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Enantioselective synthesis of rumphellaone A via epoxy nitrile cyclization

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ABSTRACT

The first enantioselective synthesis of rumphellaone A, a cytotoxic 4,5-*seco*-caryophyllane derivative incorporating a γ-lactone ring as its structural feature, has been achieved by using base-induced intramolecular cyclization of an epoxy nitrile intermediate to install its cyclobutane skeleton as well as three contiguous stereocenters as the key transformation.

Rumphellaone A (**1**), recently isolated from the gorgonian coral *Rumphella antipathies* by Chung and co-workers as a cytotoxin with moderate activity against CCRF-CEM tumor cells (IC_{50} = 12.6 μg/mL),[1] belongs to a small family of natural products known as 4,5-*seco*-caryophyllanes, which consists of only four compounds including **1** (Fig. 1). Unlike the other three members of this family,[2] which are merely oxidative cleavage products of caryophyllene at the C4–C5 double bond such as **2**, rumphellaone A (**1**) is characterized by the presence of a γ-lactone ring which might possibly be derived biosynthetically from **2** via acid-catalyzed lactonization. In contrast to a considerable number of synthetic studies on caryophyllane-type natural products,[3] no report on the synthesis of the 4,5-*seco* congeners has appeared in the literature, which prompted our synthetic efforts toward this class of natural products. In this letter, we describe the first enantioselective synthesis of **1** using epoxy nitrile cyclization as the key transformation.

Our retrosynthetic analysis of **1** is shown in Scheme 1. We envisaged that the keto lactone **1** would be obtainable by chain elongation at both the C2 and C7 positions of **3**. To construct the cyclobutane ring of **3**, we planned to apply Stork's epoxy nitrile cyclization protocol to optically active epoxide **4**, which might simultaneously be able to install the three contiguous stereogenic centers appropriately. The epoxide **4** would be prepared by the Sharpless asymmetric epoxidation of **5**, which in turn should readily be accessible from known olefinic alcohol **6**.

According to the synthetic plan, the known compound **6**,[4] prepared in two steps from methyl isobutylate by its allylation and subsequent reduction, was converted into nitrile **8** via the corresponding tosylate **7** (Scheme 2).[5] Ozonolytic cleavage of the double bond of **8** afforded **9**, which was then subjected to the Wittig chain elongation to give **10** in a 51% overall yield from **6** after chromatographic removal of the corresponding *Z* isomer from the crude reaction product (*E*/*Z* = 8.3:1). The ester **10** was reduced to **5**, and the allylic alcohol was exposed to the Sharpless asymmetric epoxidation conditions to provide **11** with 92% enantiomeric excess, as judged by ^{1}H NMR analyses of the corresponding (*R*)- and (*S*)-MTPA esters. After protection of **11** as its TBS ether **12**, the product was treated with NaHMDS in refluxing toluene for 2.5 h to give a >20:1 mixture of **13** and its C1-epimer in an excellent yield of 90%.[6] This epoxy nitrile cyclization, when conducted at 0 °C and quenched after 40 min, gave a mixture of the starting material **12**, the desired product **13** and its C1-epimer in a ratio of 7:1:1. This means that the highly stereoselective formation of **13** was due to its thermodynamic stability, which was supported by our observation that a mixture of **13** and its C1 epimer converged into **13** upon exposure to the same cyclization conditions (NaHMDS in refluxing toluene).[7] After protection of **13** as its TMS ether **14**, the product was reduced with DIBAL to afford the aldehyde **15**, the Horner–Wadsworth–Emmons olefination of which gave enone **16**. Removal of its two silyl protecting groups

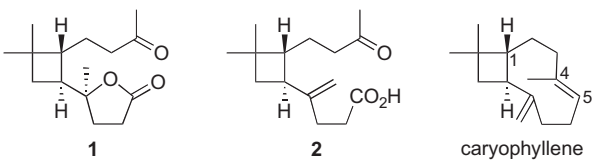

Figure 1. Structures of rumphellaone A (**1**) and related natural products.

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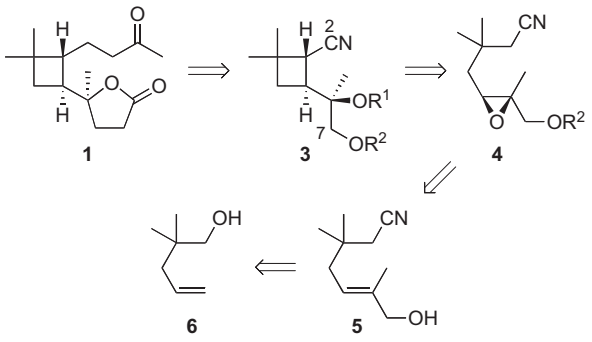
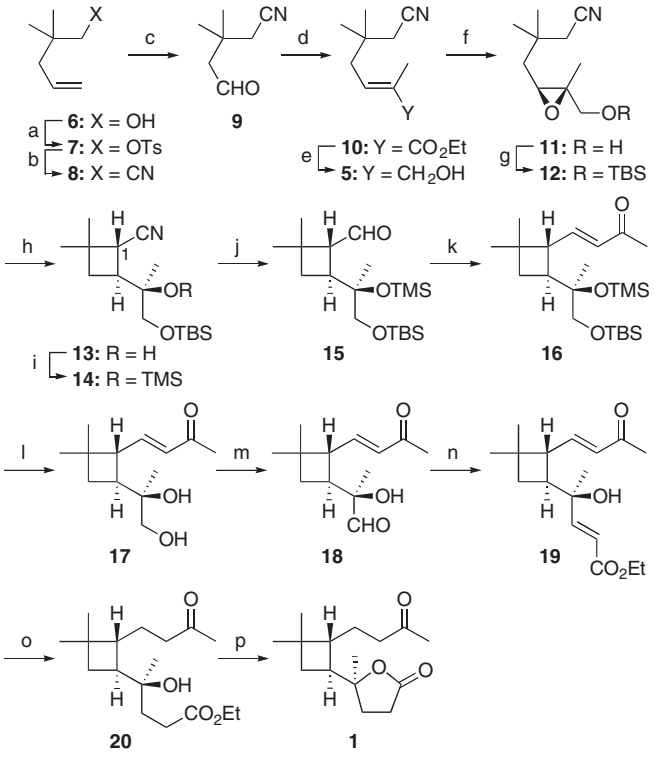


Scheme 1. Retrosynthetic analysis of **1**.



Scheme 2. Synthesis of **1**. Reagents and conditions: (a) TsCl, Et_3N, $Me_3N{\cdot}HCl$, CH_2Cl_2, 0 °C to rt, 18 h; (b) NaCN, DMSO, 150 °C, 19.3 h; (c) O_3, $NaHCO_3$, CH_2Cl_2/MeOH, −78 °C, 2 h, then Me_2S, −78 °C to rt, overnight; (d) $Ph_3P{=}C(Me)CO_2Et$, THF, 40 °C, 20.2 h (51% from **6**); (e) DIBAL, CH_2Cl_2, −78 to −30 °C, 4 h; (f) TBHP, Ti(O*i*-Pr)$_4$, L-(+)-DIPT, CH_2Cl_2, −20 °C, 17.3 h (64% from **10**); (g) TBSCl, imidazole, DMF, 0 °C to rt, 1.5 h (96%); (h) NaHMDS, PhMe, reflux, 2.5 h (90%); (i) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 45 min (80%); (j) DIBAL, CH_2Cl_2, −20 °C to rt, 25 h (85%); (k) $MeCOCH_2PO(OMe)_2$, NaH, DME, rt, 5 d (84%); (l) TBAF, THF, rt, 1 h (84%); (m) $SO_3{\cdot}Py$, $EtN(i\text{-}Pr)_2$, DMSO, rt, 55 min (83%); (n) $Ph_3P{=}CHCO_2Et$, THF, 50 °C, 3 h (71%); (o) H_2, 10% Pd/C, MeOH, rt, 1.7 h (87%); (p) CSA, CH_2Cl_2, rt, 15 min (73%).

followed by oxidation of the resulting diol **17** furnished **18**. The aldehyde **18** was then treated with $Ph_3P{=}CHCO_2Et$ to give **19**, the catalytic hydrogenation of which proceeded uneventfully to give **20**. Finally, the hydroxy ester was exposed to acidic conditions (CSA in CH_2Cl_2) to provide the target molecule **1**, the ^1H and ^{13}C NMR spectral data of which showed good agreement with those of the natural product.[1,8] The synthetic material shared the same sign of specific rotation as the natural rumphellaone A, although they were significantly different in the magnitude of specific rotation [observed data for the synthetic sample, $[\alpha]_D^{30}$ +75.8 (*c* 1.11, $CHCl_3$); reported data for natural rumphellaone A, $[\alpha]_D^{25}$ +257 (*c* 0.014, $CHCl_3$)].[9]

In conclusion, the first enantioselective total synthesis of rumphellaone A (**1**), featuring the epoxy nitrile cyclization of **12** to install the cyclobutane ring as well as the three contiguous stereogenic center (C1, C8, and C9), has been achieved in 16 steps from known olefinic alcohol **6**. Synthesis of other 4,5-*seco*-caryophyllanes and caryophyllane-related natural products is now underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.145.

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7. When treated with LDA/HMPA in THF at rt for 1 h, **12** was consumed completely and gave a 5:4 mixture of **13** and its C1-epimer, which was employed for the equilibration experiment. For the NMR spectral data of **13** and its C1-epimer, see Supplementary data.
8. *Physical and spectral data for* **1**: $[\alpha]_D^{30}$ +75.8 (*c* 1.11, $CHCl_3$) (lit.[1] $[\alpha]_D^{25}$ +257 (*c* 0.014, $CHCl_3$); IR n_{max} 1765 (vs), 1713 (s), 1248 (m), 1161 (m), 936 (m); ^1H NMR (400 MHz, $CDCl_3$) *d* 1.04 (3H, s), 1.07 (3H, s), 1.32 (3H, s), 1.43 (1H, br t, *J* = 10.3 Hz), 1.57 (1H, dd, *J* = 10.7, 8.7 Hz), 1.64–1.70 (2H, m), 1.82–1.93 (2H, m), 1.99–2.09 (2H, m), 2.13 (3H, s), 2.37 (2H, br t, *J* = 7.7 Hz), 2.54 (1H, ddd, *J* = 18.2, 10.0, 5.1 Hz), 2.64 (1H, ddd, *J* = 18.2, 9.7, 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *d* 22.5, 24.9, 25.1, 29.1, 29.9, 30.6, 30.9, 33.0, 33.5, 42.0, 44.2, 44.5, 87.2, 177.0, 208.6; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{25}O_3$ ($[M+H]^+$) 253.1804, found 253.1805.
9. The enantiomeric excess of our synthetic material (**1**) is considered to be 92% since that of the intermediate **11** was evaluated to be 92% by the Mosher ester analysis and no reaction affecting the enantiomeric excess was employed in the sequence from **11** to **1**. At present, we are unable to account for the difference in the magnitude of specific rotation, but the discrepancy might be ascribable to the very low concentration (*c* 0.014) of the natural material employed for the measurement of the specific rotation or to the presence of some impurity with a very high rotation value either in the natural or in the synthetic sample. For ^1H and ^{13}C NMR spectra of our synthetic material, see Supplementary data.