) {lit.[1] $[\alpha]_D$ +14.3 (c 6 × 10^{-3}, $CHCl_3$)}. ^{1}H (300 MHz, $CDCl_3$) δ 6.98 (d, J = 8.4 Hz, 1H; H_8), 6.58 (dd, J = 8.4, 2.5 Hz, 1H; H_7), 6.50 (d, J = 2.5 Hz, 1H; H_5), 4.71 (ddd, J = 7.0, 5.1, 1.5 Hz, 1H; H_3), 3.28 (dd, J = 16.5, 5.1 Hz, 1H; H_{4a}), 2.42 (d, J = 16.5 Hz, 1H; H_{4b}), 2.26–2.18 (m, 1H; H_{10a}), 1.98 (ddd, J = 11.5, 9.5, 3.1 Hz, 1H; H_{9a}), 1.83 (dd, J = 11.5, 7.4 Hz, 1H; H_{9b}), 1.75−1.63 (m, 1H; H_{10b}), 1.70 (s, 3H; H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 32.4, 39.5, 45.0, 76.3, 82.7, 115.0, 117.7, 126.0, 135.4, 138.1, 156.6. HRMS calcd for $C_{12}H_{14}O_2$ 190.0994, found 190.0992.

Acknowledgment. Financial support for this work was provided by the Ministerio de Educación y Ciencia of Spain (CTQ2007-61048/BQU).

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

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(6) Some other metallic complexes have been reported to catalyze the intramolecular hydroalkoxylation of alkynes. For selected recent examples see the following references. Palladium: (a) Trost, B. M.; Weis, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7664. Silver: (b) Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019 Gold: (c) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112. Ruthenium: (d) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 2528. Rhodium: (e) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2003**, *125*, 7482. Iridium: (f) Genin, E.; Antoniotti, S.; Michelet, V.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4949. Tungsten: (g) McDonald, F. E.; Reddy, K. S.; Díaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304. (h) Barluenga, J.; Diéguez, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 126. (i) Barluenga, J.; Diéguez, A.; Rodríguez, F.; Fañanás, F. J.; Sordo, T.; Campomanes, P. *Chem. Eur. J.* **2005**, *11*, 5735.

(7) Ramana's synthesis of the enantiomer of bruguierol A (see ref 2a) requires at least 10 steps (from geranyl acetate) and the global yield is approximately 1.5%.