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An Efficient Construction of Trinervitane and Kempane Skeletons from the Common Intermediate[1]

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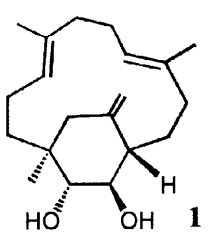
Abstract: Tricyclic trinervitane and tetracyclic kempane skeletons are constructed from the common intermediate possessing bicyclic secotrinervitane skeleton on the basis of biogenetical consideration.

Unusual bioactive terpenoids have been isolated from termite soldiers[2] and their roles are clarified as the defense chemicals in termite society. Of these terpenoids bicyclic diterpene as exemplified by **1** is known as secotrinervitane and is the proposed intermediate in the biosynthesis of other polycyclic diterpenes such as **2** and **3** from cembrene.[3] The tricyclic (**2**) and tetracyclic (**3**) diterpenes belong to trinervitane and kempane type skeletons, respectively.



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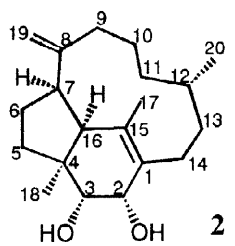

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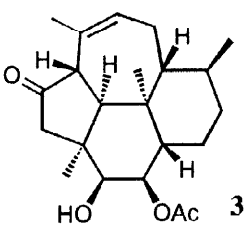

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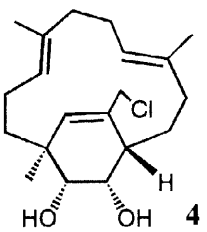

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Because of these interesting features, the synthesis of these compounds has attracted much attention.[4] We have achieved the total synthesis of *dl*-**1** by a biomimetic route involving the stereospecific cyclization of a cembrene derivative.[5] On the basis of the biogenetical consideration, we have continued the synthetic study of tricyclic and tetracyclic compounds (**2** and **3**) and found that both skeletons corresponding to **2** and **3** are constructed from the common intermediate (**4**) derived from the bicyclic compound (**1**). The result is described in this communication.

The common intermediate (**4**) was prepared from *dl*-**5**[5b] by the improved route shown in scheme 1. The configuration of 2β-hydroxy group of **6** was first converted to α-isomer (**7**), which provided epoxide (**8**) under Sharpless epoxidation conditions. The β-isomer (**6**) afforded no epoxide under the employed conditions due to equatorial nature of the β-hydroxy group of **6**. The selective epoxide ring opening of **8** was achieved after protection of the 2α-hydroxy group of **8**. The deprotection of both MOM groups afforded the triol (**9**). The primary hydroxy group of **9** was selectively converted to the corresponding chloride (**4**) through the protected intermediate (**10**).

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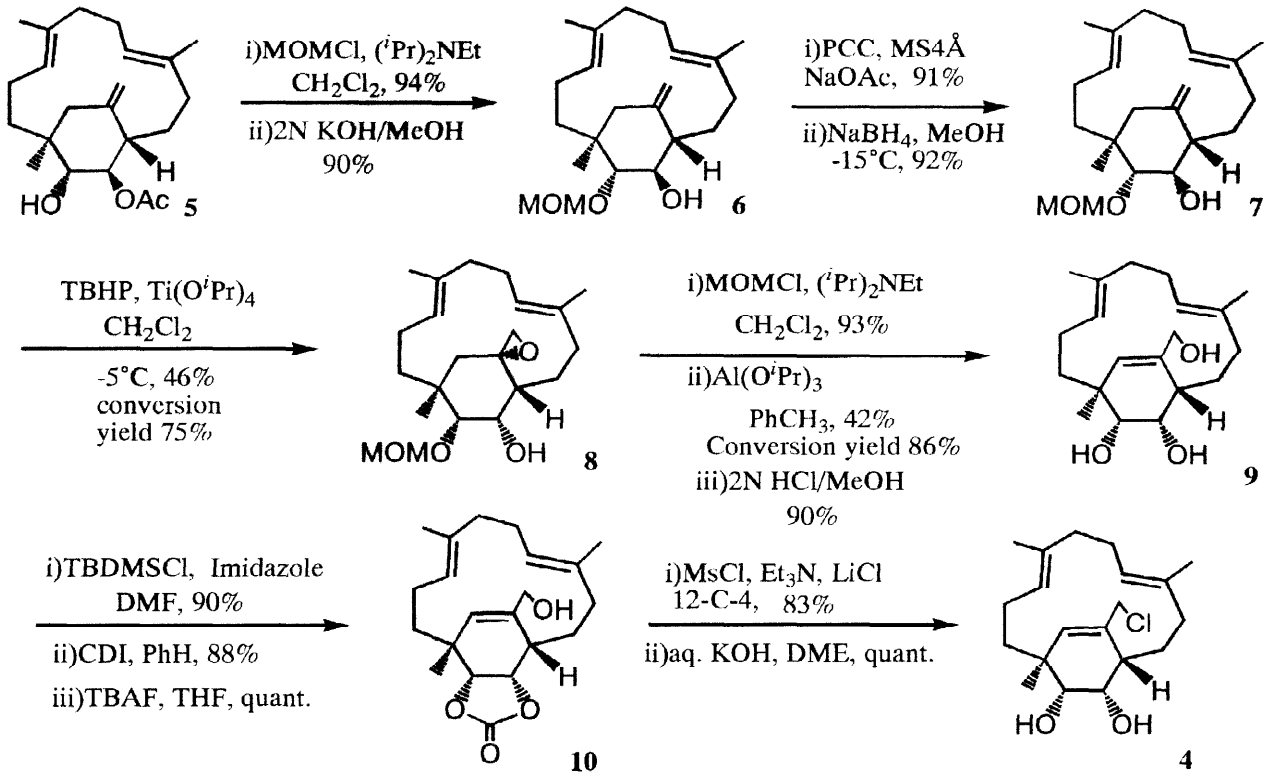
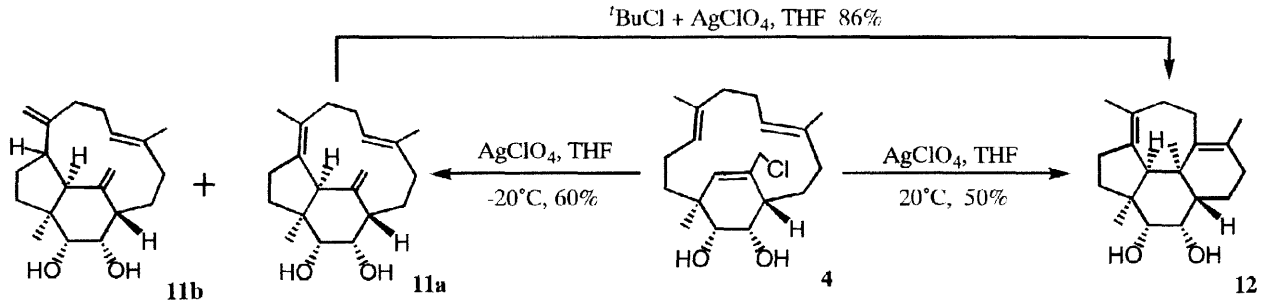


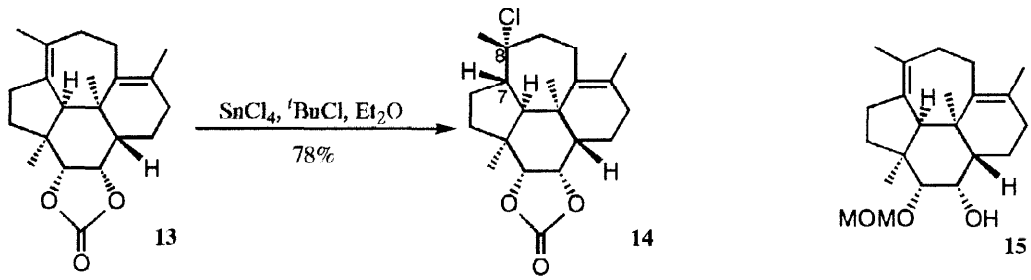
Scheme 1 Preparation of the common intermediate (**4**)

When **4** was treated with $AgClO_4$ at -20°C, the trinervitane skeletons (**11a** and **11b**) were isolated in 60 and 5 % yields, respectively.[6] In the meanwhile, the tetracyclic kempane-type compound (**12**) was isolated in 50% yield when the reaction was carried out at +20°C. The time course of the formation of **12** by TLC analysis suggested that **11a** was the intermediate, which may be transformed to **12** by the action of $HClO_4$ liberated in the reaction medium. In fact, **11a** was effectively converted to **12** by $HClO_4$ prepared *in situ* from ^{t}BuCl and $AgClO_4$.[7]

The structures of the trinervitane (**11a**) and kempane skeleton (**12**) was elaborated from the detailed inspection of NMR spectra including H-H COSY, C-H COSY and NOESY. The results are summarized in Table 1. In the NMR spectra of **12**, two *tert*-methyl and two olefinic methyl groups were clearly observed while no olefinic proton was detected on the two double bonds, suggesting the tetracyclic kempane skeleton. The stereogenic centers at 4, 16 and 15 positions were demonstrated from clear NOEs between C_{16}-H and both C_4- and C_{15}-methyl groups. These groups and C_{16}-H showed no NOE between each proton at 1, 2, and 3 positions while clear NOEs were observed among these protons.



Thus, it was found that four stereogenic centers of ring junction of kempane skeleton were formed from the bicyclic intermediate (**4**). Directed toward the synthesis of kempane type natural products, some preliminary experiments concerning chemical properties of functional groups in **12**[8] were carried out. The 2,3-dihydroxy group of **12** were converted to the corresponding carbonate (**13**) in 92% yield by the action of CDI in benzene at room temperature. The regio- and stereoselective HCl addition was observed when the carbonate (**13**) was treated with $SnCl_4$ and ^tBuCl to give the adduct (**14**) in 78% yield.[9] The structure of **14** was deduced from the detailed analysis of the NMR spectra listed in Table 1.[10]



13 14 15

Table 1. ^1H and ^{13}C NMR spectra of **11a**, **12** and **14** ($CDCl_3$, ^1H 500MHz; ^{13}C 125MHz)

atom	11a		12		14	
number	^{13}C δ (m)	^1H δ (m *J* Hz)	^{13}C δ (m)	^1H δ (m *J* Hz)	^{13}C δ (m)	^1H δ (m *J* Hz)
1	44.0 (d)	2.20(br)	40.5 (d)	1.54 (m)	36.7 (d)	1.56 (m)
2	78.3 (d)	3.75 (br s)	76.4 (d)	3.87 (dd 2.0, 4.0)	78.1 (d)	4.89 (dd 4.9, 9.5)
3	72.8 (d)	3.40 (d 3.0)	72.6 (d)	3.46 (br s)	79.7 (d)	4.67 (d 9.5)
4	50.7 (s)		47.2 (s)		43.2 (s)	
5	37.3 (t)	(a)1.09 (m)	38.6 (t)	(a)1.15 (br)	39.2 (t)	(a)1.20 (dt 6.7, 12.5)
		(b)1.99 (m)		(b)1.88 (dd 2.4, 6.3)		(b)1.40 (dd 5.7, 12.1)
6	30.6 (t)	2.39 (br)	30.9 (t)	2.25 (br)	25.7 (t)	(a)1.64(br)
						(b)1.73 (br)
7	136.1 (s)		135.5 (s)		54.3 (d)	1.77(m)
8	129.4 (s)		126.2 (s)		77.5 (s)	
9	32.9 (t)	(a)1.69 (br)	37.7 (t)	(a)2.10 (m)	46.9 (t)	(a)1.60 (br)
		(b)2.53 (dt 4.0, 12.5)		(b)2.24 (m)		(b)2.17 (br)
10	24.2 (t)	(a)2.02 (m)	23.9 (t)	(a)2.27 (br)	22.7 (t)	(a)2.12 (br)
		(b)2.15 (m)		(b)2.40 (dt 4.0, 13.4)		(b)2.22 (br)
11	125.8 (d)	4.99 (dd 5.5, 11.0)	140.6 (s)		137.3 (s)	
12	132.7 (s)		122.1 (s)		127.2 (s)	
13	40.1(t)	(a)1.88 (dt 4.5, 12.5)	30.9 (t)	(a)2.00 (m)	31.9 (t)	(a)2.02 (dd 6.1, 17.4)
		(b)2.14 (m)		(b)2.10 (m)		(b)2.11 (br)
14	25.9 (t)	(a)1.45 (m)	23.2 (t)	(a)1.49 (br)	20.3 (t)	(a)1.66 (br)
		(b)1.94 (m)		(b)2.09 (br)		(b)1.87 (m)
15	148.4 (s)		43.1 (s)		38.0 (s)	
16	61.1 (d)	2.94 (br s)	57.3 (d)	2.93 (br)	52.4 (d)	2.25 (m)
17	112.5 (t)	(a)4.93 (s)	24.9 (q)	1.30 (s)	21.5 (q)	1.09 (s)
		(b)5.06 (s)				
18	21.6 (q)	0.99 (s)	25.1 (q)	1.34 (s)	26.7 (q)	1.27 (s)
19	18.7 (q)	1.64 (s)	22.4 (q)	1.52 (s)	32.7 (q)	1.53 (s)
20	15.6 (q)	1.54 (s)	18.8 (q)	1.57 (s)	19.0 (q)	1.59 (s)
21					154.7 (s)	

When **12** was treated with equimolar amount of MOMCl and $^{i}Pr_2NEt$, 3-hydroxy group was selectively protected to give **15** in 76% yield.

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References and Notes

1. This constitutes part 57 of the series of "Cyclization of Polyenes". Part 56, Y. Kasibuchi, T. Fukumoto, T. Hirukawa, and T. Kato, *Heterocycles*, in press (1998).
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6. The structure of **11a** was confirmed by X-ray crystallographic analysis of dihydro-derivative derived therefrom. The stereochemistry at 7 position of **11b** remains undetermined.
   Spectral data of **11b**: ^{1}H-NMR(500MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.13 (dt, 1H, *J*=7.5, 12.0 Hz), 1.27 (d, 1H, *J*=8.0 Hz), 1.52 (m, 1H), 1.54 (s, 3H), 1.75 (dt, 1H, *J*=7.5, 13.5 Hz), 1.83 (br, 1H), 1.91 (m, 1H), 1.98-2.10 (br, 4H), 2.21 (d, 1H, *J*=9.5 Hz), 2.27 (dt, 1H, *J*=6.5, 11.5 Hz), 2.33 (br, 1H), 2.43 (br, 2H), 2.62 (d, 1H, *J*=12.5 Hz), 2.84 (br, 1H), 3.47 (dd, 1H, *J*=3.5, 9.0 Hz), 3.67 (dt, 1H, *J*=3.5, 8.0 Hz), 4.91 (s, 1H), 5.07 (s, 1H), 5.10 (s, 1H), 5.12 (s, 1H), 5.03-5.20 (br, 1H); ^{13}C-NMR (125MHz, $CDCl_3$) δ 15.5 (q), 22.1 (q), 25.2 (t), 25.9 (t), 28.9 (t), 35.9 (t), 37.8 (t), 38.1 (t), 41.4 (d), 49.4 (d), 50.2 (s), 59.7 (d), 72.3 (d), 77.9 (d), 109.6 (t), 115.0 (t), 129.5 (d), 130.6 (s), 145.6 (s), 150.2 (s).
7. Treatment of **11a** with other Lewis acids such as BF_3-OEt_2 or $SnCl_4$ gave no satisfactory result concerning the cyclization.
8. The synthetic study of trinervitane type natural products from **11a** has been currently undertaken and the results will be published.
9. The scope and limitation of this reagent system to the polyene compounds will be reported.
10. The newly formed streogenic centers at 7 and 8 positions of **14** were deduced from NOESY, where C_7-H showed positive NOE between C_8-methyl while it exhibited on NOE between C_{16}-H and C_4-methyl group.