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The First Total Synthesis of Gravicycle

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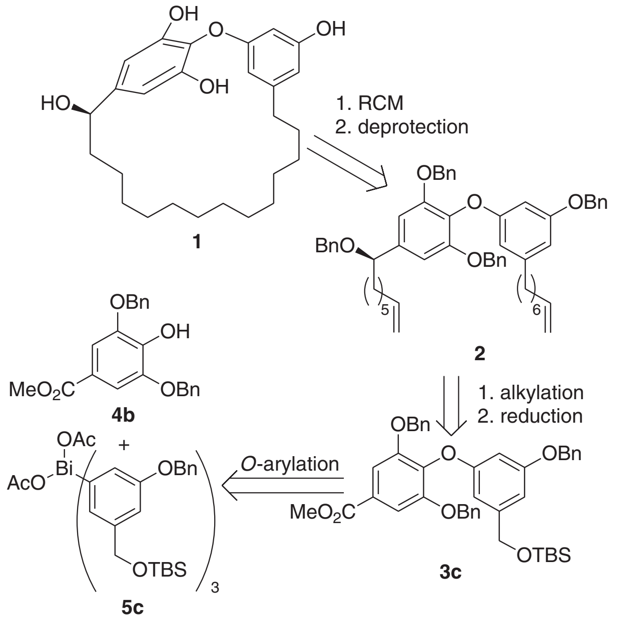
The total synthesis of gravicycle, isolated from *Grevillea robusta*, has been achieved for the first time. The key step of our synthetic process is the efficient assembly of a highly functionalized biaryl ether via the copper-catalyzed *O*-arylation of suitably protected pyrogallol-5-carboxylate, using triarylbismuth(V) diacetate.

Gravicycle, a novel cyclic biaryl ether, was first isolated from *Grevillea robusta* A. Cunn. (Proteaceae) in 2007.[1] This compound has demonstrated significant cytotoxicity against human breast carcinoma (MCF-7), lung carcinoma (NCI-H460), and central nervous system carcinoma (SF-268) cell lines. As shown in Scheme 1, the structure of **1** includes a biaryl ether formed from two resorcinol units, resulting in a 22-membered cyclic ether which contains a chiral benzylic alcohol. Although highly functionalized biaryl ether linkages are common in a variety of natural products,[2] their production by synthetic methods has been quite limited to date.[3]

The bond formations resulting in biaryl ethers have often been achieved through the use of transition-metal-catalyzed reactions between aryl halides and phenols,[4] including Ullmann-type reactions.[3,4d,4e] However, these reactions generally require harsh reaction conditions.[3a–3c] Under such conditions, good yields via *O*-arylation are realized only in the case of simple phenols and aryl halides, whereas reactions of 2,6-disubstituted phenols and functionalized aryl halides have resulted in low yields.[5] There are few methods that allow the preparation of highly substituted biaryl ethers under mild conditions.



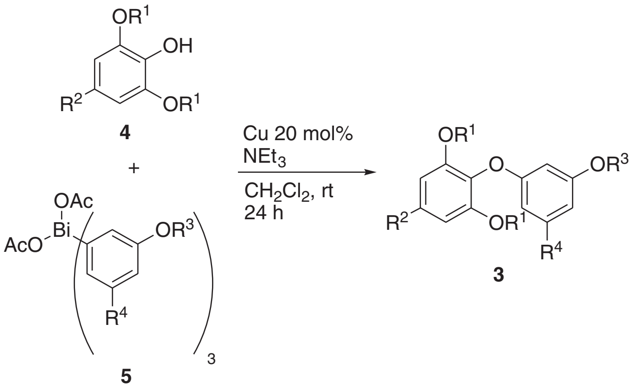
Scheme 1. Retrosynthetic analysis of gravicycle (**1**).

In the 1980s, Barton and Finet developed a copper-catalyzed *O*-arylation of phenol which proceeded at room temperature using phenylbismuth(V) reagents.[6] No examples have been reported, however, in which this methodology has been used for the synthesis of more sterically crowded biaryl ethers. Herein, we describe copper-catalyzed coupling reactions of crowded phenols using triarylbismuth(V) diacetate. In addition, we present the first total synthesis of gravicycle (**1**).

Our synthetic strategy is outlined in Scheme 1. The macrocycle of **1** was to be produced by ring-closing metathesis (RCM)[7] of **2**. The biaryl ether **3c** was to be synthesized via copper-catalyzed *O*-arylation of properly protected pyrogallol-5-carboxylate **4b**[8] with the triarylbismuth diacetate **5c**.

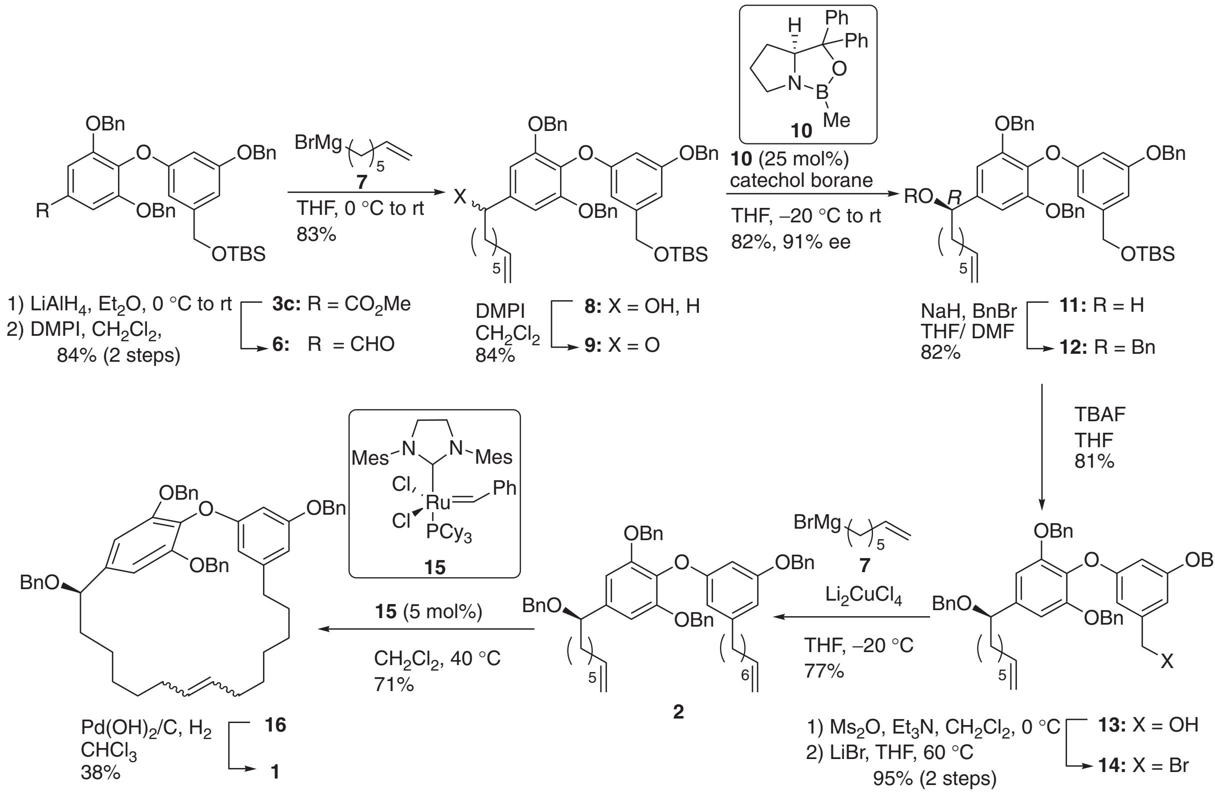
Initially, we examined the copper-catalyzed *O*-arylation of a series of pyrogallol derivatives **4** with a series of triarylbismuth diacetate derivatives **5**[9] (Table 1). When 3,5-dimethoxy-4-hydroxybenzaldehyde (**4a**) was treated with **5a** and copper powder in the presence of triethylamine, formation of the biaryl

Table 1. Copper-catalyzed *O*-arylation of pyrogallol derivatives **4** using bismuth diacetate derivatives **5**



Entry	**4**			**5**[a]			Yield/%
		R^1	R^2		R^3	R^4	
1	**a**	Me	CHO	**a**	Me	H	83 (**3a**)
2[b]	**a**	Me	CHO	**b**	Me	CH_2OTBS	90 (**3b**)
3[b,c]	**a**	Me	CHO	**b**	Me	CH_2OTBS	68 (**3b**)
4[b]	**b**	Bn	CO_2Me	**c**	Bn	CH_2OTBS	50 (**3c**)
5	**b**	Bn	CO_2Me	**c**	Bn	CH_2OTBS	68 (**3c**)

[a]1.5 molar equivalents used. [b]NEt_3 (6.0 mol equiv) not added. [c]1.2 mol equiv of **5** used.



Scheme 2. Synthesis of gravicycle (**1**).

ether proceeded at room temperature to give the ether **3a** in good yield (Entry 1). The reaction of **4a** with **5b** also gave the biaryl ether **3b** in high yield (Entry 2). Triethylamine was necessary to obtain **3c** in good yield reproducibly (Entries 4 and 5). These results show that arylbismuth(V) reagents are suitable for use with crowded phenols in copper-catalyzed Ullmann-type coupling reactions.

Our total synthesis of **1** commenced with **3c** (Scheme 2). Reduction of methyl ester **3c** with LiAlH$_4$ followed by oxidation with Dess–Martin periodinane (DMPI)[10] afforded aldehyde **6** in 84% yield (2 steps). Addition of the Grignard reagent **7** to **6** gave benzyl alcohol **8** in 83% yield. Following the oxidation of **8**, the resultant ketone **9** was reduced with oxazaborolidine **10**[11] and catecholborane in THF at −20 °C to give chiral benzyl alcohol **11** in 82% yield. The enantiomeric excess of this chiral product was found to be 91% by HPLC using Chiralpak AD-H® analysis. The (*R*)-configuration of **11** was determined using the modified Mosher's method.[12] The hydroxy functional group of **11** was protected by conversion to a benzyl ether to give **12** in 82% yield. The TBS ether of **12** was cleaved by reaction with TBAF in THF. Mesylation of **13** with methanesulfonic anhydride (Ms$_2$O) and triethylamine in CH$_2$Cl$_2$ at 0 °C, followed by bromination with lithium bromide in THF at 60 °C, afforded benzyl bromide **14** in 95% yield.[13] Alkylation of **14** with **7** in the presence of Li$_2$CuCl$_4$ in THF at −20 °C proceeded efficiently to give **2** in 77% yield.[14] Cyclization of **2** via RCM was conducted using the Grubbs second generation catalyst **15**[15] at 40 °C in a 2.5 mM CH$_2$Cl$_2$ solution. Under these conditions, **2** was consumed completely, and only the desired cyclic product **16** was obtained as a 2.6:1 mixture of (*E*)- and (*Z*)-olefins in 71% yield. When the *E*/*Z* olefin mixture **16** was mixed with palladium hydroxide on carbon in CHCl$_3$ under a hydrogen atmosphere, hydrogenation of the olefin and hydrogenolysis of the four benzyl ethers proceeded to give **1** (38% yield). The use of CHCl$_3$ as a solvent in this step was necessary in order to dissolve **16**, since it was insoluble in both ethyl acetate and alcohols. The hydrogenolysis was slow and not completed under these conditions. The spectral data (^{1}H, ^{13}C, IR, and HRMS) of the synthetic product **1** were identical with those reported for a sample of **1** obtained from natural sources.[16]

In conclusion, we have achieved the first total synthesis of gravicycle (**1**), via a process which features the copper-catalyzed *O*-arylation of the pyrogallol derivative **4b** using triarylbismuth diacetate **5c**. Furthermore, the development of this synthesis demonstrated that the formation of highly functionalized biaryl ethers can be carried out under mild reaction conditions. The methodology presented here should be more generally applicable to the *O*-arylation of sterically crowded alkyl alcohols[18] as a means to the synthesis of highly functionalized alkyl aryl ethers. Further research along these lines is currently underway in our laboratory.

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Reference and Notes

1 T.-H. Chuang, P.-L. Wu, *J. Nat. Prod.* **2007**, *70*, 319.
2 a) D. A. Evans, M. R. Wood, B. W. Trotter, T. I. Richardson, J. C. Barrow, J. L. Katz, *Angew. Chem., Int. Ed.* **1998**, *37*,

2700. b) K. C. Nicolaou, H. J. Mitchell, N. F. Jain, N. Winssinger, R. Hughes, T. Bando, *Angew. Chem., Int. Ed.* **1999**, *38*, 240. c) H. Shimamura, S. P. Breazzano, J. Garfunkle, F. S. Kimball, J. D. Trzupek, D. L. Boger, *J. Am. Chem. Soc.* **2010**, *132*, 7776. d) D. L. Boger, S. M. Sakya, D. Yohannes, *J. Org. Chem.* **1991**, *56*, 4204. e) W. Schuehly, W. Voith, H. Teppner, O. Kunert, *J. Nat. Prod.* **2010**, *73*, 1381.

3 a) S. V. Ley, A. W. Thomas, *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. b) R. Frlan, D. Kikelj, *Synthesis* **2006**, 2271. c) F. Theil, *Angew. Chem., Int. Ed.* **1999**, *38*, 2345. d) J. R. Cannon, B. W. Metcalf, *Aust. J. Chem.* **1973**, *26*, 2277.

4 a) M. Palucki, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 10333. b) G. Mann, C. Incarvito, A. L. Rheingold, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 3224. c) Q. Shelby, N. Kataoka, G. Mann, J. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 10718. d) D. Maiti, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 17423. e) D. Maiti, S. L. Buchwald, *J. Org. Chem.* **2010**, *75*, 1791.

5 C. Paizs, U. Bartlewski-Hof, J. Rétey, *Chem.—Eur. J.* **2007**, *13*, 2805.

6 a) D. H. R. Barton, J.-P. Finet, J. Khamsi, C. Pichon, *Tetrahedron Lett.* **1986**, *27*, 3619. b) D. H. R. Barton, B. Charpiot, W. B. Motherwell, *Tetrahedron Lett.* **1982**, *23*, 3365. For related *O*-arylation with arylboronic acid, see: c) D. A. Evans, J. L. Katz, T. R. West, *Tetrahedron Lett.* **1998**, *39*, 2937.

7 a) *Handbook of Metathesis*, ed. by R. H. Grubbs, Wiley-VCH, Weinheim, **2003**, Vol. 2, pp. 296–319. b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.

8 G. Cainelli, C. Angeloni, R. Cervellati, P. Galletti, D. Giacomini, S. Hrelia, R. Sinisi, *Chem. Biodiversity* **2008**, *5*, 811.

9 J.-P. Finet, A. Yu. Fedorov, *J. Organomet. Chem.* **2006**, *691*, 2386.

10 a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155. b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277.

11 a) E. J. Corey, C. J. Helal, *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. b) C. Y. Hong, N. Kado, L. E. Overman, *J. Am. Chem. Soc.* **1993**, *115*, 11028.

12 I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092.

13 H. Hashizume, H. Ito, T. Morikawa, N. Kanaya, H. Nagashima, H. Usui, H. Tomoda, T. Sunazuka, H. Kumagai, S. Ōmura, *Chem. Pharm. Bull.* **1994**, *42*, 2097.

14 a) T. B. Nguyen, A.-S. Castanet, T.-H. Nguyen, K. P. P. Nguyen, J.-F. Bardeau, A. Gibaud, J. Mortier, *Tetrahedron* **2006**, *62*, 647. b) M. Schlosser, H. Bossert, *Tetrahedron* **1991**, *47*, 6287.

15 M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953.

16 **1**: Colorless amorphous solid, $[\alpha]_D^{23} = +11.5$ (c 0.45, MeOH) [lit[1,17] $[\alpha]_D = +13.1$ (c 0.45, $CHCl_3$)]; IR (film): ν 3343, 1597, 1501, 1460 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 1.27 (20H, m), 1.45 (2H, m), 1.73 (2H, m), 2.34 (2H, t, $J = 6.0$ Hz), 4.46 (1H, t, $J = 6.0$ Hz), 5.82 (1H, dd, $J = 2.4$, 1.6 Hz), 6.26 (1H, dd, $J = 2.4$, 1.6 Hz), 6.46 (2H, brs), 6.48 (1H, dd, $J = 2.4$, 2.4 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 26.4, 27.9, 28.5, 28.6, 28.8, 28.9, 29.0, 29.1, 29.4, 30.1, 32.2, 37.0, 40.0, 75.3, 102.7, 105.2, 106.7, 109.9, 130.4, 143.9, 146.0, 151.8, 159.2, 160.8; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{26}H_{36}NaO_5$ 451.2460, found 451.2460.

17 The optical rotation of **1** was not measured in $CHCl_3$, because synthetic product **1** was insoluble in $CHCl_3$.

18 T. Mukaiyama, N. Sakurai, K. Ikegai, *Chem. Lett.* **2006**, *35*, 1140.