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# Stereoselective synthesis of (+)-lauthisan

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**Abstract**—Stereoselective synthesis of (+)-lauthisan has been accomplished starting from D-glyceraldehyde acetonide by combination of diastereoselective alkylation and ring-closing metathesis. High degree of 1,3-asymmetric induction has been realized in ether system.


Numerous cyclic ethers have been isolated from the wide range of marine organism, particularly from *Laurencia* red algae.[1] Many compounds of this class contain an eight-membered oxocane or oxocene ring usually with *syn*-stereochemistry in the alkyl substituents on both the carbons flanking the ether linkage. Among them, lauthisan and laurencin (Fig. 1) have been the subject of significant synthetic effort within the past decade.[2,3] The synthetic effort had mainly focused on the construction of eight-membered ring, because the synthesis of eight-membered ring from acyclic precursors is difficult due to conformational entropy factors and developing transannular repulsions as the ring is formed. Since the advent of RCM developed by Grubbs and co-workers, however, focal point has been moved to the stereocontrolled synthesis of acyclic diene for RCM.[4] Stereoselective creation of two chiral centers around ether oxygen has become a major subject on the synthesis of cyclic ethers. In view of efficiency, it is desirable to induce the second chirality from the resident first stereogenic center. However, many approaches have employed the resolution technique or the additional chiral auxiliary for the induction of second stereogenic center.[5] It implies the difficulty in realizing the high degree of 1,3-induction in ether system due to its higher flexibility compared to alkane system.

Our interest in these molecules arises from our recent success with the highly diastereoselective alkylation of

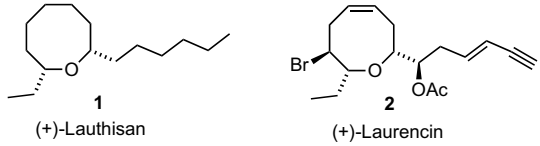


**Figure 1.**

glycolate as applied to the asymmetric synthesis of α-hydroxy esters.[6] In this paper, we will describe the extension of this methodology to the asymmetric synthesis of (+)-lauthisan. Our synthetic strategy for lauthisan was based on the approach outlined in Scheme 1, which involves 1,3-asymmetric induction by diastereoselective alkylation and ring-closing metathesis as key steps. We envisioned that the chelation-controlled asymmetric alkylation of chiral glycolic acid derivative **3**, followed by introduction of double bonds via functional group manipulation of **4** would provide the acyclic diene **5** with the requisite stereogenicity around ether oxygen. Completion of the synthesis of (+)-lauthisan would then entail cyclization of acyclic diene using RCM, and functional groups elaboration.

Critical to the efficiency of our plan is to find out the best $R_1$ and $R_2$ groups suitable for the high asymmetric induction and finally convertible to ethyl and hexyl group for lauthisan. We began our synthesis by finding the optimum reaction condition for the asymmetric alkylation of chiral glycolate derived from D-glyceraldehyde. Lithium enolate of chiral glycolic acid derivatives **6** were reacted with alkyl iodide to give alkylation products **7** and **8**, respectively.

*Keywords*: (+)-Lauthisan; Diastereoselective alkylation; Ring-closing metathesis; Cyclic ether.
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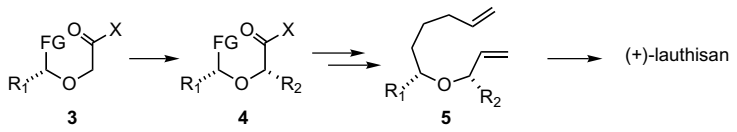
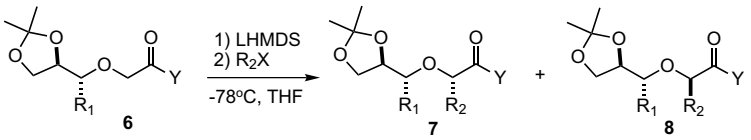



**Scheme 1.**

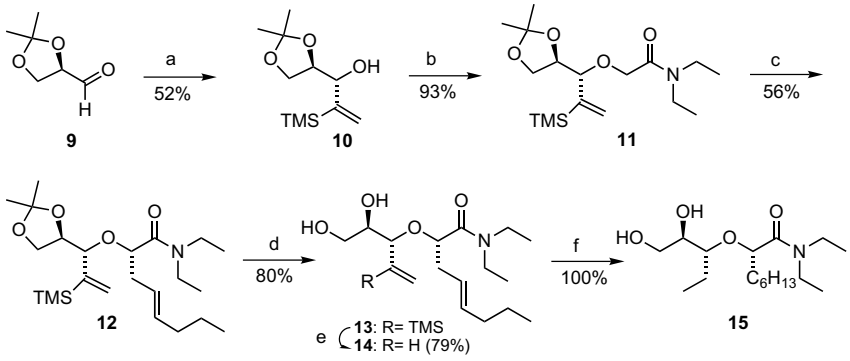
**Table 1.**



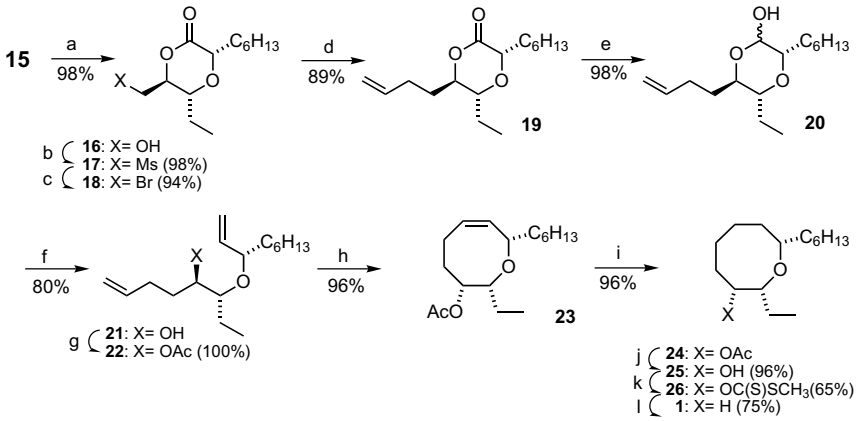

| Entry | $R_1$ | Y | $R_2X$ | Yield (%) | **7**:**8**[a] |
|---|---|---|---|---|---|
| 1 | *p*-Anisyl | OEt | Methyl iodide | 86 | 100:1 |
| 2 | Ethyl | $OBu^t$ | Hexyl iodide | 74 | 3:1 |
| 3 | Hexyl | $OBu^t$ | Ethyl iodide | 25 | 1:1 |
| 4 | 1-TMS-vinyl | $OBu^t$ | *trans*-2-Hexenyl iodide | 56 | 13:1 |
| 5 | 1-TMS-vinyl | $NEt_2$ | *trans*-2-Hexenyl iodide | 56 | 21:1 |
| 6 | 1-TMS-vinyl | $NEt_2$ | *cis*-2-Hexenyl iodide | 30 | 16:1 |

[a] The ratio was determined by capillary GC (HP-1 column).

As shown in Table 1, $R_1$ group showed a significant effect on stereoselectivity. Compared to *p*-anisyl group of the previously developed chiral auxiliary,[6] compound **6** with ethyl or hexyl group (entry 2 and 3) necessary for lauthisan did not show any acceptable diastereoselectivity. Despite the various attempts to increase the diastereomeric ratio, it did not exceed 3. As another attempt to increase diastereoselectivity, we introduced 1-trimethylsilylvinyl group as a bulky ethyl substitute for $R_1$. The diastereoselectivities were increased dramatically. When *trans*-2-hexenyl iodide was used as a reactive electrophile for hexyl group, the diastereoselectivity was increased up to 21:1. Encouraged with the result, we set about the asymmetric synthesis of (+)-lauthisan. Introduction of side chain for lauthisan via diastereoselective alkylation is shown in Scheme 2. The starting (*R*)-glyceraldehyde acetonide **9**, readily available from D-mannitol, reacted with trimethylsilylvinylmagnesium bromide and CuI in DMS–THF at −78 °C to give the *syn* alcohol **10** in high diastereoselectivity (>98:2).[7] After purification by silica gel column chromatography, **10** was converted to the corresponding alkoxide with NaH, followed by O-alkylation with *N*,*N*-diethyl chloroacetamide in DME afforded the ether **11** in 93% yield. Treatment of **11** with LHMDS in THF at −78 °C to generate the corresponding enolate, followed by addition of *trans*-2-hexenyl iodide produced **12** and its *anti* isomer in a 21:1 ratio in favor of *syn* isomer **(12)** in 56% combined yield. After separation of the diastereomers by silica gel column chromatography, *syn* isomer **12** was subjected to desilylation. Many attempts to remove TMS group in vinylsilane **12** found to be in vain. After finding a report that KH–HMPA is effective for the protodesilylation of γ-trimethylsilyl-




**Scheme 2.** Reagents and conditions: (a) 1-(trimethylsilyl)vinylmagnesium bromide, CuI, THF–$Me_2S$ (5:1), −78 °C; (b) NaH, then chloro-*N*,*N*-diethylacetamide, DME, −10 °C to room temperature; (c) LHMDS, then *trans*-1-iodohex-2-ene, THF, −78 °C; (d) PPTS, MeOH, reflux; (e) NaH, THF–HMPA (1:2); (f) Pd/C, $H_2$.




**Scheme 3.** Reagents and conditions: (a) PPTS, toluene, reflux; (b) MsCl, pyridine, 0 °C; (c) LiBr, acetonitrile, reflux; (d) allyltributyltin, AIBN, benzene, reflux; (e) DIBAH, $CH_2Cl_2$, −78 °C; (f) NaH, DMSO (10 equiv), methyl triphenylphosphonium bromide, THF; (g) $Ac_2O$, TEA, DMAP; (h) $(Cy_3P)_2Cl_2Ru{=}CHPh$ (10 mol%), $CH_2Cl_2$ (0.0025 M), reflux; (i) $H_2$, Pd/C, methanol; (j) $K_2CO_3$, $H_2O$–MeOH; (k) NaH, $CS_2$, $CH_3I$; (l) $Bu_3SnH$, AIBN, benzene, reflux.

homoallyl alcohol,[8] we treated **12** with PPTS in MeOH to give homoallylic alcohol **13** in 86% yield. The alcohol **13** in hand was treated immediately with metal hydride. In our case, NaH was better than KH. Thus, treatment of **13** with NaH in HMPA–THF (2:1) produced the desired desilylated vinyl compound **14** in 79% yield. Saturation of two double bonds in **14** via hydrogenation (Pd/C, $H_2$) led to **15** in quantitative yield.

After installing ethyl and hexyl substituents for lauthisan, our attention was focused to the synthesis of the requisite acyclic diene **21** for ring-closing metathesis. Subsequent cyclization and completion of synthesis of (+)-lauthisan is outlined in Scheme 3. Selective protection of secondary alcohol in **15** was accomplished by acid-catalyzed cyclization to **16**. The primary alcohol **16** was then transformed to the bromide **18** via two steps sequence in 96% yield. Radical allylation of **18** to **19** with allyltributyltin, followed by DIBAH reduction gave **20** in 87% yield.

Then, we explored Wittig olefination of **20** with a variety of reagents and conditions. Unfortunately, all attempts were unsuccessful. Only the reaction of **20** with $Ph_3PCH_3Br$ and dimsyl anion (NaH, DMSO) in THF under elevated temperature (40 °C) delivered the desired diene **21** in 80% yield.[9] The diene **21** in hand, we have initially tried RCM reaction without protection of alcohol functionality. However, the yield was very low, presumably due to the unfavorable conformation resulted from internal hydrogen bonding between the hydroxyl group and ether oxygen. Thus, the hydroxyl group was transformed into the acetate **22** under standard procedure in quantitative yield. The stage was thus set for the RCM. Exposure of **22** to the Grubbs catalyst [10 mol% $(Cy_3P)_2RuCl_2(CHPh)$] as $2.5 \times 10^{-3}$ M solution in dichloromethane at refluxing temperature cleanly produced eight-membered oxocene **23** in 96% yield. The remarkably enhanced yield was presumably due to the additional favorable *gauche* effect displayed by two oxygens.[10] The stereochemistry of the Δ-6-oxocene **23** was confirmed by inspection of NOESY spectrum. As

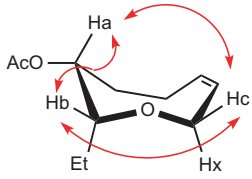



**Figure 2.**

shown in Figure 2, a substantial cross-peak was observed between Hb and Hc, indicating a *cis* relationship on the Δ-6-oxocene. A significant interaction was also observed for Ha and Hb, indicating their *cis* relationship. In addition, the long distance interaction between Ha and Hc was also detected.

With the cyclic ether **23** in hand, the total synthesis of (+)-lauthisan was accomplished in a straightforward manner. Hydrogenation and deacetylation, followed by xanthate formation (NaH/$CS_2$, then $CH_3I$) afforded **26** in 60% yield over three steps. Finally, treatment of **26** with $Bu_3SnH$ and AIBN in refluxing benzene provided (+)-lauthisan in 75% yield. The synthetic **1** was identical in all respect ($^1H$ NMR, $^{13}C$ NMR, IR) to those reported for natural (+)-lauthisan.[11] The specific rotation of synthetic sample [+13.3 (*c* 0.08, $CHCl_3$)] was virtually identical to the value reported by Kotsuki et al. [+13.9 (*c* 0.15, $CHCl_3$)].[11]

In summary, we have shown that (+)-lauthisan can be prepared efficiently from our chiral auxiliary via chelation-controlled diastereoselective alkylation and ring-closing metathesis. High degree of 1,3-asymmetric induction has been realized in ether system. Although we chose (+)-lauthisan as an initial target to demonstrate our tactic, compound **12** or **23** could be a very versatile intermediate for the synthesis of chiral cyclic ethers.[12] Thus, our synthetic method offers an efficient entry into chiral cyclic ethers, especially in the ether system containing the oxygen flanked by two chiral centers.

## Acknowledgements

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12. Selected data for compounds **12** and **23**. Compound **12**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 5.78 (1H, dd, $J = 0.8$, 2.6 Hz), 5.55 (1H, d, $J = 2.6$ Hz), 5.45–5.37 (1H, m), 5.36–5.28 (1H, m), 4.15–4.08 (2H, m), 3.83–3.77 (2H, m), 3.73–3.69 (1H, m), 3.58–3.49 (1H, m), 3.44–3.34 (1H, m), 3.31–3.14 (2H, m), 2.37–2.26 (2H, m), 1.89–1.78 (2H, m), 1.27 (3H, s), 1.21 (3H, s), 1.24 (2H, m), 1.02 (3H, t, $J = 7.2$ Hz), 0.97 (3H, t, $J = 7.2$ Hz), 0.73 (3H, t, $J = 7.2$ Hz); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 170.51, 149.02, 133.82, 130.69, 125.38, 109.82, 84.94, 77.92, 76.26, 66.45, 41.17, 40.35, 36.72, 34.89, 26.78, 23.06, 22.66, 14.81, 13.93, 13.18, 0.00; $[\alpha]_D^{20}$ −18.2 (*c* 0.62, $CHCl_3$); IR (neat) 2959, 2873, 1655 cm$^{-1}$; HRMS (CI) calcd for $C_{23}H_{44}NO_4Si$ ($M+H^+$) 426.3030, found 426.3029. Compound **23**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 5.58 (1H, ddt, $J = 11.6$, 7.2, 1.6 Hz), 5.34 (1H, ddd, $J = 11.6$, 2.8, 1.6 Hz), 5.05 (1H, ddd, $J = 6.8$, 4.0, 2.8 Hz), 3.93 (1H, m), 3.39 (1H, ddd, $J = 8.0$, 5.2, 2.8 Hz), 3.00–2.91 (1H, m), 2.01 (3H, s), 1.88–1.79 (1H, m), 1.78–1.72 (1H, m), 1.61–1.55 (1H, m), 1.54–1.44 (4H, m), 1.42–1.17 (8H, m), 0.90 (3H, t, $J = 7.6$ Hz), 0.81 (3H, t, $J = 6.8$ Hz); $^{13}$C (100 MHz, $CDCl_3$): $\delta$ 171.1, 133.4, 128.1, 81.1, 80.7, 71.8, 36.4, 32.1, 30.2, 29.5, 25.9, 25.0, 22.9, 21.6, 21.5, 14.3, 11.0; $[\alpha]_D^{22}$ +91.7 (*c* 0.28, $CHCl_3$); IR (neat) 3012, 2930, 2857, 1739, 1452, 1371, 1241 cm$^{-1}$; HRMS (CI) calcd for $C_{17}H_{31}O_3$ ($M+H^+$) 283.2273, found 283.2273.