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Studies toward the total synthesis of sarsolilide A: preparation of the proper precursor for the macrocyclization

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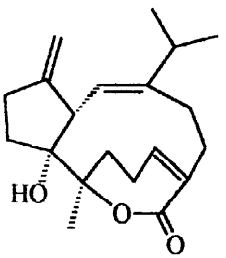
Abstract

A strategically functionalized chiral cyclopentane, as a proper precursor for the synthesis of Sarsolilide A, has been synthesized with complete stereochemical control.

Keywords: *Sarsolilide A; zirconium-mediated ring-contraction; chiral cyclopentane; E-trialkyl -substituted alkene*

Sarsolilide A **1**,[1] isolated from the marine *Sarcophyton Solidun* Tixier-Durivault (Alcyoniidae), has an unusual tricyclic framework composed of a [9. 3. 0] tetradecane nucleus and a seven-membered α,β-unsaturated lactone whose double-bond resides at a bridgehead site. Although the structure has been determined, its absolute stereochemistry remains unsolved, and the biological activity also was not tested owing to the scarcity of natural material. It was these factors that prompted us to study its enantioselective total synthesis.



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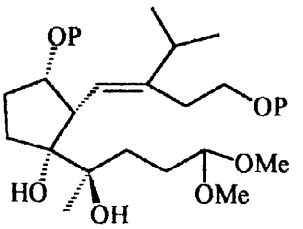

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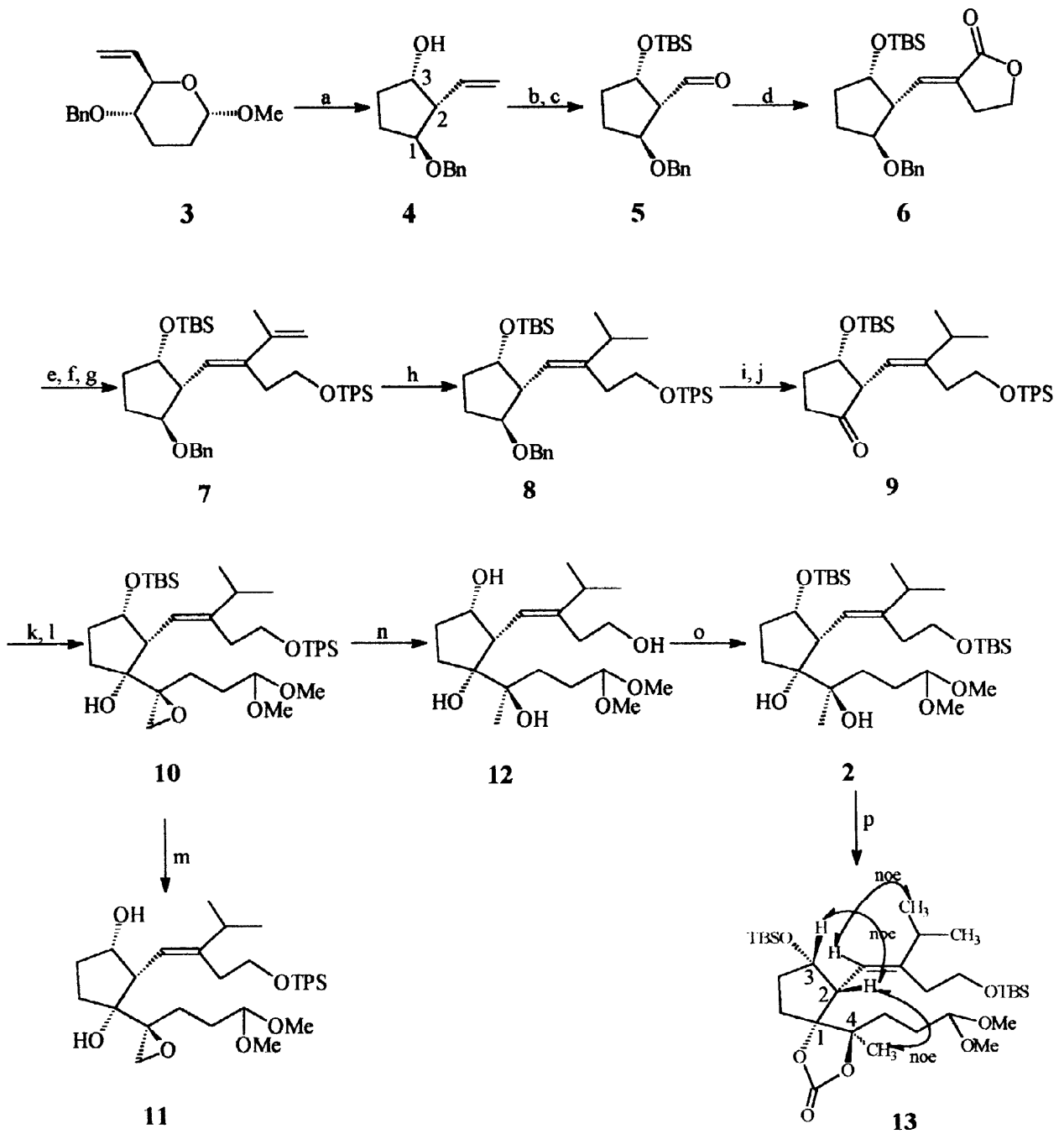

Scheme 1. Reagents and conditions: a) 1.1eq. Cp_2ZrCl_2, 2.2eq. n-BuLi, THF, -78°C to rt, 4hr; then 1.2eq. $BF_3{\bullet}Et_2O$, 0°C to rt, 2hr, 54%; b) TBDMSCl, imid., DMF, rt, 12hr, 95%; c) CH_2Cl_2, O_3, -78°C; then Ph_3P, -78°C to rt, 1.5hr; d) 1-butyrolactonylidene triphenylphosphorane, toluene, 100°C, 10hr, 65% (2 steps); e) CH_3Li, Et_2O, -78°C to rt, 10min, 95%; f)TBDPSCl, imid., DMF, rt, 2hr, 90%; g) MsCl, DMAP, Et_3N, -78°C to rt, 2hr, 80%; h) excess NH=NH, DMF, 95°C, 10hr, 80%; i) 20%$Pd(OH)_2$/C, cyclohexene, EtOH, reflux, 5hr, 95%; j) Dess-Martin oxid., 80%; k) 1.2eq. $LiC(=CH_2)(CH_2)_2C(OMe)_2$, THF, -78°C to rt, 2hr, 80%; l) $VO(acac)_2$, TBHP, PhH, rt, 1hr, 85%; m) $LiAlH_4$, Et_2O, rt, 4hr, 90%; n) $LiAlH_4$, THF, reflux, overnight, 60%; o) TBDMSCl, imid., DMF, rt, 12hr, 80%; p) $CO(OCCl_3)_2$, pyridine, CH_2Cl_2, -78°C to rt, 2hr, 60%.

According to our synthetic strategy, the first goal would be to construct a chiral cyclopentane with two side-chains, as in compound **2**, one side-chain with an *E*-trialkyl-substituted double-bond and the other with a tertiary *vic*-diol, and then to establish the three chiral centers inherent in the molecule. Here we communicate our results. The synthetic route is shown in **Scheme 1.**

Following the scheme, we began the investigation with the preparation of chiral cyclopentane **4**, which could be accomplished by modeling the zirconium-mediated ring-contraction developed by T. Taguchi[2] starting from the compound **3**.[3] The yield was 54%. Based on the mechanism and the configuration of the 1-benzyloxyl group, the configurations of the 2- and 3-carbons were assigned as shown and further confirmed by a NOESY experiment on the 3-acylated product.[4]

After conversion of **4** into aldehyde **5**, our attention was focused on the elaboration of the upper side chain. On several attempts, an indirect pathway was chosen which involved reaction of 1-butyrolactonylidene triphenylphosphorane[5] with aldehyde **5** and then conversion of the lactone to an isopropyl group. These transformations were carried out successfully. The Wittig product **6** was obtained in 65% yield (2steps).[6] Then **6** was treated with excess methyl lithium followed by dehydration and the resulting terminal double-bond was selectively reduced by diimide (generated *in situ* from ethyl acetate and hydroxylamine in DMF[7]) to afford the desired compound **8**.

Installation of the second side chain was executed as follow. Treatment of ketone **9** with the vinyllithium (prepared from t-BuLi and 2-bromo-5, 5-dimethoxy-1-pentene[8]) and epoxidation of the resulting allylic alcohol by Bu^tOOH-$VO(acac)_2$ system[9] provided epoxide **10** in 70% yield (2 steps). In general, $LiAlH_4$ is the preferred reagent for the reductive opening of epoxides, and silyl ethers are stable unless there is a near hydroxyl in the molecule.[10] Interestingly, treatment of epoxide **10** with $LiAlH_4$ in ether afforded only the desilylated product **11**, implying that the resulting tert-hydroxyl and 3-silyloxyl groups are situated on the same side of cyclopentane, i.e. α-orientation. Treatment of epoxide **10** with $LiAlH_4$ in THF, under reflux, gave compound **12**, and protection of the pri- and sec-hydroxyls gave compound **2** (p=TBS).

In order to determine the configuration of the last created chiral center in compound **2**, the spiro-carbonate **13**[11] was prepared. The observed intense correlation between H-C(2) and CH_3-C(4) in a NOESY experiment indicated that the configuration of C(4) was as expected. The configuration of the trisubstituted double-bond was again confirmed by the NOESY experiment.

In summary, we have established the highly-hindered trisubstituted double-bond and all the three chiral centers inherent in the target molecule, which should be an efficient precursor for the total synthesis of Sarsolilide A. Synthetic studies of Sarsolilide A are now actively being conducted in our laboratory.

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References and notes:

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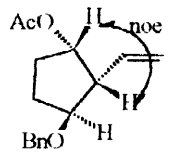
2. (a) Ito, H.; Motoki,Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, 115, 8835-8836; (b) Hanzawa, Y.; Ito, H.; Taguchi,T. Synlett **1995**, 299-305.
3. Stamatatos, L.; Sinay, P.; Pougny, J.R. *Tetrahedron Lett.* **1984**, 40, 1713-1719.
   This compound was prepared from D-glucose in a ten-step procedure in 25% overall yield with modifications by us.
4. We also obtained the minor isomer (**14:15** = 15:1). The stereochemistries were unambiguosly determined by NOESY experiment of compound **14** and **15**.



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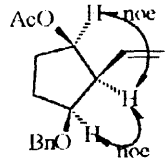

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Data for **14**: ^{1}HNMR δ (400MHz, $CDCl_3$): 7.28-7.19 (m, 5H), 5.72 (ddd, J=8.3, 10.3, 17.3Hz, 1H), 5.21-5.18 (m, 1H), 5.13 (d,17.3Hz, 1H), 5.07 (d, J=10.3Hz, 1H), 4.47 (s, 2H), 3.95-3.91 (m, 1H), 2.73-2.65 (m, 1H), 2.09-2.06 (m, 2H), 1.94 (s, 3H), 1.67-1.60 (m, 2H).

15: ^{1}HNMR δ (400MHz, $CDCl_3$): 7.33-7.26 (m, 5H), 5.98 (ddd, J=7.1, 10.0, 20.0Hz, 1H), 5.19-5.09 (m, 3H), 4.53, 4.48 (2H of AB system, J=12.1Hz), 3.99-3.94 (m,1H), 2.95-2.90 (m, 1H), 2.03 (s, 3H), 2.02-1.85 (m, 4H).

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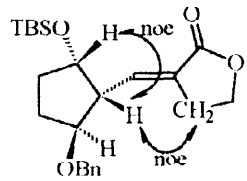
6. Minor isomer **16** was also obtained (**6:16** = 20:1). The configuration of the double bond was determined by the value of δ. Compound **6** was characterized by NOESY experiment as shown below.



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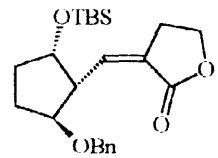

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Data for **6**: ^{1}HNMR δ (300MHz, $CDCl_3$), 7.34-7.22 (m, 5H), 6.91 (dt, J=2.9, 10.0Hz, 1H), 4.47, 4.42 (2H of AB system, J=11.7Hz), 4.33-4.26 (m, 3H), 4.13-4.08 (m, 1H), 2.97-2.82 (m, 2H), 2.68-2.61 (m, 1H), 2.31-2.17 (m, 1H), 2.07-2.00 (m, 1H), 1.74-1.66 (m, 2H), 0.86 (s, 9H), 0.00 (s, 6H).

16:^{1}HNMR δ (300MHz, $CDCl_3$), 7.35-7.23 (m, 5H), 6.30 (dt, J=2.2, 9.3Hz, 1H), 4.50 (s, 2H), 4.43-4.40 (m, 1H), 4.33 (t, J=7.4Hz, 2H), 4.06-4.00 (m, 2H), 2.94-2.88 (m, 2H), 2.23-2.07 (m, 2H), 1.75-1.61 (m, 2H), 0.86 (s, 9H), -0.01 (s, 3H), -0.05 (s, 3H).

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11. Data for **13**: ^{1}HNMR δ (400MHz, $CDCl_3$), 5.45 (d, J=9.9Hz, 1H), 4.34 (t, J=5.2Hz, 1H), 4.20-4.19 (m, 1H), 3.67-3.61 (m, 1H), 3.58-3.53 (m, 1H), 3.32 (s, 3H), 3.31 (s, 3H), 2.65 (dd, J=5.7, 9.9Hz, 1H), 2.38-2.23 (m, 4H), 1.94-1.88 (m, 5H), 1.75-1.50 (m, 2H), 1.29 (s, 3H), 1.03 (d, J=7.0Hz, 3H), 1.01 (d, J=7.0Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.07 (s, 6H), 0.00 (s, 3H), -0.35 (s, 3H).