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A stereoselective synthesis of the C_{15}–C_{25} subunit of (+)-lasonolide A

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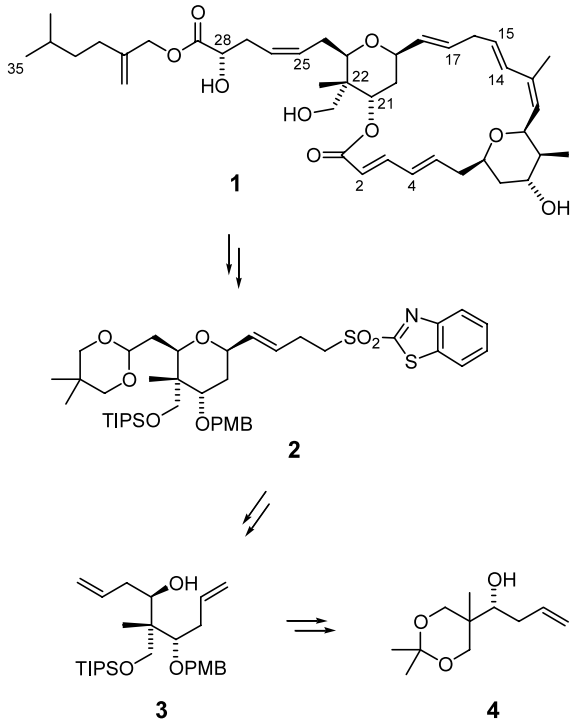
Abstract—The C_{15}–C_{25} upper THP segment **2** of (+)-lasonolide A has been synthesized efficiently via diastereomeric differentiation, iodocyclization and Julia–Kocieński's sulfone olefination to install its quaternary chiral center, *cis*-2,6-disubstituted THP and *trans*-olefin, respectively.

In conjunction with discovering new antitumor agents from marine organisms, lasonolide A was isolated from the shallow water Carribean marine sponge, *Forcepia* sp., by McConnell et al.[1] It displays potent in vitro cytotoxic activity against A-549 human lung carcinoma cells and inhibition of cell adhesion in a cell assay for searching signal transduction agents.[2] Although the relative stereochemistry of lasonolide A was proposed by extensive spectroscopic studies, it was recently revised, and the undetermined C_{28} hydroxy group and the absolute configuration were suggested as **1** by synthetic studies.[3] The attractive structural and biological features of lasonolide A directed us to be involved in its total synthesis. In this paper, we report an enantioselective synthesis of the C_{15}–C_{25} fragment comprising four stereogenic centers with a quaternary carbon center and one *trans*-olefinic double bond.[4]

Based on the retrosynthetic analysis toward **1**, the C_{15}–C_{25} segment was chosen as our immediate synthetic target, which was appositely functionalized to build the C_{14} *trans*-double bond by sulfone chemistry and the C_{25} *cis*-double bond by Wittig reaction (Scheme 1). We envisaged that the THP ring of **2** could be formed by iodocyclization of δ-hydroxyalkene **3** and its double bond by another sulfone protocol. The quaternary asymmetric center of **3** was planned to be established by diastereomeric differentiation of the two alkoxymethyl groups of **4**.



Scheme 1. Retrosynthetic analysis.

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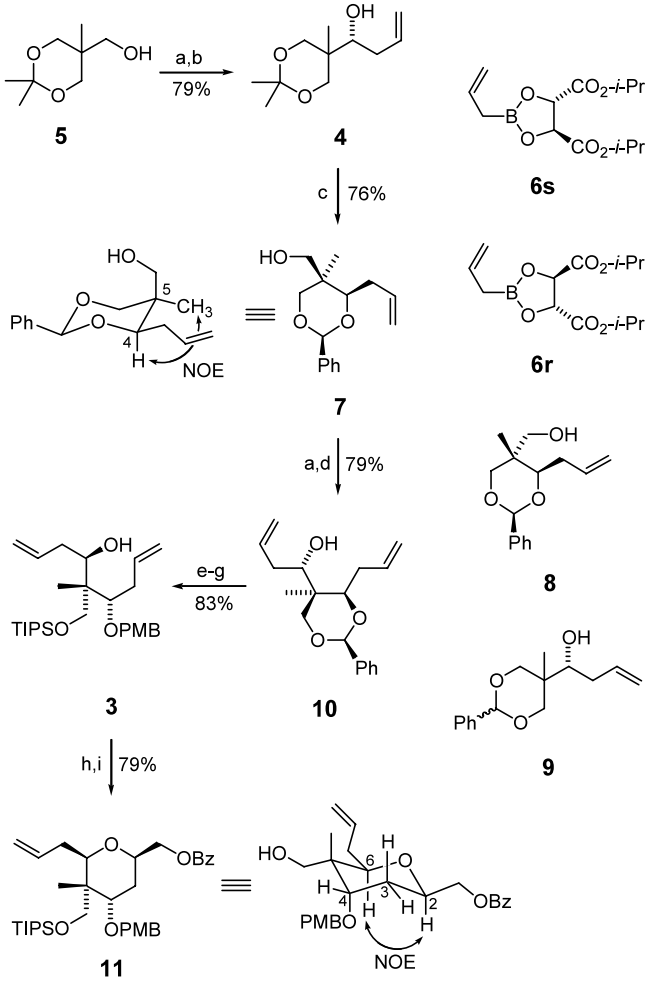
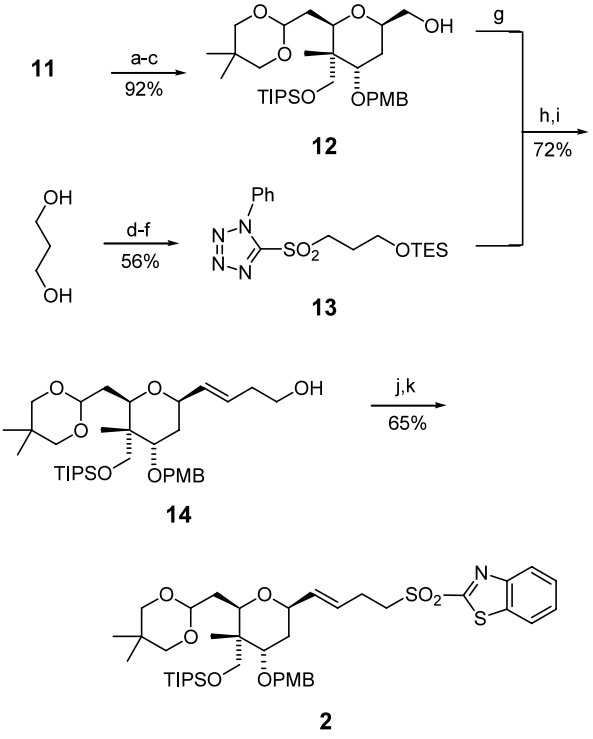
The known alcohol **5**[5] was sequentially subjected to Swern oxidation[6] and asymmetric allylation using allylboronate **6s**[7] to afford homoallyl alcohol **4** in 78% ee and 79% overall yield (Scheme 2). To differentiate the two alkoxymethyl groups of **4**, it was treated with benzaldehyde in the presence of 3 mol% of *p*-TsOH to give rise to a 1:1 mixture of the desired benzylidene **7** and its diastereomer **8** in 80% combined yield along with 14% of the other diastereomers **9**. After two more resubmission of **8** and **9** to benzylidene formation, **7** was obtained in 76% combined yield, the stereochemistry of which was corroborated by observing the NOE enhancements between the C_4 hydrogen and the C_5 methyl group. Another Swern oxidation and asymmetric allylation using allylboronate **6r** furnished alcohol **10** in 91% increased ee and 77% yield. Its protecting groups were adjusted by *p*-methoxybenzylation, acidic hydrolysis of the benzylidene group and silylation in sequence to give δ-hydroxyalkene **3** in 83% overall yield. Stereoselective formation of tetrahydropyranyl ring was attained by iodocyclization[8] of **3** to produce a 12:1 inseparable mixture of *cis*- and *trans*-2,6-disubstituted THP derivatives. After converting the mixture into benzoates by sodium benzoate in 1-methyl-2-pyrrolidinone (NMP), the desired benzoate **11** was separated in 79% overall yield, and its *cis*-stereochemistry was manifested by NOE enhancements between C_2 hydrogen and C_6 hydrogen, and the coupling constants ($J_{2H,3H}=10.1$ and 2.5 Hz, $J_{3H,4H}=2.6$ and 2.6 Hz).



Scheme 2. *Reagents and conditions*: (a) Swern oxidation; (b) **6s**, 4 Å MS, PhMe, −78°C to rt; 2N NaOH, 0°C; (c) PhCHO, *p*-TsOH, PhMe, rt; (d) **6r**, 4 Å MS, PhMe, −78°C to rt; 2N NaOH, 0°C; (e) *p*-$MeOC_6H_4CH_2Cl$, KH, *n*-Bu_4NI, THF, 0°C to rt; (f) *p*-TsOH, MeOH, rt; (g) TIPSCl, DMAP, Et_3N, CH_2Cl_2, rt; (h) I_2, K_2CO_3, MeCN, −25 to −15°C; (i) PhCOONa, NMP, 100°C.

With access to the right THP part **11** secure, the left three carbon equivalent **13** was prepared in 56% overall yield by Mitsunobu reaction of 1,3-propanediol using 1-phenyl-1*H*-tetrazole-5-thiol[9] followed by MCPBA oxidation and silylation (Scheme 3). The olefinic double bond of **11** was oxidatively cleaved, the generated aldehyde was protected as acetal using 2,2-dimethyl-1,3-propanediol and the benzoate group was hydrolyzed to provide alcohol **12** in 92% overall yield. After Swern oxidation of **12**, the resulting aldehyde was olefinated with sulfone **13** using KHMDS to afford an inseparable mixture of alkenes. Desilylation of the alkenes gave a 9:1 separable mixture of *trans*-alkene **14** and *cis*-isomer in 80% combined overall yield. Alcohol **14** was transformed into sulfide under Mitsunobu conditions using 2-mercaptobenzothiazole[10] and oxidized to sulfone with



Scheme 3. *Reagents and conditions*: (a) OsO_4, $NaIO_4$, MeOH, H_2O, THF, 0°C; (b) $HOCH_2C(Me)_2CH_2OH$, *p*-TsOH, PhMe, 80°C; (c) K_2CO_3, MeOH, rt; (d) 1-phenyl-1*H*-tetrazole-5-thiol, DEAD, Ph_3P, THF, 0°C; (e) MCPBA, $NaHCO_3$, CH_2Cl_2, 0°C to rt; (f) TESCl, DMAP, Et_3N, CH_2Cl_2, 0°C; (g) Swern oxidation; (h) KHMDS, DME, −60°C to rt; (i) PPTS, THF, MeOH, 0°C; (j) 2-mercaptobenzothiazole, DEAD, Ph_3P, THF, 0°C; (k) 30% H_2O_2, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, THF, EtOH, rt.

heptamolybdate to produce the C_{15}–C_{25} upper THP subunit **2**[11] in 71% overall yield along with 13% of corresponding sulfoxide, which could be reoxidized to sulfone **2** in 81% yield.

In summary, a stereocontrolled synthesis of the C_{15}–C_{25} fragment **2** of (+)-lasonolide A has been developed via diastereomeric differentiation for the C_{22} quaternary stereogenic center, asymmetric allylation for the C_{21} and C_{23} asymmetric centers, and iodocyclization for the C_{19} chiral center.

Acknowledgements

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11. *Spectral data of* ***2***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (1H, dd, $J=8.5$, 1.0 Hz), 7.99 (1H, dd, $J=8.1$, 0.6 Hz), 7.62–7.56 (2H, m), 7.19 (2H, d, $J=8.5$ Hz), 6.82 (2H, d, $J=8.5$ Hz), 5.57–5.55 (2H, m), 4.55–4.52 (1H, m), 4.42 (1H, d, $J=11.1$ Hz), 4.35 (1H, d, $J=11.1$ Hz), 4.10 (1H, dt, $J=11.8$, 2.7 Hz), 3.78 (3H, s), 3.79–3.72 (1H, m), 3.73 (1H, d, $J=9.1$ Hz), 3.61–3.58 (2H, m), 3.54–3.51 (3H, m), 3.42–3.35 (3H, m), 2.64–2.59 (2H, m), 1.67–1.57 (3H, m), 1.46–1.39 (1H, m), 1.13 (3H, s), 1.06–0.99 (21H, m), 0.90 (3H, s), 0.67 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 158.9, 152.7, 136.7, 134.5, 131.3, 128.9, 128.0, 127.6, 125.4, 125.0, 122.3, 113.5, 100.0, 77.2, 76.8, 72.6, 71.6, 70.9, 66.3, 55.2, 54.1, 41.9, 35.9, 30.9, 30.1, 25.3, 23.0, 21.8, 18.1, 15.2, 12.0.