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An enantiospecific formal total synthesis of (−)-aplysin and (−)-debromoaplysin

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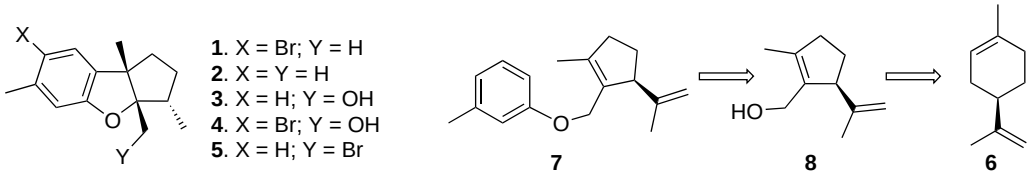
Abstract—An enantiospecific approach to marine sesquiterpenes (−)-debromoaplysin and (−)-aplysin, starting from (*R*)-limonene employing a Claisen rearrangement as the key step, is described.

Aplysin **1**, one of the first halogenated marine sesquiterpenes to be reported, was isolated from the red alga *Laurencia* and the sea hare *Aplysia*. The logical biogenetic precursor debromoaplysin **2** and the related debromoaplysinol **3**, aplysinol **4** and isoaplysin **5** have also been isolated from these species,[1] and some of them exhibit antifeedant properties. The presence of an interesting tricyclic structure and associated properties made these compounds attractive synthetic targets.[2] Besides a few approaches to racemic aplysins, two enantioselective strategies have been reported for debromoaplysin and aplysin.[2] Herein, we report an enantiospecific approach to debromoaplysin **2** and aplysin **1** starting from the monoterpene (*R*)-limonene **6** and employing a Claisen rearrangement as the key step. It was anticipated that a stereoselective Claisen rearrangement[3] of the *m*-cresyl ether **7** of the allyl alcohol **8** followed by cyclisation could generate the aplysin carbon framework directly. The synthetic sequence starting from (*R*)-limonene **6** is depicted in Scheme 1. To begin with, (*R*)-limonene **6** was converted into the allyl alcohol **8** in three steps[4] viz controlled ozonolysis, intramolecular aldol condensation and reduction of the aldehyde. The key intermediate **7**, $[\alpha]_D^{24}$ +81.5 (*c* 1.4, $CHCl_3$), was obtained by coupling the allyl alcohol **8** with *m*-cresol under Mitsunobu conditions[5] employing triphenylphosphine and diisopropyl azodicarboxylate (DIAD) in 83% yield. Thermal activation of the ether **7** in *N*,*N*-dimethylaniline in a sealed tube at 180°C for 72 h generated a 5:1:2 mixture of the cyclised products **9**† and **10** derived from the *ortho* Claisen rearrangement, and the *para* Claisen rearrangement product **11**, in 64% yield, which were separated by silica gel and silver nitrate impregnated silica gel column chromatography. Next, attention was turned towards conversion of **9** into aplysins via degradation of the isopropenyl group employing a Criegee rearrangement.[6] Thus, ozonolysis of the compound **9** in methanol–methylene chloride followed by treatment of the resulting methoxyhydroperoxide with acetic anyhydride, triethyl-



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† All the compounds exhibited spectral data consistent with their structures. Selected spectral data for the compound **9**: isolated yield 40%; $[\alpha]_D^{22}$ −50.2 (*c* 1.4, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1645, 1621, 1591, 1090, 887. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.90 (1H, d, *J* 7.5 Hz), 6.61 (1H, d, *J* 7.5 Hz), 6.50 (1H, br s), 4.87 (1H, s), 4.69 (1H, s), 2.64 (1H, t, *J* 9.0 Hz), 2.28 (3H, s), 2.10–1.80 (2H, m), 1.86 (3H, s), 1.70–1.55 (2H, m), 1.20 (3H, s), 1.15 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 157.1 (C), 144.9 (C), 137.7 (C), 135.4 (C), 122.8 (CH), 121.3 (CH), 111.4 (CH_2), 110.7 (CH), 98.5 (C), 56.3 (CH), 53.4 (C), 39.2 (CH_2), 26.6 (CH_2), 24.7 (CH_3), 23.6 (CH_3), 21.6 (CH_3), 16.8 (CH_3). For the acetate **12**: $[\alpha]_D^{24}$ −49.9 (*c* 4.5, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1742. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.94 (1H, d, *J* 7.2 Hz), 6.61 (1H, d, *J* 7.2 Hz), 6.47 (1H, br s), 5.20 (1H, br s), 2.29 (3H, s), 2.07 (3H, s), 2.00–1.55 (4H, m), 1.35 (3H, s), 1.30 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 169.3 (C), 157.7 (C), 138.1 (C), 132.5 (C), 122.5 (CH), 121.5 (CH), 110.0 (CH), 98.8 (C), 81.8 (CH), 53.2 (C), 41.3 (CH_2), 28.9 (CH_2), 22.9 (CH_3), 21.6 (CH_3), 21.1 (CH_3), 17.0 (CH_3).

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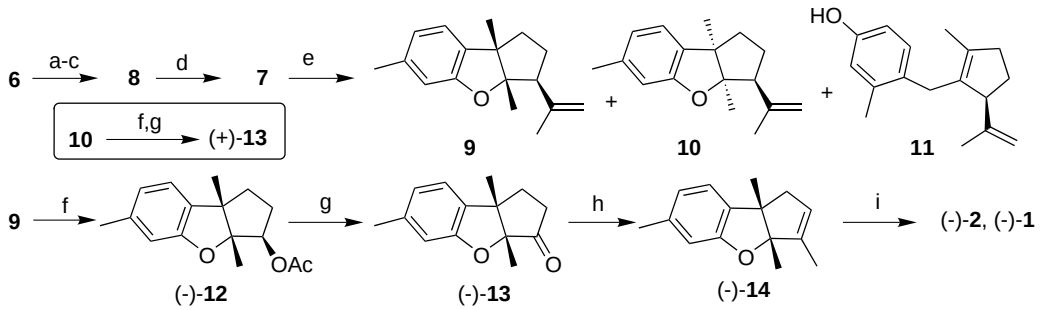

Scheme 1. *Reagents, conditions and yields:* (a) O_3/O_2, CH_2Cl_2–MeOH (5:1), −70°C; Me_2S, rt, 5 h; 70%; (b) piperidine, AcOH, C_6H_6, reflux, 1 h, 75%; (c) $CeCl_3{\cdot}6H_2O$, $NaBH_4$, MeOH, 0°C, 0.5 h, 92%; (d) *m*-cresol, PPh_3, DIAD, rt, 10 h, 83%; (e) $PhNMe_2$, sealed tube, 180°C, 72 h, 64%; (f) O_3/O_2, CH_2Cl_2–MeOH (5:1), −70°C; Ac_2O, NEt_3, DMAP, C_6H_6, reflux, 75%; (g) K_2CO_3, MeOH, rt, 2 h; PCC, NaOAc, CH_2Cl_2, rt, 1 h; 86%; (h) MeMgI, Et_2O; $POCl_3$–py, rt;[7] (i) reference 2d.

amine and 4-dimethylaminopyridine (DMAP) in refluxing benzene generated the acetate **12**† in 75% yield. Hydrolysis of the acetate followed by oxidation of the resultant alcohol with PCC–NaOAc transformed the acetate **12** into the ketone **13**, $[\alpha]_D^{24}$ −313 (*c* 3.6, $CHCl_3$), which exhibited spectral data identical to that of the racemic[7] compound. As expected, the same sequence transformed the minor isomer **10** into the enantiomeric ketone (+)-**13**, $[\alpha]_D^{23}$ +295 (*c* 0.35, $CHCl_3$). The ketone (−)-**13** was then transformed[7] into the olefin (−)-**14**, $[\alpha]_D^{23}$ −102 (*c* 0.5, $CHCl_3$) {lit.[2d] $[\alpha]_D^{25}$ −113 (*c* 0.2, $CHCl_3$}, via a Grignard reaction followed by dehydration, which exhibited ^1H and ^{13}C NMR spectral data identical to that reported.[2d] Since the olefin (−)-**14** has already been transformed[2c,d] into (−)-debromoaplysin **2** and (−)-aplysin **1**, via catalytic hydrogenation and bromination, the present sequence constitutes an enantiospecific total synthesis of these marine sesquiterpenes. Currently, we are investigating the extension of this methodology to other related sesquiterpenoids.

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