A New Synthesis of (+)-Didemnenones A and B

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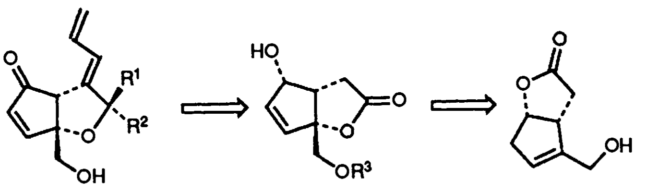
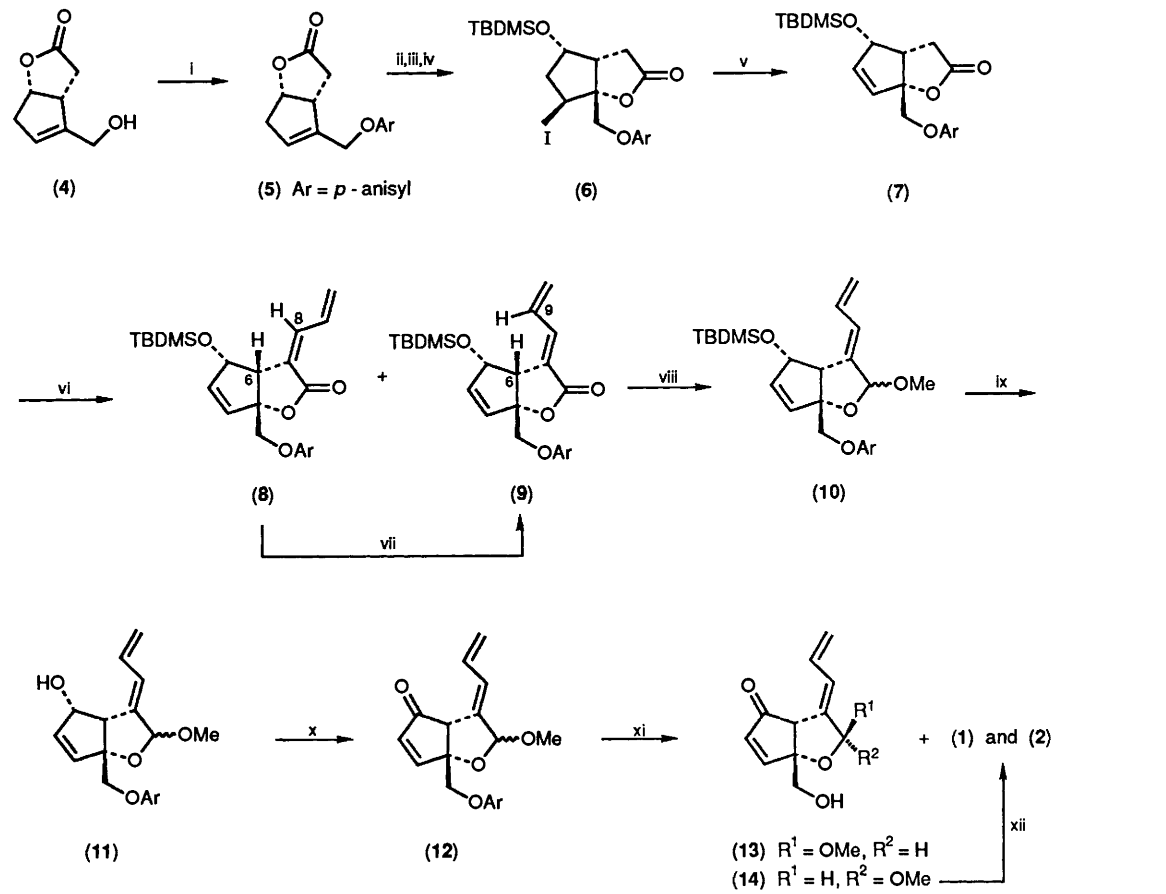
(+)-Didemnenones A (**1**) and B (**2**), unique and biologically active C_{11}-cyclopentenone metabolites from a tunicate, were synthesized from the optically active lactone (**4**).

In 1988 Fenical *et al.*[1] reported the isolation and the structure determination of (+)-didemnenones A (**1**) and B (**2**) as an inseparable mixture, from the Caribbean tunicate *Trididemnum cf. cyanophorum*, which showed antibacterial and antifungal activity. The first synthesis and the establishment of absolute configurations of (**1**) and (**2**) was achieved by Clardy *et al.*[2] We wish to report here a new and practical synthesis of (+)-didemnenones A (**1**) and B (**2**).



(1) R^1 = H, R^2 = OH
(2) R^1 = OH, R^2 = H
(3)
(4)

Scheme 1.



Scheme 2. *Reagents and conditions:* i, p-$MeOC_6H_4OH$ (1.5 equiv.), Ph_3P (1.5 equiv.), DEAD (1.5 equiv.), CH_2Cl_2, 25 °C, 3 h; ii, 30% NaOH (3.3 equiv.), 25 °C, 10 h; iii, KI (11 equiv.), I_2 (4 equiv.), H_2O, 0 ⟶ 5 °C, 60 h; iv, TBDMSCl (1.1 equiv.), imidazole (2.5 equiv.), DMF, 30 °C, 12 h; v, DBN (1.2 equiv.), THF, reflux, 11 h; vi, (*a*) $LiN(SiMe_3)_2$ (1.5 equiv.), THF, −78 °C, 1 h then acrolein (1.2 equiv.), 1 h, (*b*) MsCl (1.3 equiv.), Et_3N (2.5 equiv.), 25 °C, 4 h, (*c*) DBU (2 equiv.), THF, reflux, 1 h; vii, *i*-PrSLi (0.1 equiv.), THF, 25 °C, 48 h; viii, (*a*) DIBALH (1.5 equiv.), toluene, −78 °C, 3 h, (*b*) BF_3–OEt_2 (catalytic), MeOH, 0 °C, 15 min; ix, TBAF (1.7 equiv.), THF, 25 °C, 2 h; x, PDC (1.5 equiv.), CH_2Cl_2, 25 °C, 10 h; xi, CAN (2.4 equiv.), CH_3CN–H_2O, 0 °C, 5 min; xii, HCl (catalytic), THF–H_2O, 0 ⟶ 25 °C, 2.5 h).

Our retrosynthetic analysis of didemnenones A and B involves the construction of a diene, oxidation of an allylic alcohol and reduction of the lactone alcohol (3). Compound (3) would be prepared from optical active lactone alcohol (4) *via* halolactonization (Scheme 1).

The synthesis started with the protection[4] of the optically active lactone alcohol (4)† with p-methoxyphenol, triphenylphosphine and diethyl azodicarboxylate (DEAD) in CH_2Cl_2 to afford the p-methoxyphenylether (5)‡ {93.5%, m.p. 64–65 °C (AcOEt–hexane); $[\alpha]_D$ +51.9° (*c* 0.985 in $CHCl_3$)} (Scheme 2). Hydrolysis of (5) with 30% aqueous NaOH followed by halolactonization (KI, I_2) afforded an iodo alcohol and the resulting hydroxyl group was directly protected as the t-butyldimethylsilyl (TBDMS) derivative [TBDMSCl, imidazole–dimethylformamide (DMF)] to give (6) in 83% overall yield. Treatment of (6) with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) provided the bicyclic lactone (7) {100%, m.p. 93–94 °C (Et_2O–light petroleum); $[\alpha]_D$ +48.59° (*c* 0.992 in $CHCl_3$)}.

Condensation of (7) with acrolein in the presence of lithium hexamethyldisilazide [$LiN(SiMe_3)_2$, THF, −78 °C] followed by treatment with methanesulphonyl chloride (MsCl) and triethylamine (Et_3N) gave the mesyl derivative which was directly reacted with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give a separable mixture of *Z*-diene compound (8)§ {61% yield from (7); m.p. 105–106.5 °C (Et_2O–hexane); $[\alpha]_D$ +142° (*c* 0.99 in $CHCl_3$)} and *E*-diene compound (9) {26% yield from

† Compound (4) was readily prepared (Reference 3) from the commercially available (−)-3α, 5α-dihydroxy-2β-(hydroxymethyl)-cyclopentane-1α-acetic acid γ-lactone 3-benzoate (Corey lactone benzoate).

‡ All new compounds gave satisfactory spectral and analytical data.

§ The structure of (9) and (10) was elucidated by nuclear Overhauser enhancement (NOE) experiments in addition to 500 MHz ^1H NMR spectra. Irradiation of the proton 6-H gave a 5.2% NOE enhancement for the proton 8-H but not for the proton 9-H on the compound (9). In the case of compound (10), a 7.1% NOE enhancement was found between the proton 6-H and 9-H but not between the proton 6-H and 8-H proton (didemnenone numbering is used).

(7); m.p. 123–124 °C (Et_2O–hexane); $[\alpha]_D$ +205.3° (*c* 0.99 in $CHCl_3$)}].

Exposure of *Z*-diene compound (**8**) to lithium isopropylthiolate (*i*-PrSLi)[5] at room temperature for 48 h gave the *E*-diene compound (**9**) (75%) along with the starting material (25%). Reduction of (**9**) with di-isobutylaluminium hydride (DIBALH) at −78 °C followed by treatment with MeOH in the presence of catalytic BF_3–OEt_2 at 0 °C afforded a mixture of cyclic methyl acetal anomers (**10**) (81.6%). The TBDMS protecting group in (**10**) was removed under usual conditions [tetrabutylammonium fluoride (TBAF), THF, 25 °C] to give a separable mixture of (**11**) in a ratio of 3:1 (100%). Alcohol (**11**) was oxidized to the α,β-unsaturated ketone (**12**) with pyridinium dichromate (PDC)[6] in 78% yield. Deprotection[4] of *p*-methoxyphenyl protecting group in (**12**) with cerium(IV) ammonium nitrate (CAN) in CH_3CN–H_2O at 0 °C for 5 min gave didemnenones A (**1**) and B (**2**) (44%) directly along with a separable mixture of alcohol (**13**) (6.5%), and (**14**) (20%). The alcohol (**14**) showed identical spectroscopic data (^1H and ^{13}C NMR) with those of the compound (**14**)[1] derived from natural products. Hydrolysis of (**14**) with catalytic HCl in THF–H_2O also afforded (+)-didemnenones A (**1**) and B (**2**) (60% yield). The spectroscopic data (^1H and ^{13}C NMR) of synthetic (**1**) and (**2**) were closely correlated to the published data for didemnenones A (**1**) and B (**2**).

Experimental

(+)-*Didemnenones A* (**1**) *and B* (**2**).—CAN (317 mg, 0.58 mmol) was added to α,β-unsaturated ketone (**12**) (95 mg, 0.29 mmol) in a mixture of acetonitrile (3.3 ml) and water (0.83 ml) at 0 °C, and stirred (5 min) under argon. The mixture was made alkaline with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The extract was washed with brine and dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (5:1) gave recovered starting material (**12**) (5 mg); elution with hexane–ethyl acetate (4:1) gave the alcohol (**13**) (4 mg, 6.5%) and (**14**) (12 mg, 20%); and elution with hexane–ethyl acetate (1:4) gave (+)-didemnenones A (**1**) and B (**2**) (25 mg, 44%).

The alcohol (**13**) a colourless powder (Found: M^+, 222.0891; $C_{12}H_{14}O_4$ requires *M*, 222.0892); $\nu_{max}(CHCl_3)$ 3 300–3 500 (OH), and 1 720 (C=O).

The alcohol (**14**), m.p. 128–130 °C (AcOEt) [lit.,[2] m.p. 127–128 °C (no solvent specified)] (Found: M^+, 222.0888; $C_{12}H_{14}O_4$ requires M^+, 222.0892); $[\alpha]_D^{24}$ +375.2° (*c* 1.04 in $CHCl_3$) {lit.,[1] $[\alpha]_D$ +371.8° (*c* 0.86 in $CHCl_3$)}; $\nu_{max}(CHCl_3)$ 3 600, 3 500 (OH), and 1 720 (C=O).

Didemnenones A (**1**) and B (**2**), a colourless powder (Found: M^+, 208.0755 $C_{11}H_{12}O_4$ requires M^+, 208.0736); $[\alpha]_D^{28}$ +520.5° (*c* 0.44 in DMSO) {lit.,[1] $[\alpha]_D$ +576.1° (*c* 0.49, in DMSO)}; ν_{max}(Nujol) 3 300 (OH) and 1 710 (C=O); δ_H(500 MHz; CD_3OD) 3.63–3.80 (6 H, m), 5.28 (2 H, d, *J* 10.2 Hz), 5.35 (2 H, d, *J* 17 Hz), 5.50 (1 H, br s), 5.73 (1 H, s), 6.115 (1 H, d, *J* 5.5 Hz), 6.21 (1 H, d, *J* 5.5 Hz), 6.28 (2 H, br d, *J* 11 Hz), 6.91 (2 H, ddd, *J* 17, 11 and 10.2 Hz), 7.55 (1 H, d, *J* 5.5 Hz), and 7.62 (1 H, d, *J* 5.5 Hz).

Acknowledgements

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