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A synthetic study of briarane-type marine diterpenoid, pachyclavulide B

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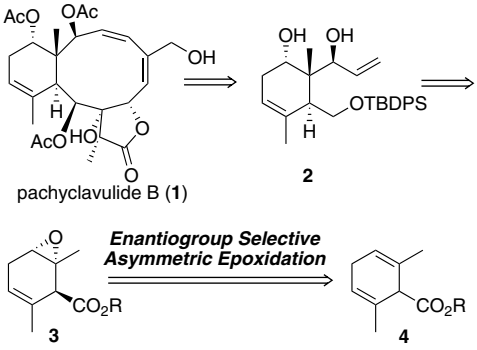
Abstract—Enantioselective preparation of the six-membered ring of pachyclavulide B, a briarane-type diterpenoid, was achieved. The key step is desymmetrization of an achiral symmetric substrate by enantiogroup- and diastereoselective epoxidation. The asymmetric epoxidation proceeded with up to 99% de and 94% ee.

Pachyclavulide B (**1**) isolated from the Okinawan soft coral *Pachyclavularia violacea* by our group is a briarane-type diterpenoid containing eight chiral centers and a highly oxygenated tricyclic system,[1] and it exhibited moderate growth-inhibitory activity against cancer cells (SNB-75) of the central nervous system. Over 350 of the briarane-type diterpenoids were isolated from various organisms.[2,3] Details of various attractive biological activities of several of these compounds were reported. Synthetic studies of briarane-type diterpenoids were reported by several groups;[4] however, total synthesis has not yet been reported. Therefore, the total synthesis of pachyclavulide B (**1**) was examined because **1** would be converted easily to other briarane-type diterpenoids. We report here the enantioselective synthesis of the six-membered ring fragment through enantiogroup- and diastereoselective epoxidation.

Our synthetic plan of pachyclavulide B (**1**) is shown in Scheme 1. Construction of the 10-membered ring would be achieved through elongation of the carbon chain of **2** and ring-closing reaction. Therefore, compound **2** was selected for a key intermediate. During consideration of the preparation of **2**, we found that compound **2** has a latent symmetric feature. Compound **2** could be prepared from compound **3** by carbon–carbon bond forming reaction with the construction of the quaternary carbon on the cyclohexene ring. Compound **3**



Scheme 1. Retrosynthetic analysis of pachyclavulide B.

could be synthesized through enantiogroup and diastereoselective asymmetric epoxidation of achiral substrate **4**. Compound **4** can be easily prepared by Birch reduction of 2,6-dimethylbenzoic acid.

Prior to the synthesis of **2**, we examined the enantiogroup- and diastereoselective epoxidation of symmetric 1,4-cyclohexadiene derivatives.[5] In this reaction system, both enantiogroup selectivity and diastereoselectivity were important, that is, the reagent attacks not only from the *Re* or *Si* face of the tri-substituted carbon–carbon double bond but also from the less hindered site to avoid the steric repulsion of the substituent such as an alkoxycarbonyl or alkoxymethylene group. The substrate was prepared from 2,6-dimethylbenzoic acid through Birch reduction as shown in Scheme 2. All reactions were carried out in excellent yield. The asymmetric epoxidation of these substrates was examined using a

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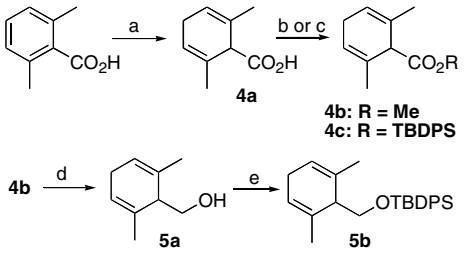


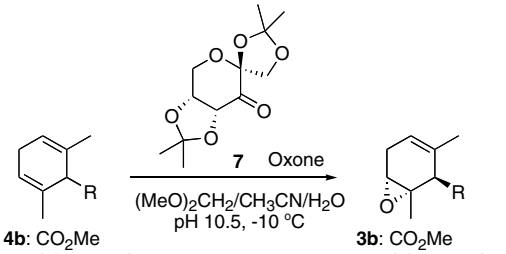
Scheme 2. Preparation of the substrates for epoxidation. Reagents and conditions: (a) Na, NH_3, EtOH, −50 °C, 96%; (b) CH_2N_2, ether, 0 °C, quant; (c) TBDPSCl, imidazole, CH_2Cl_2, rt, quant; (d) LAH, THF, 0 °C, 97%; (e) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 98%.

chiral ketone as a catalyst with Oxone developed by Shi et al.[6] and the results are shown in Table 1.

For optimization of the reaction conditions, a catalyst **7**, which was prepared from D-fructose,[6] was employed to provide the antipode of the desired mono-epoxide. In the case of substrate **4b**, the yield was strongly dependent on the amount of the catalyst (entries 1 and 2). In the presence of 50 mol % of the catalyst, compound **3b**[7] was obtained in 55% yield with 75% de and 87% ee. The use of 100 mol % of the catalyst increased the de to 82% but the yield was significantly decreased (44% yield, entry 3). A more bulky substituent (TBDPS) was employed to increase the diastereoselectivity (entries 4–6). The reaction of **4c** proceeded to provide **3c** in 70% yield with excellent diastereoselectivity (99% de) and enantioselectivity (94% ee) in the presence of 100 mol % of the catalyst (entry 6). We also examined a silyloxymethyl substituent; however, the diastereoselectivities were not satisfactory (entries 7 and 8). At this point, the absolute stereochemistry of epoxides was tentatively assigned based on mechanistic consideration reported by Shi et al.[5,6] We also confirmed the absolute stereochemistry of epoxide **ent-3b** after converting to compound **9** (vide infra).

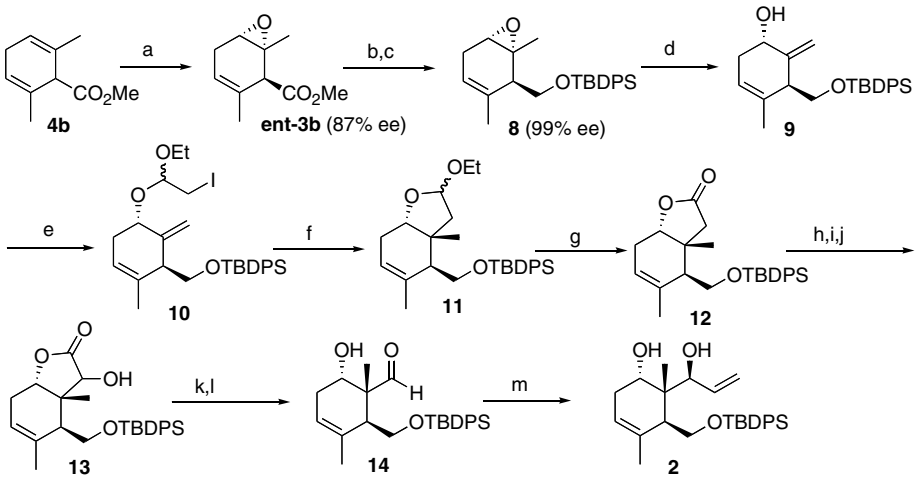
As mentioned above, asymmetric epoxidation was achieved to obtain the mono-epoxide **3** with up to 99% de and 94% ee. At first, we tried to convert **3c** to compound **8** through a reduction–protection sequence. The epoxide moiety on **3c**, however, was decomposed under the reduction condition because relatively strong reduction condition was required to reduce the TBDPS ester due to the steric repulsion of the TBDPS group. Therefore, we employed **3b** for the synthetic study of pachyclavulide B (**1**). The asymmetric epoxidation of **4b** was performed by the use of the enantiomer of **7** as a catalyst, which was prepared from D-sorbose,[6] to give compound **ent-3b** in 44% yield with 81% de and 87% ee (Scheme 3). The reduction of the methoxycarbonyl group successively proceeded to give an alcohol by using DIBAL–H in 93% yield. After the protection of the hydroxyl group with the TBDPS group, compound **8** was purified by recrystallization and almost enantiomerically pure **8** (99% ee) was obtained. Compound **8** was converted to allylic alcohol derivative **9** by treating with Et_2AlTMP.[8] The absolute stereochemistry of compound **9** was determined after conversion to MTPA esters by the Kusumi–Kakisawa method.[9] For the construction of the quaternary center on the cyclohexene ring, intramolecular radical cyclization was performed.[10] The substrate **10** was prepared by treating **9** with ethyl vinyl ether in the presence of NIS in 80% yield.[11] Although the yield was unsatisfactory (32% yield), the intramolecular radical cyclization proceeded

Table 1. Enantiogroup and diastereoselective asymmetric epoxidation[a]



Entry	Substrate	Cat (mol %)	Time (h)	Product	Yield (%)[b]	de (%)[c]	ee (%)[d,e]
1	**4b**	30	2	**3b**	27 (52)	75	88
2	**4b**	50	4.5	**3b**	55 (58)	75	87
3	**4b**	100	4.5	**3b**	44	82	87
4	**4c**	30	2	**3c**	37 (69)	99	93
5	**4c**	50	3.5	**3c**	56 (76)	99	93
6	**4c**	100	6	**3c**	70 (93)	99	94
7	**5b**	50	3.5	**6b**	56 (67)	75	84
8	**5b**	100	3.5	**6b**	49 (59)	83	84

[a] Reaction conditions were reported by Shi et al.
[b] Isolated yield. Numbers in parentheses were conversion yield after recovery of the substrate.
[c] De was determined by ^1H NMR.
[d] Ee was determined for major diastereomer.
[e] Ee was determined by CHIRALCEL OJ-H for **3b**, CHIRALPAK AD-H for **3c** and CHIRALPAK AS-H for **6b**.



Scheme 3. Reagents and conditions: (a) **ent-7**, Oxone, CH_3CN–DMM, 44%; (b) DIBAL–H, toluene, −78 °C, 93%; (c) TBDPSCl, imidazole, CH_2Cl_2, rt, quant; (d) Et_2AlTMP, toluene, 0 °C, 97%; (e) ethyl vinyl ether, NIS, CH_2Cl_2, −20 to 0 °C, 80%; (f) Bu_3SnH, AIBN, toluene, 100 °C, 32%; (g) Jones reagent, acetone, rt, 94%; (h) TBAF, THF, rt, 99%; (i) LDA, 2-(phenylsulfonyl)-3-phenyloxaziridine, THF, −30 to −10 °C, 62%; (j) TBDPSCl, imidazole, DMF, rt, 90%; (k) $LiAlH_4$, THF, rt; (l) $NaIO_4$, THF–H_2O, rt, then aq $NaHCO_3$, THF–MeOH, rt, two steps 74%; (m) vinylmagnesium chloride, THF, 0 °C, quant.

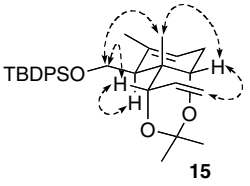


Figure 1. NOE correlations of **15**.

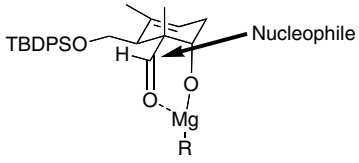


Figure 2.

to give compound **11** along with a significant amount of iodine-reduced and 6-*endo* cyclized products.[12] For the conversion of compound **11** to aldehyde **14** with one carbon degradation, the acetal moiety of **11** was directly oxidized to a lactone using Jones reagent and **12** was obtained in 94% yield. The incorporation of a hydroxyl group at the α-position of lactone **12** was found to be difficult due to the steric repulsion of the TBDPS group; however, the reaction proceeded in a diastereoselective manner (>95% de) after removal of the TBDPS group. Although the stereochemistry of the product **13** was not determined, it could be speculated that the Davis reagent[13] approached from the convex face of lithium enolate of **12**. After conversion of **13** to a diol derivative, oxidative cleavage was achieved by treating with $NaIO_4$ and aldehyde **14** was obtained.

The diastereoselective addition reaction of vinylmagnesium chloride to **14** was achieved to give compound **2** as a single diastereomer in quantitative yield.[14] The stereochemistry of **2** was determined by NOESY spectra after conversion of **2** to compound **15** as shown in Figure 1.

The mechanism of the diastereoselectivity was speculated as shown in Figure 2. The chelation of magnesium between the carbonyl oxygen and the hydroxyl group on the cyclohexene ring fixed the conformation of the aldehyde carbonyl group. The nucleophile approached from the *Si* face of the carbonyl group to avoid the steric repulsion of the TBDPS group to create an (*S*) chiral center bearing a hydroxyl group.

The enantioselective preparation of key intermediate **2** for the synthesis of the briarane-type diterpenoid, pachyclavulide B (**1**), was achieved. Enantiogroup and distereoselective epoxidation of the symmetric substrate succeeded to give the optically active mono-epoxide. Work on the total synthesis of pachyclavulide B and related briarane-type diterpenoids is now under way.

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7. Compound **3b**: Colorless oil. $[\alpha]_D$ +154.0 (*c* 1.0, $CHCl_3$) (87% ee). IR (film) *v* cm^{-1}; 2968, 2912, 1741, 1454, 1435. ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (3H, s), 1.68 (3H, br s), 2.51–2.68 (2H, m), 3.18 (1H, s), 3.34 (1H, s), 3.73 (3H, s), 5.33 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 22.3, 26.4, 52.2, 52.9, 57.5, 58.1, 119.2, 128.3, 172.2. HRESIMS Calcd for $C_{10}H_{15}O_3$ $(M+H)^+$ 183.1021, found 183.1013.
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14. Compound **2**: Colorless oil. $[\alpha]_D$ +83.7 (*c* 0.95, $CHCl_3$). IR (film) *v* cm^{-1}; 3307, 2930, 2857, 1590, 1471, 1455, 1428. ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.11 (3H, s), 1.50 (3H, br s), 2.14 (1H, br s), 2.15 (1H, br d, $J = 18.5$ Hz), 2.43 (1H, br d, $J = 18.5$ Hz), 3.15 (1H, d, $J = 2.2$ Hz), 3.32 (1H, br d, $J = 6.0$ Hz), 3.70 (1H, dd, $J = 4.7$, 11.1 Hz), 3.78 (1H, dd, $J = 3.1$, 11.1 Hz), 4.27 (1H, td, $J = 5.7$, 7.4 Hz), 4.44 (1H, d, $J = 7.4$ Hz), 5.17 (1H, dd, $J = 1.7$, 18.0 Hz), 5.19 (1H, dd, $J = 1.7$, 10.6 Hz), 5.41 (1H, br s), 5.87 (1H, ddd, $J = 7.4$, 10.6, 18.0 Hz), 7.37–7.42 (6H, m), 7.64–7.68 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 19.1, 22.3, 26.8, 32.3, 42.2, 47.5, 61.9, 73.2, 77.6, 117.6, 121.3, 127.6, 127.7, 129.7, 132.6, 133.1, 133.3, 135.6, 135.7, 137.3. HRESIMS Calcd for $C_{28}H_{39}O_3Si$ $(M+H)^+$ 451.2668, found 451.2645.