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Diastereoselective synthesis of the 19-*epi*-C_{18}–C_{25} segment of (−)-lasonolide A and an unusual inversion at C_{19}

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Abstract—Diastereoselective construction of the 19-*epi*-C_{18}–C_{25} segment of (−)-lasonolide A was achieved using a 5-*exo*-trigonal mode of radical cyclization for the creation of the contiguous quaternary and tertiary stereogenic centers at C_{22} and C_{23} as the key reaction step. During the dehydration stage, it was found that an unusual inversion of configuration took place.

Lasonolide A, a polyketide-derived natural product isolated from extracts of the Caribbean marine sponge *Forcepia* sp. by McConnell and co-workers,[1] was discovered to inhibit the in vitro proliferation of A-549 human lung carcinoma cell as well as cell adhesion in a newly-developed whole cell assay that detects signal transduction agents. Because of its intriguing structural features, interesting biological profile and limited availability, lasonolide A is an attractive target for total synthesis. To date, two total syntheses[2,3] have been communicated by Korean groups. In particular, Lee and co-workers[2] revised the proposed structure and established the absolute structure by their first total synthesis. We attempted the synthesis of the C_{18}–C_{25} segment (**2**) of (−)-lasonolide A (**1**),[4] the unnatural enantiomer, using a 5-*exo*-trigonal mode of radical cyclization for the construction of the crucial quaternary and tertiary stereogenic centers[5] at C_{22} and C_{23} as the key reaction step. Herein we report a diastereoselective construction of the 19-*epi*-C_{18}–C_{25} segment (**3**) of (−)-lasonolide A and an unusual inversion at C_{19} during the dehydration stage (Fig. 1).

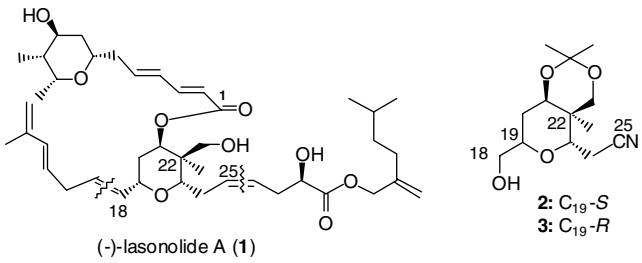

Figure 1.

We envisaged constructing the C_{22} quaternary stereogenic center of the target segment (**2**) using a 5-*exo*-trigonal mode of radical cyclization of the dihydropyran (**6**) to give the radical intermediate (**5**) with the (22*R*) configuration. This radical species would abstract hydrogen of metal hydride, for example, tri-*n*-butyltin hydride, from the opposite face of the C_{19} alkoxymethyl moiety to furnish the (23*R*)-tetrahydropyran (**4**), which would be transformed to the target molecule (**2**) via sequential one-carbon elongation, oxidation of the carbon–silicon bond and protection of the resulting 1,3-diol (Scheme 1).

Aldol condensation of **7**,[6] derived from (*S*)-malic acid, with (*S*)-3-(1-oxopropyl)-4-benzyl-2-oxazolidinone in the presence of dibutylboron triflate and Hunig's base gave the aldol product (**8**) diastereoselectively in 95% yield. Acidic hydrolysis followed by selective protection of the primary alcohol moiety of the resulting triol as the *t*-butyldiphenylsilyl (TBDPS) ether provided the diol (**9**). Hydrolytic removal of the chiral auxiliary produced the carboxylic acid, which was treated with EDC, HOBT, and triethylamine to provide the lactone (**10**)[7] in 59% yield from **8**. After protection of the secondary hydroxyl group as the *t*-butyldimethylsilyl (TBS) ether, the benzyloxymethyl anion,[8] generated in situ from benzyloxymethyl(tributyl)stannane, was added to the C_{23}

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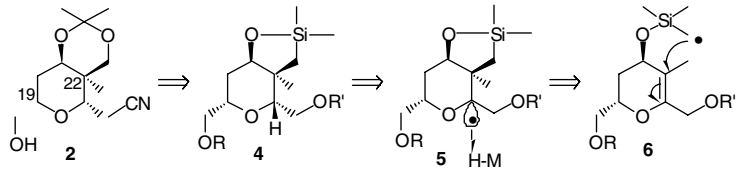
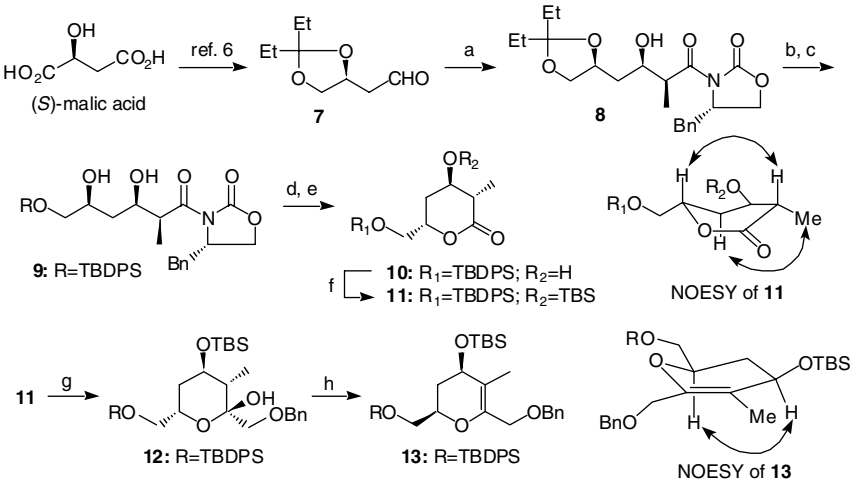


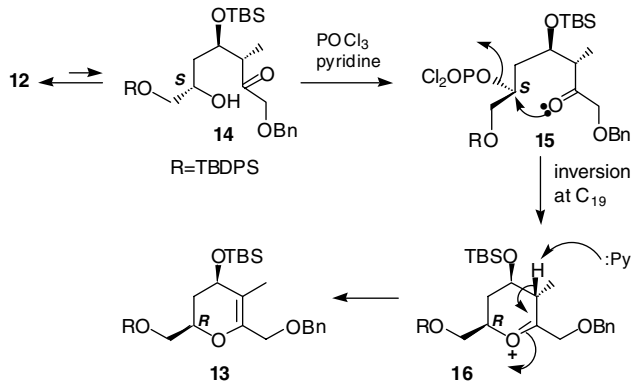
Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) (*S*)-3-(1-oxopropyl)-4-benzyl-2-oxazolidinone, *n*-Bu_2OTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 1 h, 95%; (b) Dowex®, aq MeOH, reflux, 12 h; (c) *t*-$BuPh_2SiCl$, imidazole, 4-DMAP, CH_2Cl_2, 0 °C, 1.5 h, 86% for the two steps; (d) $LiOH{\cdot}H_2O$, 35% H_2O_2, H_2O, THF, 0 °C, 1.5 h; (e) EDC, HOBT, Et_3N, CH_2Cl_2, rt, 1.5 h, 68% for the two steps; (f) TBSOTf, 2,6-lutidine, DMF, rt, 13 h, 97%; (g) *n*-Bu_3SnCH_2OBn, *n*-BuLi, THF, −78 °C, 2 h, 97%; (h) $POCl_3$, pyridine, rt, 48 h, 51%.

position of **11** to give the hemiacetal (**12**) as a single product,[9] which was exposed to dehydration conditions using phosphorus oxychloride in pyridine at room temperature. The simple dehydrated product could not be obtained; however, surprisingly, the epimeric product at C_{19} was generated in 51% yield. The structure was deduced by a NOESY spectrum, in which a distinct correlation between the C_{19} and C_{21} methine protons was observed (Scheme 2).

As a plausible mechanistic explanation for the unusual and interesting inversion at C_{19}, we propose that inversion takes place via an intramolecular S_N2-type displacement process, as shown in Scheme 3. Initially, the



Scheme 3. A plausible mechanism.

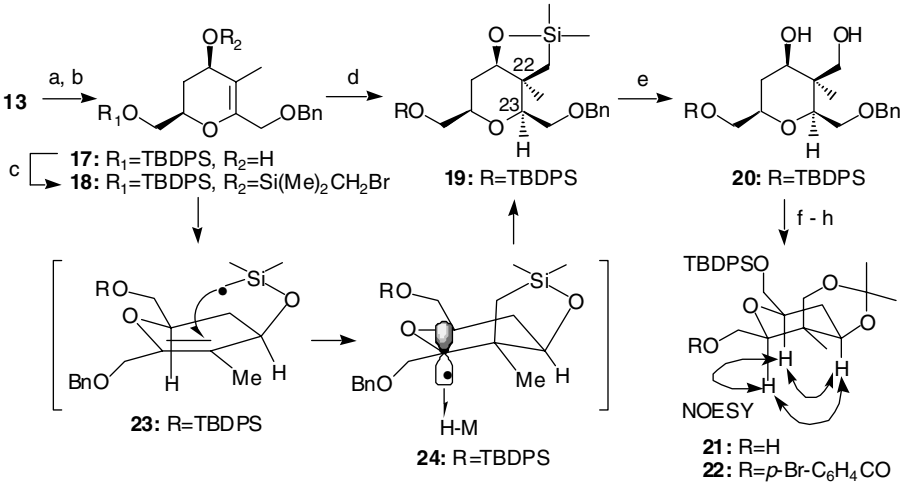
lactol (**12**) opens up to the hydroxy ketone (**14**) and the C_{19} hydroxyl function is activated as the chlorophosphonate (**15**), which is then displaced by the carbonyl oxygen in an intramolecular S_N2-type reaction. This process would invert C_{19} and give the oxonium intermediate (**16**), which would be converted to **13** with the 19*R* configuration.

Although disappointing, this result did not deter us from examining further transformations because, ultimately, we were interested in the stereochemical outcome of the radical cyclization for the construction of contiguous quaternary and tertiary stereogenic centers. Thus deprotection of the silyl ethers in **13** followed by selective protection of the primary hydroxyl group as TBDPS ether gave the alcohol (**17**), which was treated with bromomethyldimethylchlorosilane and triethylamine to provide **18**, the substrate for the key radical reaction, in 57% yield from **13**. Treatment of **18** with a catalytic tri-*n*-butyltin chloride, sodium cyanoborohydride, and AIBN in refluxing *t*-butanol[10] for 3 h provided the bicyclic silyl ether (**19**) as a single product. Since this compound was slightly unstable, it was immediately exposed to Tamao oxidation conditions[11] to produce the 1,3-diol (**20**) in 59% yield for the two steps. The stereochemistry of the newly generated stereogenic centers (C_{22} and C_{23}) was confirmed by NOESY experiments on **22**, which was prepared from **20** by sequential acetonide formation, debenzylation, and *p*-bromobenzoylation of **21**. The exclusive formation of

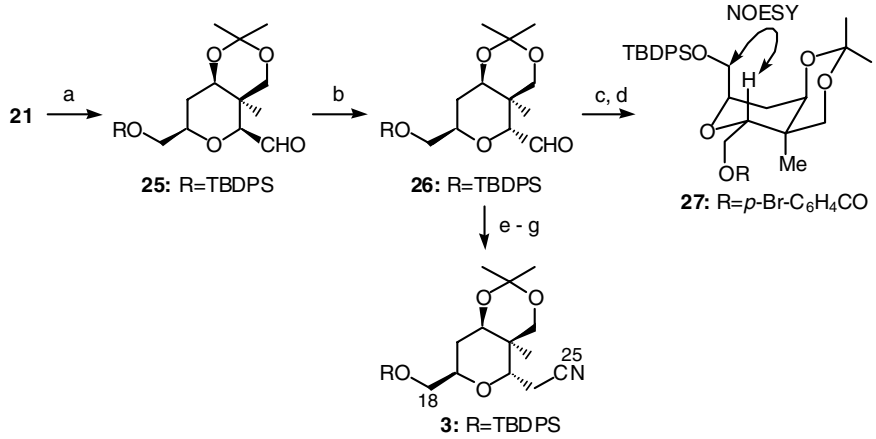
19 could be explained by considering the intermediate radical species **24**, generated from **23** via a diastereoselective 5-*exo*-trigonal mode of radical cyclization, in which, after inversion at the C_{19} stereogenic center, the bottom face turned out to be more convex, and the hydrogen abstraction took place from the α-face to yield the (22*R*,23*S*)-isomer (**19**) (Scheme 4).

Although we obtained the (23*S*) isomer selectively, our initial target was the (23*R*) isomer. Consequently, we examined the epimerization at the C_{23} stereogenic center. The alcohol **21** was oxidized with Dess–Martin reagent to give the aldehyde (**25**), which was subjected to a variety of epimerization conditions. After numerous attempts, the use of DBU provided the best result. Thus, treatment of **25** with DBU at 90 °C for 0.5 h provided the epimerized product (**26**) in 46% yield. The structure was determined by NOESY experiments on the *p*-bromobenzoate (**27**), as shown in Scheme 5. Finally, one carbon elongation of the aldehyde (**26**) was realized via sequential $NaBH_4$ reduction, triflate formation, and cyanation to give the cyanide (**3**). The structure and relative configuration of **3** was firmly established by X-ray crystallographic analysis[12] (Fig. 2).

In summary, we have completed a diastereoselective construction of the 19-*epi*-C_{18}–C_{25} segment of (−)-lasonolide A using a 5-*exo*-trigonal mode of radical cyclization for the creation of the contiguous quaternary and tertiary stereogenic centers at C_{22} and C_{23} as the key reaction step. The synthetic route we developed here would contribute to the synthesis of a variety of lasonolide A analogs. In addition, it should be emphasized that an unusual and unprecedented inversion of configuration was found during the dehydration leading to the formation of the dihydropyran. A generalization of this



Scheme 4. Reagents and conditions: (a) *n*-Bu_4NF, THF, rt, 1 h; (b) *t*-$BuPh_2SiCl$, imidazole, 4-DMAP, CH_2Cl_2, rt, 2 h, 66% for the two steps; (c) bromomethyldimethylchlorosilane, Et_3N, 4-DMAP, CH_2Cl_2, rt, 1 h, 86%; (d) *n*-Bu_3SnCl, $NaBH_3(CN)$, AIBN, *t*-BuOH, 100 °C, 3 h; (e) $KHCO_3$, H_2O_2, THF, MeOH, 90 °C, 1.5 h, 59% for the two steps; (f) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, reflux, 10 h, 90%; (g) Li, liq. NH_3, THF, −78 °C, 20 min, 77%; (h) *p*-Br–C_6H_4COCl, Et_3N, H_2Cl_2, rt, 3.5 h, 74%.



Scheme 5. Reagents and conditions: (a) Dess–Martin periodinane, CH_2Cl_2, rt, 0 °C, 85%; (b) DBU, 90 °C, 0.5 h, 46%; (c) $NaBH_4$, MeOH, 0 °C, 2 h; (d) *p*-Br–C_6H_4COCl, Et_3N, CH_2Cl_2, rt, 2.5 h, 70% for the two steps; (e) $NaBH_4$, MeOH, 0 °C, 2 h, 97%; (f) Tf_2O, pyridine, CH_2Cl_2, −78 °C, 20 min; (g) KCN, 18-crown-6, DMSO, rt, 12 h, 32% for the two steps.

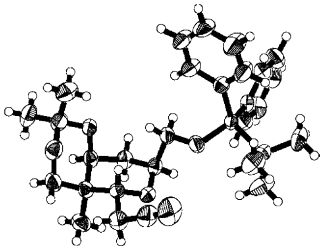


Figure 2. ORTEP drawing of **3** (R = TBDPS).

interesting inversion will be made in our laboratories in due course.

Acknowledgements

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12. Crystal data of **3**: $C_{29}H_{39}NO_4Si$, $M = 493.72$, monoclinic, space group $P2_1$, $a = 10.833(1)$ Å, $b = 9.862(2)$ Å, $c = 13.138(1)$ Å, $\beta = 91.039(9)°$, $V = 1403.4(4)$ Å^3, $Z = 2$, $Dc = 1.168\,Mg\,m^{-3}$, $F(000) = 532$, $\mu(Mo\,K_\alpha) = 1.160\,cm^{-1}$. The final R and wR were 0.037 and 0.042 for 316 parameters. The crystallographic data will be sent on quoting the CCDC number, CCDC 249373 (e-mail; deposit@ccdc.cam.ac.uk).