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A novel convergent approach to *trans*-fused polyether frameworks based on the reaction of vinylstannanes and triflates and its application to a synthetic study of the EFGH ring system of gambierol

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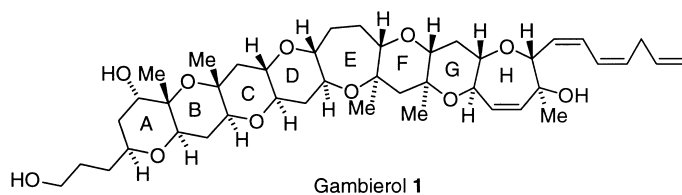
Abstract

A new strategy for the convergent assembly of six-membered polycyclic ether ring fragments has been developed based upon the novel reaction between vinylstannanes with triflates in the presence of a strong base. The application of the present method has allowed for a synthetic study of the EFGH ring of gambierol to be achieved. © 2000 Elsevier Science Ltd. All rights reserved.

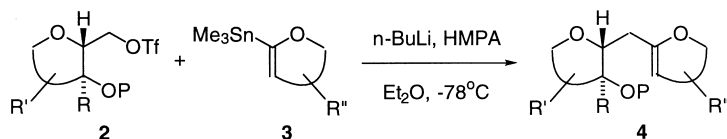
Keywords: polycyclic ether; coupling; vinylstannane; triflate.

The wide ranging and potent level of biological activity exhibited by isolated polycyclic ethers originating from marine bioorganisms has continuously attracted the interest of synthetic chemists.¹ Along with their novel intricate structures and rarity in nature, these compounds have, not surprisingly, become significant targets for synthesis.² In contrast to recent advances in the development of synthetic routes to medium-sized cyclic ethers,³ only a handful of protocols describing the convergent assembly of six-membered ether ring fragments have been reported to date.⁴ In connection with synthetic studies directed towards the synthesis of the EFGH ring system of gambierol **1**,^{5,6} we now report herein a novel expedient coupling procedure that relies upon the ability of a variety of cyclic triflates to undergo S_N2 substitution with anionic cycloalkoxyvinyl intermediates generated in situ, and its application to a model study of the EFGH ring system of gambierol **1**.⁷

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The coupling of six-membered cyclic ethers **2** with stannyl bicyclic ether **3** was initially chosen as the model system to establish the reaction conditions (Scheme 1 and Table 1). Thus, addition of *n*-BuLi at -78°C to an azeotropically dried mixture of tetrahydropyran **2** and vinylstannane **3a**



Scheme 1.

Table 1
Coupling of triflate **2** with vinylstannane **3** in the presence of *n*-BuLi

Entry	Triflate 2	Vinylstannane 3	Product 4	Yield/ %
1				46(71)
2	2b , P = TBS, R = Me	3a	4b , P = TBS, R = Me	28
3	2c , P = TES, R = H	3a	4c , P = TES, R = H	55(59)
4	2d , P = MPM, R = H	3a	4d , P = MPM, R = H	55
5	2d	3a	4d	16 ^b
6		3a		29
7		3a		18
8		3a		16
9	2b			25
10	2d	3b		15

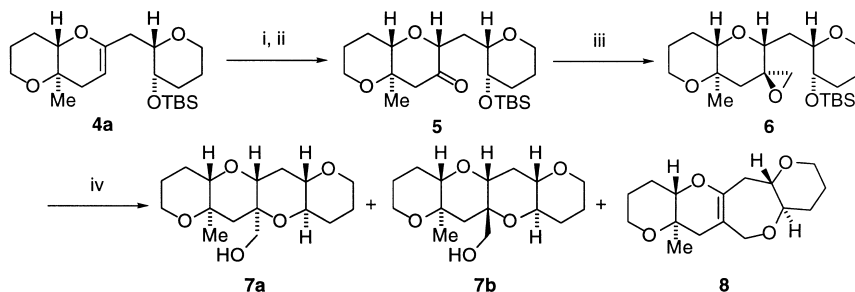
^aYields in parathesis based on recovery of triflate **2**; ^bTo a solution of the stannane **3** in Et_2O treated with *n*-BuLi for 20min., was added a Et_2O solution of the triflate **2**.

furnished the coupling products **4a–d** in moderate to good yields (entries 1–4).⁸ As seen in Table 1, under the applied conditions the reaction was best carried out using the TBS protected triflate **2a** (entry 1). Although better isolated yields could be obtained when using either the MPM or TES protected triflates of **2** (entries 3–4), recovery of **2a** and **3a** in 34 and 24% yield, respectively, after purification allowed for starting material recyclization and subsequent overall yield optimization of the present coupling reaction.

At this juncture, it is noteworthy to highlight the eloquent nature of the present procedure as a useful synthetic tool for the convergent construction of six-membered polycyclic ethers. This is more so when compared to work in our laboratory showing the cuprate-mediated version of this reaction to be ineffective whilst a survey of a variety of other possible substitution partners gave either lower yields, decomposition or no reaction.⁹ It is also interesting to note the dependency of the present method on the order of addition of substrates with optimum yields obtained when the reactions were carried out in situ. The reaction between triflate **2d** and vinylstannane **3a**, for example, gave superior yields of **4d** when a mixture of both starting materials were treated with base when compared to the sequential addition of **2d** to a solution of **3a** treated with base (entries 4–5).

The generality of the present coupling procedure was next investigated. The coupling of seven-membered triflates **2e–g** with **3a**, however, was found to be more problematic. Regardless of the reaction conditions employed, only low to moderate yields of the corresponding adducts **4e–g** were obtained (entries 6–8). The reaction of the analogous seven-membered stannyl ether **3b** to either **2b** or **2d** also gave the desired products **4a–b** in low to moderate yields of 15 and 25%, respectively, along with the corresponding protonated vinyl ether of **3b** in yields of 50 and 60%, respectively (entries 9 and 10).

The usefulness of the present coupling procedure was demonstrated in a simple model synthesis of the EFGH ring system of gambierol **1** by preparing the *trans*-fused tetracyclic ether **7**. Hydroboration of olefin **4a** followed by oxidation of the resultant secondary alcohol readily afforded the cyclic ketone **5** in 86% overall yield over two steps. Subsequent epoxidation to furnish the epoxide **6** in 87% yield and acid-mediated ring opening then afforded **7** as the major product in 69% yield and as an inseparable 1:1 mixture of diastereomers, and the undesired seven-membered cyclic ether **8** in 31% yield (Scheme 2). Further work to improve the regio- and diastereoselectivity of this step and the removal of the hydroxy group of **7a** are currently in progress.



Scheme 2. Reagents and conditions: (i) $\text{BH}_3\cdot\text{SMe}_2$, then H_2O_2 , NaOH , 86%; (ii) Dess–Martin periodinane, NaHCO_3 , CH_2Cl_2 , quant.; (iii) $\text{Me}_2\text{S}(\text{O})\text{CH}_2\text{I}$, DMSO , NaH , 87%; (iv) CSA , CH_2Cl_2 , $0\rightarrow 30^\circ\text{C}$, quant.

In conclusion, we have demonstrated a novel method for the assembly of *trans*-fused polyether frameworks based on the reaction of vinylstannanes and triflates and its potential application to

the total synthesis of gambierol **1**. Further studies towards the total synthesis of gambierol **1** are underway and will be reported in due course.

Acknowledgements

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8. Typical procedure: Diethyl ether (10 ml) followed by HMPA (0.17 ml, 1.0 mmol) was added to an azeotropically dried mixture of the triflate **2a** (343 mg, 0.91 mmol) and stannane **3a** (287 mg, 0.91 mmol) flushed with argon at room temperature. On cooling to -78°C, *n*-BuLi was then slowly added and the reaction mixture was allowed to stir for 50 mins. The reaction was quenched at -78°C with NaHCO₃, standard aqueous work-up with Et₂O and column chromatography afforded **4a** in 46% yield. ¹H NMR δ (500 MHz, C₆D₆) 4.68 (d, *J*=5.3, 1H), 3.75 (m, 1H), 3.65, (dd, *J*=11.0, 4.4, 1H), 3.48 (ddd, *J*=9.5, 9.5, 1.7, 1H), 3.41 (ddd, *J*=11.2, 11.2, 2.8, 1H), 3.33–3.22 (m, 1H), 3.11 (ddd, *J*=11.4, 11.4, 2.1, 1H), 2.87 (d, *J*=14.4, 1H), 2.39 (d, *J*=15.9, 1H), 2.20 (dd, *J*=14.3, 9.6, 1H), 2.02 (dd, *J*=15.9, 5.7, 1H), 1.86–1.71 (m, 2H), 1.60–1.12 (m, 10H), 0.93 (s, 9H), 0.00 (d, *J*=2.7, 6H).
9. The in situ reaction of vinylstannane **3a** with **2d** where the leaving group was modified to bear a triflate (FSO₂⁻) functional group, gave product **4d** in 20% yield. In contrast, no reaction was observed for either the tosylate or mesylate versions of **2d**. Reaction of **2d** where the triflate was replaced by iodide furnished unknown decomposition products. Also, no coupling was observed for the in situ reaction of the vinyl iodide equivalent of **3b** with **2d**. Reaction of **3a** with the aldehyde of **2d** resulted in only enolization of the aldehyde.