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Application of phenolic oxidation chemistry in synthesis: preparation of the BCE ring system of ryanodine

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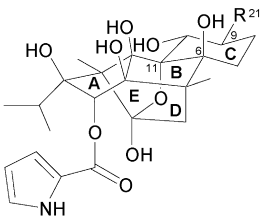
Abstract—A reaction sequence involving phenolic oxidation followed by singlet oxygen addition was used to assemble a model system containing the *trans*-fused, bridgehead oxygenated bicyclo[4.3.0] ring system found in the ryanoid group of natural products.

1. Introduction

Ryanodine (**1**) and 9,21-didehydroryanodine (**2**, Fig. 1), two natural products isolated from *Ryania speciosa vahl*, are the main active components of Ryania-derived insecticidal formulations, which were in use until a few years ago.[1,2] Their mode of action involves binding to intracellular calcium release channels known as ryanodine receptors.[3,4] Due to its strong interaction with this class of proteins, ryanodine remains a preferred probe for their study.



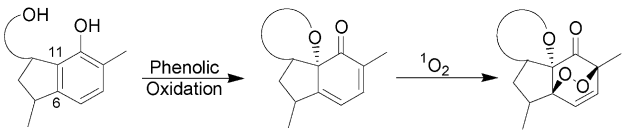
R = CH_3: Ryanodine (**1**)
R = CH_2: 9,21-Didehydroryanodine (**2**)

Figure 1. R=CH_3: ryanodine (**1**); R=CH_2: 9,21-didehydroryanodine (**2**).

Ryanodine's complex molecular structure comprising a highly oxygenated pentacyclic core with 11 contiguous stereocenters makes it a formidable target for organic synthesis. As a result, the only member of the ryanoid family that has succumbed to total synthesis is ryanodol, a saponification product of ryanodine.[5,6]

Preliminary inspection of ryanodine's structure led us to the conclusion that the *trans*-fused, bridgehead-oxygenated [4.3.0] bicycle comprising the B,C-ring system of the molecule presents one of the major synthetic challenges. Consequently, synthesis of this subunit became the focus of our initial investigations.

Ongoing studies in our laboratory led us to consider a phenolic oxidation/intramolecular trapping/singlet oxygen sequence to provide an appropriately functionalized intermediate possessing the correct relative stereochemistry at the bridgehead positions (see, C6 and C11 in Scheme 1).[7,8]



Scheme 1.

2. Results and discussion

To explore the hypothesis described above, we prepared a phenolic substrate (**5**) from 7-hydroxy-3,6-dimethyl-indan-1-one (**3**, Scheme 2), which was readily prepared from *o*-cresol following a literature procedure.[9] In the event, indanone **3** was treated with ethyl bromoacetate under Reformatsky conditions to form a β-hydroxyester addition product which, upon further heating, underwent dehydration and lactonization to afford lactone **4** in 62% isolated yield. Subsequent hydrogenation of **4** using Pearlman's catalyst furnished ester **5** as a single diastereomer in excellent yield. Saponification of the ester gave carboxylic acid **6** (93% yield) and set the stage for testing the phenolic oxidation chemistry.

Oxidation of phenol **6** with [bis(trifluoroacetoxy) iodo]-benzene (BTIB) led to formation of the intramolecular trapping product **7** (Scheme 3), albeit in a low 35% yield.[10]

Keywords: ryanodine; phenolic oxidation.
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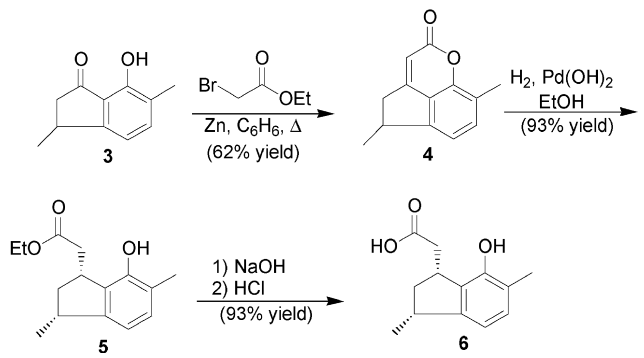
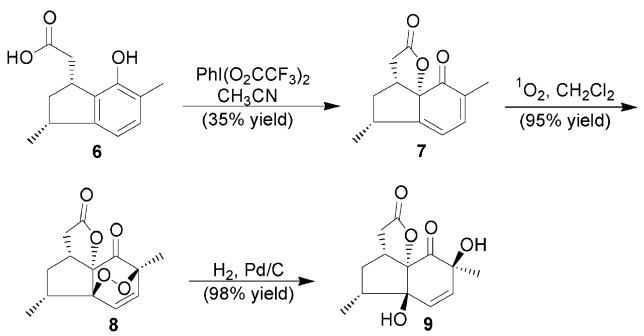


Scheme 2.



Scheme 3.

With this material in hand we tested the next oxidation in our sequential oxidation approach to the *trans*-fused oxygenated BC-bicyclic ring system of ryanodine. We were delighted to find that singlet oxygen oxidation of diene **7** led to the formation of a single diastereomeric endoperoxide (**8**) in excellent yield. Simple reduction of **8** with hydrogen in the presence of palladium on carbon furnished diol **9** (98% yield, Scheme 3).

The structure and relative stereochemistry of triol **9** was confirmed by X-ray crystallographic analysis (Fig. 2). As anticipated, singlet oxygen addition to diene **7** occurs on the face of the molecule opposite to that on which trapping in the phenolic oxidation step took place, thus producing the desired *trans* relationship between the angular groups at C6 and C11.[11]

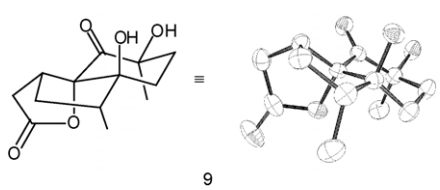
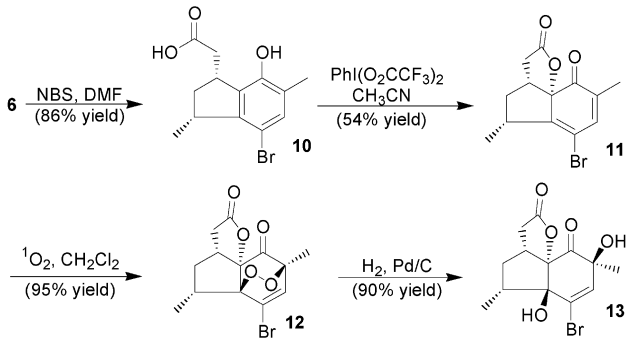


Figure 2.

Having demonstrated the feasibility of our synthetic approach, our attention turned to improving the low yielding phenolic oxidation step (i.e. **6** to **7**, Scheme 3).

Careful accounting for material in the oxidation step soon revealed the formation of an acetamide-containing product, a component that apparently arises from incorporation of acetonitrile at the *para* position.[12] Reasoning that this side reaction could be avoided by introducing a suitable blocking group we converted phenol **6** to bromophenol **10** using NBS in DMF (86% yield). As expected, treatment of this acid with BTIB produced **11** as the only isolable product (54% yield).[13] As before, singlet oxygen addition to **11** and exhaustive hydrogenation of the resulting endoperoxide (**12**) proceeded in excellent yields (95 and 90%, respectively) to deliver diol **13** (Scheme 3).

Diol **13** represents the complete right-hand portion of the ryanoid skeleton, with the α-hydroxyketone functionality providing an option for elaboration toward ryanodine (via deoxygenation) or 9,21-didehydroryanodine (via dehydration) (Scheme 4).



Scheme 4.

3. Conclusion

In summary, we report herein an efficient approach for the synthesis of *trans*-fused bridgehead-oxygenated [4.3.0]-bicycles similar to that found in ryanodine and 9,21-didehydroryanodine. The strategy employs a consecutive phenolic oxidation singlet oxygen addition sequence to deliver the desired relative stereochemistry. Efforts to extend this strategy toward a total synthesis of ryanodine are currently underway.

4. Experimental

4.1. Data for compounds

4.1.1. Lactone (±)-4. A solution of hydroxyindanone **3** (1.7 g, 9.6 mmol, 1 equiv.) and ethyl bromoacetate (5 mL, 7.6 g, 45.6 mmol, 4.75 equiv.) in benzene (10 mL) was added to a refluxing mixture of zinc (6.7 g, 102.7 mmol, 10.7 equiv.) and benzene (90 mL). The reaction mixture was allowed to reflux for 3 h, after which more ethyl bromoacetate (5 mL, 4.75 equiv.) and zinc (6.7 g, 10.7 equiv.) were added. After refluxing overnight, the reaction mixture was filtered and an equal volume of 1N HCl was added to the filtrate. The phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give a yellow oil (3.08 g). Column chromatography of this crude product (10:1 hexanes/EtOAc) afforded lactone **4** as a light yellow, crystalline solid (1.2 g, 6.0 mmol, 61.9% yield). Mp 73.2–74.4°C; FTIR (thin film/NaCl) 2959 (w), 2925 (w), 2870 (w), 1727 (s), 1613 (s), 1493 (w), 1361 (w), 1250 (w), 1112 (w), 1081 (w), 963 (w), 882 (w), 832 (w) cm^{-1}; ^1H NMR

(500 MHz, $CDCl_3$) δ 7.34 (d, J=7.6 Hz, 1H), 7.03 (d, J=7.6 Hz, 1H), 6.13 (t, J=1.7 Hz, 1H), 3.64 (m, 1H), 3.41 (ddd, J=1.8, 7.5, 19.0 Hz, 1H), 2.70 (ddd, J=1.8, 3.5, 19.1 Hz, 1H), 2.40 (s, 3H), 1.39 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 162.8, 149.2, 148.4, 134.9, 124.7, 122.3, 118.6, 107.4, 39.1, 38.7, 21.1, 14.1; HRMS (ESI) *m/z* found 201.0915 [calcd for $C_{13}H_{13}O_2$ (M+H) 201.0916].

4.1.2. Ethyl ester (±)-5. A mixture of lactone **4** (645 mg, 3.2 mmol, 1 equiv.), Pearlman's catalyst (22.5 mg, 0.16 mmol, 0.05 equiv.) and ethanol (15 mL) was pressurized under hydrogen (100 psi) and stirred overnight. Filtration through celite and concentration under reduced pressure yielded ethyl ester **5** as a pale yellow oil (750 mg, 3.0 mmol, 93% yield). FTIR (thin film/NaCl) 3316 (br m), 2957 (m), 2868 (m), 1706 (s), 1587 (m), 1480 (m), 1461 (m), 1449 (m), 1428 (m), 1376 (m), 1303 (m), 1260 (s), 1212 (s), 1029 (m), 1098 (w), 805 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.00 (d, J=7.6 Hz, 1H), 6.66 (d, J=7.6 Hz, 1H), 4.23 (q, J=7.2 Hz, 2H), 3.55 (m, 1H), 3.08 (m, 1H), 2.95 (dd, J=9.0, 17.5 Hz, 1H), 2.68 (dd, J=3.5, 17.4 Hz, 1H), 2.66 (ddd, J=8.3, 8.3, 12.7 Hz, 1H), 2.23 (s, 3H), 1.42 (ddd, J=5.6, 5.6, 12.8 Hz, 1H), 1.29 (t, J=7.2 Hz, 3H), 1.29 (d, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 151.4, 148.6, 130.2, 130.1, 123.1, 115.0, 61.6, 42.9, 41.7, 38.4, 37.6, 21.9, 15.9, 14.3; HRMS (FAB) *m/z* found 248.1413 [calcd for $C_{15}H_{20}O_3$ (M+) 248.1412].

4.1.3. Carboxylic acid (±)-6. A mixture of ester **5** (625 mg, 2.5 mmol, 1 equiv.), 1N NaOH (3 mL, 3 mmol, 1.2 equiv.), and H_2O (3 mL) was allowed to stir overnight. After washing once with Et_2O, the reaction mixture was brought to pH 6 with 1N HCl and extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to yield acid **6** as a colorless solid (513 mg, 2.3 mmol, 93% yield). Mp 143–144°C; FTIR (thin film/NaCl) 3516 (m), 2988 (m), 2947 (m), 2867 (m), 1699 (s), 1478 (w), 1448 (w), 1398 (w), 1285 (w), 1232 (w), 1199 (w), 1105 (w), 920 (w), 799 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (br s, 1H), 7.01 (d, J=7.5 Hz, 1H), 6.69 (d, J=7.5 Hz, 1H), 6.43 (br s, 1H), 3.60 (m, 1H), 3.17 (dd, J=7.5, 17.4 Hz, 1H), 3.11 (m, 1H), 2.66 (dd, J=5.2, 17.4 Hz, 1H), 2.66 (ddd, J=8.2, 8.2, 12.8 Hz, 1H), 2.23 (s, 3H), 1.43 (ddd, J=6.4, 6.4, 12.8 Hz, 1H), 1.30 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.5, 151.0. 148.9, 130.3, 130.0, 122.2, 115.4, 42.6, 40.6, 38.4, 37.8, 21.5, 15.7; HRMS (FAB) *m/z* found 220.1099 [calcd for $C_{13}H_{16}O_3$ (M+) 220.1099].

4.1.4. Diol (±)-9 from 6. *Phenolic oxidation*. A solution of acid **6** (74 mg, 0.34 mmol, 1 equiv.) and bis(trifluoroacetoxy)iodobenzene (202 mg, 0.47 mmol, 1.4 equiv.) in CH_3CN (5 mL) was allowed to stir for 45 min, after which the reaction mixture was concentrated in vacuo and subjected to flash chromatography (5:1 hexanes/EtOAc) to yield diene **7** (22 mg, 0.10 mmol, 30% yield) which was used directly in the next step.

Singlet oxygen addition. A solution of diene **7** (8 mg, 0.036 mmol, 1 equiv.) and a trace of methylene blue in $CDCl_3$ (3 mL) was cooled to 0°C. A stream of oxygen was passed through the solution while subjecting it to irradiation with a 650 W Sylvania tungsten halogen lamp for 20 min. Removal of the sensitizer by addition of charcoal and filtration through celite, followed by concentration under reduced pressure afforded peroxide **8** (8.5 mg, 0.034 mmol, 95% yield), which was immediately reduced to diol **9**.

Reduction. A mixture of peroxide **8** (8 mg, 0.032 mmol, 1 equiv.), palladium on carbon (trace), and deuterochloroform (2 mL) was allowed to stir under hydrogen for 3 h. Filtration through celite and concentration under reduced pressure yielded diol **9** as a crystalline solid (8 mg, 0.031 mmol, 98% yield).

4.1.5. Bromoacid (±)-10. NBS (61 mg, 0.35 mmol, 1 equiv.) was added to a solution of acid (±)-**6** (76 mg, 0.35 mmol, 1 equiv.) in DMF (4 mL). After stirring overnight, Et_2O was added, and the reaction mixture was washed with 1N HCl (2×) and H_2O (1×). After drying over Na_2SO_4, the solution was concentrated under reduced pressure to yield bromoacid **10** as a crystalline solid (91 mg, 0.30 mmol, 86% yield). Mp 137–140°C; FTIR (thin film/NaCl) 3196 (m), 2962 (m), 2870 (m), 1701 (s), 1572 (w), 1471 (m), 1447 (m), 1407 (m), 1313 (m), 1271 (m), 1248 (m), 1202 (s), 1023 (w), 908 (m), 869 (w), 816 (w), 792 (w), 734 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (br s, 1H), 7.13 (s, 1H), 3.64 (ddd, J=4.0, 9.1, 9.1 Hz, 1H), 3.25 (m, 1H), 2.98 (dd, J=9.1, 18.4 Hz, 1H), 2.84 (dd, J=4.1, 18.3 Hz, 1H), 2.69 (ddd, J=9.1, 9.1, 13.3 Hz, 1H), 2.19 (s, 3H), 1.62 (app d, J=13.3 Hz, 1H), 1.36 (d, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl???δ 180.6, 150.5, 146.9, 133.4, 131.8, 125.6, 109.2, 42.3, 41.1, 40.5, 37.9, 21.5, 15.7; HRMS (ESI) *m/z* found 297.0125 [calcd for $C_{13}H_{15}BrO_3$ (M+) 297.0126].

4.1.6. Diol 13 from 10. *Phenolic oxidation*. To a cooled (0°C), stirred solution of acid **10** (71 mg, 0.24 mmol, 1 equiv.) in CD_3CN (3 mL) was added a solution of bis(trifluoroacetoxy)-iodobenzene (123 mg, 0.29 mmol, 1.2 equiv.) in CD_3CN (2 mL). After 30 min, the reaction was filtered through a mixture of $NaHCO_3$ and SiO_2, and then concentrated under reduced pressure. Flash chromatography (5:1 hexanes/EtOAc) of the resulting yellow oil yielded diene **11** (38 mg, 0.13 mmol, 54% yield) which was immediately used in the next reaction.

Singlet oxygen addition. A solution of diene **11** (38 mg, 0.13 mmol, 1 equiv.) and a trace of methylene blue in $CDCl_3$ (5 mL) was cooled to 0°C. A stream of oxygen was passed through the solution while subjecting it to irradiation with a 650 W Sylvania tungsten halogen lamp for 20 min. Removal of the sensitizer by addition of charcoal and filtration through celite, followed by concentration under reduced pressure afforded peroxide **12** (40 mg, 0.12 mmol, 95% yield), which was immediately reduced to diol **13**.

Reduction. A mixture of endoperoxide **12** (20 mg, 0.06 mmol, 1 equiv.), palladium on carbon (trace), and deuterochloroform (2 mL) was allowed to stir under hydrogen overnight. Filtration through celite and concentration under reduced pressure yielded diol **13** as a crystalline solid (14 mg, 0.06 mmol, 90% yield). Mp 166.6–169.3°C; FTIR (thin film/NaCl) 3429 (br m), 2967

(w), 2934 (w), 2876 (w), 1780 (s), 1725 (m), 1449 (w), 1224 (m), 1112 (s), 1062 (w), 1022 (m), 988 (m), 912 (m), 888 (w), 847 (w) cm^{-1}; ^1H NMR (500 MHz, CDCl3) δ 3.38 (ddd, J=4.7, 7.9, 10.8 Hz, 1H), 2.87 (dd, J=7.9, 17.7 Hz, 1H), 2.85 (ddd, J=9.5, 10.9, 14.5 Hz, 1H), 2.42 (d, J=17.8 Hz, 1H), 2.09–2.31 (m, 4H), 1.83 (ddd, J=2.4, 4.8, 14.0 Hz, 1H), 1.53 (s, 3H), 1.19 (ddd, J=2.4, 4.7, 14.4 Hz, 1H), 1.08 (d, J=7.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1, 174.8, 96.5, 86.2, 76.8, 45.0, 39.3, 37.4, 36.3, 36.1, 27.6, 26.2, 17.9; HRMS (CI) m/z found 255.1231 [calcd for $C_{13}H_{19}O_5$ (M+H) 255.1232].

Acknowledgements

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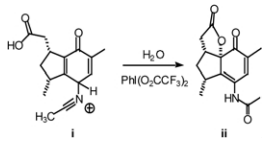
10. The low isolated yield is due to instability of **7** to chromatographic purification.
11. The only comparable reaction sequence that we are aware of occurs in Danishefsky's elegant work towards the total synthesis of lactonamycin, see: Cox, C.; Danishefsky, S. *J. Org. Lett.* **2000**, *2*, 3493.
12. Although the structure of this product has yet to be fully delineated, spectroscopic evidence is consistent with **ii**, a product derived from acetonitrile adduct **i**



13. Isolation of **11** also proved problematic due to decomposition upon chromatographic purification; thus the yield for this tranforation was estimated based on ^1H NMR analysis.