SYNTHESIS OF *O*-METHYLTOPSENTIN

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Abstract: *O*-Methyl ether **16** of an indolylimidazole marine alkaloid, topsentin **1** [4-(3-indolyl)-2-(6-hydroxy-3-indolyl)carbonyl-1*H*-imidazole], was synthesized by acylation of 5-(1-*tert*-butyldimethylsilyl-3-indolyl)-2-lithio-1-(2-trimethylsilylethoxymethyl)-1*H*-imidazole with a Weinreb amide **12** of 1-(*tert*-butyldimethylsilyl)-6-methoxy-3-indolylcarboxylic acid followed by desilylation with 20% hydrochloric acid.

Topsentin **1** is a marine diindolylimidazole alkaloid, isolated from a sponge, and has antiviral and antitumorigenic activities (1). (Fig. 1) In this communication, we would like to report the first synthesis of *O*-methyltopsentin **16** starting from a 1,2-protected imidazole derivative.

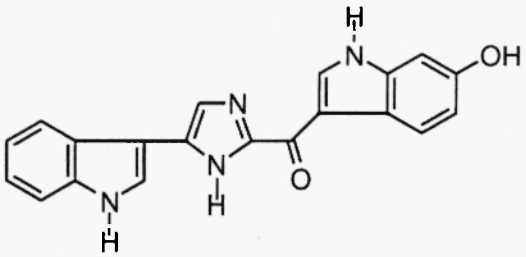
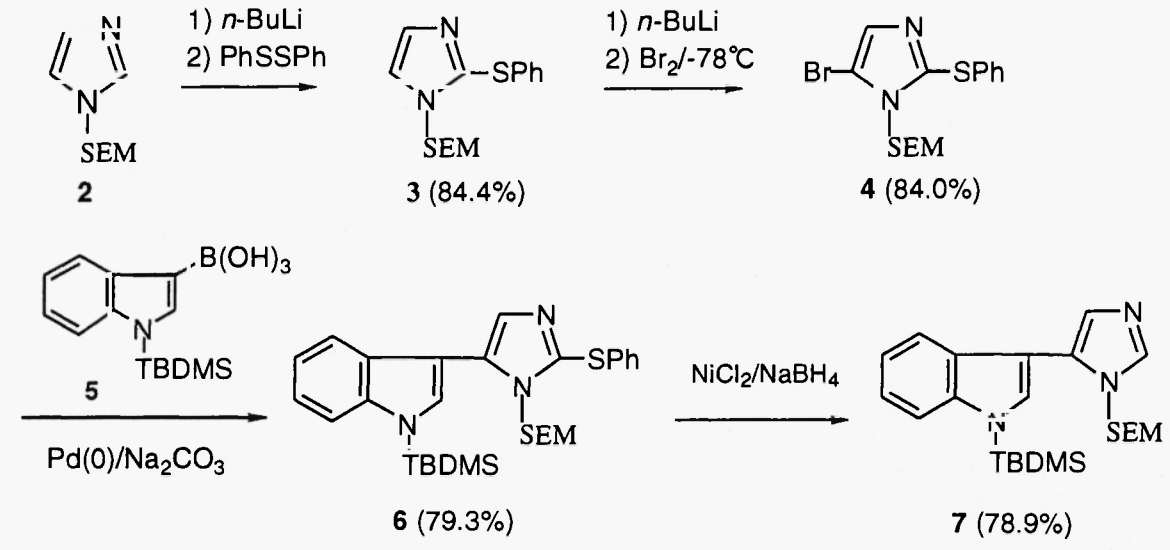


Fig. 1. **1** (topsentin)

The left hand part of topsentin **1** was prepared as follow. Lithiation of 1-SEM-imidazole **2** with *n*-BuLi (2) followed by treatment with diphenyldisulfide afforded the 1,2-protected imidazole **3** in 84.4 % yield. Lithiation of **3** with *n*-BuLi at -78 °C (3) followed by bromination with bromine at -78 °C gave the 5-bromoimidazole **4** in 84.0 %. It was found after several attempts that the bromide **4** successfully coupled with 1-TBDMS-3-indolylboronic acid **5** to give the 5-(3-indolyl)imidazole **6** in 79.3 % yield. Desulfurization of **6** with sodium borohydride in the presence of $NiCl_2$ afforded **7** in 78.9 % yield (4). (Chart 1)

The right hand part **12** of **1** using for acylation of the left hand part **7** was prepared as follow. The 1-position of 6-methoxyindole **8** (5) was protected by TBDMS group in a usual manner, and then brominated at the 3-position by treatment with NBS to give **10** (6) in 89.1 % yield. The bromide **10** was converted to the lithio derivative with *t*-BuLi, and then treated with methyl chloroformate to give the indole-3-carboxylate **11** in 78.6 % yield. The *N*, *O*-dimethylhydroxamic acid amide (**12**, Weinreb amide) was prepared in 68.5 % yield

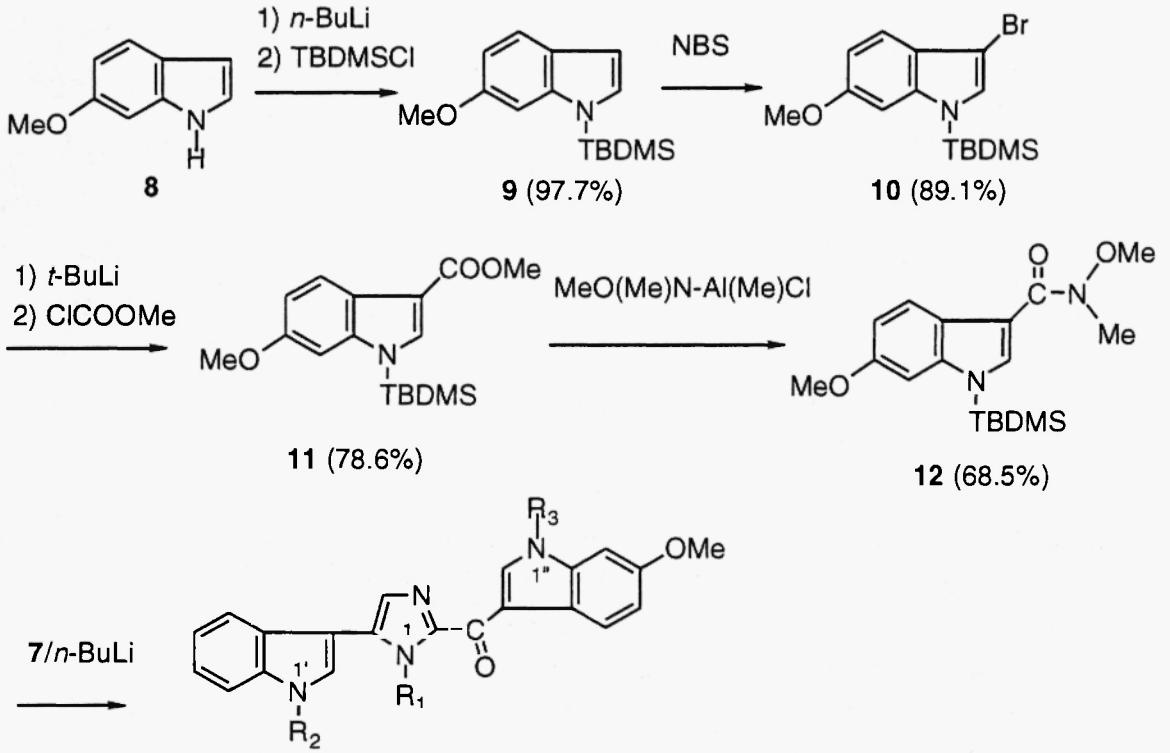


2 **3** (84.4%) **4** (84.0%)

5

6 (79.3%) **7** (78.9%)

Chart 1



8 **9** (97.7%) **10** (89.1%)

11 (78.6%) **12** (68.5%)

13 : R_1=SEM; R_2=R_3=TBDMS (34.1%)
14 : R_1=SEM; R_2=TBDMS; R_3=H (32.6%)
15 : R_1=SEM; R_2=R_3=H (5.8%)

16 : R_1=R_2=R_3=H (66.0%)

Chart 2

according to the literature procedure, by which carboxylic ester was treated with methylaluminum *N, O*-dimethylhydorxyamide chloride (7).

The acylation of **7** was achieved by treatment with *n*-BuLi followed by addition of the Weinreb amide **12** to give a mixture of **13** (34.1 % yield), **14** (32.6 %) and **15** (5.8 %). Presence of the TBS group at the 1'-position of **14** was confirmed on the basis of NOE experiment, in which NOE (3.7 %) was observed between C2'-H and CH_2 of the SEM group. The mixture of **13**, **14** and **15** was finally deprotected by treating with 20% hydrochloric acid to give *O*-methyltopsentin (**16**, mp 304 - 306 °C, pale yellow crystals) in 66.0 % yield (Chart 2) (8)

Cleavage of the methyl ether group in **16** is in progress (9).

References and Notes

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(8) Recrystallized from AcOEt - hexane. IR (KBr tab.): 3396, 2903, 1582, 1516 cm^{-1}. ^{1}H-NMR (acetone-d_6): 3.79 (s, 3H, OCH_3), 6.84 and 6.87 (s each, total 1H, H-5"), 7.05 (s, 1H, H-7"), 7.08 - 7.21 (m, 2H, H-5' and H-6'), 7.42 and 7.47 (d each, total 1H, J = 7.92 and 6.83 Hz, H-7'), 7.57 and 7.67 (d each, total 2H, H-4 and H-5), 7.80 and 8.04 (s each, total 1H, H-2'), 7.91 and 8.18 (d each, total 1H, J = 7.6 Hz, H-4'), 8.31 and 8.32 (d each, total 1H, J = 8.7 Hz, H-4"), 9.23 and 9.46 (s each, total 1H, H-2"), 10.37 and 10.62 (br each, total 1H, H-1), 10.91 and 10.96 (br each, total 1H, H-1'), 12.00 and 12.07 (br each, total 1H, H-1"). This NMR spectrum reflects the presence of the tautomers at the imidazole ring (cf. ref. 1). HRMS *m/z*: Calcd for $C_{21}H_{16}N_4O_2$, 356.1270. Found, 356.1249 (M^+).

(9) Structures of the newly prepared compounds, appeared in this paper, were confirmed on the basis of their spectral and analytical data.

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