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ONE-POT STEREOSPECIFIC CONSTRUCTION OF CIS-CLERODANE SKELETON BY MEANS OF DOUBLY STEREOCONTROLLED CYCLIZATION: TOTAL SYNTHESIS OF LINARIDIAL

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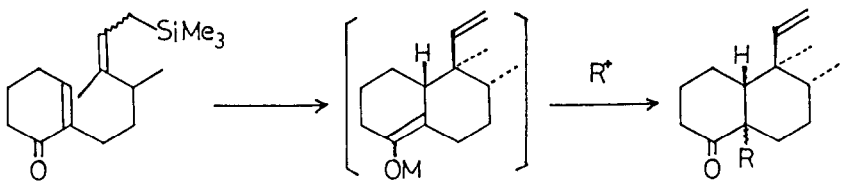
Abstract: Doubly stereocontrolled cyclization of the allylsilane derivative **1** followed by trapping of the enolate with $ClCH_2SMe$ gives in one-pot manner the decalone derivatve **5** in which all of the four contiguous diastereomeric centers of cis-clerodane skeleton have been secured. The total synthesis of linaridial **4** have been accomplished from **5**.

In previous letter,[1] we reported a doubly stereocontrolled cyclization of 2-(3',4'-dimethyl-6'-trimethylsilyl-4'-hexenyl)-2-cyclohexenone **1** to the decalone derivative **3** (R = H) and reasoned this remarkable result in terms of orientation and folding strain controls.[1] If the stereoselective introduction of a C_1 synthon at the angular position could be possible through the trapping of intermediary enolate **2**, our cyclization will lead in one-pot process to the construction of clerodane diterpenoid skeleton **3**[2] which involves four contiguous diastereomeric centers. We delineate here the realization of this aim and the application for the first total synthesis of linaridial **4**, a cis-clerodane diterpene isolated from Linaria japonica.[3]



1 2 3

The trapping of the enolate formed in the Hosomi-Sakurai reaction was already reported.[4] However the reaction of **1** in this procedure - i.e. the addition of an electrophile after the enolate formation - gave none of the desired product even by the use of trimethyl orthoformate, which was described to be most effective, or by the agency of Lewis acids other than $TiCl_4$. Perhaps steric requirement in **2** would be problematic. To overcome this difficulty we focussed our attention to the use of the electrophile, sterically less demanding and highly active, and the choice of more effective procedure. After extensive experimentation the formation of alkylated product **5**[5] in a minute amount was observed firstly in the reaction with chloromethyl methyl sulfide ($ClCH_2SMe$). Then we found that the addition of a mixture of the allylsilane **1** and $ClCH_2SMe$ to a CH_2Cl_2 solution of $TiCl_4$ was most effective

Table 1. Cyclization-Enolate Trapping Reaction of Allylsilane 1*

entry	Equiv of Reagents		temp (°C)	solvent	Products (yield, %)	
	$TiCl_4$	$ClCH_2SMe$			**5**	**3** (R = H)
1	1	10	-78	CH_2Cl_2	0	∿ 85
2	1	2	-78	CH_2Cl_2	21	64
3	2	1.1	-78	CH_2Cl_2	51	34
4	2	1.1	-12	CH_2Cl_2	64	21
5	2	1.1	0	CH_2Cl_2	77	8
6	2	1.1	-12	PhMe	0	∿ 85
7	2	1.1	-12	$ClCH_2CH_2Cl$	57	28

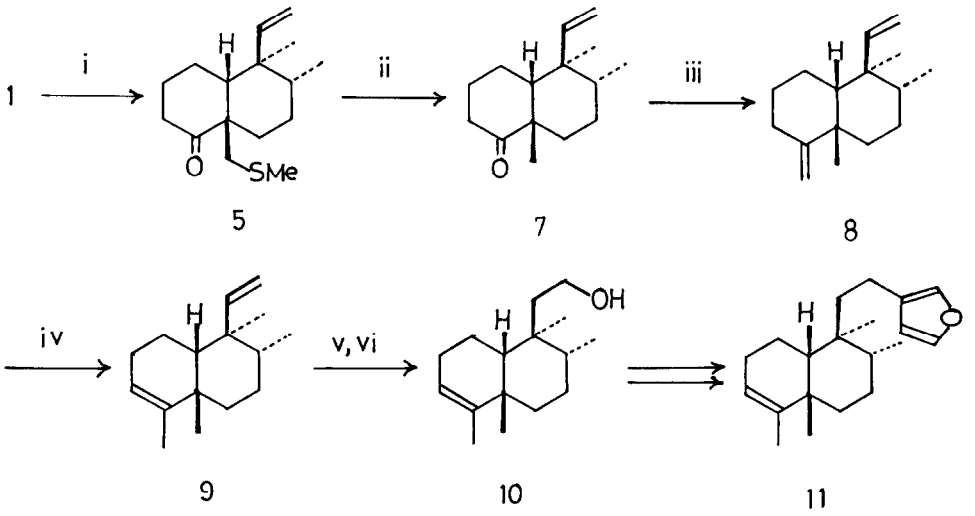
*The reactions were conducted by adding a mixture of the allylsilane (50 mg) and $ClCH_2SMe$ in CH_2Cl_2 (1 ml) to a solution of $TiCl_4$ in CH_2Cl_2 (2 ml) kept at a fixed temperature.

Table 1 lists the result of the investigation to improve the yield of **5** in relevance with the stoichiometry of $TiCl_4$ and $ClCH_2SMe$, reaction temperature, and solvents. The best result was achieved by the reaction of **1** with 2 equiv of $TiCl_4$ and 1.1 equiv of $ClCH_2SMe$ in CH_2Cl_2 at 0 °C.(entry 5)[6] The high reactivity of $ClCH_2SMe$ could be ascribed to the formation of the sulfonium species **6** which should be very reactive and less sterically demanding. This assumption is in conformity with the requisite equivalents of $TiCl_4$, one extra molar equiv being consumed for the production of **6**. The excess of $ClCH_2SMe$ would solvate to the cationic species **6** and render it more bulky. The stereochemistry of the methylthiomethyl group introduced at the angular position can be assigned to be cis when we assume the attack of the reagent from convex side of the molecule. This assumption was supported by the observation of NOE effect between the methylene proton signal of the group in question and the vinyl group proton signal in the ^1H NMR spectrum. Thus the one-pot preparation of cis-clerodane skeleton has become feasible.

$Me\overset{+}{S}=CH_2 \cdot \overset{-}{Ti}Cl_5$

6

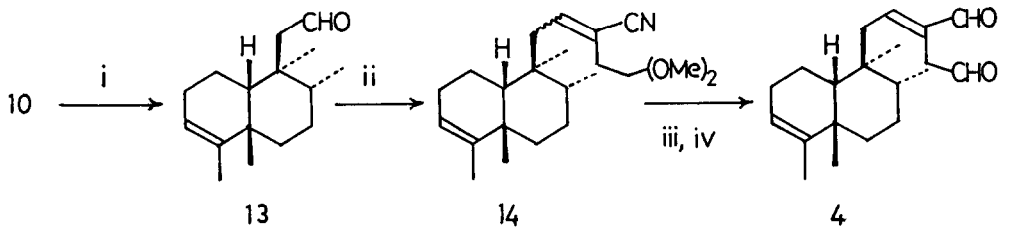
Next we concerned with its conversion to the alcohol **10** which was already synthesized and transformed by us[2b] to the natural cis-clerodane diterpene **11** isolated from Solidago arguta.[7](Scheme 2) Reductive removal of the methylthio group in **5** gave the decalone derivative **7**[8] with cis-methyl group. For the installation of a methyl group at the carbonyl position of **7** we routinely investigated the reaction with methyl lithium. However it gave only minute amount (< 10%) of the corresponding tertiary alcohol as the result of extensive enolization due to the severe steric hindrance inherent with the carbonyl group in **7**. MeLi-$CeCl_3$ procedure[9] was also ineffective, the yields being less than 20%. The tertiary alcohol in the yield up to 50% could be obtained by the repetition of the methylation (MeLi) and protonation (MeOH) several times,[10] but this method is rather tedious. Moreover the dehydration of the tertiary alcohol by thionyl chloride-pyridine afforded a mixture of exo and endo olefins, **8** and **9** in 4:1 ratio. Therefore an alternate sequence was explored. The methylenation by Nozaki procedure[11] worked excellently to give **8** in high yield, which could be isomerized cleanly to the endo olefin **9**[12] by



Scheme 2. Reagents: i,$TiCl_4$,$ClCH_2SMe$,0 °C; ii,Raney Ni,EtOH; iii,CH_2Br_2-Zn-$TiCl_4$,THF; iv,$KNH(CH_2)_3NH_2$,$NH_2(CH_2)_3NH_2$,rt, 5 h; v,$Me_2CHMe_2CBH_2$,THF; vi,H_2O_2, NaOH

Brown's method.[13] The selective hydroboration followed by oxidation provided the alcohol **10**. This product was identified by spectroscopic comparison (IR, ^1H and ^{13}C NMR). Accordingly the conversion above implies the affirmation of the configuration assigned for the cyclization-alkylation product **5** as well as the formal total synthesis of **11**.

The utility of our key intermediate **5** for the synthesis of cis-clerodane diterpenoids has been further demonstrated by a facile access to the antifungal compound, linaridial **4**. First the alcohl **10** was converted by Swern oxidation to aldehyde **13**. The Horner-Emmons condensation of **13** with diethyl (1-cyano-3,3-dimethoxypropyl)phosphonate **12**[14] gave **14** as a mixture of stereoisomers (E/Z = 1:5).[15] Reduction of **14** with Bu^i_2AlH(DIBAL) resulted only in poor production of the corresponding aldehyde and entailed a special device. With the consideration that the coordination of DIBAL to the acetal grouping of **14** might bring the complication of the reaction we examined the effect of Lewis acid addends to prevent it. Actually the addition of diethylaluminum chloride does improve the situation and the reduction of **14** in a mixture of ether and toluene (1:2) proceeded smoothly and, after acidic treatment,



Scheme 3. Reagents: i,$(COCl)_2$,DMSO,CH_2Cl_2,then NEt_3; ii, **12**,NaH,THF; iii, DIBAL(1.5equiv),Et_2AlCl(1.5equiv),Et_2O-PhMe(1:2),-78∿40 °C; iv,1MHCl,THF

afforded linaridial **4** in 73% yield as single stereoisomer. The isomerization of Z-isomer to **4** had occurred during the reduction-hydrolysis process. The identity with the natural product has been secured by the comparison of IR and ^{1}H NMR spectra.[16]

In conclusion a unique and efficient method for the stereospecific synthesis of cis-clerodane diterpenoid has been developed. The mode with which the ring skeleton with four diastereomeric centers is constructed in one-pot reaction would provide a remarkable instance of multiple stereocontrol.

Acknowlegements. We are indebted to Prof. I. Kitagawa, Osaka University for providing us copies of IR and ^{1}H NMR spectra of linaridial. This work was partly supported by Grand-in-Aid from the Ministry of Education, Science and Culture, which is gratefully acknowledged.

References and Notes

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2. For our other approaches to the stereospecific synthesis of clerodan diterpenoids see: (a)T. Tokoroyama, K. Matsuo, and T. Kubota, Tetrahedron, **34**, 1907(1978); (b)T. Tokoroyama, K. Fujimori, T. Shimizu, Y. Yasmagiwa, M. Monden, and H. Iio, J. Chem. Soc., Chem. Commun., 1516(1983); (c)H. Iio, M. Monden, K.Okada, and T. Tokoroyama, ibid., 358(1987).
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5. **5**: mp 60-62 °C; IR(neat) 2960,1705,1640,1460,1210,920cm^{-1}; ^{1}H NMR δ 0.72 (d,J=6Hz), 0.86(3H,s),1.00-1.60(12H,m),2.13(3H,s),2.93(2H,ABq,J=12Hz),4.91 (1H,dd,J=3,16.5Hz),5.10(1H,dd,J=3,13.5Hz),5.43(1H,dd,J=13.5,16.5Hz).
6. Even at this condition we could not completely avoid the formation of the unsubstituted product **3** (R = H). In the preparations of larger scale, the ratio **5**/**3**(R = H) improved up to 18:1.
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8. **7**, IR($CHCl_3$)2930,1700,1631,1450,1200,910cm^{-1}; ^{1}H NMR δ 0.72(3H,d,J=6Hz), 0.86(3H,s), 1.33(3H,s),0.90-2.80(12H,m),4.89(1H,dd,J=3,16.5Hz),5.09(1H,dd, J=3,10.5Hz),5.43(1H,dd,J=10.5,16.5Hz).
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10. We thank professor M. Kodama and Dr. T. Tsunoda for the information on this procedure.
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12. **9**: ^{1}H NMR δ 0.70(3H,d,J=6.6Hz),0.89(3H,s),1.04(3H,s),1.10-2.16(10H,m),1.69 (3H,d,J=2Hz),4.90(1H,dd,J=1.5,17.6Hz),5.06(1H,dd,J=1.5,10.7),5.28(1H,br s), 5.45(1H,dd,J=10.7,17.6Hz).
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15. **14**: ^{1}H NMR δ 0.82(3H,d,J=6Hz),0.93(3H,s),1.06(3H,s),1.70,(3H,br s),1.10-2.80(14H,m),3.39,3.41*(6H in total,s),4.53(1h,t,J=6Hz),5.30(1H,br s),6.30, 6.53*(1H in total,t,J=7.5Hz). Asterisks (*) denote the minor signal due to the E isomer.
16. **4**: IR($CHCl_3$) 2720,1732,1692,1640cm^{-1}; ^{1}H NMR(400 MHz) δ 0.82(3H,d,J=6.7Hz), 0.93(3H,s),1.04(3H,s),1.06-1.35(7H,m),1.47(1H,ddq,J=3,12,6.7Hz),1.68(3H,d, J=1.7Hz),1.95-2.20(2H,m),2.26(1H,dd,J=6.7,16.7Hz),2.54(1H,dd,J=8.2,16.5Hz), 3.41(2H,d,J=17.2Hz), 3.46(1H,d,J=17.2Hz),5.31(1H,br s),6.91(1H,t,J=7.3Hz), 9.49(1H,s),9.62(1H,t,J=1.5Hz). In the ^{1}H NMR chart (90 MHz) of natural product[3] additional trivial signals are observed at δ 6.50(t,J=7Hz), 9.59 (br s), and 10.04(s). These signals should most probably be attributed on the basis of ^{1}H NMR spectra of the related compounds in this work to the presence of Z isomer in minor amount, the first corresponding to the vinyl proton of the side chain and the last two to aldehyde protons.

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