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Enantioselective total synthesis of enokipodins A–D

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Abstract—The first enantioselective total synthesis of enokipodins A–D, highly oxidized α-cuparenone-type sesquiterpenoids with antimicrobial activity, was accomplished by using Meyers' diastereoselective alkylation protocol for the construction of the C7-quaternary asymmetric center. The present synthesis also constitutes a formal enantioselective synthesis of (*S*)-1,4-cuparenediol and (*S*)-cuparene-1,4-quinone.

Cuparene-type sesquiterpenoids constitute a family of natural products featuring a *p*-tolylcyclopentane framework bearing two contiguous quaternary centers on the cyclopentane ring, and quite interestingly, are known to exist in both enantiomeric forms in nature [e.g., (*R*)-cuparene [(*R*)-**3a**][1] and (*S*)-α-cuparenone [(*S*)-**3b**][2] from higher plants; (*S*)-cuparene [(*S*)-**3a**][3,4] and (*R*)-α-cuparenone [(*R*)-**3b**][5] from liverworts] (Fig. 1). Since the isolation of (*R*)-(+)-cuparene from the heartwood extracts of some conifers,[1] the sterically congested molecular architecture of this class of terpenoids has attracted considerable interest of synthetic chemists, and thereby many synthetic studies on cuparenes, either as racemic or as optically active forms, have been reported so far.[6] Most of the synthetic efforts, however, have been focused on two simple cuparenes, **3a** and **3b**,[6,7] while syntheses of cuparenes bearing oxygen functionalities at the aromatic ring portion did not appear in the literature until two recent reports on the synthesis of (±)-HM-1 methyl ether (methyl ether of **3c**),[8] (±)-1,4-cuparenediol (**3d**),[9] and (±)-cuparene-1,4-quinone (**4**).[9] Most recently, Srikrishna and Rao reported the synthesis of (±)-enokipodins A and B (**1a** and **2a**, respectively),[10] previously isolated by Ishikawa et al. from a culture broth of an edible mushroom (*Flammulina velutipes*, enokitake in Japanese).[11] These two cuparenoids and two additional α-cuparene derivatives isolated later from the same mushroom [enokipodin C (**1b**) and enokipodin D (**2b**)][12] showed significant antimicrobial activity against a fungus (*Cladosporium herbarum*) and Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*). Their structural uniqueness (both the cyclopentane and the aromatic ring portions are oxidized) combined with the fact that no enantioselective synthesis of cuparenes bearing oxygen functionalities on the aromatic ring moiety has been reported to date, as well as our own interest in elucidating the biological activities of enokipodins and their analogs in detail prompted us to embark on the synthesis of optically active enokipodins A–D.

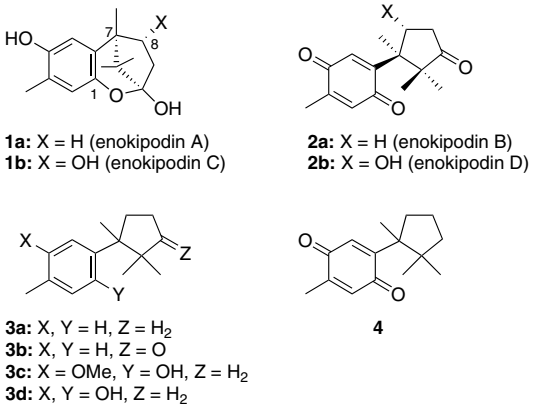

Figure 1. Structures of enokipodins A–D and related compounds.

Keywords: Enokipodin; Terpenoids; Antibiotics; Cuparene.
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Our synthesis began with methallylation of known aromatic ester **5**, which in turn could readily be obtained

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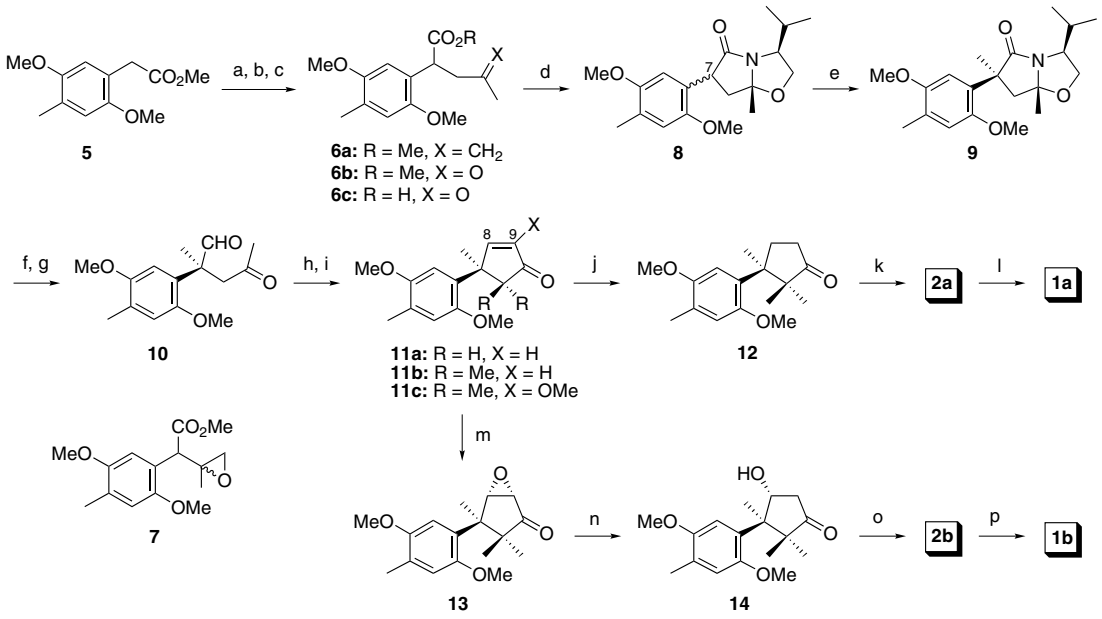

Scheme 1. Reagents and conditions: (a) LDA, methallyl chloride, NaI, THF–HMPA (7:1), −78 °C, 3.5 h (98%); (b) OsO_4, NMO, $NaIO_4$, THF–H_2O (3:1), rt, 18 h (98%); (c) 2 M aq KOH, THF, 50 °C, 12 h (98%); (d) (*S*)-valinol, toluene, reflux, 15 h (85%); (e) *s*-BuLi, MeI, THF, −78 °C, 2 h (88%); (f) Red-Al®, THF, 0 °C to rt, 1.5 h; (g) 1 M aq $(n\text{-Bu})_4NH_2PO_4$, EtOH, rt, 24 h; (h) K_2CO_3, *t*-BuOH, reflux, 4.5 h (82% from **9**); (i) NaH, MeI, THF–HMPA (5:1), rt, 17 h (61%); (j) H_2, Pd/C, EtOAc, rt, 16 h; (k) CAN, CH_3CN–H_2O (3:2), rt, 30 min (79% from **11b**); (l) $Na_2S_2O_4$, EtOH–H_2O, rt, 30 min (55%); (m) 30% aq H_2O_2, NaOH, MeOH, 60 °C, 6.5 h (51%); (n) PhSeSePh, $NaBH_4$, EtOH, AcOH, rt, 1 h (68%); (o) CAN, CH_3CN–H_2O (3:2), rt, 30 min (78%); (p) $Na_2S_2O_4$, EtOH–H_2O, rt, 30 min (89%).

from 2,5-dimethoxy-4-methylbenzaldehyde in three steps following the literature procedure (Scheme 1).[13] The resulting olefinic product (**6a**) produced in 98% yield was subjected to the Lemieux–Johnson oxidation to give keto ester **6b** almost quantitatively. When this oxidative cleavage was conducted by using ozonolysis, a substantial degree of undesirable oxidation at the aromatic ring moiety took place, and attempted direct alkylation of **5** with bromoacetone into **6b** was unsuccessful due to preferential attack of the enolate of **5** to the keto group of bromoacetone, leading eventually to a 3:2 mixture of diastereomeric epoxides **7**. The ester group of **6b** was then saponified to afford keto acid **6c** (96% overall yield from **6a**). In order to construct the C7-quaternary stereogenic center of enokipodins by Meyers' diastereoselective alkylation protocol,[14] the keto acid (**6c**) was converted in 85% yield into chiral bicyclic lactam **8** as an inseparable 6:5 epimeric mixture at the C7 position by treating with (*S*)-valinol in refluxing toluene.[15] The mixture of lactams was alkylated with iodomethane to give **9** in 88% isolated yield together with its C7-epimer (3% yield). The methylated lactam (**9**) was successively treated with Red-Al® and an aqueous solution of tetrabutylammonium dihydrogenphosphate to give keto aldehyde **10**, which upon exposure to aldol condensation conditions (K_2CO_3, *t*-BuOH, reflux)[16] furnished cyclopentenone derivative **11a** in 82% overall yield from **9**. Dimethylation of **11a** with excess amounts of iodomethane and sodium hydride was first attempted in DMF, which had been used as the solvent for dimethylation of an analogous cyclopentenone derivative.[7,14] In this solvent, however, substantial amounts of the starting ketone (**11a**) and the corresponding mono-methylated product remained even after 3 days of heating at 100 °C. On the other hand, this reaction proceeded smoothly in THF–HMPA (5:1) even at room temperature, to give the desired dialkylation product (**11b**) in 61% yield. Catalytic hydrogenation of **11b** afforded **12**, which upon oxidation with ceric ammonium nitrate gave (−)-enokipodin B (**2a**) as orange needles [mp 146–147 °C, $[\alpha]_D^{22}$ −65 (*c* 0.40, MeOH); lit.[11] semisolid, $[\alpha]_D^{24}$ −63 (*c* 0.05, MeOH)] in 79% overall yield from **11b**. Finally, reduction of the benzoquinone moiety with sodium dithionite afforded (+)-enokipodin A (**1a**) as colorless prisms [mp 180–182 °C, $[\alpha]_D^{23}$ +48 (*c* 0.50, MeOH); lit.[11] mp 138.5–138.9 °C, $[\alpha]_D^{23}$ +48 (*c* 0.5, MeOH)] in 55% yield. The ^1H and ^{13}C NMR spectra of synthetic **1a** and **2a** were completely identical with those of natural enokipodins A and B, respectively.[11]

Having completed the synthesis of (+)-**1a** and (−)-**2a**, we next turned our attention to the elaboration of intermediate **11b** to enokipodins C (**1b**) and D (**2b**). Stereoselective epoxidation of the C8–C9 double bond of **11b** with alkaline hydrogen peroxide in methanol occurred from the less hindered α-face opposite the aromatic ring moiety to give **13** as a single stereoisomer in a moderate isolated yield of 51%.[17] In this reaction, prolonged reaction time caused formation of **11c**, which probably resulted from epoxide ring opening of **13** at the C9 position by methanol followed by dehydration. Reductive cleavage of the epoxide ring was carried out by using Miyashita's organoselenium chemistry to afford **14** in 68% yield.[18] The ^1H NMR spectrum of **14** was exactly the same as that of an authentic sample prepared previously from natural enokipodin C by Ishikawa et al.[12] to determine the absolute configuration of **1b**. Finally, in the same manner as described for the synthesis of **1a** and

2a, **14** was converted into enokipodin D [**2b**: yellow needles, mp 146–147°, $[\alpha]_D^{26}$ −130 (*c* 0.20, MeOH); lit.[12] mp 116.0–117 °C, $[\alpha]_D^{24}$ −130 (*c* 0.1, MeOH)][19] and then enokipodin C [**1b**: $[\alpha]_D^{24}$ −9.2 (*c* 0.50, MeOH); lit.[12] $[\alpha]_D^{24}$ −9.4 (*c* 1.0, MeOH)]. The spectral data (^{1}H and ^{13}C NMR) of **1b** and **2b** were identical with those of natural enokipodins C and D, respectively.[12]

In conclusion, the first enantioselective total synthesis of enokipodins A, B, C, and D was accomplished starting from known aromatic ester **5** in 12, 11, 13, and 12 steps, and in overall yields of 15%, 28%, 8%, and 10%, respectively. The ^{1}H and ^{13}C NMR spectra and specific rotation values of synthetic enokipodins were matched those of the natural enokipodins, while the melting points of synthetic **1a** and **2b** were considerably higher than those of the corresponding natural samples of enokipodins. Since (±)-**12** has previously been converted into (±)-**3d** and (±)-**4**,[9,10] this synthesis also constitutes a formal synthesis of (*S*)-**3d** and (*S*)-**4**.

Acknowledgements

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