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Synthesis of the napalilactone and pathylactone A spirocyclic skeleton†

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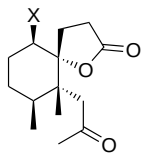
Abstract—The spirolactone core of napalilactone and pathylactone A was synthesized in five steps from 2-methyl-2-cyclohexen-1-one or 2,3-dimethyl-2-cyclohexen-1-one. This spirolactone contains all of the carbon atoms and three of the four stereocenters of napalilactone and pathylactone A.

Napalilactone (**1**)[1] and pathylactone A (**2**)[2] are novel norsesquiterpenoid spirolactones isolated from marine sources. Their structures contain four contiguous stereocenters and differ only in the nature of the heteroatom substituent (Cl versus OH) adjacent to the spirolactone ring junction (Fig. 1). Although no biological activity data has yet been reported for **1**, pathylactone A (**2**) was reported to be a Ca^{2+} antagonist.[3] An efficient total synthesis would provide access to these compounds for further biological testing. The synthetic challenge presented by the stereochemically dense skeleton of **1** and **2** and our interest in spirolactones[4] prompted us to undertake their synthesis. In this Letter we describe the preparation of ketospirolactone **10**, which contains all of the carbon atoms and three of the four stereocenters of **1** and **2**, and its diastereomer **12**.



1 X = Cl napalilactone

2 X = OH pathylactone A

Figure 1. Structures of napalilactone (**1**) and pathylactone A (**2**).

Ketone **5** (Scheme 1) was chosen as the starting point for constructing the spirolactone moiety of the target molecules. Unfortunately the one-pot conjugate addition of lithium dimethylcuprate to 2-methylcyclohex-2-enone (**3**)[5] followed by alkylation with allyl bromide failed to provide **5** in the reported yield and diastereomeric ratio.[6,7] We then resorted to a stepwise protocol[8] in which **3** was treated with lithium dimethylcuprate, and the resulting enolate was trapped with chlorotrimethylsilane. The resulting trimethylsilyl enol ether was isolated, and treated with methyllithium to form the enolate that was alkylated with excess allyl bromide to produce **5** as a 7:1 ratio of diastereomers in 51% yield for the two steps (Scheme 1). Due to the difficulty encountered separating **5** from its *anti* 2,3-dimethyl diastereomer, we explored other routes to **5**. Reduction of 2,3-dimethylcyclohex-2-enone (**4**)[9] with lithium in liquid ammonia, followed by monoprotonation, and alkylation with excess allyl bromide gave a 10:1 ratio of **5** and its *anti* diastereomer in 85% yield.[10,11] Ketone **5** was separated from its diastereomer by careful medium pressure liquid chromatography (MPLC) on silica gel.

We next turned our attention to construction of the spirolactone. Numerous methods for the construction of spirolactones of the type found in **1** and **2** have been reported.[12,13] Our initial plan called for opening a spiroepoxide intermediate with the aluminum enolate of *tert*-butyl acetate.[4,14] We were able to prepare the

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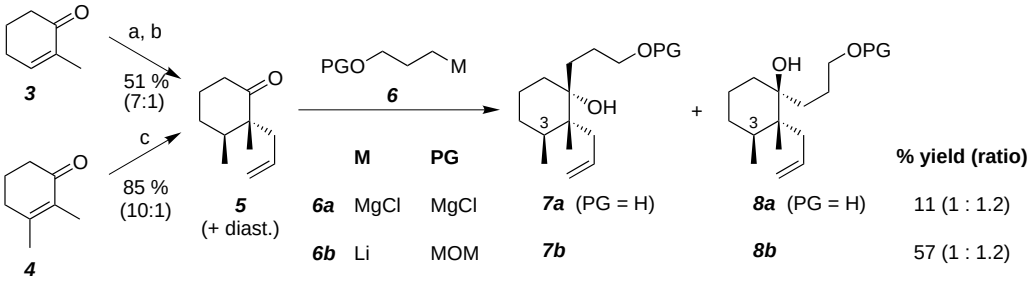


Scheme 1. *Reagents and conditions*: (a) (i) $(CH_3)_2CuLi{\cdot}LiBr$, ether, 0°C; (ii) TMSCl; (b) CH_3Li, THF, 0°C then allyl bromide; (c) Li (2 equiv.), NH_3, −78°C, H_2O (1 equiv.), allyl bromide (4 equiv.).

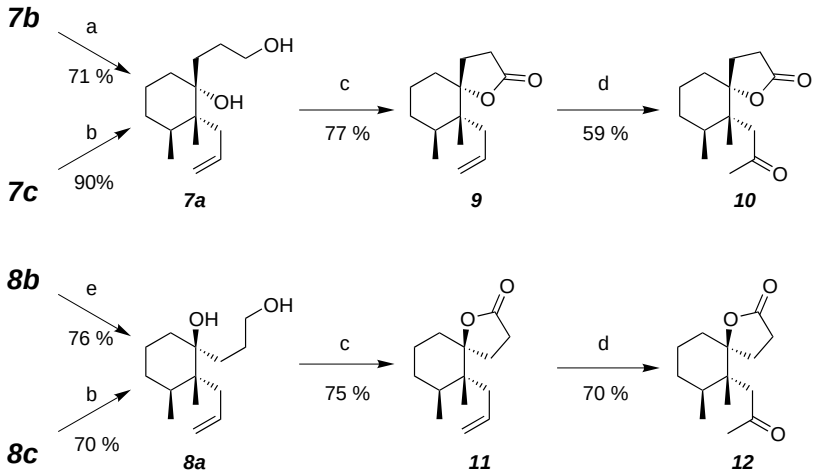
required spiroepoxide from **5**, but addition of the aluminum enolate was unsuccessful, presumably due to the steric hindrance of the adjacent quaternary center.

We then shifted our attention to the addition of nucleophiles directly to the carbonyl of **5**. Addition of Normant reagent **6a**[15] to **5** produced a 1:1.2 ratio of tertiary alcohols **7a** and **8a** in a disappointing 11% yield.[16] The majority of the starting ketone was recovered, however, leading us to suspect that enolization of **5** was to blame, but conducting the reaction in the presence of anhydrous $CeCl_3$ or excess **6a** did not improve the yield.[17] Alkyllithium reagent **6b**[18,19] improved the yield of addition product considerably, producing **7b** and **8b** in 57% yield, but the diastereoselectivity of the addition was unchanged.[20] Use of 3-*tert*-butyldimethylsiloxypropyllithium (**6c**)[21] improved the yield further, affording **7c** and **8c** in 71% yield as a 1:2 ratio of diastereomers.[22]

Diastereomers **7** and **8** were easily separated in all cases, and their relative stereochemistry was initially assigned based on their polarity and the chemical shift of the C(3) methine hydrogen (2.18 ppm in C_6D_6) in the ^1H NMR spectrum of **7a**, which is deshielded due a 1,3-diaxial relationship with the tertiary hydroxyl oxygen in the lowest energy conformation.[23] This assignment was subsequently confirmed by X-ray analysis of diastereomer **8a**.[24] The slight preference for formation of **8** over **7** in these additions of can be rationalized by axial attack of the nucleophile on the lowest energy conformer of **5**.[25]

Removal of the methoxymethyl ether protecting group present in **7b** and **8b** was complicated by competitive dehydration of the tertiary alcohol under acidic conditions, particularly in the case of **7b** (Scheme 2). A variety of conditions for cleaving the MOM group[26] were screened before settling on those listed in Scheme 2. Tetrabutylammonium fluoride cleaved the silyl ether groups from **7c** and **8c** without incident to yield the corresponding diols **7a** and **8a**, respectively. Oxidation of diol **7a** with excess pyridinium dichromate[27] afforded spirolactone **9**[28] in good yield, and **8a** was converted to spirolactone **11**[29] in identical fashion. Finally, Wacker oxidation of the terminal alkene[11,30] in **9** and **11** generated ketolactones **10**[31] and **12**[32] in 59 and 70% yields, respectively. Keto lactone **10** contains all of the carbons and three of four stereocenters found in napalilactone (**1**) and pathylactone A (**2**).

In summary, the complete carbon skeleton of napalilactone and pathylactone A has been prepared for the first



Scheme 2. *Reagents and conditions*: (a) 10% HCl, THF, 42 h; (b) TBAF, THF, 0°C; (c) PDC (2.7 equiv.), CH_2Cl_2, 24 h; (d) CuCl (10 mol%), $PdCl_2$ (10 mol%), DMF, H_2O, O_2, 24 h; (e) conc. HCl (cat), *tert*-butyl alcohol, 42 h.

time. The synthesis covers five steps and produces keto lactone **10** in 8% yield from **4**. Diastereomeric keto lactone **12** was produced in 15% yield from **4** using the same sequence of reactions. Our current focus in on the installation of the heteroatom substituent and control of absolute stereochemistry in the preparation of **1** and **2**.

Note added in proof. The authors were alerted to a nearly identical synthesis of spirolactone **10** carried out by Diaz and Coelho after acceptance of this paper.[33]

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29. Characterization data for **11**: IR (neat) ν 3074, 1771 (s), 1636, 1217, 1168, 1001, and 921 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.94 (dddd, $J=15.0$, 11.5, 9.0, 6.3 Hz, 1H), 4.85 (m, 2H), 2.57–2.18 (m, 4H), 2.02 (dd, $J=15.0$, 9.0 Hz, 1H), 1.9–1.1 (m, 8H), 1.05 (s, 3H), and 0.93 (d, $J=6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.9, 136.0, 115.1, 91.8, 43.2, 36.8, 41.9, 33.7, 28.8, 28.7, 26.0, 21.0, 15.6, and 14.5. Anal. calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.36; H, 10.20.
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32. Characterization data for **12**: mp 106–108°C; IR (KBr) ν 1765, 1689, 1244, 1221, 1168, and 1143 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.60 (d, $J=13.0$ Hz, 1H), 2.52 (m, 3H), 2.35 (d, $J=13.0$ Hz, 1H), 2.23 (s, 3H), 2.2–1.3 (m, 8H), 1.30 (s, 3H,), and 0.86 (d, $J=6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 210.1, 176.4, 91.1, 52.4, 45.5, 37.6, 32.5, 32.0, 28.6, 28.5, 25.6, 21.5, and 15.6. Anal. calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.44; H, 9.49.
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