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Total synthesis of 6-*epi*-sarsolilide A

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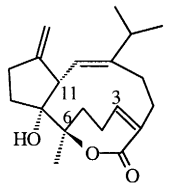
Abstract

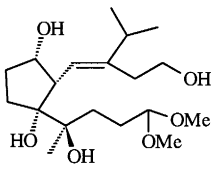
This paper describes an asymmetric synthesis of 6-*epi*-sarsolilide A. The 11-membered carbocycle and seven-membered lactone were established by an intramolecular HWE reaction and iodolactonization.

Keywords: sarsolilide A; intramolecular HWE reaction; total synthesis.

Sarsolilide A **1**[1] has been isolated from the marine *Sarcophyton solidun* Tixier-Durivault (Alcyoniidae). Due to the scarcity of the natural material, its absolute stereochemistry and biological activity are not known. The unique structure of sarsolilide A make it of synthetic interest.



Sarsolilide A 1



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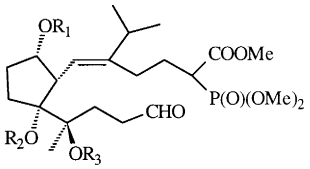

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In a preliminary report[2] we have described the synthesis of compound **2** containing three of the necessary chiral centers. However, experiments showed that it was very troublesome to convert **2** into the required precursor **3** for macrocyclization because of the presence of the C6–OH. So we changed our plan and attempted to firstly establish the 11-membered carbocycle from compound **7**, and then construct the last chiral center by iodolactonization. However, the results revealed that the chiral center created by iodolactonization was different from sarsolilide A **1**, as communicated herein. The synthetic route is shown in Scheme 1.

The synthesis commenced with compound **4**.[2] Selective desilylation[3] and then protection of the two hydroxyl groups gave carbonate **5**[4] in 86% yield. Cleavage of the TBDPS ether followed by iodination produced iodide **6** in 92% yield. The compound **6** was treated with three phosphonate reagents[5] and then hydrolysis[6] of the acetal with Amberlyst-15 afforded the corresponding precursors for intramolecular HWE reaction, that is **7**, **8** and **9** in 73%, 64% and 60% yield, respectively (two steps).

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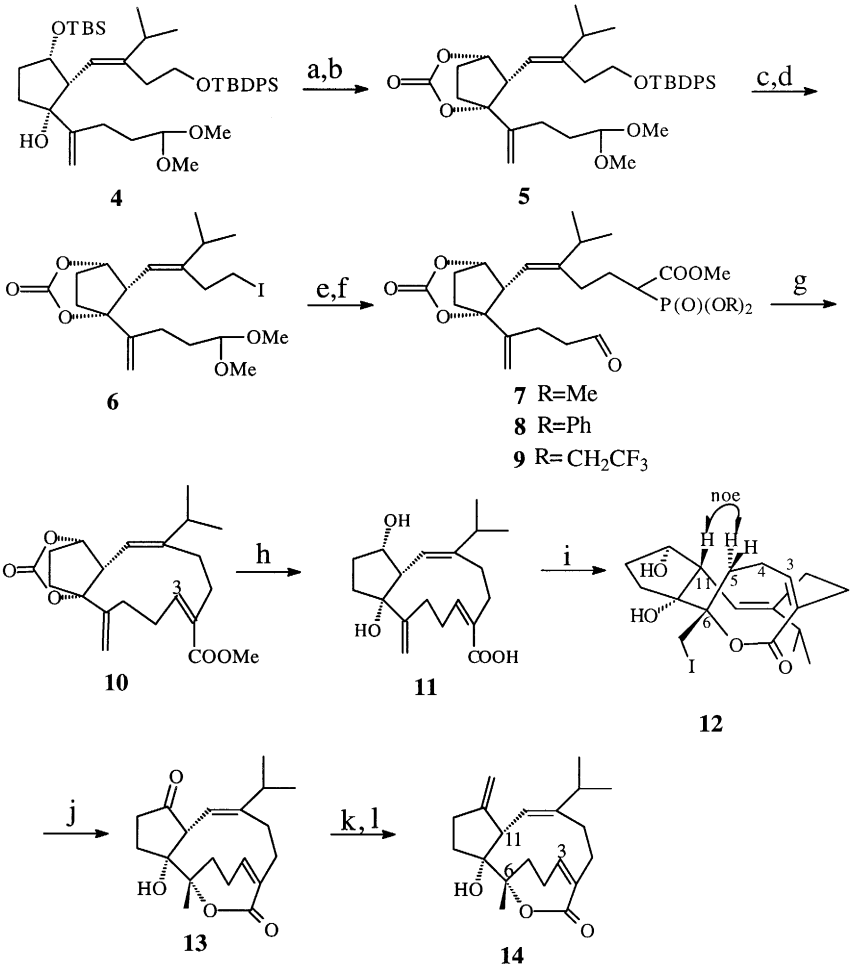

Scheme 1. Reagents and conditions: (a) $LiAlH_4$, Et_2O, rt, overnight; (b) triphosgene, pyridine, CH_2Cl_2, −78°C→0°C; (c) Bu_4NF, THF, rt, 1 h; (d) I_2, Ph_3P, imidazole, THF:CH_3CN (3:1), rt; (e) (i) $(RO)_2P(O)CH_2COOMe$, NaH, DMSO, rt, 30 min; (ii), **6**, DMSO, 50°C, 4 h; (f) Amberlyst-15, acetone–H_2O, rt, 2 h; (g) NaH, DME, rt, 20 h; (h) NaOH, THF–H_2O, reflux, overnight; (i) I_2, $NaHCO_3$, CH_3CN, rt, 1 h; (j) Bu_3SnH, AIBN, benzene, reflux, 30 min; (k) Dess–Martin oxid., CH_2Cl_2, rt, 30 min; (l) CH_2I_2, Zn, $TiCl_4$, THF, rt, 30 min

In our efforts at macrocyclization, exposure of the phosphono ester aldehyde **7** to NaH in DME at room temperature provided a mixture of cyclized products enriched in the undesired *E*-olefin in a 50% total yield (2:1 ratio of *E*:*Z*).[7] Examining the phenyl phosphonate aldehyde **8**[8] in the macrocyclization, showed that this reaction exhibited a surprising trend, and provided a mixture of product enriched in the desired *Z*-olefin in a 30% total yield (3:8 ratio of *E*:*Z*). We also had the occasion to examine the trifluoromethyl phosphonate aldehyde **9**; a variety of conditions for the cyclization of **9** were tried, but the results were disappointing and almost no product was obtained.

Subsequently, hydrolysis of the methyl ester of compound **10** was accompanied by the deprotection of the carbonate and iodolactonization was in situ performed. On treatment with a large excess of iodine at room temperature[9] for prolonged periods, lactone **12** was obtained in only 30% overall yield (two steps).[10] The most efficient iodolactonization condition was I_2–CH_3CN, resulting in reaction completed in 1 h, to give **12** in 32% yield. Reduction of the iodide **12** with tributyltin hydride and oxidation of the resulting alcohol by Dess–Martin reagent gave compound **13** in 45% yield (two steps).

Finally, methylenation of ketone **13** by the mild CH_2I_2–Zn–$TiCl_4$ system[11] yielded the target **14**. However, it was notable that there was a remarkable difference on comparison of the ^{1}H NMR of compound **14** with that of sarsolilide A **1**[12] in the chemical shifts of C11–H and C6–CH_3 (compound **14**: C11–H, δ 3.63; C6–CH_3, δ 1.52; sarsolilide A **1**: C11–H, δ 3.01; C6–CH_3, δ 1.40). Consequently, it appears that the final chiral center created at the C6-position is different from sarsolilide A **1**.

To confirm the assignment of the C6-configuration, the iodide **12** was studied by ^{1}H NMR, TOCOSY, DQCOSY and NOESY spectra. The C5 proton position was identified through the correlation of the C3–C4–C5 protons in the TOCOSY and DQCOSY spectra. The observed intense correlation between C5–H and C11–H in the NOESY experiment indicated that the configuration of C6 was different from that in the natural product.

In summary, we have achieved the first enantioselective synthesis of 6-*epi*-sarsolilide A.

Acknowledgements

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7. The *E*- and *Z*-isomers of the ester-substituted double bond could be separated by column chromatography (3:1 petroleum:ethyl acetate), their configurations were readily identified by the chemical shifts of the characteristic vinylic hydrogen in ^{1}H NMR (*E*-olefin: δ 6.93 for C3–H; *Z*-olefin δ 5.79 for C3–H). Selected data for the *Z*-isomer **10**: $[\alpha]_D^{15}$=+217.9 (*c* 0.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (t, 1H, *J*=8.3 Hz), 5.61 (s, 1H), 5.24 (d, 1H, *J*=1.9 Hz), 5.19 (d, 1H, *J*=9.6 Hz), 4.48 (t, 1H, *J*=3.1 Hz), 3.77 (s, 3H), 3.00–2.94 (m, 1H), 2.72–2.67 (m, 1H), 2.57 (dd, 1H, *J*=2.6, 9.6 Hz), 2.48–2.43 (m, 1H), 2.32–2.09 (m, 7H), 2.00–1.92 (m, 1H), 1.87–1.73 (m, 2H), 1.04 (d, 3H, *J*=6.8 Hz), 1.03 (d, 3H, *J*=6.8 Hz). Selected data for the *E*-isomer: $[\alpha]_D^{15}$=+174.4 (*c* 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (dd, 1H, *J*=6.7, 9.1 Hz), 5.52 (s, 1H), 5.16 (d, 1H, *J*=10.2 Hz), 5.13 (s, 1H), 4.56–4.54 (m, 1H), 3.75 (s, 3H), 2.95 (dd, 1H, *J*=2.6, 10.2 Hz), 2,72–2.45 (m, 4H), 2.38–2.18 (m, 5H), 2.11–1.98 (m, 3H), 1.85–1.75 (m, 1H), 1.03 (d, 3H, *J*=6.9 Hz), 1.01 (d, 3H, *J*=6.9 Hz).
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10. Selected data for **12**: $[\alpha]_D^{20}$=+32.0 (*c* 0.19, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.34 (dd, 1H, *J*=5.4, 9.0 Hz), 5.44 (d, 1H, *J*=10.2 Hz), 4.05 (d, 1H, *J*=11.1 Hz), 4.01 (br s, 1H), 3.40 (d, 1H, *J*=11.1 Hz), 3.17 (dd, 1H, *J*=5.1, 10.2 Hz), 2.93 (dd, 1H, *J*=5.4, 13.8 Hz), 2.83 (dd, 1H, *J*=5.4, 13.2 Hz), 2.70 (s, 1H), 2.34–2.16 (m, 6H), 2.06–1.96 (m, 4H), 1.90 (dt, 1H, *J*=2.4, 11.2 Hz), 1.69–1.63 (m, 1H), 1.08 (d, 3H, *J*=6.9 Hz), 1.05 (d, 3H, *J*=6.9 Hz).
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12. Selected data for **14**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.32 (dd, 1H, *J*=9.0, 6.0 Hz), 5.16 (d, 1H, *J*=10.2 Hz), 4.94 (s, 1H), 4.63 (s, 1H), 3.63 (dd, 1H, *J*=2.4, 10.2 Hz), 2.82 (dt, 1H, *J*=3.6, 13.6 Hz), 2.66–2.59 (m, 1H), 2.43–2.36 (m, 2H), 2.33–2.15 (m, 5H), 1.99 (dd, 1H, *J*=5.1, 13.2 Hz), 1.78 (ddd, 1H, *J*=2.4, 8.4, 13.2 Hz), 1.67 (ddd, 1H, *J*=9.3, 11.1, 13.2 Hz), 1.52 (s, 3H), 1.07 (d, 3H, *J*=6.9 Hz), 1.05 (d, 3H, *J*=6.9 Hz); HRMS found 316.2043; calcd: 316.2039. Selected data for sarsolilide A **1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (dd, 1H, *J*=9.0, 6.0 Hz), 5.18 (d, 1H, *J*=10.3 Hz), 4.89 (d, 1H, *J*=1.9 Hz), 4.64 (d, 1H, *J*=1.9 Hz), 3.01 (d, 1H, *J*=10.3 Hz), 2.91 (m 1H), 2.63–2.43 (m, 2H), 2.40 (m, 2H), 2.35 (m, 1H), 2.20 (m, 1H), 2.07 (m, 2H), 1.97 (m, 2H), 1.78 (m, 2H), 1.60 (br s, 1H, OH), 1.40 (s, 3H), 1.04 (d, 3H, *J*=6.8 Hz), 1.04 (d, 3H, *J*=6.8 Hz).