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A Convenient Method for Synthesis of Novel Cyclic Ethers (1R, 2R, 3R, 5S, 7S, 9R, 12R)-3-(*t*-Butyldimethylsilyl)oxy-7-methoxymethyl-oxy-2, 10-dimethyl-12-oxatricyclo [7.2.1.0^{5,12}] dodecane

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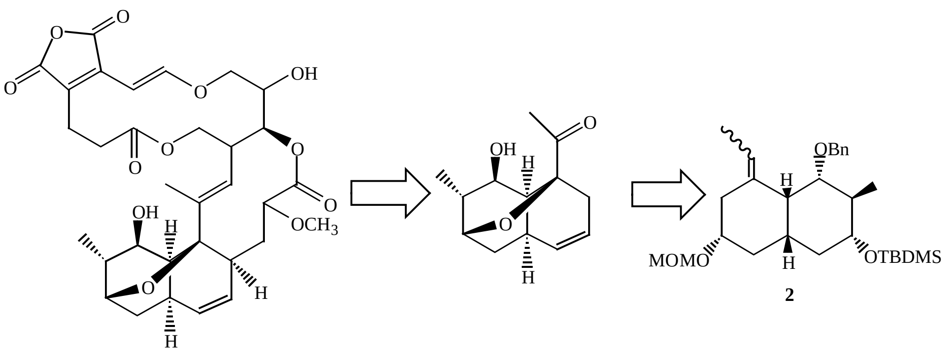
Abstract: Novel cyclic esters (1R, 2R, 3R, 5S, 7S, 9R, 12R)-3-(*t*-butyldimethylsilyl)oxy-7-methoxymethyloxy-2, 10-dimethyl-12-oxatricyclo [7.2.1.0^{5,12}] dodecane were prepared when their precursor **1** was treated with $SOCl_2$/pyridine. A plausible mechanism was hypothesized.

Keywords: (1R, 2R, 3R, 5S, 7S, 9R, 12R)-3-(*t*-Butyldimethylsilyl)oxy-7-methoxymethyloxy-2, 10-dimethy-12-oxatricyclo [7.2.1.0^{5,12}] dodecane, synthesis, mechanism.

Coloradocin, a novel macrolide antibiotic from cultures of *Actinoplanes coloradoensis*[1] exhibits activity against pathogenic anaerobic and microaerophilic species[2]. Because its low toxicity and substantial oral activity[3, 4], as well as its unusual structure[5], several research groups initiated approaches towards the synthesis of coloradocin[6], which culminated in the synthesis of 18-deoxynargenicin A_1 by Kallmerten *et al*.[7].

Scheme 1



Coloradocin

2

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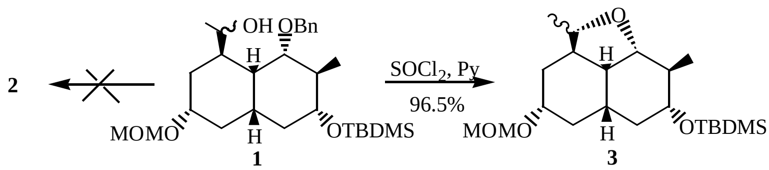
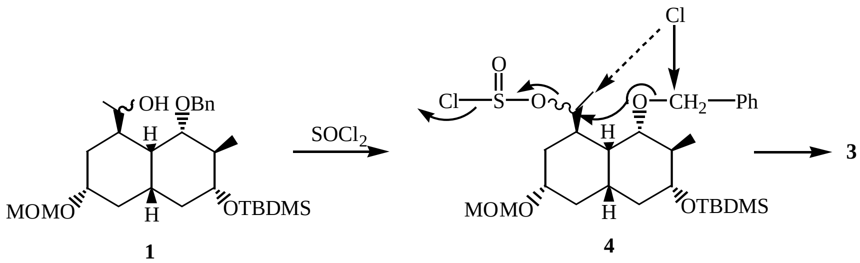
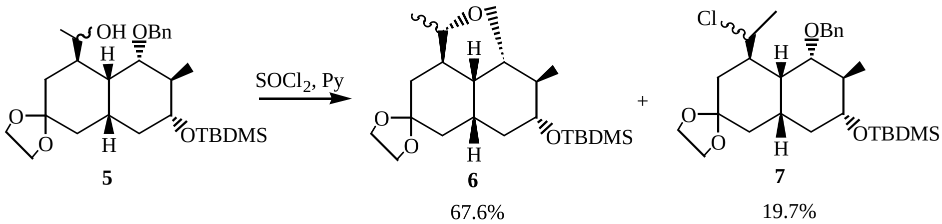
Scheme 2



Scheme 3



Scheme 4



In order to synthesize the oxygen bridged decalin subunit of coloradocin **2 (Scheme 1)**, we prepared (1R, 2S, 3R, 4R, 6R, 8S, 10R)-2-benzyloxy-4-(*t*-butyldimethylsilyl)oxy-10-(1-hydroxyethyl)-8-methoxymethyloxy-2-methyl [4.4.0] decane **1**[8] as starting material. We found when **1** was treated with $SOCl_2$/pyridine in short time at 0℃, this result was different from that obtained by Geossinger[9], novel diastereomeric mixture of cyclic ethers (1R, 2R, 3R, 5S, 7S, 9R, 12R)-3-(*t*-butyldimethylsilyl)-oxy-7-methoxymethyloxy-2, 10-dimethy-12-oxatricycl [7.2.1.$0^{5,12}$] dodecane **3** (ratio 60:40 by ^{1}H-NMR) were the only products in 96.5% yield, but not the desired olefine **2 (Scheme 2)**.

The unusual result was exciting because the normal method for preparation of cyclic ethers was the intramolecular reaction of hydroxyl and alkene functions[9-12], this method for cyclic ethers had not been reported before. A plausible mechanism was as follows: when **1** was treated with $SOCl_2$, the intermediate **4** was formed, then Cl^- attacked the benzyl group, following an intramolecular substitution to give product **3.** Cl^- hardly attacked the leaving group directly, because benzyloxy group blocked the attack route **(Scheme 3)**.

In order to prove above mechanism, we prepared compound **5**[8] and treated it with $SOCl_2$/pyridine in the same reaction conditions. After workup we got the desired major product **6**[8] and also separated the minor chloride **7**[8] (**Scheme 4**).

General procedure for the synthesis of compounds **3**:

Under argon atmosphere, 5 µL freshly distilled $SOCl_2$ (0.058 mmol) was added in 0.5 mL dry pyridine and the mixture was cooled to 0℃. A solution of 5.5 mg **1** (0.0116 mmol) in 1 mL dry pyridine was added slowly. After the addition was completed the mixture was stirred for 0.5 h at 0℃. The reaction was quenched with sat. aq $NaHCO_3$, the water layer was extracted with ethyl acetate, the combined organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation the crude product was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate (5:1) to afford 4.1 mg (96.5 %) inseparable two diastereomers **3** (ratio 60:40) as colorless oil. ^{1}H-NMR (400MHz, $CDCl_3$, δ_{ppm}): -0.003 (s, 3H); 0.00 (s, 3H); 0.91 (s, 9H); 1.16 (d, 3H, *J*=5.8Hz); 1.22 (d, 3H, *J*=6.3Hz); 1.41-1.49 (m, 2H); 1.55-1.69 (m, 4H); 1.78 (d, 1H *J*=4.1Hz); 1.92-2.03 (m, 2H); 2.09 (dd, 1H, *J*=22.5, 11.1Hz); 2.94 (dd, 1H, *J*=10.3, 3.5Hz); 3.04 (s, 3H); 3.46-3.56 (m, 2H); 3.65-3.69 (m, 1H); 4.31 (d, 1H, *J*=6.8Hz); 4.35 (d, 1H, *J*=6.8Hz); IR (film, cm^{-1}): 2930, 2910, 2850; EI-MS (3KV, *m/z*): 384 (M^+, 100); HRMS: Calcd. for $C_{21}H_{40}O_4Si$ =384.6366, found M^+ =384.6334.

References and Notes

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8. Spectral data: **1**: ^{1}H-NMR (400MHz, $CDCl_3$, δ ppm): 0.00 (s, 6H); 0.85 (s, 9H); 0.97 (d, 3H, *J*=6.3Hz); 1.15 (d, 3H, *J*=6.3Hz); 1.46-1.54 (m, 2H); 1.58-1.86 (m, 5H); 1.97-2.14 (m, 1H); 2.40 (ddd, 1H, *J* =11.6, 4.3, 4.3Hz); 2.85 (dd, 1H, *J*=11.1, 4.8Hz); 3.00 (ddd, 1H, *J*=17.8, 9.8, 4.5Hz); 3.07 (ddd, 1H, *J*=12.0, 12.0, 3.0Hz); 3.10-3.17 (m, 1H); 3.31(s, 3H); 3.73 (b, 1H); 3.86-3.90 (m, 1H); 4.01 (d, 1H, *J*=11.1Hz); 4.35 (d, 1H, *J*=11.1Hz); 4.52 (d, 1H, *J*=6.6Hz); 4.60 (d, 1H, *J*=6.8Hz); 7.23-7.29 (m, 5H). IR (film, cm^{-1}): 3385, 3020, 2950. EI-MS (3KV, *m/z*): 493 (M^+, 35.7). HRMS: Calcd. for $C_{28}H_{48}O_5Si$ =492.7632, found M^+ =492.7601. **5**: ^{1}H-NMR (400MHz, $CDCl_3$, δ ppm): 0.00 (s, 3H); 0.01 (s, 3H); 0.85 (s, 9H); 0.98 (d, 3H, *J*=6.3Hz); 1.07 (d, 3H, *J*=6.3Hz); 1.14 (dd, 1H, *J*=13.8, 13.8Hz); 1.42 (d, 1H, *J*=13.6Hz); 1.61 (d, 1H, *J*=12.9Hz); 1.71-1.87 (m, 4H); 1.91-1.99 (m, 1H); 1.99-2.13 (m, 2H); 3.03 (dd, 1H, *J*=11.2, 3.7Hz); 3.05-3.12 (m, 1H); 3.82-3.96 (m, 5H); 4.35 (b, 1H); 4.46 (d, 1H, *J*=11.6Hz); 4.72 (d, 1H, *J*=11.4Hz); 7.27-7.31 (m, 5H). IR (film, cm^{-1}): 3420, 3032, 2950. EI-MS (3KV, *m/z*): 491 (M^+, 48.6). HRMS: Calcd. for $C_{28}H_{46}O_5Si$ =490.7473, found M^+ =490.7434. **6:** ^{1}H-NMR (400MHz, $CDCl_3$, δ ppm): -0.001 (s, 3H); 0.00 (s, 3H); 0.90 (s, 9H); 1.16 (d, 3H, *J*=5.8Hz); 1.23 (d, 3H, *J*=6.3Hz); 1.43-1.52 (m, 2H); 1.55-1.65 (m, 4H); 1.75 (d, 1H *J*=4.1Hz); 1.96-2.03 (m, 2H); 2.09 (dd, 1H, *J*=21.5, 11.0Hz); 2.94 (dd, 1H, *J*=10.3, 3.5Hz); 3.08 (s, 3H); 3.53-3.60 (m, 2H); 3.71-3.74 (m, 1H); 3.75-3.89 (m, 4H); 4.33 (d, 1H, *J*=6.8Hz); 4.38 (d, 1H, *J*=6.8Hz). IR (film, cm^{-1}): 2933, 2910, 2855. EI-MS (3KV, *m/z*): 382 (M^+, 21.1). HRMS: Calcd. for $C_{21}H_{38}O_4Si$ =382.5880, found M^+ =382.5867. **7**: ^{1}H-NMR (400MHz, $CDCl_3$, δ ppm): -0.01- 0.01 (m, 6H); 0.84 (s, 4.5H); 0.85 (s, 4.5H); 0.88 (d, 1.5H, *J*=6.6Hz,); 0.99 (d, 1.5H, *J*=6.6Hz); 1.17 (dd, 3H, *J*=13.4, 6.4Hz); 1.32-1.53 (m, 2H); 1.54-2.08 (m, 6H); 2.14 (qt, 1H, *J*=11.6, 2.5Hz); 2.46-2.58 (m, 1H); 2.93 (dd, 0.5H, *J*=11.4, 3.8Hz); 3.06 (ddd, 0.5H, *J*=20.4, 9.6, 5.0Hz); 3.48 (ddd, 0.5H, *J*=11.7, 6.3, 2.2Hz); 3.57 (ddd,

0.5H, *J*=10.4, 10.4, 4.7Hz); 3.79-3.99 (m, 4H); 4.36 (dd, 1H, *J*=11.6, 2.2Hz); 4.51-4.58 (m, 1.5H); 5.03-5.12 (m, 0.5H) 7.19-7.31 (m, 5H). IR (film, cm^{-1}): 3028, 2932, 2857. EI-MS (3KV, *m/z*): 508 (M^+, 100). HRMS: Calcd. for $C_{28}H_{44}ClO_4Si$ =508.1848, found M^+ =508.1802.

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