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METATHESIS REACTIONS OF UNSATURATED ESTERS CATALYZED BY HOMOGENEOUS TUNGSTEN COMPLEXES. SYNTHESES OF CIVETONE AND MACROLIDES

JIRO TSUJI and SHOHEI HASHIGUCHI
Tokyo Institute of Technology, Meguro, Tokyo 152 (Japan)

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Summary

The metathesis reactions of methyl 10-undecenoate, methyl oleate and oleyl acetate have been carried out using WCl_6 and $WOCl_4$ as primary catalysts and $SnMe_4$, $PbMe_4$, Cp_2TiMe_2, and Cp_2ZrMe_2 as cocatalysts. The catalyst system $WOCl_4/Cp_2TiMe_2$ was found to be very active for the metathesis of the unsaturated esters and is somewhat better than the system $WCl_6/SnMe_4$. Diethyl 9-octadecene-1,18-dioate, obtained by the metathesis of ethyl oleate, was subjected to the Dieckmann cyclization. The cyclized product was decarboxylated to give civetone as a mixture of the *cis* and *trans* isomers. Preliminary studies of macrolide synthesis by the intramolecular metathesis of oleyl oleate and 10-undecenyl 10-undecenoate to afford 9-octadecen-18-olide and 10-eicosen-20-olide, respectively, have been carried out.

Olefin metathesis, expressed by the following general scheme, is a unique and remarkable reaction which was discovered in recent years [1].

$$2\ R^1{-}CH{=}CH{-}R^2 \rightleftharpoons R^1{-}CH{=}CH{-}R^1 + R^2{-}CH{=}CH{-}R^2$$

The reaction proceeds under the influence of homogeneous and heterogeneous tungsten, molybdenum, and rhenium catalysts. As homogeneous catalysts, a combination of tungsten or molybdenum salts with organoaluminum compounds is typical. In solution the metathesis reaction of simple olefins proceeds rapidly when using $WCl_6/AlEtCl_2$ as a catalyst. The reaction offers a synthetic method very useful in both industry and academic laboratories. However, one drawback in applying the olefin metathesis to organic synthesis is the fact that the common catalysts for metathesis prepared from tungsten or molybdenum chlorides as the principal catalyst and organoaluminum compounds as a cocatalyst are inactive for olefins with functional groups. In order to exploit the metathesis reactions as a truly useful synthetic methodology, it is essential to discover

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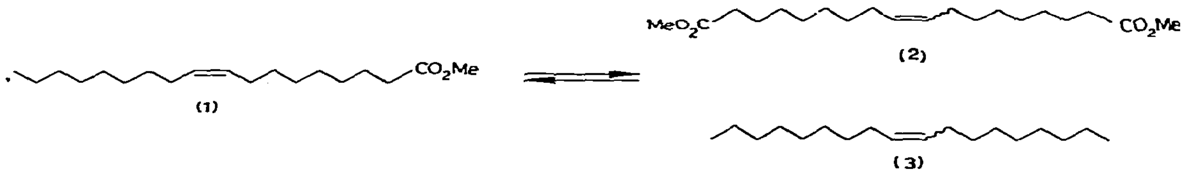
a new catalyst system which can tolerate the presence of various functional groups in the olefin molecules. From this standpoint, the discovery made by Van Dam, Mittelmeijer, and Boelhouwer in 1972 that the catalyst prepared from WCl_6 as the principal catalyst and $SnMe_4$ as the cocatalyst can be used for the metathesis of some unsaturated esters was an important breakthrough [2,3]. They converted methyl oleate [(*Z*)-9-octadecenoate] (1) into dimethyl 9-octadecenedioate (2) and 9-octadecene (3) using 1—2 mol % of WCl_6 and $SnMe_4$ in 1 : 1 molar ratio as the catalyst.



Since this study, many investigations have been carried out on the metathesis of functionalized olefins. In addition to the $WCl_6/SnMe_4$ system, other catalysts such as WCl_6/Et_3B, $WCl_6/Me_3Al_2Cl_3$, and $Mo(OEt)_2Cl_3/Me_3Al_2Cl_3$ have been proposed [4,5]. Olefins with functional groups such as esters, halogens, amines, and ethers were subjected to metathesis with considerable success [6—12]. But $WCl_6/SnMe_4$ seems to be the most active catalyst. However, it is still important to discover a better catalyst for functionalized olefins. The present investigation has been undertaken with the intension of finding more active catalyst systems for functionalized olefins. We have carried out screening experiments, and found that the catalyst system of $WOCl_4/Cp_2TiMe_2$ is highly active for unsaturated esters. We have used this catalyst system for the syntheses of macrolides and civetone. A part of this study has already been reported briefly [13] and the details of these studies are presented in this paper.

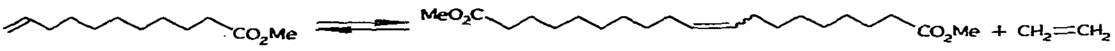
Results and Discussion

Since the work of Van Dam et al., several reports have appeared on the metathesis of unsaturated esters using $SnMe_4$ [7—12]. We have carried out screening experiments of catalyst systems which are active for the metathesis of unsaturated esters. As the principal catalysts we used WCl_6, $WOCl_4$, $WOCl_3$, WO_2Cl_2, $WOCl_2$, $WO(OMe)_6$, and $MoO_2(acac)_2$. As the cocatalysts we selected the following alkyl derivatives of Group IVB elements: Cp_2TiMe_2, $Cp_2TiClMe$, and Cp_2ZrMe_2. These alkyl compounds have not previously been used for the metathesis. Also, we have compared the activity of the following alkyl derivatives of Group IVA elements: $SnMe_4$, $PbMe_4$, Et_3SiH, and Et_2SiH_2. Organoaluminium compounds such as $AlMe_3$, $AlEt_2Cl$, $AlEtCl_2$, which are known to be somewhat active for functionalized olefins [5], were used as the cocatalysts in this study, As substrates we selected methyl 10-undecenoate (4), methyl oleate (methyl [*Z*]-9-octadecenoate) (2), and oleyl acetate ([*Z*]-9-octadecenyl acetate) (6).

Throughout this study all products except ethylene were isolated by column chromatography and the yields shown in tables are all isolated yields.

1. *Metathesis of methyl 10-undecenoate (4)*

As a typical unsaturated ester with a terminal double bond we selected the readily available methyl 10-undecenoate. Baker carried out the metathesis of ω-olefinic esters with $WCl_6/SnMe_4$ [9]. We found that WCl_6/Cp_2TiMe_2 is an active catalyst for the metathesis of this ester to afford dimethyl 10-eicosenedioate (5) and ethylene.



(4) (5)

At first we investigated the solvent effect. As shown in Table 1, aliphatic and aromatic hydrocarbons and their chloro-derivatives can be used. We decided to use benzene throughout this study, since it can be purified easily and gives satisfactory results. In this reaction methyl 10-chloroundecanoate was formed in a small amount by hydrochlorination.

The catalytic activity of WCl_6 combined with alkyl derivatives of Pb, Ti, and Zr was compared by using somewhat higher concentrations. Interestingly, the Zr compound showed the highest activity (exp. 9). Yields greater than 50% were obtained in experiments 11, 12, 13, and 16. The results mean that the reaction proceeded by shifting the equilibrium to the right-hand side with removal of volatile ethylene from the reaction sphere.

The catalytic activity of $WOCl_4$ was studied in the expectation of higher activity, since Muetterties and coworkers reported that a combination of $WOCl_4$ with alkylaluminium chlorides is more active than that of WCl_6 and organoaluminums [14]. As shown in Table 2, a better result was obtained with Cp_2TiMe_2 (exp. 12) than by using $SnMe_4$ (exp. 11). No 10-chloroundecanoate was formed when $WOCl_4$ was used as the principal catalyst. We used carbon disulfide in the preparation of $WOCl_4$, and thought that the higher activity of $WOCl_4$ may be due to the presence of carbon disulfide. Therefore,

TABLE 1

METATHESIS REACTIONS OF METHYL 10-UNDECENOATE WITH WCl_6 [a]

Exp. No.	WCl_6 (mol %)	Cocatalysts [b] (eq.)	Time (h)	Solvents	Yields (%) [c]	
					A	B
1	5	Cp_2TiMe_2 (1)	6	toluene	28.6	1.5
2	5	Cp_2TiMe_2 (1)	6	toluene	31.5	2
3	5	Cp_2TiMe_2 (1)	19	benzene	34.5	1.5
4	5	Cp_2TiMe_2 (1)	3	chlorobenzene	28	1
5	5	Cp_2TiMe_2 (1)	14	*o*-dichlorobenzene	0	0
6	5	Cp_2TiMe_2 (1)	6	n-hexane	38	2.5
7	5	Cp_2TiMe_2 (1)	6	CCl_4	41	4
8	10	$PbMe_4$ (1.2)	20	benzene	26.7	0
9	10	Cp_2ZrMe_2 (1.2)	20	benzene	50	1
10	10	$Cp_2TiClMe$ (1.2)	20	benzene	29.6	2

[a] The reactions were carried out under argon at 70°C. [b] Mol equivalents of the cocatalysts for WCl_6. [c] Isolated yields; A: dimethyl 10-eicosenedioate; B: methyl 10-chloroundecanoate.

TABLE 2

METATHESIS OF METHYL 10-UNDECENOATE WITH $WOCl_4$ AND WCl_6 [a]

Exp.	Catalyst [b]	Cocatalyst [c]	Time (h)	Yield (%) [d]
11	$WOCl_4$	$SnMe_4$	18	54
12	$WOCl_4$	Cp_2TiMe_2	18	71
13	$WOCl_4$	$Cp_2TiClMe$	20	50.7
14	$WOCl_4$	Cp_2TiMe_2	20	60 [e]
15	WCl_6	$SnMe_4$	20	48.6 [e]
16	WCl_6	Cp_2TiMe_2	20	37.4 [e]

[a] The reactions were carried out at 70°C in benzene. [b] 10 mol %. [c] 1.2 mol equiv. for WCl_6 or $WOCl_4$. [d] Isolated yields of dimethyl 10-eicosenedioate. [e] CS_2 (0.5 ml) was added.

the reactions were carried out by using $WOCl_4/Cp_2TiMe_2$, WCl_6/Cp_2TiMe_2, and $WCl_6/SnMe_4$ in the presence of a small amount of carbon disulfide (exp. 14—16). The activity was lowered by the addition of carbon disulfide, but the combination of $WOCl_4/Cp_2TiMe_2$ showed higher activity than $WCl_6/SnMe_4$.

2. *Metatheses of methyl oleate (1) and oleyl acetate (6)*

As examples of unsaturated esters with an internal double bond we selected

TABLE 3

METATHESIS OF METHYL OLEATE [a]

Exp. No.	Catalyst [b]	Cocatalyst [c]	Time (h)	Yields (%) [f]	
				C	D
17	WCl_6	$SnMe_4$	17	38.6	43.3
18	WCl_6	Cp_2TiMe_2	17	16.3	39.0
19	WCl_6	$PbMe_4$	17	29.9	33.3
20	WCl_6	Cp_2ZrMe_2	17	35.8	30.1
21	WCl_6	$Cp_2TiClMe$	19	30.2	25.2
22	$WOCl_4$	$SnMe_4$	10	29.4	33.2
23	$WOCl_4$	Cp_2TiMe_2	10	45.4	42.7
24	$WOCl_4$	$PbMe_4$	20	0	0
25	$WOCl_4$	Cp_2ZrMe_2	20	0	0
26	$WOCl_4$	$Cp_2TiClMe$	19	39.4	40.8
27	$WOCl_4$	$Me_3Al_2Cl_3$	20	10.3	3.7
28	$WOCl_4$	MeLi	19	0	0
29	$WO(OMe)_4$	$EtAlCl_2$ [d]	14	13.3	12.4
30	$WO(OMe)_4$	Et_2AlCl	14	18.8	18.7
31	$WO(OMe)_4$	Me_3Al [e]	16	trace	trace
32	$WO(OMe)_4$	$Me_2Al_2Cl_3$	23	0	0
33	$WO(OMe)_4$	$Cp_2TiClMe$	23	1.6	3.3
34	WCl_6	Et_2SiH_2	23	1.2	8.2
35	WCl_6	Et_3SiH	23	8.0	8.5
36	WCl_6	$Me_3SiSiMe_3$	23	trace	trace
37	$WOCl_4$	Et_3SiH	21	18.3	9.2
38	$WOCl_4$	Et_2SiH_2	21	3.0	6.5
39	$WOCl_4$	$Me_3SiSiMe_3$	21	0	0

[a] The reactions were carried out in benzene at 70°C. [b] 10 mol %. [c] 1.2 mol equiv. were used. [d] 2.0 mol equiv. were used. [e] 1.1 mol equiv. [f] Isolated yield; C: dimethyl-9-octadecenedioate; D: 9-octadecene.

TABLE 4

METATHESIS OF OLEYL ACETATE [a]

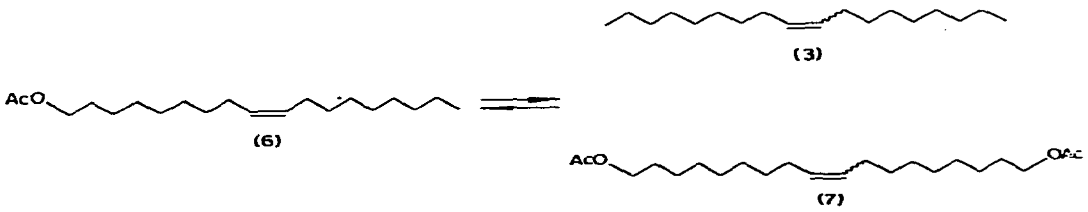
Exp. No.	Catalyst [b]	Cocatalyst [c]	Yield (%) [d]	
			D	E
40	WCl_6	$SnMe_4$	38.0	36.7
41	WCl_6	Cp_2TiMe_2	33.2	34.5
42	WCl_6	$Cp_2TiClMe$	13.1	12.5
43	$WOCl_4$	$SnMe_4$	29.8	30.6
44	$WOCl_4$	Cp_2TiMe_2	37.4	41.9
45	$WOCl_4$	$Cp_2TiClMe$	27.9	29.7

[a] The reactions were carried out at 70°C for 17 h in benzene. [b] 10 mol %. [c] 1.2 mol equiv. [d] Isolated yields; D: 9-octadecene; E: 1,18-diacetoxy-9-octadecene.

the readily available methyl oleate and oleyl acetate. Both esters have an internal *cis* double bond. At first the activity of catalysts prepared from WCl_6 and alkyl derivatives of Sn, Ti, Pb and Zr was studied. As shown in Table 3, $SnMe_5$ showed the highest activity (exp. 17), but other alkyl compounds also gave satisfactory results.

When $WOCl_4$ was used instead of WCl_6, the highest activity was observed with Cp_2TiMe_2. The $WOCl_4/Cp_2TiMe_2$ system (exp. 23) was clearly superior to $WCl_6/SnMe_4$ (exp. 17). Interestingly, no activity was observed with Zr and Pb compounds combined with $WOCl_4$ for the metathesis of oleate (exp. 24,25). Also, the activity of $WO(OMe)_4$ was studied, which was claimed to be active for simple olefins by Muetterties [14]. As shown in Table 3, a considerable activity was observed by its combination with ethylaluminums. $EtAlCl_2$ and Et_2AlCl gave yields of 18.8% and 13.3% (exp. 29,30). A very low yield (1.6%) was obtained when $Cp_2TiMeCl$ was used (exp. 33). Other tungsten compounds such as $W(OMe)_6$, WO_2Cl_2, $WOCl_3$ and $WOCl_2$ were tested in combination with the alkyl derivatives of Ti, Sn, Pb, and Zr, but they were all inactive. $W(CO)_6$ in CCl_4 under irradiation, which is known to be active for simple olefins, was inactive for methyl oleate [15—18]. Also, $MoO_2(acac)_2$ was not effective. Slight activity was observed with WCl_6 or $WOCl_4$ combined with hydrosilanes, but they were not very promising (exp. 34—39).

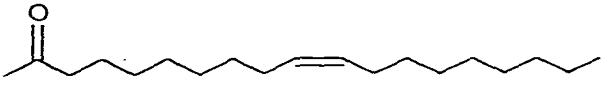
The metathesis of oleyl acetate (6) was carried out by using WCl_6 and $WOCl_4$ in combination with Ti and Sn compounds. Metathesis of acetates of ω-unsaturated alcohols, including oleyl acetate, using $WCl_6/SnMe_4$ has been reported [12]. As shown in Table 4, the yields of 1,18-diacetoxy-9-octadecene (7) were somewhat lower than those of dimethyl 9-octadecenedioate (2) with the same catalyst systems. The mixtures of $WCl_4/SnMe_4$ and $WOCl_4/Cp_2TiMe_3$ gave satisfactory yields (38% and 37.4%) (exp. 40, 44).



From these studies it can be concluded that the $WOCl_4/Cp_2TiMe_2$ system is somewhat better than the $WCl_6/SnMe_4$ system for the metathesis of the unsaturated esters.

3. *Metathesis of olefins with other functional groups*

We also studied other functionalized olefins. Metathesis of unsaturated ketones using the Re_2O_7/Al_2O_3 or $SnMe_4/CCl_4$ systems has been reported by Mol [7]. We have attempted the metathesis of 10-nonadecen-2-one (**8**) and 5,10-undecadien-2-one (**9**) with our catalyst systems.



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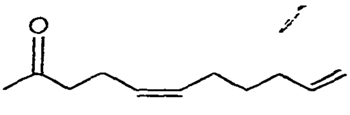
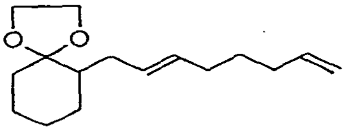


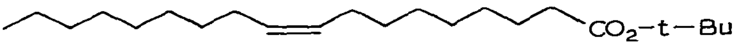
(9)

None of the catalyst systems we used for the unsaturated esters were active for the unsaturated ketones. It is known that low-valent titanium and tungsten species react with ketones to give products of reductive dimerization [19—25]. Thus it is conceivable that the metathesis of ketones is not possible with tungsten catalysts. We attempted the metathesis of ketones protected by acetal formation. However, no success was achieved with the protected unsaturated ketone **10**. The protecting group was removed during the reaction.



(10)

We also tested the bulky t-butyl oleate **11** (instead of the methyl ester), expecting the steric effect to protect the ester group from the interaction with catalytic species. But in this case hydrolysis of the ester was observed without it undergoing metathesis.



(11)

4. *Syntheses of civetone from oleate*

As shown above, satisfactory results were obtained from the metathesis reaction of methyl oleate (**1**) by using $WOCl_4/Cp_2TiMe_2$ to give dimethyl octadecenedioate (**2**) in one step. This diester is a good starting material for the synthesis of civetone (9-*cis*-cycloheptenone) (**12**), a naturally occurring 17-membered cyclic ketone with musk odor. A few studies on the total synthesis of civetone have been reported [26—34]. We intended to synthesize this 17-membered unsaturated cyclic ketone by the cyclization of diethyl 9-octadecene-1,18-dioate (**13**) by the scheme shown below [35,36]. We have carried out the meta-

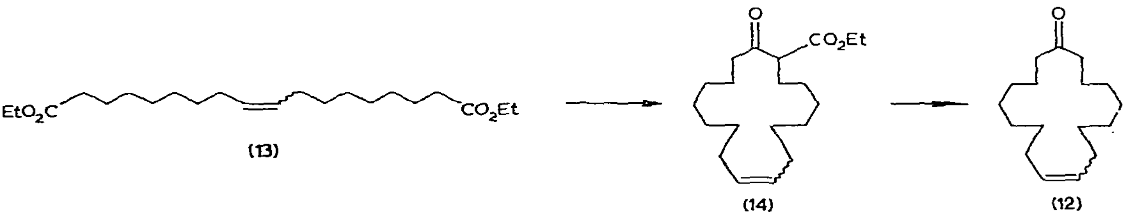
TABLE 5

METATHESIS OF ETHYL OLEATE WITH $WOCl_4/Cp_2TiMe_2$ [a]

Exp. No.	$WOCl_4$ (mol %)	Yields [b]	
		D	F
46	10	41.2	43.5
47	5	39.0	39.8
48	2	35.7	36.3

[a] The reactions were carried out at 70°C for 20 h using 1.2 mol equiv. of Cp_2TiMe_2 for $WOCl_4$. [b] Isolated yields; D: 9-octadecene; F: diethyl 9-octadecenedioate.

thesis of ethyl oleate, instead of methyl oleate, using $WOCl_4/Cp_2TiMe_2$, since ethyl esters are better than methyl esters in the Dieckmann condensation [37]. The results are shown in Table 5. The metathesis is an equilibrium reaction and the reaction mixture always contains ethyl oleate, the diester 13 and 9-octadecene (3).



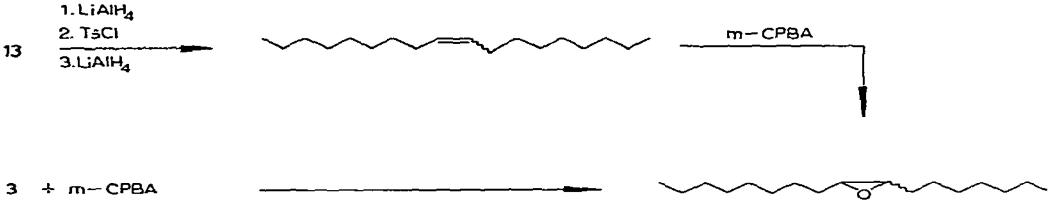
(13)

(14)

(12)

The catalyst was quenched with 10% sodium hydroxide solution. After the usual workup, the reaction mixture was subjected to silica gel column chromatography. The diester 13 and 9-octadecene (3) were isolated in 43% yields.

It is known that *cis—trans* double bond isomerization takes place during the metathesis reaction. Although the ethyl oleate used as the starting material is predominantly *cis*, the *cis* to *trans* double bond isomerization took place during metathesis. The ratio of the *cis* and *trans* double bonds in the products were determined by converting 13 and 3 to the epoxide 15 by the following sequences of reactions, as reported by Baker [9].

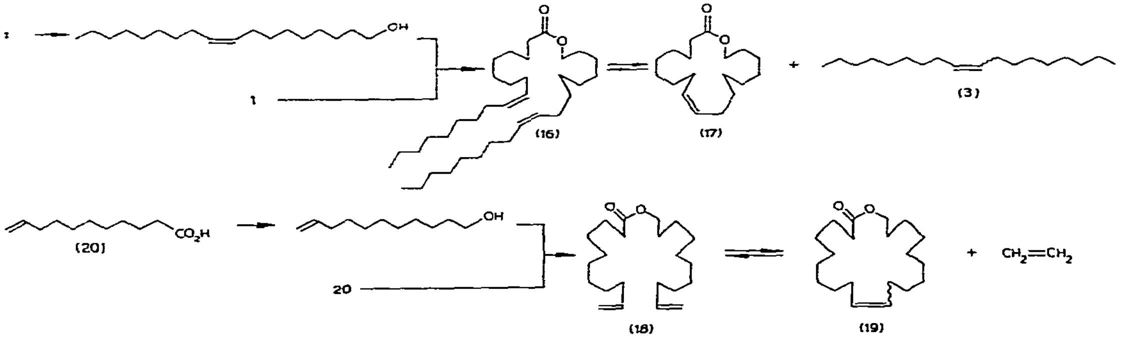


(15)

Gas chromatographic analyses of the epoxides showed that the *cis*/*trans* ratios in the diester and octadecene were 1/1.3. By the same analysis it was found that the *cis*/*trans* ratio of ethyl oleate before the reaction was 10.3/1. But the ratio of oleate recovered after the 20 h reaction was 5.4/1 [38].

The Dieckmann condensation of the diester 13 was carried out. In order to attain a high yield of the cyclized product **14** it is essential to carry out the reaction under high dilution conditions to minimize the intermolecular reaction. After several trials, we obtained the cyclized product **14** in satisfactory yields by carrying out the reaction in THF using potassium hydride as a base, by slow addition of the diester to the solution of the base. Also, the sodium salt of hexamethyldisilazane was used as the base in benzene. The crude keto ester **14** was hydrolysed. The reaction mixture was acidified and subjected to decarboxylation. After decarboxylation, purified cyclo-9-heptadecenone (civetone), **12**, was obtained by column chromatography. The overall yields from the diester **13** were 54.4% and 52% on using potassium hydride in THF and the sodium salt of hexamethyldisilazane in benzene, respectively. Since there is no possibility of *cis—trans* isomerization during the cyclization, it is assumed that the civetone thus prepared is a mixture of the *cis* and *trans* forms in a ratio of 1/1.3. These could not be separated.

We have also carried out a preliminary study of macrolide synthesis based on cyclization by the intramolecular metathesis reaction of oleyl oleate (**16**). The substrate **16** was prepared from oleic acid and oleyl alcohol. The metathesis reaction, carried out in benzene using WCl_6 (20 mol %) and Cp_2TiMe_2, afforded 9-octadecen-18-olide (**17**) in 18% yield. Also, 10-eicosen-20-olide (**19**) was obtained in 12% yield by the metathesis of 10-undecenyl 10-undecenoate (**18**) using $WOCl_4$ (20 mol %) and Cp_2TiMe_2 (24 mol %). The ester **18** was prepared from commercially available 10-undecenoic acid (**20**). Although the yield was still unsatisfactory, the method is simple, and the separation of the product and recovery of the starting material are easy. Therefore, this method may be a good synthetic method for macrolides after further improvement. Since our study, the metatheses of 1-pentenyl and 1-hexenyl 10-undecenoates have been carried out by Villemin to give 15- and 16-membered unsaturated lactones in 65% and 60% yields respectively [39].



6. *Mechanistic considerations*

In this study no effort has been made to isolate intermediate complexes formed in the reactions of tungsten compounds with Cp_2TiMe_2, and it is premature to discuss the mechanism of formation of the active species. But the following report is instructive. Muetterties and coworker identified the formation of complex **21** by the reaction of $WOCl_4$ and dimethylmagnesium [40]. From this complex, the carbene complex **22** is believed to have been formed as the olefin metathesis catalyst precursor. It seems likely that a similar complex could be formed in the reaction of $WOCl_4$ with Cp_2TiMe_2.

$$WOCl_4 + Me_2Mg \rightarrow \underset{(21)}{CH_3WOCl_3} \rightarrow \underset{(22)}{CH_2WOCl_2}$$

Furthermore, it should be noticed that complexes such as $W(O)(CRH)(PR_3)_2Cl_2$ and $W(O)(CRH)(PR_3)Cl_2$, including R = H, have in fact been isolated, structurally characterized, and shown to be metathesis catalysts [41].

Experimental

1. Preparation of the reagents

a. $WOCl_4$ was prepared by the procedure of Funk [42] and sublimed at 100°C/2 Torr in 84% yield as dark red crystals.

b. $WO(OMe)_4$ was prepared from $WOCl_4$ by Funk's procedure [42] as colorless crystals in 98% yield.

c. Cp_2TiMe_2 was prepared by the procedure of Wilkinson and coworkers as orange crystals in 87% yield and used as a benzene solution [43—45].

d. Cp_2ZrMe_2 was prepared by Wilkinson's procedure in 82% yield [44,45].

e. $Cp_2TiMeCl$ was prepared by the procedure of Long in 69% yield as dark orange crystals [46,47].

2. General procedure for the metathesis

A suspension of the principal catalyst in dry benzene (3 ml, freshly distilled over sodium diphenylketyl) was prepared in a 30 ml Schlenk tube equipped with a magnetic bar. The cocatalyst was added to the suspension at room temperature under argon with stirring. Then, a solution of the substrate in dry benzene (3 ml) was added to the mixture in one portion. The reaction mixture was stirred for 2—26 h at 70°C under argon and quenched with 10% NaOH solution. The resulting mixture was extracted with hexane/ether (5/1) and the organic layer was washed with 6 *N* HCl solution, sat. $NaHCO_3$ solution and brine. The extract was dried over $MgSO_4$. Filtration of the extract, concentration of the filtrate in vacuo, and column chromatographic purification of the residue on silica gel afforded products.

3. Structure determination of the reaction products

9-Octadecenedioate (2). (Silica gel column: hexane/ether = 25/1 as eluent) NMR (CCl_4): δ 5.55—5.03 (m, olefinic, 2 H), 3.59 (s, 6 H), 2.45—1.75 (m, 8 H), 1.75—1.00 (m, 20 H); IR (neat): 1740 (C=O), 970 (*trans* olefin), 720 (*cis* olefin) cm^{-1}.

Methyl 10-chloroundecanoate. (Silica gel column; hexane/ether = 40/1 as eluent.) NMR (CCl_4): δ 4.25—3.26 (m, -*C*HCl-, 1 H), 3.54 (s, 3 H), 2.50—2.00 (m, 2 H), 2.00—0.56 (m, 17 H); IR: (neat) 1740 (C=O) cm^{-1}.

Dimethyl 10-eicosenedioate (5). (Silica gel column; hexane/ether = 15/1 as eluent.) NMR (CCl_4): δ 5.40—5.08 (m, olefinic, 2 H), 3.57 (s, 6 H), 2.45—1.73 (m, 8 H), 1.73—0.78 (m, 48 H); IR (Nujol): 2910 (C—H), 1735 (C=O), 960 (*trans* olefin), 710 (*cis* olefin) cm^{-1}.

1,18-Diacetoxy-9-octadecene (7)
(Silica gel column; hexane/ether = 25/1 as eluent.) NMR (CCl_4): δ 5.40—5.12 (m, 2 H), 3.92 (t, J = 6.0 Hz, 5 H), 1.93 (s, 6 H), 2.17—0.81 (m, 28 H); IR (neat): 2920 (C—H), 1740 (C=O), 970 (*trans* olefin), 720 (*cis* olefin) cm^{-1}.

4. Synthesis of civetone (12)

Diethyl 9-octadecenedioate (13). (Silica gel column; hexane/ether = 25/1 as eluent.) NMR (CCl_4): δ 5.48—5.12 (m, 2 H), 4.01 (qt, J = 7 Hz, 4 H), 2.39—1.74 (m, 8 H), 1.74—0.72 (m, 20 H); IR (neat): 1735 (C=O), 970 (*trans* olefin), 720 (*cis* olefin) cm^{-1}.

Dieckmann condensation. A mixture of base (KH, 370 mg) in dry benzene (40 ml) was prepared in a 100 ml three-necked round-bottomed flask, equipped with a magnetic bar, a rubber septum, a stopper and a dropping funnel. A solution of diethyl ester **13** (425 mg) in dry benzene (10 ml) was added dropwise to the mixture with stirring at 50—60°C under argon over 2.5 h. The resulting mixture was stirred for an additional 20 min and poured into a vigorously stirred suspension of ice, NH_4Cl, and hexane/ether (5/1). The resulting mixture was extracted twice with hexane/ether (5/1) and the combined organic layer was washed with brine, and dried over $MgSO_4$. Filtration of the extract, concentration of the filtrate in vacuo, and column chromatographic purification of the residue on silica gel (hexane/ether = 50/1) gave the keto ester **14**. A solution of the keto ester **14** in 5% NaOH solution/EtOH/THF (5/10/5 ml) was refluxed for 5 h. The mixture was made slightly acidic with conc. H_2SO_4 at 0°C, and then refluxed for 10 min. Most of the solvent was removed in vacuo and the residue was extracted with hexane/ether (5/1). The organic layer was washed with sat. $NaHCO_3$ solution and brine, and dried over $MgSO_4$. Filtration, concentration of the filtrate in vacuo, and chromatographic purification of the residue on silica gel (hexane/ether = 50/1) gave civetone 157 mg (54.4%) (**12**). The structure was determined by mass spectroscopy, and by comparison of the NMR and IR spectra with those of an authentic sample of the civetone prepared in this laboratory [14].

Civetone (12). NMR (CCl_4): δ 5.39—5.09 (m, 2 H), 2.46—1.72 (m, 8 H), 1.72—0.61 (m, 20 H); IR (neat): 1710 (C=O), 960 (*trans* olefin), 710 (*cis* olefin) cm^{-1}; MS: m/e = 250 (M^+).

5. Syntheses of macrolides

Preparation of oleyl oleate (16). This ester was prepared from oleic acid (3 g, 10.6 mmol), and oleyl alcohol (2.87 g, 10.6 mmol) via chloride in 82% yield (silica gel column: hexane/ether = 150/1 as eluent). NMR (CCl_4): δ 5.38—5.08 (m, 4 H), 3.91 (t, J = 6.0 Hz, 2 H), 2.42 (m, 58 H); IR (neat): 1740 (C=O), 720 (*cis* olefin) cm^{-1}.

Preparation of 10-undecenyl 10-undecenoate (18). This ester was prepared from 10-undecenoic acid (3 g, 16.3 mmol), and 10-undecen-1-ol (2.76 g, 16.3 mmol) via chloride in 64% yield (silica gel column: hexane/ether = 200/1 as eluent). NMR (CCl_4): δ 6.09—5.32 (m, olefinic, 2 H), 5.10—4.69 (m, olefinic, 4 H), 3.95 (t, J = 7.0 Hz, 2 H), 2.46—1.77 (m, 26 H); IR (neat): 1735 (C=O), 1635 (C=O), 910 (olefin) cm^{-1}.

6. *Intramolecular metathesis*

General procedure. A suspension of the principal catalyst in dry benzene was prepared in a 100 ml Schlenk tube equipped with a magnetic stirring bar and a dropping funnel. The cocatalyst was added to the suspension at room temperature under argon with stirring. The resulting mixture was warmed at 70°C and then a benzene solution of the substrate was added dropwise to the mixture for 1 h. The reaction mixture was stirred at 70°C for an additional 30 min and quenched with 10% NaOH solution. The resulting mixture was extracted with hexane/ether (5/1) and the organic layer was washed with 6 *N* HCl solution, sat. $NaHCO_3$ solution and brine, and dried over $MgSO_4$. Filtration of the extract, concentration of the filtrate in vacuo and column chromatographic purification of the residue on silica gel gave the product.

9-Octadecen-18-olide (17). (Catalyst: WCl_6 (20 mol %) + Cp_2TiMe_2 (24 mol %), in dry benzene, 40 ml); substrate in dry benzene, 15 ml; silica gel column; hexane/ether = 100/1 as eluent.) NMR (CCl_4): δ 5.51—5.08 (m, olefinic, 2 H), 4.02 (t, J = 5.0 Hz, 2 H), 2.44—1.78 (m, 6 H), 1.78—0.64 (m, 22 H); IR (neat): 1730 (C=O), 960 (*trans* olefin), 710 (*cis* olefin) cm^{-1}.

10-Eicosen-20-olide (19). (Catalyst: $WOCl_4$ (20 mol %) + Cp_2TiMe_2 (24 mol %), in dry benzene, 60 ml; substrate in dry benzene, 10 ml; silica gel column; hexane/ether = 150/as eluent.) NMR (CCl_4): 5.42—5.09 (m, 2 H), 4.21—3.71 (m, 2 H), 2.40—1.73 (m, 6 H), 1.73—0.90 (m, 26 H); IR (neat): 1735 (C=O), 960 (*trans* olefin), 715 (*cis* olefin) cm^{-1}.

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