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Stereocontrolled synthesis of the aminocyclitol moiety of (+)-trehazolin via C–H insertion reaction of alkylidenecarbene

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Abstract—The aminocyclitol moiety of (+)-trehazolin, a powerful trehalase inhibitor, was synthesized in a stereocontrolled manner from *cis*-2-butene-1,4-diol via C–H insertion reaction of the alkylidenecarbene, followed by regioselective opening of the epoxide ring. It was obtained in an enantiomerically pure form by twice using Sharpless asymmetric epoxidation.

Trehazolin (**1**) was isolated from a culture broth of *Micromonospora*, strain SANK 62390 by Ando and co-workers in 1991.[1] This compound is a powerful trehalase inhibitor, whose structure was independently determined through the synthetic work by Ogawa and co-workers[2] and Shiozaki and co-workers[3] groups. Structure–activity relationships were also studied extensively by these groups based on their own synthetic strategies for **1**.[4] After their seminal work, the unique structure and biological activity attracted other synthetic chemists, and many syntheses related to **1**[5] and its analogues were reported. The aminocyclitol part of **1** (**2**) or its hexaacetate (**3**) is the common target, which is convertible to **1**.[3c] The success of synthesizing **2** or **3** is due to the effective construction of a skeleton with the proper stereochemistry. As chiral sources, sugars or amino acids were used in most previous chiral syntheses. In this study, we describe the stereocontrolled asymmetric synthesis of **3** starting from *cis*-2-butene-1,4-diol. This investigation was pursuant to our continual interest to use the C–H insertion reaction of the alkylidenecarbene to construct the functionalized cyclopentene[6,7] (Fig. 1).

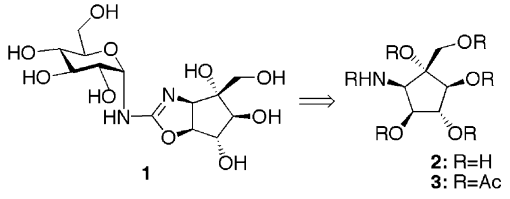

Figure 1.

Among the previous synthesis, the approaches via functionalized acyclic intermediates derived from the chiral pool looked most concise and efficient. Characteristic intramolecular reactions, for example, [2+3] cycloaddition, pinacol coupling, RCM were applied for construction of the five membered ring from the acyclic intermediates. Our early plan for **3** was also along this line, and direct synthesis of cyclopentene **6** was attempted with acyclic ketone **4** derived from D-tartrate. With the hope that the bulky protecting group of vicinal diol would make each reaction sites close as described by Saito et al.,[8] **4** was treated with lithiotrimethylsilyldiazomethane ($TMSCLiN_2$)[9] to generate the alkylidenecarbene. The main product obtained, however, was a compound, which arose from the oxonium ylide intermediate.[10] The yield of **6** was only 5% at maximum. To suppress formation of oxonium ylide, pivalate **5** was prepared and subjected to the same reaction, although in this case only decomposition of **5** occurred (Fig. 2).

After these preliminary studies, our attention turned to the disubstituted epoxide **8** that seemed to be a good precursor of trisubstituted epoxide **7**. It was expected that addition of oxygen nucleophile (R_2OH) occurs at

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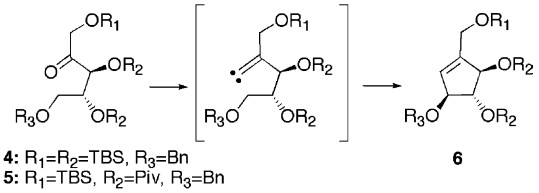


Figure 2.

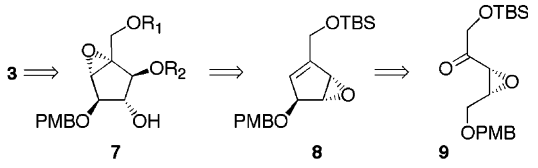
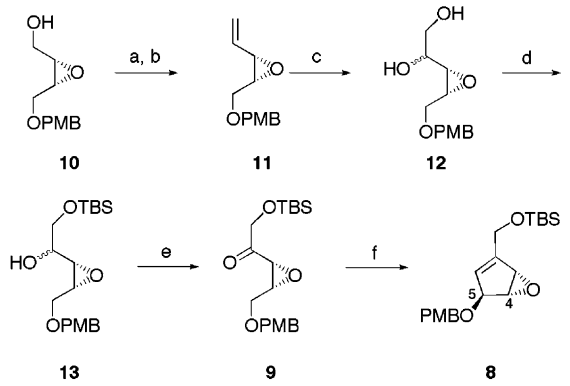


Figure 3.



Scheme 1. Reagents and conditions: (a) IBX, Py, DMSO, 45 °C; (b) Ph_3PCH_3Br, KHMDS, toluene, THF, −20 °C to rt (83% in two steps); (c) OsO_4, NMO, THF–H_2O, rt (95%); (d) TBSCl, imidazole, DMF, rt (88%); (e) Dess–Martin periodinane, CH_2Cl_2, rt (85%); (f) $TMSCLiN_2$, DME, 0 °C to rt (51%).

the allylic position of **8**, and resulting substituents around the cyclopentene ring possibly assist the diastereoselective epoxidation. Epoxide **8** was presumably obtainable from ketone **9** by C–H insertion of alkylidenecarbene without oxonium ylide formation[7d] and preferable orientation of the alkoxy group of **8** on the convex face was anticipated in view of our observation with the bicyclo [3.3.0] system[6d] (Fig. 3).

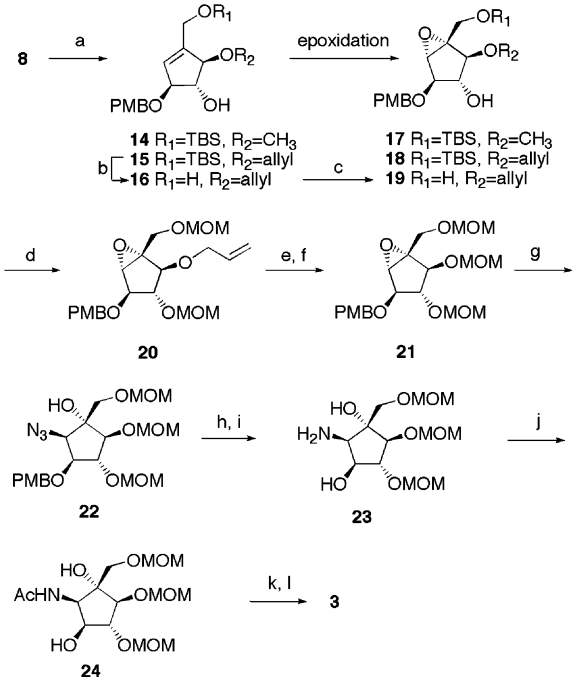
According to the procedure by Trost et al., *cis*-2-butene-1,4-diol was converted into epoxide **10** via Sharpless asymmetric epoxidation with 88% ee.[11] Oxidation of **10** with IBX, followed by a Wittig reaction with methyltriphenylphosphonium bromide and KHMDS produced a good yield of olefin **11**. The use of another base, such as BuLi or NaH in DMSO, considerably lowered the yield. Dihydroxylation of the double bond of **11** with OsO_4 furnished the diol **12** and the primary hydroxyl group was protected as TBS ether. Oxidation of the secondary alcohol of **13** with Dess–Martin periodinane produced the epoxy ketone **9**, a precursor of the alkylidenecarbene. The reaction between $TMSCLiN_2$ and **9** in DME was conducted at 0 °C. Warming the reaction mixture to an ambient temperature (20–25 °C) produced the cyclized product **8** as a single diastereomer with a 51% yield. The stereochemistry of the C-5 position of **8** was deduced based on the correlation between the C-4 proton and benzyl protons of the PMB group in its NOESY spectra.[12] To improve the yield, this reaction was attempted under various reaction conditions, however, a better yield was not obtained probably due to the instability of **8** under these reaction conditions (Scheme 1).

Opening of the epoxide ring of **8** was successful with methanol or allyl alcohol under acidic conditions to provide **14** or **15**. Using acetic acid and benzyl alcohol, the corresponding alcohol was produced in a much lower yield. Epoxidation of **14** with *m*-CPBA gave the desired epoxide **17** and its isomer with a 2.5:1 ratio with an 88% combined yield. Although epoxidation of **15** gave epoxide **18** stereoselectively (3.5:1), the yield was less than 10% due to the competitive reaction with the allyl group. Methyl ether **17** was elaborated to some later stages, however, demethylation was unsuccessful at any stage. Thus, we decided to abandon the substrate-controlled epoxidation and to turn to the asymmetric epoxidation. Since the Shiozaki group reported effective Sharpless epoxidation with a similar system,[3c] we expected that the undesired enantiomer of **16** (6%, calculated from ee of **10**) would be removable as a minor diastereomer after the second asymmetric epoxidation.

Removal of the TBS group using TBAF in THF produced the desired diol **16**.[13] Sharpless epoxidation of diol **16** and purification by silica gel chromatography produced the desired epoxide **19** as a single isomer. Minor diastereomers included in crude by-products could not be isolated. ^1H NMR spectra of (*S*)- and (*R*)-MTPA esters of **19** indicated that both are single diastereomers, namely, **19** is enantiomerically pure.

After protecting two hydroxyl groups of **19** as MOM ether, the allyl group of **20** was removed cleanly with $PdCl_2$ in acetic acid[14] and the resulting hydroxyl group was protected as MOM ether. Epoxide opening of **21** with sodium azide and ammonium chloride and the subsequent removal of the PMB group using DDQ followed by the reduction of the azido group of **22** provided a good yield of amino diol **23**. Direct conversion of **22** to **23** was attempted using H_2 over Pd/C, but the reaction was incomplete and gave a low yield. Treatment of **23** with methanolic hydrogen chloride and acetylation of the crude product resulted in a complex mixture containing hexaacetate **3**, therefore, the amino group of **23** was acetylated at this stage. Acetamide **24** was subjected to deprotection followed by acetylation to provide a good yield of the final compound **3**. The ^1H NMR spectra of the synthetic sample of **3** were identical with those of the Shiozaki group's sample, and the other physical properties were identical with those reported[3c,5h,15] (Scheme 2). Therefore, synthesis of hexaacetate **3**, which means the formal total synthesis of (+)-trehazolin (**1**), was completed in 20 steps.

Although circumvention of the direct construction of the vicinal trans oxygenated cyclopentene apparently



Scheme 2. Reagents and conditions: (a) MeOH or allyl alcohol, *p*-TsOH, −78 to 0 °C; (b) TBAF, THF, rt (69% in two steps); (c) L-(+)-DET, Ti(O*i*Pr)$_4$, TBHP, CH_2Cl_2, −20 °C (73%); (d) MOMCl, *i*Pr$_2$NEt, CH_2Cl_2, rt (87%); (e) $PdCl_2$, NaOAc, AcOH, H_2O, rt (85%); (f) MOMCl, *i*Pr$_2$NEt, CH_2Cl_2, rt (86%); (g) NaN_3, NH_4Cl, DMF–ethylene glycol, 120 °C (78%); (h) DDQ, CH_2Cl_2–H_2O, rt (87%); (i) 10%Pd–C, H_2, EtOAc, rt (97%); (j) Ac_2O, MeOH, rt (quant.); (k) AcCl, MeOH, rt; (l) Ac_2O, DMAP, Py, rt (40% in two steps).

reduced the total efficiency of the synthesis, it is notable that C–H insertion of alkylidenecarbene is still useful for the synthesis of such an oxygenated cyclopentene and its related natural product.

Acknowledgements

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12. ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.91 (s, 9H), 3.75 (d, 1H, J = 2.4 Hz) 3.81 (s, 3H), 3.94 (t, 1H, J = 2.6 Hz), 4.38–4.41 (m, 3H), 4.60 (d, 2H, J = 6.4 Hz), 5.87 (d, 1H, J = 2.1 Hz), 6.89 (d, 2H, J = 8.6 Hz), 7.30 (d, 2H, J = 8.6 Hz). Correlation was observed between signals of δ 3.94 and δ 4.60.
13. $[\alpha]_D^{20}$ + 69.1 (*c* 0.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 4.15 (ddt, 1H, J = 1.4 Hz, 5.6 Hz, 12.9 Hz), 4.18–4.29 (m, 6H), 4.55 (d, 1H, J = 11.5 Hz), 4.63 (d, 1H, J = 11.5 Hz), 5.21 (ddd, 1H, J = 1.3 Hz, 2.8 Hz, 10.4 Hz), 5.31 (ddd, 1H, J = 1.6 Hz, 3.2 Hz, 17.2 Hz), 5.77 (br s, 1H), 5.95 (ddt, 1H, J = 5.4 Hz, 10.6 Hz, 17.2 Hz), 6.89 (d, 1H, J = 8.6 Hz), 7.30 (d, 1H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 55.29, 60.27, 70.95, 71.30, 86.25, 86.27, 87.26, 113.95, 117.26, 126.22, 129.45, 130.38, 134.90, 144.17, 159.34.

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15. $[\alpha]_D^{20} + 4$ (*c* 0.13, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.02 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.09 (s, 3H), 2.12 (s, 3H), 2.14 (s, 3H), 4.56 (d, 1H, J = 12.2 Hz), 4.63 (d, 1H, J = 12.2 Hz), 5.24 (t, 1H, J = 5.2 Hz), 5.33 (dd, 1H, J = 8.3 Hz, 9.4 Hz), 5.38 (dd, 1H, J = 4.8 Hz, 7.8 Hz), 5.81 (d, 1H, J = 5.5 Hz), 5.89 (d, 1H, J = 9.5 Hz); ^{13}C NMR ($CDCl_3$) δ 20.55, 20.65, 20.68, 20.95, 21.66, 23.15, 52.75, 59.48, 73.29, 76.42, 78.93, 86.61, 168.91, 168.94, 169.52, 169.74, 169.90, 170.39.