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Synthesis and Endothelin Receptor Binding Activity of Synthetic Analogues of RES-1149-2

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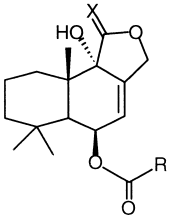
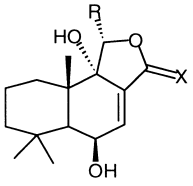
Abstract—A direct synthesis of analogues **6** and **7** is described. The key transformations are the addition of dibromomethyl lithium to a ketone and the subsequent mild hydrolysis to a hemiacetal.

Drimane sesquiterpenes have been reported to exhibit a broad range of useful biological activities, including anticancer, antiviral and anti-inflammatory activity. RES-1149-2 (**1**) and related lactols **2** and **3** were isolated from the fungus *Aspergillus ustus* var. *pseudoflectus* in 1995.[1] Pereniporin A (**4**) and B (**5**) were isolated as metabolites from microorganisms *Perreniporia medullaepanis* Aj 8345.[2] Compounds **1**–**3** exhibit endothelin receptor binding activity at the μg/mL level in the rabbit ETA assay and at the μg/mL level in the human ETA assay. Alcohols **4** and **5** show antibiotic activity against *Bacillus subtilis* Aj 1316 and exhibit cytotoxicity against the Friend leukemia virus at the μg/mL level.



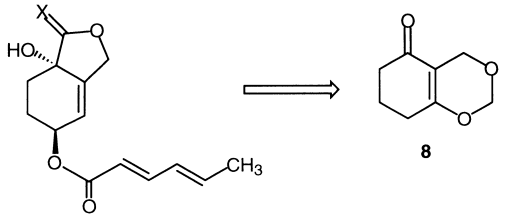


1: X=O, R= CH=CHCH=CHCH=CHCH$_3$
2: X=H, OH, R= CH=CHCH=CHCH=CHCH$_3$
3: X=H, OH, R= CH=CHCH=CHCH$_3$

4: R=OH, X=H,H
5: R=H, X=O

Syntheses and synthetic approaches to pereniporin A and B have been reported. Urones and co-workers prepared **4** by modifying 12-acetoxy-7,9(11)-drimadiene.[3] Burke and co-workers synthesized **5** via a clever vinyl silane intermediate.[4] Vidari and co-workers converted cinnamodial into **4**.[5] Mori and Takaishi produced both **4** and **5** by a 33-step synthesis from (*S*) 3-hydroxy-2,2-dimethylcyclohexanone.[6] However, no synthesis or synthetic approaches to **1**–**3** have been communicated. As part of a program to identify and synthesize sesquiterpene antiviral agents that exert useful biological activity,[7] we have developed direct preparations of analogues **6** and **7** from ketone **8**. Compounds **6** and **7** represent bicyclic analogues that possess most of the key functionality contained in compounds **1**–**3**.

The key transformation is the direct installation of the hemiacetal and lactone carbonyl carbon atom via the addition of dibromomethyl lithium followed by the high-yield conversion of the dibromomethyl group into a lactol. The hydrolysis of dibromomethyl groups to aldehydes has been reported to proceed in modest yield. We attribute the successful conversion to neighboring group participation by the alkoxide of the primary allylic alcohol.



6: X= H, OH **7**: X=O

The synthetic route begins with bicyclic ketone **8**, readily available from 1.3-cyclohexanedione and formaldehyde.[8] Ketone **8** was converted into silyl ether **9** in 83% yield over two steps by treatment with lithium diisopropylamide (LDA) and trimethylchlorosilane at −20 °C followed by oxidation with MCPBA. Desilylation using potassium carbonate in methanol provided alcohol **10**. The reaction of **9** with LAH followed by

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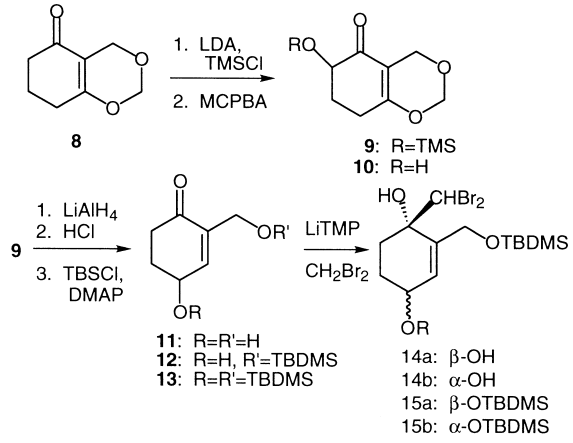
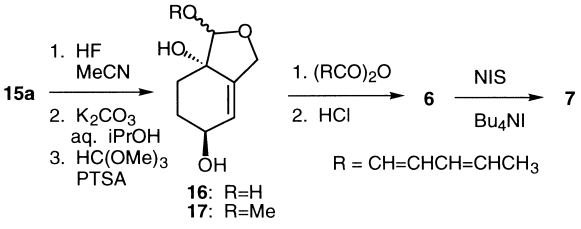
work up with 3 N HCl afforded diol **11** in 73% yield by a sequence involving reduction of the ketone and acid-mediated rearrangement. Monosilylation of diol **11** using **1** equiv of *tert*-butyldimethylchlorosilane (TBSCl) with triethylamine and dimethylaminopyridine in methylene chloride generated alcohol **12** in 87% yield. Monosilylation favored the less sterically hindered alcohol. The use of 2 equiv of TBSCl provided **13**. The reaction of **12** with dibromomethyl lithium, prepared by a modification of Taguchi's procedure,[9] at −78 °C provided a 91% yield of **14a** and **14b** in a ratio of 1.5:1. The addition of dibromomethyl lithium to **13** provided **15a** and **15b** in 91% yield in a 15:1 ratio of diastereomers.



The reaction of **15a** and **15b** with HF in acetonitrile afforded a triol in 97% yield that, without purification, was treated with potassium carbonate in aqueous isopropanol to afford lactol **16** in 93% yield. The excellent yield in the hydrolysis of the dibromomethyl group is likely due to neighboring group participation from the alkoxide of the primary allylic alcohol. The reaction of **16** with trimethyl orthoformate and a catalytic amount of PTSA produced diols **17** in 86% yield as a 3:1 mixture at the anomeric center.



The acylation of diol **17** using either the acid chloride of sorbic acid or sorbic acid and dimethylaminopyridine produced the desired ester along with elimination products and some aromatized products. However, the reaction of **17** with the anhydride of sorbic acid and triethylamine and dimethylaminopyridine in methylene chloride at 0 °C gave the ester **18** in 75% yield which could be hydrolyzed to hemiacetal **6** in 88% yield using aqueous HCl in THF at 50 °C. Compound **6** was a single stereoisomer. Lactone **7** was synthesized from **6** using *N*-iodo succinimide (NIS) and tetrabutylammonium iodide in 91% yield.

Table 1. The IC_{50} values of natural products and analogues

Compound	Rabbit ET_A (μM)	Rabbit ET_B (μM)	Human ET_A (μM)	Human ET_B (μM)
1	155	50	135	73
2	65	21	62	41
3	50	70	>250	148
6			2.5	>25
7			2.6	>25
18			8.2	>25

The binding activity of analogues **6**, **7**, and **18** is depicted above in Table 1. All three compounds exhibit substantial endothelin receptor binding activity in the human ETA assay. Interestingly, the analogues appear to be more effective than the natural products at the ETA receptor.[10]

The direct synthesis of **6** and **7** illustrates the synthetic utility of the dibromomethyl lithium addition/hydrolysis sequence.[11] The mild methodology for the introduction of a hemiacetal carbon should have broad utility in synthesis. Analogues **6** and **7** may stimulate the development of novel synthetic probes for the endothelin receptor site, since a majority of the endothelin receptor antagonists that have been reported are peptide-based compounds. In recent years a number of heterocyclic aromatic endothelin receptor antagonists have also been developed.[12]

Acknowledgements

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10. Table 1 compares results from two different research groups.
11. Experimental and spectra: To a solution of ketone (10 mmol) and CH_2Br_2 (50 mmol) in THF (50 mL), 3 to 5 equiv of LiTMP (30 mmol, prepared from tetramethylpiperidine (4.23 g, 30 mmol) and *n*-butyllithium (12 mL of 2.5 M solution in hexanes)), were added slowly at −78 °C. The reaction was stirred at −78 °C for 3 h and monitored by TLC. Saturated NH_4Cl solution (15 mL) was added at −78 °C. The mixture was then extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by sgc, eluting with hexanes and ethyl acetate, to give dihalomethyl carbinol. To the dihalomethyl carbinol (100 mg) in a mixture of *i*-PrOH (5 mL) and water (5 mL), K_2CO_3 (100 mg) was added. It was stirred at rt for 1 to 12 h (TLC). The *i*-PrOH was removed in vacuo. The aqueous solution was saturated with NaCl and extracted with ethyl acetate. The organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by sgc (eluting with hexanes and ethyl acetate) to give the lactol. **16**: ^{1}H NMR (acetone-d_6, δ): 5.64 (s, 1H), 5.10 (m, 1H), 4.2–4.5 (m, 3H), 3.5–3.9 (m, 3H), 2.0 (m, 2H). ^{13}C NMR (acetone-d_6, δ): 140.8, 128.3, 123.2, 102.9, 75.9, 67.6, 27.0, 23.9. IR (neat) cm^{-1}: 3540, 1627, 1604. MS *m*/*z* (CI): 172, 154. HRMS *m*/*z* (M−H_2O): 154.0631 for $C_8H_{10}O_3$: 154.0630. **6**: ^{1}H NMR ($CDCl_3$, δ): 7.12–7.29 (m, 1H), 6.13–6.19 (m, 2H), 5.75 (dd, *J* = 15, 1.5 Hz, 2H), 5.49 (d, *J* = 16 Hz, 1H), 5.26 (s, 1/2H), 4.93 (s, 1/2H), 4.59 (dt, *J* = 16, 2.4 Hz, 1H), 4.34 (dt, *J* = 16, 2.4 Hz, 1H), 1.5–2.0 (m, 4H). ^{13}C NMR ($CDCl_3$, δ): 167.1, 145.8, 142.5, 140.1, 129.8, 123.4, 118.8, 102.4, 76.4, 70.3, 67.5, 29.7, 24.0, 18.8. IR (neat) cm^{-1}: 3450, 3368, 2959, 2921, 1716, 1616, 1558, 1539 ,1050, 1018. MS *m*/*z* (CI–NH_3): 252, 110.
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