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A concise route to the C_2-symmetric tricyclic skeleton of ryanodine

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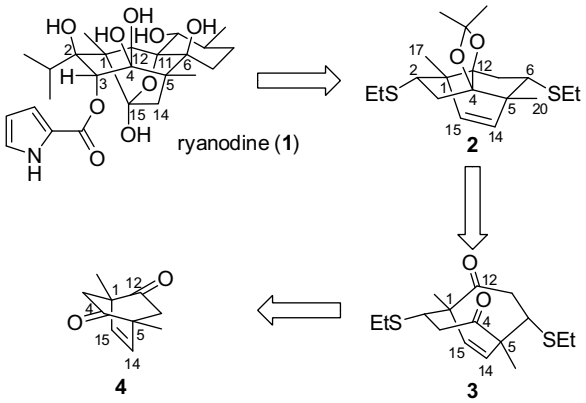
ABSTRACT

Ryanodine is a potent calcium channel modulator. In this Letter, we report the 10-step synthesis of the highly substituted tricyclic ring system of ryanodine. Diels–Alder reaction via dearomatization of 2, 5-dimethylbenzene-1,4-diol and subsequent SmI_2-mediated reductive coupling of eight-membered 1,5-diketone efficiently introduced the four consecutive fully substituted carbons of the tricyclo[3.3.2.0^{2,6}]decane system.

Ryanodine (**1**, Scheme 1),[1] a natural product isolated from the plant *Rynia speciosa* Vahl, is a potent modulator of the calcium release channel that is known as the ryanodine receptor.[2] The complex molecular architecture of **1** includes five rings and 11 stereogenic centers. From a synthetic perspective, ryanodine **1** and its related structures present an ideal platform to devise efficient strategies for building highly oxygenated multi-cyclic carboskeletons.[3,4] In addition, development of a flexible synthetic scheme to **1** would enable generation of chemical derivatives with distinct functional properties toward the ryanodine receptors. As an initial phase of this study, we established a new concise route to the highly substituted tricyclic core of **1**.

To simplify the synthetic scheme to **1**, we planned to exploit its embedded symmetric element (Scheme 1): the functionalized C_2-symmetric tricyclo[3.3.2.0^{2,6}]decane system **2** was designed as a platform structure for efficient construction of **1**.[5] Specifically, the C2- and C6-sulfides, and C14/15-olefin of **2** would be used as the handles for necessary functional group transformations en route to **1**. The four consecutive tetra-substituted carbons (C1, C4, C5, and C12) in the compact skeleton **2** were considered to be the most challenging structural feature. The fused 5/5-ring system of **2** was envisioned to be cyclized through a transannular reductive coupling of eight-membered 1,5-diketone **3** with simultaneous construction of the C4- and C12-tertiary alcohols.[6] By taking advantage of its symmetry, the eight-membered ring of **3** would be efficiently constructed by applying a two-directional



Scheme 1. Retrosynthesis of ryanodine.

ring-expansion[7] to the C_2-symmetric bicyclo[2.2.2]octane ring system **4**, followed by pairwise introduction of the sulfides. The two quaternary carbons of **4** at C1 and C5 were to be introduced via Diels–Alder reaction.

As shown in Scheme 2, upon heating 2,5-dimethylbenzene-1,4-diol **5** and maleic anhydride **6** (2.8 equiv) at 210 °C,[8] the desired adduct **7** was generated as a racemate in regioselective fashion. This intriguing Diels–Alder reaction occurred through dearomatization and set the two quaternary centers (C1 and C5) in a single step. Hydrolysis of anhydride **7** and subsequent electrolysis of the resultant bis(carboxylic acid)[9] in one pot gave rise to C_2-sym-

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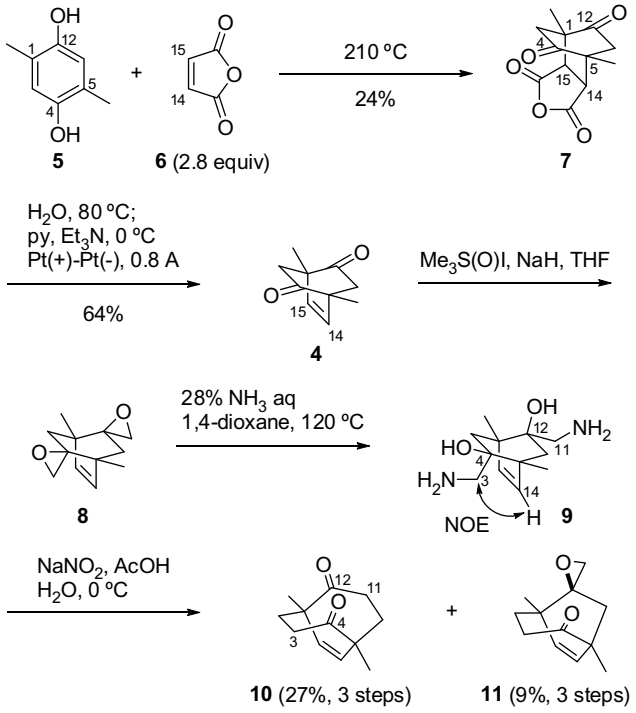
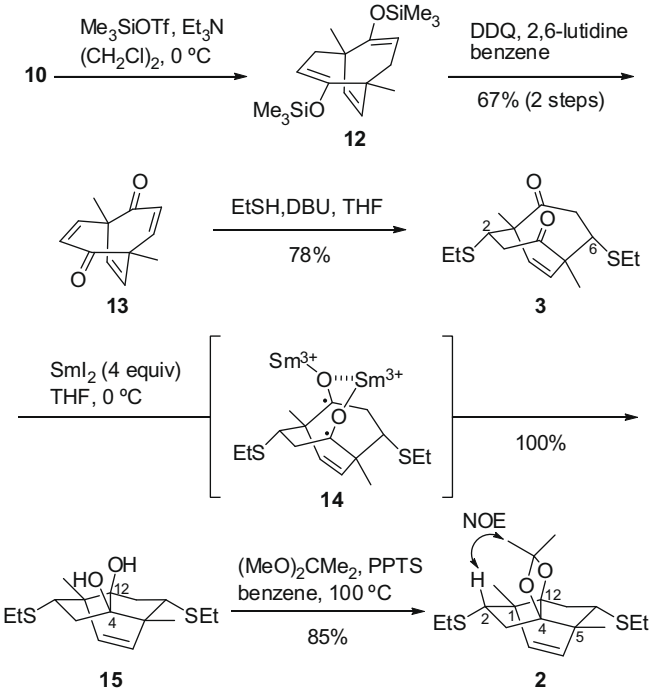


Scheme 2. Synthesis of C_2-symmetric bicyclo[3.3.2]decane system.



Scheme 3. Synthesis of tricyclo[3.3.2.0^{2,6}]decane system via transannular reductive coupling.

metric **4**. To prepare for the two-directional ring-expansion, the two 1,2-amino alcohols of **9** were constructed through stereoselective epoxide formation using dimethyloxosulfonium methylide,[10] followed by regioselective nucleophilic addition of ammonia on the epoxides of **8** at 120 °C. The newly formed stereochemistries at C4 and C12 of symmetric **9** were determined by an NOE between C3–H and C14–H. Sodium nitrite in aqueous acetic acid at 0 °C then effected the regioselective ring-expansion of the six-membered ring **9**, resulting in formation of the eight-membered ring **10** as the major product along with the seven-membered ring **11**.[11] Despite the modest overall yield from **5** to **10**, this five-step procedure routinely provides multi-gram quantities of C_2-symmetric **10**.

Having established a scalable route to bicyclo[3.3.2]decane ring **10**, we turned our attention to the transannular reaction for construction of the tricyclic system **2** (Scheme 3). Before doing so, the β-positions of the ketones of **10** needed to be functionalized. Treatment of diketone **10** with trimethylsilyl trifluoromethanesulfonate and triethylamine led to bis(enol ether) **12**, which was converted to bis(α,β-unsaturated ketone) **13** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of 2,6-lutidine.[12] Facile 1,4-addition of ethanethiol from the α-face of **13** was promoted by DBU, affording **3** as a single diastereomer.

Samarium iodide[13] was successfully applied to the reductive transannular cyclization of the eight-membered ring into the 5/5-fused ring system, and simultaneously introduced the fully substituted C4- and C12-carbons (Scheme 3). Namely, treatment of bis(β-sulfide ketone) **3** with 4 equiv of SmI_2 in THF at 0 °C delivered the desired C_2-symmetric tricyclo[3.3.2.0^{2,6}]decane system **15** in quantitative yield. Next, the 1,2-diol of **15** was masked with acetonide under acidic conditions to afford **2**, the stereochemistries of which were unambiguously established by the physical data including an NOE between C2–H and the methyl group of the acetonide.[14] Therefore, the functionalized tricycle was synthesized from **5** in only 10 steps.

In summary, a concise route to the core tricyclic framework of ryanodine was developed by taking advantage of the C_2-symmetry of the intermediates. Key reactions of the synthesis include (i) the direct Diels–Alder reaction of 2,5-dimethylbenzene-1,4-diol to introduce two quaternary carbons (**5** + **6**→**7**); (ii) two-directional ring expansion (**9**→**10**); and (iii) SmI_2-mediated reductive cyclization to construct the two-tetrasubstituted carbons (**3**→**15**). Further studies toward the total synthesis of ryanodine will be reported in due course.

Acknowledgments

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14. *Physical data for* ***2***: IR (film) 2961, 2927, 2870, 1449, 1377, 1368, 1064, 792, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 1.19 (6H, s, H17, H20), 1.23 (6H, t, J = 7.5 Hz, SCH_2CH), 1.50 (6H, s, C(*CH*), 1.86 (2H, dd, J = 14.3, 9.2 Hz, H3, H11), 2.03 (2H, dd, J = 14.3, 8.6 Hz, H3, H11), 2.54 (4H, q, J = 7.5 Hz, SCH_2CH), 3.49 (2H, dd, J = 9.2, 8.6 Hz, H2, H6), 5.48 (2H, s, H14, H15); ^{13}C NMR (125 MHz, $CDCl_3$) 14.6 (CH_3), 15.3 (CH_3), 26.7 (CH_2), 28.3 (CH_3), 40.1 (CH_2), 55.35 (CH), 55.39 (C), 96.4 (C), 113.7 (C), 134.1 (CH); HRMS (ESI), calcd for $C_{19}H_{30}O_2S_2Na$ 377.1579 ($M+Na^+$), found 377.1581.