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Construction of Functionalized Dolabellane Framework via the Stereocontrolled Cope Rearrangement of a 1,3,2-Dioxasilacycloheptane Derivative

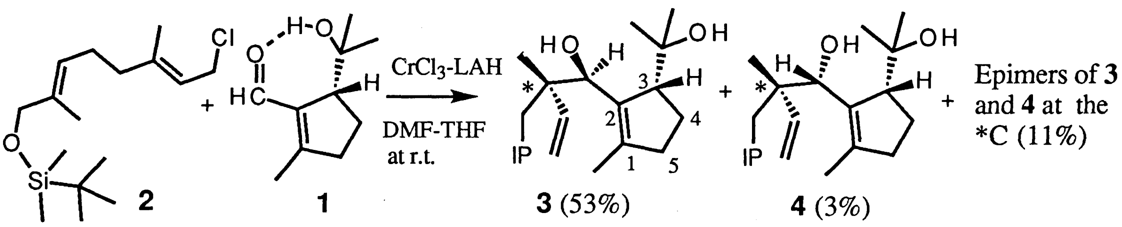
Nobuo KATO, Atsushi HIGO, Kohji NAKANISHI, Xue WU, and Hitoshi TAKESHITA*
Institute of Advanced Material Study, 86, Kyushu University, Kasuga-koen, Kasuga, Fukuoka 816

Dolabellane, a biogenetic precursor of fusicoccane and dolastane diterpenoids, was constructed stereoselectively via Cope rearrangement of an appropriately functionalized 1,3,2-dioxasilacycloheptane derivative to generate the trans-geometry at C-1 and C-12.

The dolabellane derivatives, possessing a conformationally flexible eleven-membered ring with olefinic linkages or oxygenated functions derived therefrom at the particular positions, have been continuously isolated as the natural products.[1)] Since they are regarded to be the biogenetic precursors of fusicoccanes and dolastanes,[2)] syntheses of them are focus of attentions.[3)] In this paper, we describe a successful application of stereocontrolled Cope rearrangement with incorporated siloxane segment to furnish the dolabellane framework.

In the synthetic studies of 5-8-5-membered tricyclic higher terpenoids, we have already developed a lactol-regulated Cope rearrangement strategy to control the stereochemistry of quaternary carbon center by enforcing to take chair or boat transition geometries.[4,5)]

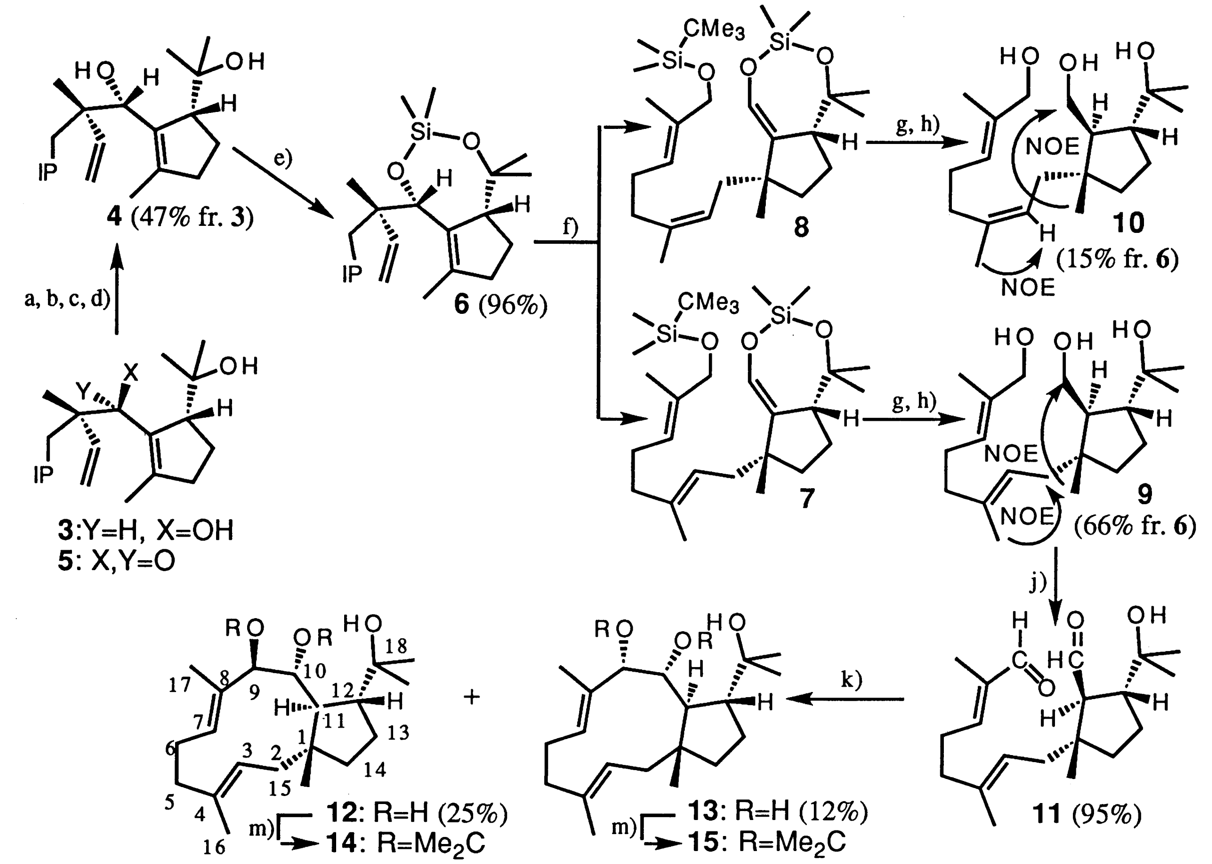
Low-valent chromium salt-mediated coupling of (3*R*)-8-hydroxy-1-iriden-7-al (**1**) and (*E,E*)-8-chloro-2,6-dimethylocta-2,6-dienyl *tert*-butyldimethylsilyl (TBS) ether (8-(*tert*-butyldimethylsiloxy)geranyl chloride, **2**; IP= C_5H_8OTBS) was investigated; after several trials, the reaction in a mixture of DMF and THF was shown to give the highest yield of one product (**3**), together with other three condensates (**4** and two epimers).



It is predicted that the Cope rearrangement of **3** and **4** should proceed on a steric ground to form 1-β-attacked products, having the *trans*-relationship for C-1 and C-3 (which should become C-1 and C-12 according to the adopted numbering for dolabellane as shown in **12**).[6)] This stereochemistry is opposite to the most of the dolabellane derivatives, although there are many natural products having C-3 (C-12) being sp^2-hybridized. Therefore, it is important to design functional groups to furnish the *cis*-products from the major product, **3**. However, it can only be realized by placing the migrating allyl group on the sterically-crowded α-side of the molecule via a ring-formation with two hydroxyl groups of **4**.[4,5)] In addition, the molecular model inspections suggested that the required (*E,E*)-geometry of the double bonds should be generated if the rearrangement proceeds through the chair-transition geometry. And, a conversion of **3** into **4** was carried out in the begining; i.e.,

3 was oxidized with pyridinium dichromate (PDC) to a ketone (**5**), which, after protection of the tertiary alcohol as a TMS ether, was reduced with diisobutylaluminum hydride (DIBAH) and deprotected the TMS ether to **4**.

Then, functionalization was achieved by treatment of **4** with dichlorodimethylsilane in pyridine to give a cyclic siloxane, a 1,3,2-dioxasilacycloheptane derivative (**6**).



Reagents and conditions: a) PDC/CH_2Cl_2; b) TMSCl/pyridine; c) DIBAH/toluene; d) PPTS/aqTHF; e) Me_2SiCl_2/benzene, pyridine; f) 200 °C, M.S. (4 Å)/xylene; g) NaOH, Bu_4NF/THF; h) LAH/THF; j) $(CCl_3CO)_2O/CH_2Cl_2$, DMSO, -60-50 °C, then Et_3N; k) $TiCl_4$/Zn/THF, pyridine; m) $Me_2C(OMe)_2$, PPTS/CH_2Cl_2.

Cope rearrangement of **6** occurred at 200 °C to form an enol siloxane (**7**) and its geometrical isomer (**8**): Formation of two thermolysates should be attributable to two transition geometries, chair for **7** and boat for **8** (Fig. 1). Deprotection of masked oxygen functions by treatment with tetrabutylammonium fluoride and subsequent LAH-reduction afforded triols (**9** and **10**). The major product (**9**) was identified as (1*R*,2*S*,3*R*)-(*E*,*E*)-1-(8-hydroxy-3,7-dimethylocta-2,6-dienyl)iridane-7,8-diol from the NOE evidence, and the minor, **10**, the (*Z*,*E*)-derivative. Subsequently, **9** was converted into a dialdehyde (**11**) by Swern oxidation. Rather unstable **11** was, without purification, subjected to low-valent titanium chloride-coupling(7) by Mukaiyama's procedure to give two cyclisates (**12** and **13**), in 25 and 12% yields, respectively.

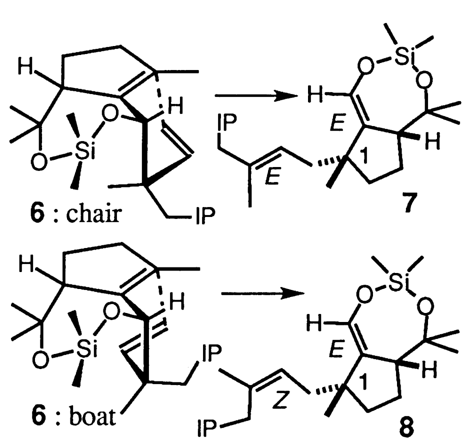


Fig. 1. Cope Transition geometries of **6**.

Stereochemical differentiation of epimers was done after formations of conformationally more rigid dioxolane derivatives (**14** and **15**), respectively. In the ^{1}H NMR spectrum of **14**, the singlet methyl signal of C-1 showed an NOE with the methine proton signal of C-10, while that of isopropyl methyl singlet revealed an NOE with signals ascribable to allylic methine proton signal of C-9 and methine proton at C-11.

Therefore, **14** has the 9β,10α-glycol function. On the other hand, similar NOE experiment established the stereochemistry of **15** as 9α,10α-glycol by positive NOE between C-1 methyl signal and two methine proton signals of C-9 and C-10 and isopropyl methyl and C-11 methine proton signal.[8)]

Consequently, the functionalized dolabellane skeleton has been constructed by introduction of geranyl group followed by cyclization. It should be noted that **14** has the same stereochemistry with the B-ring of fusicoccins and its biomimetic conversion will be the next aim.

References

1) e.g., A. G. Gonzälez, J. D. Martin, M. Norte, R. Përez, V. Weyler, S. Rafii, and J. Clardy, *Tetrahedron Lett.*, **24**, 1075 (1983); S. Huneck, G. A. Baxter, A. F. Cameron, J. D. Connolly, L. J. Harrison, W. R. Phillips, D. S. Rycroft, and G. A. Sim, *J. Chem. Soc., Perkin Trans. 1*, **1986**, 809; J. Shin and W. Fenical, *J. Org. Chem.*, **56**, 3392 (1991); C. B. Rao, F. Trimurtulu, D. V. Rao, S. C. Babzin, D. M. Kushlan, and J. D. Faulkner, *Phytochem.*, **30**, 1971 (1991); G. M. Koenig, A. D. Wright, and O. Sticher, *ibid.*, **30**, 3679 (1991).

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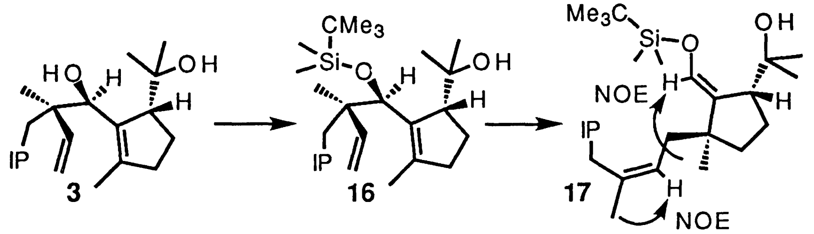
5) N. Kato, H. Kataoka, S. Ohbuchi, S. Tanaka, and H. Takeshita, *J. Chem. Soc., Chem. Commun.*, **1988**, 354; *J. Chem. Soc., Perkin Trans. 1*, **1989**, 165.

6) Indeed, the Cope rearrangement of *tert*-butyldimethylsilyl ether (**16**) of **3** afforded a *trans*-derivative (**17**) in 95% yield. The stereochemistry was assigned with NOE experiment.



7) For medium and large ring formations mediated by low-valent titanium species, seeJ. E. McMurry and J. G. Rico, *Tetrahedron Lett.*, **30**, 1169 (1989).

8) The ^{1}H and ^{13}C NMR spectra (270 and 67.5 MHz, respectively, in CDCl$_3$ solutions) of key compounds are listed below:

2: δ(H)=0.06(6H, s), 0.91(9H,s), 1.59(3H, br s), 1.73(3H, br s), 2.0-2.15(4H, m), 4.00(2H, br s), 4.09 (2H, d, *J*=8 Hz), 5.36(1H, m), and 5.44(1H, m). δ(C)=−5.3(2C), 13.5, 16.1, 18.4, 25.6, 26.0(3C), 39.1, 41.1, 68.5, 120.4, 123.4, 134.9, and 142.6.

3: δ(H)=0.06(6H, s), 0.90(9H, s), 0.92(3H, s), 1.03 (3H, s), 1.26(3H, s), 1.3-1.6(3H, m), 1.57(3H, br s), 1.73(3H, br s), 1.8-2.0(3H, m), 2.0-2.4(2H, m), 3.03(1H, br d, *J*=9 Hz), 3.99(2H, br s), 4.31(1H, s),

5.02 (1H, dd, *J*=18, 2 Hz), 5.16(1H, dd, *J*=11, 2 Hz), 5.35 (1H, m), and 6.01(1H, dd, *J*=18, 11 Hz). δ(C)=–5.2 (2C), 13.4, 15.4, 18.0, 18.4, 22.3, 23.5, 26.0(3C), 27.2, 30.4, 37.0, 38.4, 46.3, 58.2, 68.7, 73.9, 74.2, 113.9, 125.3, 133.9, 135.0, 141.6, and 145.3.

4: δ(H)=0.06(6H, s), 0.91(9H, s), 1.06(3H, s), 1.16(3H, s), 1.24(3H, s), 1.4-1.6(3H, m), 1.57(3H, br s), 1.7-2.0(3H, m), 1.89(3H, br s), 2.09(1H, m), 2.32(1H, m), 2.56(1H, br d, *J*=8.5 Hz), 3.99(2H, br s), 4.56 (1H, s), 5.01(1H, dd, *J*=18, 2 Hz), 5.13(1H, dd, *J*=11, 2 Hz), 5.36(1H, m), and 5.82(1H, dd, *J*= 18, 11 Hz). δ(C)=–5.2(2C), 13.4, 17.6, 18.3, 18.4, 22.4, 25.99(3C), 26.02, 26.3, 30.2, 36.8, 39.3, 47.7, 60.8, 68.7, 75.9, 77.9, 114.1, 125.2, 134.0, 136.2, 139.7, and 144.1.

5: δ(H)=0.06(6H, s), 0.90(3H, s), 1.10(3H, s), 1.15(3H, s), 1.27(3H, s), 1.57(3H, br s), 1.6-1.85(3H, m), 1.65(3H, br s), 1.85-2.1(3H, m), 2.2-2.45(2H, m), 3.19(1H, br d, *J*=9 Hz), 3.99(2H, br s), 5.10(1H, dd, *J*=17.5, 1 Hz), 5.17(1H, dd, *J*=11, 1 Hz), 5.35(1H, m), and 6.02(1H, dd, *J*=17.5, 11 Hz). δ(C)=–5.2 (2C), 13.4, 15.7, 18.4, 19.1, 22.3, 24.7, 26.0(3C), 26.4, 28.9, 37.6(2C), 55.0, 61.6, 68.6, 74.5, 114.2, 124.3, 134.6, 139.2, 142.1, 142.4, and 214.0.

6: δ(H)=0.06(6H, s), 0.07(3H, s), 0.14(3H, s), 0.91(9H, s), 1.12(3H, s), 1.13(3H, s), 1.27(3H, s), 1.4-1.6(3H, m), 1.56(3H, br s), 1.81(3H, br s), 1.85-2.1(3H, m), 2.16(1H, m), 2.31(1H, m), 2.60(1H, br d, *J*=9 Hz), 4.00(2H, br s), 4.18(1H, s), 5.01(1H, dd, *J*=18, 2 Hz), 5.02(1H, dd, *J*=11, 2 Hz), 5.37(1H, m), and 6.45(1H, dd, *J*=18, 11 Hz). δ(C)=–5.2(2C), –1.3, 0.7, 13.1, 18.3, 18.4, 22.4, 23.8, 26.0(3C), 26.5(2C), 31.4, 37.0, 40.9, 43.3, 65.1, 68.7, 77.6, 79.7, 111.1, 125.2, 134.1, 135.0, 137.3, and 145.9.

9: δ(H)=0.78(3H, s), 1.14(3H, s), 1.2-1.55(2H, m), 1.25(3H, s), 1.61(3H, br s), 1.65(3H, br s), 1.7-2.05 (4H, m), 2.1-2.25(6H, m), 3.33(1H, t, *J*=10 Hz), 3.72(1H, dd, *J*=10, 2.5 Hz), 3.97(2H, br s), 5.22(1H, br t, *J*=7 Hz), and 5.37(1H, br t, *J*=5.5 Hz). δ(C)=13.7, 16.1, 21.0, 23.4, 25.6, 27.1, 31.0, 38.6, 39.45, 39.51, 45.3, 49.7, 56.3, 64.2, 68.5, 72.7, 121.4, 125.3, 134.9, and 136.3.

12: δ(H)=1.00(3H, s), 1.15-1.6(3H, m), 1.23(3H, s), 1.27(3H, s), 1.50(3H, br s), 1.54(3H, br s), 1.7-1.9 (3H, m), 1.95-2.4(5H, m), 2.47(1H, dt, *J*=11, 9 Hz), 2.74(1H, br s; OH), 3.29(1H, br t, *J*=9.5 Hz), 3.39 (1H, br s; OH), 4.01(1H, br d, *J*=9 Hz; OH), 4.09(1H, d, *J*=10 Hz), 4.72(1H, br t, *J*=5.5 Hz), and 5.21 (1H, br dd, *J*=8, 6.5 Hz).

13: δ(H)=1.01(3H, s), 1.15-1.4(2H, m), 1.25(3H, s), 1.28(3H, s), 1.51(3H, br s), 1.55(3H, br s), 1.55-1.9 (4H, m), 1.95-2.25(5H, m), 2.51(1H, td, *J*=10, 7.5 Hz), 3.60(1H, br t, *J*=2 Hz), 4.36(1H, br s), 4.77 (1H, br t, *J*=6 Hz), and 5.25(1H, br t, *J*=7.5 Hz).

14: δ(H)=0.96(3H, s), 1.15(3H, s), 1.2-1.6(3H, m), 1.24(3H, s), 1.43(3H, s), 1.46(3H, s), 1.53(3H, br s), 1.57(3H, br s), 1.75-2.5(9H, m), 3.43(1H, s; OH), 3.66(1H, dd, *J*=9, 1.5 Hz), 4.42(1H, d, *J*=9 Hz), 4.80(1H, br t, *J*=6 Hz), and 5.24(1H, br dd, *J*=10, 5 Hz). δ(C)=11.9, 16.3, 22.6, 23.4, 25.0, 26.5, 26.7, 27.5, 32.2, 38.2, 38.6, 39.0, 42.0, 46.0, 50.6, 72.0, 76.5, 86.0, 108.1, 123.5, 127.7, 133.4, and 133.9.

15: δ(H)=1.09(3H, s), 1.1-1.8(4H, m), 1.19(3H, s), 1.22(3H, s), 1.38(3H, s), 1.53(3H, s), 1.59(3H, br s), 1.67(3H, t, *J*=1 Hz), 1.95(1H, dd, *J*=10.5, 7 Hz), 2.0-2.5 (7H, m), 4.16(1H, dd, *J*=10.5, 6.5 Hz), 4.53 (1H, d, *J*=6.5 Hz), 4.81(1H, br s; OH), 4.96(1H, br dd, *J*=9.5, 4 Hz), and 5.08(1H, br dd, *J*=12, 4 Hz). δ(C)=13.6, 16.8, 23.9, 24.2, 24.9, 25.0, 26.0, 28.4, 31.9, 38.9, 39.9, 42.8, 43.3, 46.8, 56.1, 71.0, 79.9, 85.4, 106.5, 124.4, 131.4, 133.6, and 134.2.

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