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Synthesis of the C22–C37 segment of prorocentin

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ABSTRACT

The synthesis of the C22–C37 segment of prorocentin, isolated from the dinoflagellate *Prorocentrum lima*, was achieved. Because the relative stereochemical relationship between C26 and other stereocenters (C28/C31/C32 established as $R^*/R^*/R^*$) in the C22–C37 region of natural prorocentin has not yet been determined, both epimers at C26 of the C22–C37 segment were selectively constructed. The synthesis was based on a 5-*exo* epoxide ring opening reaction to form an oxolane (E-ring), Brown asymmetric methallylation to install the C26-stereocenter, acryloylation of the resulting alcohol, and ring-closing olefin metathesis to establish the *Z*-olefin at C23/C24.

Prorocentin (**1**, Fig. 1), isolated as a cytotoxic agent from the cultured dinoflagellate *Prorocentrum lima* clone PL021117001 by Lu,[1] is a novel polyketide polyether possessing an all-*E* triene, an epoxide (A-ring), a pyran-fused spirocyclic acetal (BCD-ring), an oxolane (E-ring), and 13 asymmetric centers. The full planar structure and the relative stereochemistry in the C1–C26 and C27–C35 regions of **1** have been elucidated by extensive NMR analysis, although the relative stereochemical relationship between the two regions, as well as the full absolute configuration, remains undetermined. Because the unique structure and bioactivity of **1** attracted our attention, we commenced a project toward the total synthesis and the determination of the absolute configuration of **1**. Here, the stereoselective synthesis of C26-epimeric lactones **2** and **3** (Fig. 1), corresponding to the C22–C37 segment of **1**, is described as an initial part of the project.

For the future construction of the BCD-ring of **1**, shown in Scheme 1, lactone **2**/**3** was designed as a versatile synthetic intermediate: it would function as an electrophile for the reaction with B-ring nucleophile **I** (Route A) or as a precursor for nucleophile **III** or **IV**, which would be connected with B-ring electrophile **II** (Route B). As described above, the relative stereochemical relationship between C26 and other stereocenters (C28/C31/C32 established as $R^*/R^*/R^*$) in the C22–C37 region of naturally occurring **1** has not yet been determined. Therefore, the preparation of both C26-epimeric lactones **2** and **3** was required for the synthesis of the possible stereoisomers of **1**. The spectral and optical data of the stereoisomers would then be compared with those of the natural compound to determine the absolute stereochemistry of prorocentin.

The synthesis of **2** and **3** was planned as shown in Scheme 2. The following five key reactions were scheduled in the plan: (i) the 5-*exo* cyclization of dihydroxy epoxide **10** to form E-ring **9**;

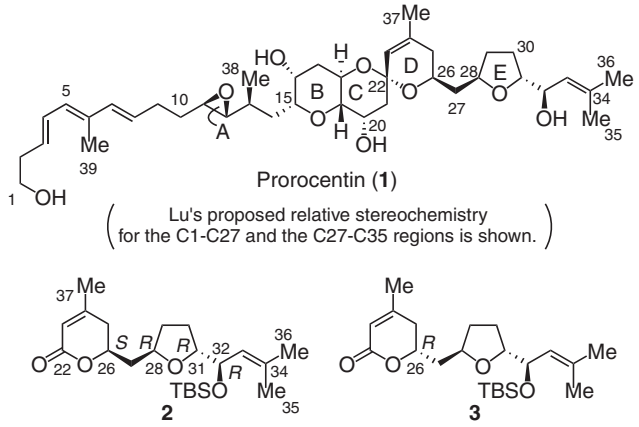
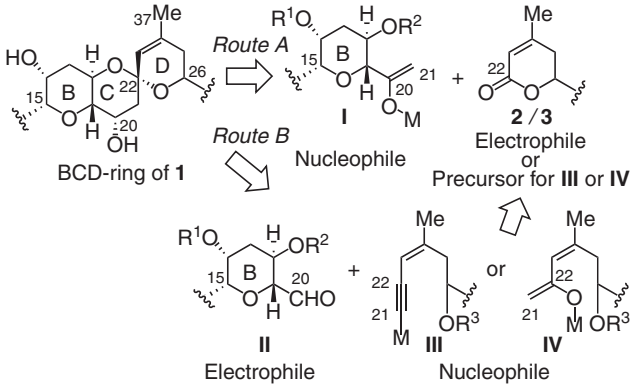


Figure 1.



Scheme 1.

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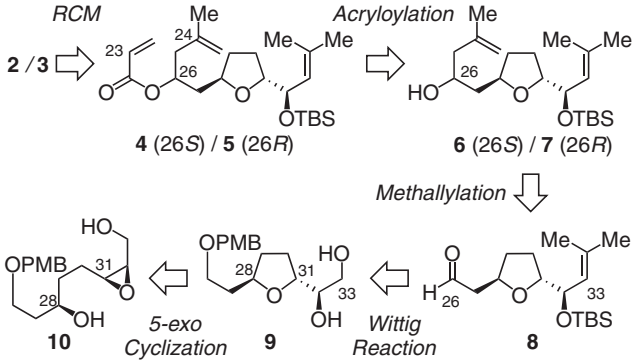
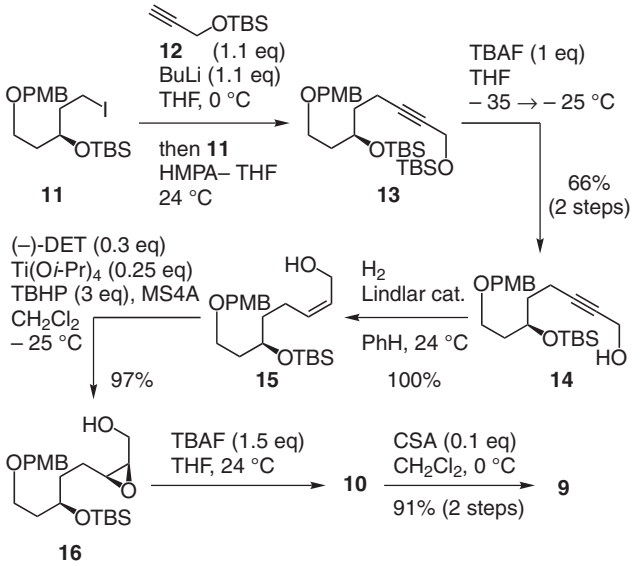


Scheme 2.

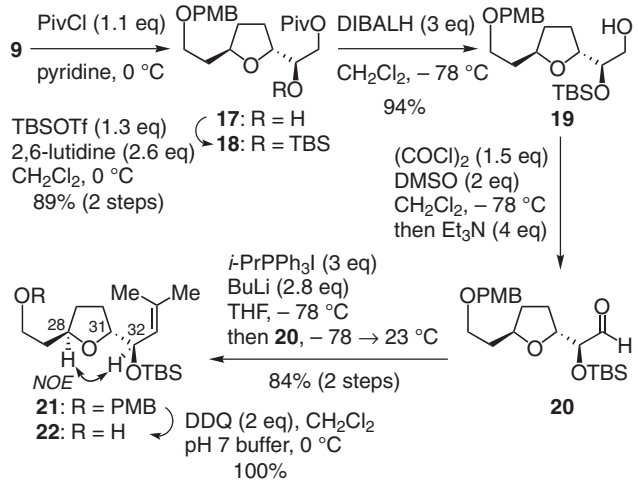
(ii) Wittig olefination to construct the isopropylidene group at C33; (iii) the methallylation of aldehyde **8** to install the C26-stereocenter; (iv) the acryloylation of alcohol **6** or **7**; and (v) the ring-closing olefin metathesis (RCM)[2] to establish the *Z*-olefin at C23/C24. The selective preparation of either **6** or **7** would require an asymmetric methallylation reaction. To generate the antipodal C26-stereocenter, the acryloylation of the preceding major alcohol (**6** or **7**) by the Mitsunobu reaction[3] was undertaken.

The synthesis of E-ring **9** began from the known chiral compound **11**[4] (Scheme 3). Iodide **11** was reacted with an acetylide, prepared from alkyne **12** with BuLi, to produce alkyne **13**. The primary TBS group of **13** was selectively removed with TBAF at low temperature (−35→−25 °C) to give alcohol **14** (66% from **11**), which was partially hydrogenated to afford *Z*-allylic alcohol **15** (100%). The Katsuki–Sharpless asymmetric epoxidation of **15** using (−)-diethyl tartrate produced **16** (97%) exclusively.[5] After the TBS removal from **16**, treatment of the resulting dihydroxy epoxide **10** with CSA-promoted 5-*exo* cyclization to furnish E-ring **9** in 91% yield from **16**.

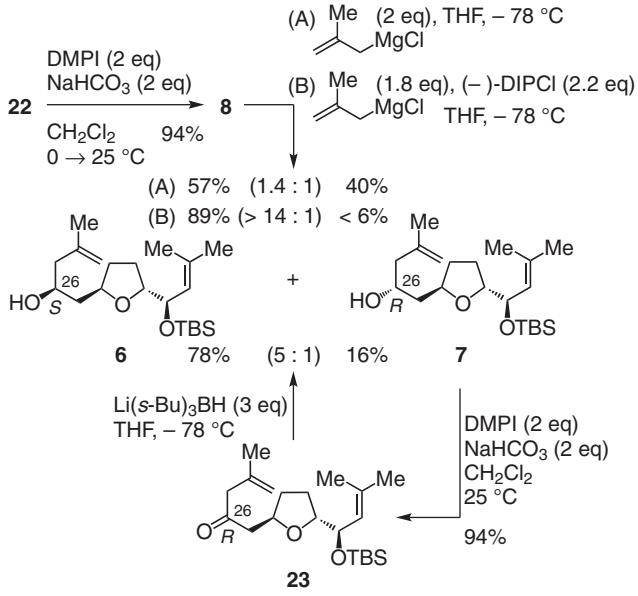
The installation of the isopropylidene group at C33 is illustrated in Scheme 4. Diol **9** was first converted to alcohol **19** (84% overall) by protecting group manipulation [(i) selective pivaloylation of the primary alcohol of **9**, (ii) TBS-protection of the secondary alcohol of **17**, and (iii) removal of the pivaloyl group of **18**]. Swern oxidation[6] of **19** followed by Wittig reaction with isopropylidene triphenylphosphorane installed the required isopropylidene group to pro-



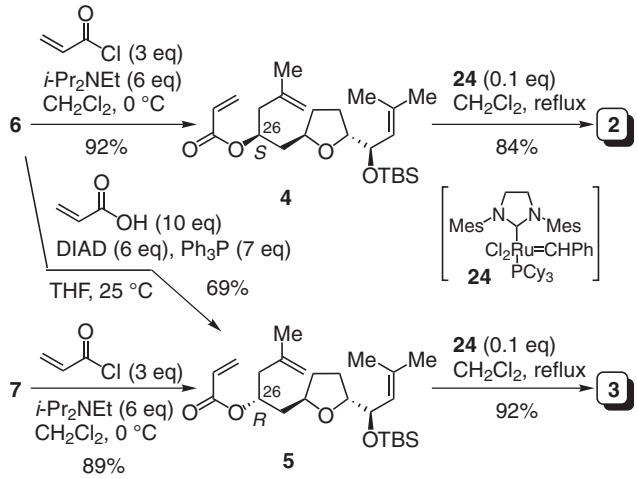
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

duce **21**[7] (84% from **19**). The *trans*-disubstitution of the E-ring was confirmed at this stage from the presence of an NOE interaction between H28 and H32. The PMB group of **21** was removed with DDQ to give alcohol **22** (100%).[8]

The construction of the C26-stereocenter was performed after Dess–Martin oxidation of **22** to give **8** (94%) (Scheme 5).[9] Aldehyde **8** was initially reacted with methallyl magnesium chloride to produce 26*S*-alcohol **6**[10] (57%) and its diastereomer **7** (40%) with modest selectivity (**6**:**7** = 1.4:1) [condition (A)]. Conversion of **7** to **6** was examined, and a process including Dess–Martin oxidation and reduction with Li(*s*-Bu)$_3$BH was found to furnish **6** with relatively high selectivity (**6**:**7** = 5:1) in good yield (73% over two steps). In the methallylation reaction, Brown's asymmetric procedure was also tested [condition (B)].[11] The reaction of **8** with a methallyl borane, prepared from (−)-*B*-chlorodiisopinocampheylborane with methallyl magnesium chloride, proceeded smoothly in THF at −78 °C to afford **6** predominantly (**6**:**7** = 14:1) in 89% yield. Thus, Brown asymmetric methallylation was employed as an efficient method for the installation of the C26-stereocenter of **6**.

Finally, lactones **2** and **3** were synthesized as shown in Scheme 6. Treatment of alcohol **6** with acryloyl chloride produced ester **4** (92%). Alternatively, the alcohol was also reacted with acrylic acid under Mitsunobu conditions to give ester **5** (69%) with complete inversion of stereochemistry, though the reaction required excess amounts of reagents because of the low reactivity of **6**. Ester **5** was also obtained by esterification of **7** with acryloyl chloride (89%). The cyclization of esters **4** and **5** was catalyzed by the second generation Grubbs catalyst (**24**)[12] to smoothly furnish **2** (84%) and **3** (92%),[13] respectively, thereby completing the synthesis of the C22–C37 segments required for determination of the absolute stereochemistry of **1**.

In conclusion, two C26-epimeric lactones **2** and **3** corresponding to the C22–C37 region of prorocentin (**1**) were stereoselectively synthesized for the determination of the absolute stereochemistry of **1** by total synthesis. The synthesis was based on (i) the 5-*exo* cyclization of dihydroxy epoxide **10** to form E-ring **9**, (ii) Wittig olefination to construct the isopropylidene group at C33, (iii) Brown asymmetric methallylation of aldehyde **8** to install the C26-stereocenter, (iv) acryloylation of alcohol **6** by a condensation or a Mitsunobu reaction, and (v) RCM of **4** and **5** to establish the *Z*-olefin at C23/C24. Further studies toward the total synthesis and the determination of the absolute configuration of **1** are in progress in this laboratory.

Acknowledgments

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13. Selected spectral data of **2**: a pale yellow oil; $[\alpha]_D^{23}$ −78.2 (*c* 1.14, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (1H, br s), 5.12 (1H, d-sp, *J* = 9.2, 1.5 Hz), 4.57 (1H, dddd, *J* = 12.0, 6.8, 5.3, 4.1 Hz), 4.23 (1H, dd, *J* = 9.2, 5.8 Hz), 4.12 (1H, tdd, *J* = 8.4, 4.0, 2.9 Hz), 3.92 (1H, td, *J* = 7.2, 5.8 Hz), 2.52 (1H, br dd, *J* = 17.8, 12.0 Hz), 2.27 (1H, dd, *J* = 17.8, 4.1 Hz), 1.95–2.08 (2H, m), 1.98 (3H, br s), 1.80–1.94 (2H, m), 1.58–1.72 (1H, m), 1.71 (3H, d, *J* = 1.5 Hz), 1.65 (3H, d, *J* = 1.5 Hz), 1.43–1.57 (1H, m), 0.86 (9H, s), 0.02 (3H, s), 0.00 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$, $^{13}CDCl_3$ as 77.0 ppm) δ 165.3 (C), 157.4 (C), 133.3 (C), 125.5 (CH), 116.2 (CH), 82.8 (CH), 75.2 (CH), 74.7 (CH), 72.3 (CH), 39.8 (CH_2), 34.1 (CH_2), 32.3 (CH_2), 27.3 (CH_2), 25.9 (CH_3), 25.8 ($CH_3 \times 3$), 22.9 (CH_3), 18.6 (CH_3), 18.1 (C), −4.4 (CH_3), −4.8 (CH_3); IR (film), ν_{max} cm^{-1}; 2928, 2856, 1724, 1648, 1472, 1462, 1442, 1390, 1360, 1290, 1248, 1194, 1154, 1066, 938, 874, 835, 813, 776, 665; HR-FDMS, calcd for $C_{22}H_{39}O_4Si$ $[M+H]^+$: 395.2618, found: 395.2635. Selected spectral data of **3**: a pale yellow oil; $[\alpha]_D^{22}$ +33.3 (*c* 1.11, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (1H, br s), 5.10 (1H, d-sp, *J* = 9.0, 1.2 Hz), 4.58 (1H, tdd, *J* = 8.3, 7.4, 4.5 Hz), 4.24 (1H, dd, *J* = 9.0, 6.5 Hz), 4.14 (1H, tdd, *J* = 9.1, 5.9, 3.1 Hz), 3.90 (1H, q, *J* = 6.5 Hz), 2.32 (2H, d, *J* = 7.4 Hz), 1.90–2.08 (3H, m), 1.97 (3H, br s), 1.58–1.78 (2H, m), 1.71 (3H, d, *J* = 1.2 Hz), 1.66 (3H, d, *J* = 1.2 Hz), 1.36–1.57 (1H, m), 0.86 (9H, s), 0.03 (3H, s), 0.01 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$, $^{13}CDCl_3$ as 77.0 ppm) δ 165.1 (C), 157.3 (C), 133.5 (C), 125.4 (CH), 116.4 (CH), 82.8 (CH), 75.7 (CH), 75.1 (CH), 72.3 (CH), 41.1 (CH_2), 35.3 (CH_2), 32.7 (CH_2), 27.4 (CH_2), 25.9 (CH_3), 25.8 ($CH_3 \times 3$), 22.9 (CH_3), 18.6 (CH_3), 18.3 (C), −4.4 (CH_3), −4.7 (CH_3); IR (film), ν_{max} cm^{-1}; 2955, 2928, 2856, 1725, 1647, 1472, 1462, 1442, 1386, 1360, 1289, 1246, 1196, 1152, 1117, 1060, 1016, 1005, 956, 939, 873, 834, 814, 776; HR-FDMS, calcd for $C_{22}H_{39}O_4Si$ $[M+H]^+$: 395.2618, found: 395.2628.