Chapter III
RESULTS AND DISCUSSION

This research was mainly focused on radical deoxygenation utilizing Barton McCombie method. This process was reported to be able to change aliphatic alcohols to alkanes efficiently under mild conditions, compatible with natural product molecules. Deoxygenation of primary and secondary alcohols, especially nucleosides, antibiotics and carbohydrates is very important in organic synthesis. The original Barton-McCombie reaction provided a solution to this problem particularly for secondary alcohols. In this research, the deoxygenation of primary and secondary alcohols has also been demonstrated. The model substrate used was mainly cyclododecanol. Other substrates such as 1-octadecanol and 2-adamantanol were selected to test the optimized conditions explored. Moreover, some natural products such as steroids, mono- and triterpenoids were chosen to test for the application of this developed procedure. For comparative studies, both organosilane and organostanane were utilized as reducing agents in this reaction. AIBN and *tert*-butyl peroxide were employed as radical initiators for this reaction.

3.1 The Optimum Conditions for the Deoxygenation of Cyclododecyl *S*-Methyl Xanthate

Cyclododecanol was selected as a chemical model for optimizing the reaction conditions. It was derivertized to *S*-methyl xanthate by the known procedure using CS_2 and CH_3I in the presence of *n*-butyllitium.[32] The yield of this transformation process is quite high approximately 75%. Various experimental parameters are studied as follows :

3.1.1 Effects of Solvent

Among various solvents examined such as benzene, toluene and *o*-xylene, toluene was found to be the most suitable solvent for this reaction. It could dissolve starting material (cyclododecyl *S*-methyl xanthate), a chain carrier and an initiator. Futhermore, its boiling point is high enough to raise up the temperature of the reaction which is important for the initiating step. The effects of the amount of toluene were found not to be of significantly difference. The results are tabulated in Table 3.1 and Fig 3.1. However, in order to keep this parameter constant, 4 mL of toluene was mainly used in this study.

Table 3.1 The effects of the volume of solvent

Solvent (mL)	Cyclododecyl *S*-methyl xanthate (mmol)	Recovery of substrate (mmol)	Cyclododecane (mmol)	Mass balance (%)	Product (%)
2	0.422	0	0.400	94.81	94.81
4	0.380	0.030	0.355	101.13	93.35

Reaction conditions : cyclododecyl-*S*-methyl xanthate (0.4 mmol), Ph_2SiH_2 (0.8mmol), AIBN (0.08 mmol), toluene (variable)

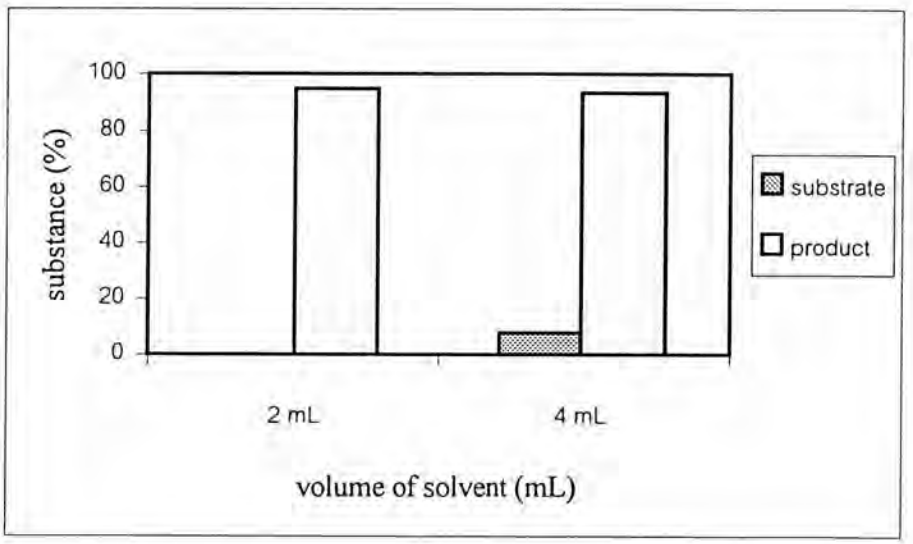


Figure 3.1 The effects of the volume of solvent

3.1.2 Comparative Studies on Employing Ph_2SiH_2 and nBu$_3$SnH as a Reducing Agent

There are many chain carriers that have been employed for this type of reaction such as organostannane[29], organogermanium[13-14], organomercury[15-17] and organosilane.[18-26] In this research, the reactivity of nBu$_3$SnH and Ph_2SiH_2 was systematically compared in the deoxygenation reaction of cyclododecyl *S*-methyl xanthate. The results are presented in Tables 3.2 and 3.3 and Fig 3.2. Considering the amount of the desired product (cyclododecane) and the reaction time, when utilizing diphenylsilane (Ph_2SiH_2) as a chain carrier in the reaction, the yield of deoxygenation products (cyclododecane) are quite impressive as much as 92-96%. Under the same circumstances, when *n*-butyltin hydride (nBu$_3$SnH) was used as a reducing agent, the reduced product was attained only 22-28%. From this section, it was found that under this particular conditions diphenylsilane (Ph_2SiH_2) was a significantly better chain carrier than *n*-butyl tin hydride (nBu$_3$SnH) in the reduction of a model compound. In addition, it can be seen from Table 3.4 and Fig 3.3 that the reaction time is another main factor of the reaction employing *n*-butyl tin hydride. To illustrate this, when the reaction was quenched at four hours, the reaction provided slightly higher amount of deoxygenated product from 16.63% to 22.45%. This means the amount of cyclododecane is increased 1.35 times as that obtained more than in 1 hour 20 minutes. Because of a shorter reaction time and more quantity of desired product attained diphenylsilane (Ph_2SiH_2) is chosen for further investigation.

Table 3.2 The effects of the amount of AIBN in deoxygenation of cyclododecyl *S*-methyl xanthate

AIBN (mmol)	Cyclododecyl *S*-methyl xanthate (mmol)	Recovery of substrate (mmol)	Cyclododecane (mmol)	Mass balance (%)	Product (%)
0	0.388	0.387	0.001	100.15	0.28
0.04	0.395	0.082	0.320	101.49	80.88
0.08	0.380	0.030	0.360	101.13	92.30
0.12	0.400	0	0.384	95.93	95.93
0.16	0.405	0	0.382	94.29	94.29

Reaction conditions : cyclododecyl-*S*-methyl xanthate (0.4 mmol), Ph_2SiH_2 (0.8 mmol), AIBN (variable), toluene (4 mL)

Reaction time : 1 hour 20 minutes

Table 3.3 The effects of the amount of AIBN and nBu$_3$SnH in deoxygenation of cyclododecyl *S*-methyl xanthate

AIBN (mmol)	Cyclododecyl *S*-methyl xanthate (mmol)	Recovery of substrate (mmol)	Cyclododecane (mmol)	Mass balance (%)	Product (%)
0	0.361	0.352	0.001	97.67	0.17
0.04	0.384	0.304	0.086	101.64	22.45
0.08	0.399	0.297	0.086	96.00	22.41
0.12	0.404	0.262	0.114	93.15	28.20
0.16	0.438	0.342	0.099	100.69	22.58

Reaction conditions : cyclododecyl *S*-methyl xanthate (0.4 mmol), nBu$_3$SnH (0.8 mmol), AIBN (variable), toluene (4 mL)

Reaction time : 4 hours

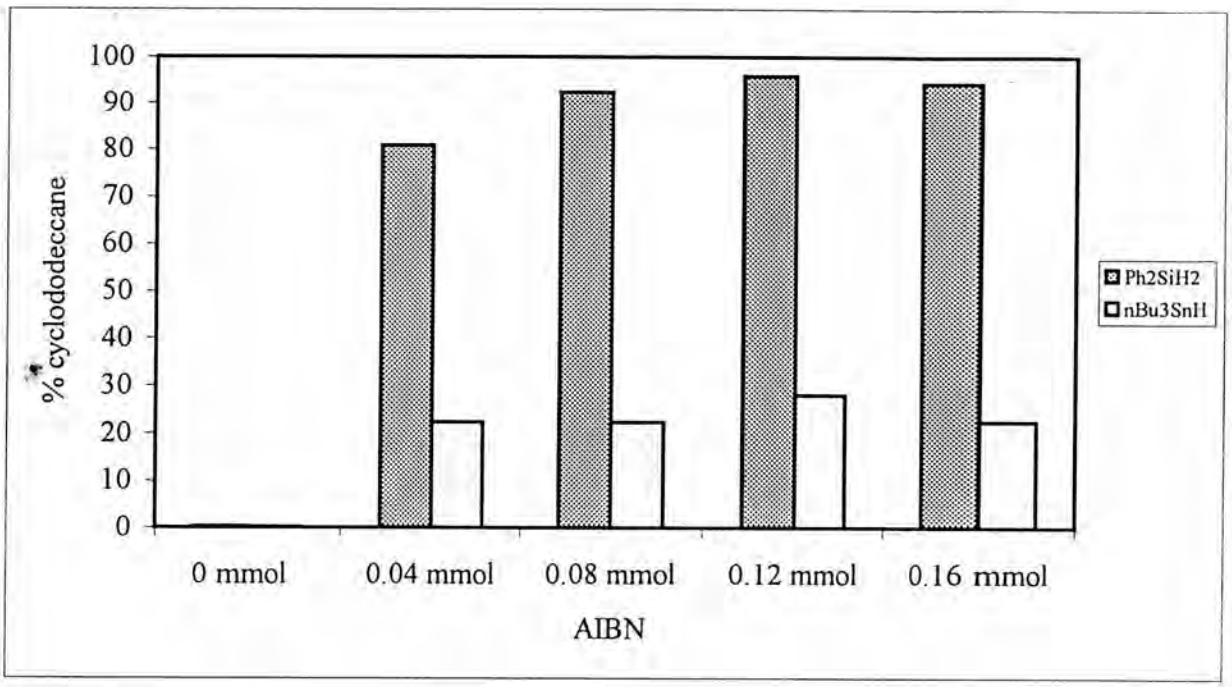


Figure 3.2 The effects of the amount of AIBN as an initator

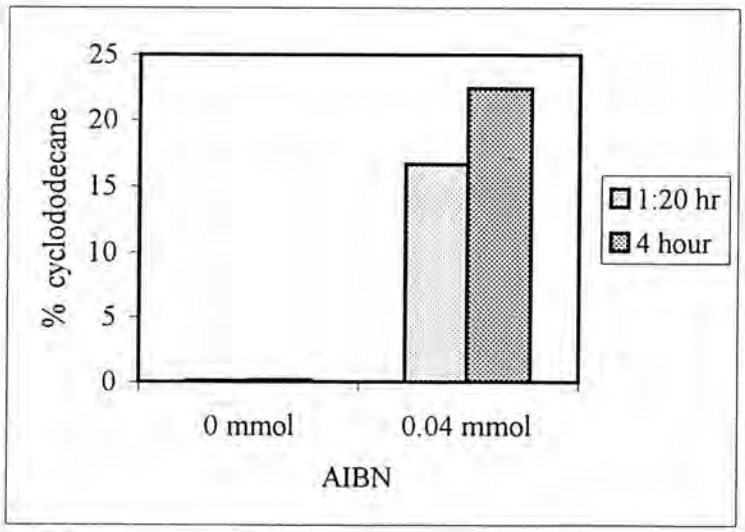


Figure 3.3 The effects of reaction time using nBu$_3$SnH in radical chain reaction

Table 3.4 The effects of the reaction time of nBu$_3$SnH as a chain carrier in radical reaction

AIBN (mmol)	Cyclododecyl *S*-methyl xanthate (mmol)	Reaction time (min.)	Recovery of substrate (mmol)	Cyclododecane (mmol)	Mass balance (%)	Product (%)
0	0.361	80	0.373	0.0003	103.49	0.08
		240	0.352	0.001	97.67	0.17
0.04	0.384	80	0.217	0.064	95.93	16.63
		240	0.304	0.086	101.64	22.45

Reaction conditions : cyclododecyl *S*-methyl xanthate (0.4 mmol), nBu$_3$SnH (0.8 mmol), AIBN (variable), toluene (4 mL)

3.1.3 Effects of Organosilane as a Chain Carrier

In order to seek for an appropriate silane compound as a reducing agent to substitute tri-*n*-butyltinhydride which was criticized to produce toxic waste. Moreover, tin residue is not easy to remove, even traces of toxic tin compounds from the reaction mixtures. This causes serious problem particularly in pharmaceutical industries. In this section, three commercially available organosilanes namely diphenylsilane (Ph_2SiH_2), triphenylsilane (Ph_3SiH) and triethylsilane (Et_3SiH) were selected to compare their ability as a chain carrier in the deoxygenation reaction of cyclododecyl xanthate (**3a**). All of these three organosilanes were reported to be ever success as a reducing agent in some radical reductions. For instance, B. P. Robert used Et_3SiH in the reduction reaction of alkyl halides and diacetyl sulphide. Later J. N. Kirwan introduced Et_3SiH as a chain carrier in deoxygenation reaction in 1990.[20] Tri-*n*-propylsilane chosen for the dehydroxylation of phenylchloroformate derivatives of alcohols was reported by R. A. Jackson and his colleagues.[19] Very recently D. H. R. Barton and coworkers disclosed the methodology to reduce thiocarbonyl derivatives employing diphenylsilane and using and triethylborane-air as an initiator.[21] The results of the effects of three organosilanes selected are presented in Table 3.5 and Fig 3.4.

Table 3.5 The effects of organosilane as a chain carrier

Organosilane	% cyclododecane (**2a**)	
	at 40 minutes	at 80 minutes
Ph_2SiH_2	87.46	99.49
Ph_3SiH	8.81	9.81
Et_3SiH	2.45	2.73

Reaction conditions : cyclododecyl *S*-methyl xanthate (0.4 mmol), organosilane (0.8 mmol), AIBN (0.08 mmol), toluene (4 mL)

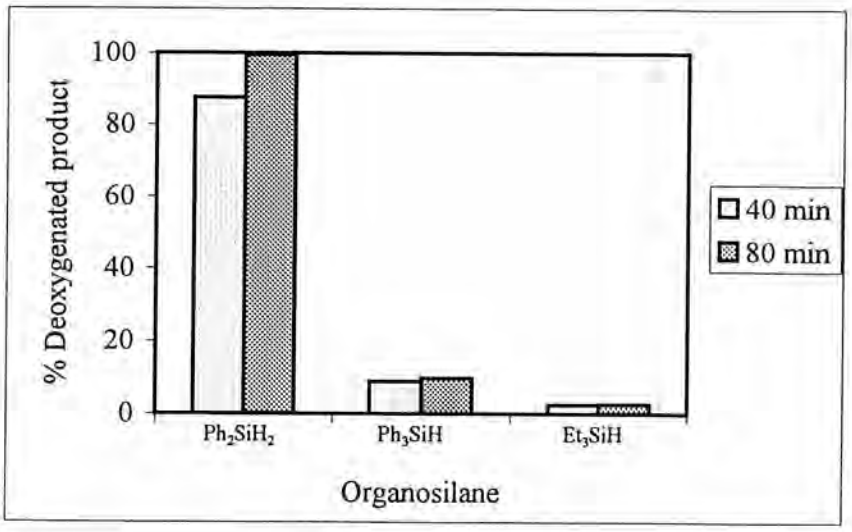


Figure 3.4 The effects of organosilane as a chain carrier

According to Fig 3.4, it was found that diphenylsilane (Ph_2SiH_2) could be employed as a good chain carrier. The cyclododecane (**2a**), the deoxygenated product was obtained about 88% and almost quantitative yield when the reaction time was 40 and 80 minutes, respectively. However, under these particular conditions, triphenyl silane (Ph_3SiH) or triethylsilane (Et_3SiH) could not be used as chain carriers. The deoxygenation reaction in the presence of both organosilanes provided only 3-10% of the desired product.

The principal reason that may be used to explain the outcome of this reaction was possibly due to the dissociation bond energy between Si-H in organosilanes. B. Giese and coworkers had reported the Sn-H bond energy of nBu$_3$Sn-H to be 74 kcal/mol, which was nearly the value of Si-H bond in *tris*(trimethylsilyl)silane (79 kcal/mol). The bond energy of Si-H in Et_3SiH is around 90 kcal/mol which was higher than previous mentioned reducing agents.[22] From this study, diphenylsilane was found to be a good hydrogen radical donor and the diphenylsilane radical generated from its chain can proceed in the radical deoxygenated cycle in well behave. However, there was no report concerning with the bond energy of Si-H in Ph_2SiH_2 available in chemical literatures. From the outcome of experiments, it may imply that Si-H bond energy of Ph_2SiH_2 was not higher than the bond energy of triethylsilane (90 kcal/mol). In addition, interestingly Ph_2SiH_2, an excellent reducing

agent from this experiment which provided the highest quantity of deoxygenated product was 30 times cheaper than tris(trimethylsilyl)silane : $(Me_3Si)_3SiH$.[21]

3.1.4 Effect of Initiator in Radical Reaction

From the results in Table 3.5 indicated that among three organosilanes studied, diphenylsilane was the best chain carrier in this standard conditions : cyclododecyl *S*-methyl xanthate 0.4 mmol, initiator 0.08 mmol and Ph_2SiH_2 0.8 mmol in toluene 4 mL. Under this curcumstance, the appropriate initiator was the next parameter to be evalulated. The results are summarized in Table 3.6 and Fig 3.5.

Table 3.6 The effects of initiator in the chain deoxygenation reaction

Initiator	% cyclododecane (**2a**)	
	at 40 minutes	at 80 minutes
AIBN	87.46	99.49
tert-butyl peroxide	97.50	97.50
benzoyl peroxide	5.79	9.57

Reaction conditions : cyclododecyl *S*-methyl xanthate (0.4 mmol), Ph_2SiH_2 (0.8mmol), initiator (0.08 mmol), toluene (4 mL)

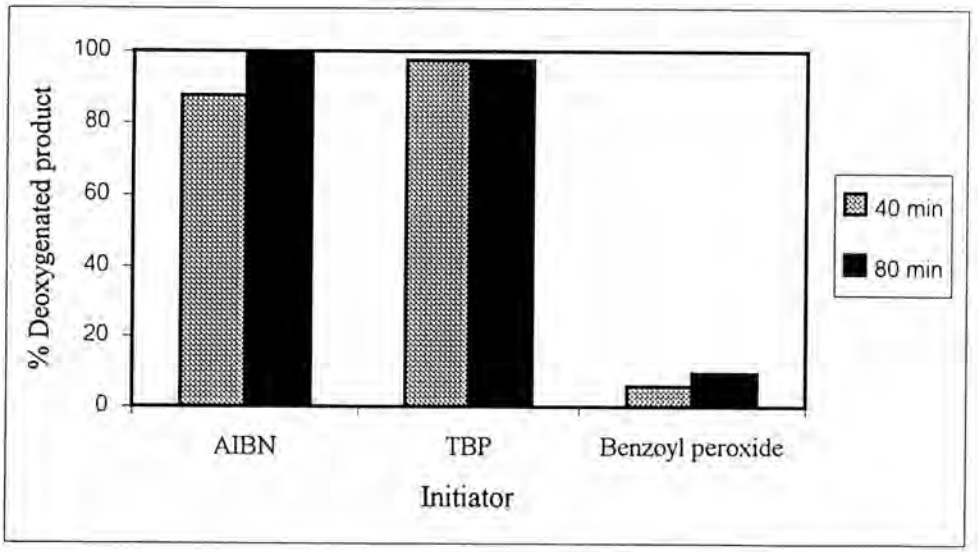


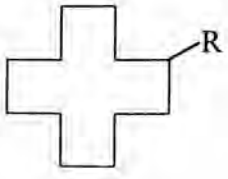
Figure 3.5 Effects of initiator in radical reaction

It was clearly seen that both AIBN and *tert*-butyl peroxide could be used as good initiators under these conditions. The deoxygenated product was obtained in an excellent yield (almost quantitative). Nevertheless, benzoyl peroxide was not a good initiator under these reaction conditions due to the oxygen-oxygen bond dissociation energy of benzoyl peroxide is higher than *tert*-butyl peroxide almost 1000 times. Thus, this made benzoyl peroxide has a decomposition rate faster than the latter. In addition, *tert*-butyl peroxide was found to proceed the deoxygenation reaction very rapidly, the reaction was almost completed within 40 minutes. This can also be illustrated in terms of an appropriate decomposition rate of O-O bond breaking.[38]

From aforementioned experimental results, it could therefore be summarized a standard condition for deoxygenation of cyclododecyl *S*-methyl xanthate as follows: cyclododecyl *S*-methyl xanthate 0.4 mmol, Ph_2SiH_2 as a chain carrier 0.8 mmol, AIBN or TBP as a radical initiator 0.08 mmol in refluxing toluene 4 mL using a reaction time 80 minutes. This standard conditions are kept constant to utilize in the next experiment.

3.1.5 Effects of Alcohol Derivatives

In this research six types of alcohol derivatives were prepared to compare its ability as a leaving group in radical deoxygenation reaction. They are cyclododecyl *S*-methyl xanthate (**3a**), cyclododecyl *N*-acetylthioxocarbamate (**4a**), cyclododecyl *N*-phenylthioxocarbamate (**5a**), cyclododecyl *O'*-phenylthioxocarbamate (**6a**), cyclododecyl acetate (**7a**) and cyclododecyl trifluoroacetate (**8a**).



R = $OC(S)SCH_3$ (**3a**)

$OC(S)NHC(O)CH_3$ (**4a**)

OC(S)NHPh (**5a**)

OC(S)OPh (**6a**)

$OC(O)CH_3$ (**7a**)

$OC(O)CF_3$ (**8a**)

All of these alcohol derivatives gave satisfactory physical and spectroscopic (IR, ^{1}H and ^{13}C NMR) data compared with those reported in literature. Some characteristic data of the prepared alcohol derivatives was summarized in Table 3.7.

Table 3.7 Characteristic data of cyclododecyl derivatives

Compound (% yield)	m.p. (°C) (solvent)	IR[a] ν (cm^{-1})	^{1}H NMR ($CDCl_3$) δ (ppm)	^{13}C NMR ($CDCl_3$) δ (ppm)
3a (70%)	47-48 (CH_2Cl_2-EtOH)	2991, 2945, 2858, 1465, 1210, 1050	1.20-1.45 (m, 18H), 1.60-1.90 (m, 4H), 2.50 (s, 3H, SMe), 5.85-5.90 (m, 1H)	18.6, 20.9 (2C), 23.2, (2C), 23.4 (2C), 23.7, 23.9, 28.7 (2C), 82.8, 215.3
4a (66%)	111-112 (hexane-EtOAc)	3211, 2929, 1710, 1523, 1298, 1201	1.33-1.88 (m, 22H), 2.3 (s, 3H), 5.58-5.64 (m, 1H), 8.70 (s, 1H)	20.9, 21.0, 23.1, 23.3 (2C), 23.8, 24.0, 24.2, 25.6, 28.6, 32.5, 69.2, 83.0, 168.7, 188.1
5a (75%)	116-117 (hexane-EtOAc)	3186, 3037, 2936, 2850, 1598, 1544, 1400, 1299, 1202, 1018, 760, 693	1.35-1.87 (m, 22H), 5.64-5.72 (m, 1H), 7.28-7.35 (m, 5H aromatic), 8.22 (br, 1H)	20.9, 21.0, 23.1, 23.2, 23.4 (2C), 23.8, 23.9, 24.0, 24.2, 28.8, 29.4, 88.5, 118.6, 121.5, 123.2, 125.2, 129.0, 137.3, 188.2
6a (75%)	60-62 (EtOH)	2937, 2863, 1488, 1253, 1189	1.25-1.60 (m, 18H), 1.64-2.00 (m, 4H), 5.45-5.58 (m, 1H), 7.04-7.18 (m, 2H), 7.20-7.30 (m, 1H), 7.32-7.45 (m, 2H)	20.9 (2C), 23.2 (2C), 23.4 (2C), 23.6, 23.9 (2C), 28.5 (2C), 83.9, 122.1 (2C), 126.4, 129.3 (2C), 153.4, 194.4
7a (60%)	oil	2942, 2877, 1723, 1464, 1243	1.30-1.71 (m, 22H), 1.97 (s, 3H), 4.89-4.99 (m, 1H)	20.9 (2C), 21.3, 23.2 (2C), 23.3 (2C), 23.8 (2C), 24.1 (2C), 29.0, 73.6, 172.3
8a (79%)	oil	2945, 2889, 1777, 1475, 1227, 1164	1.54-1.88 (m, 22H), 5.11-5.23 (m, 1H)	20.5 (2C), 20.8, 23.0, 23.2, 23.8, 23.9 (2C), 24.1, 28.6 (2C), 32.1, 77.9, 157.6

[a] KBr discs for solids, neat for oil.

Some alcohol derivatives were previously reported to be used as substrates in different radical reaction conditions. For example, cyclododecyl *S*-methyl xanthate (**3a**) and cyclododecyl *O'*-phenylthioxocarbamate (**6a**) were used as reactants in the presence of Ph_2SiH_2 as a hydrogen atom donor with the use of triethylborane-air as an initiator.[21] For other thioxocarbamate derivatives, cyclododecyl *N*-acetylthioxocarbamate (**4a**) and cyclododecyl *N*-phenylthioxocarbamate (**5a**), M. Oba and K. Nishiyama utilized triphenylsilane (Ph_3SiH), triethylsilane (Et_3SiH) or *tris*-(trimethylsilyl)silane ($(MeSi_3)_3SiH$) and di-*tert*-butylperoxide reduce them.[33-34] The results of deoxygenation using a variety of cyclododecyl derivatives using Ph_2SiH_2 and AIBN as an initiator under standard conditions studied are summarized in Table 3.8 and Fig 3.6.

Table 3.8 The effects of alcohol derivatives

Alcohol derivatives	% cyclododecane (**2a**)	
	at 40 minutes	at 80 minutes
1. *S*-methyl xanthate (**3a**)	87.46	99.49
2. *N*-acetylthioxocarbamate (**4a**)	20.35	21.44
3. *N*-phenylthioxocarbamate (**5a**)	31.37	36.22
4. *O'*-phenylthioxocarbamate (**6a**)	38.53	41.69
5. Acetate (**7a**)	0.12	0.27
6. Trifluoroacetate (**8a**)	0.04	0.10

Reaction conditions : cyclododecyl derivative (0.4 mmol), Ph_2SiH_2 (0.8 mmol), AIBN (0.08 mmol), toluene (4 mL)

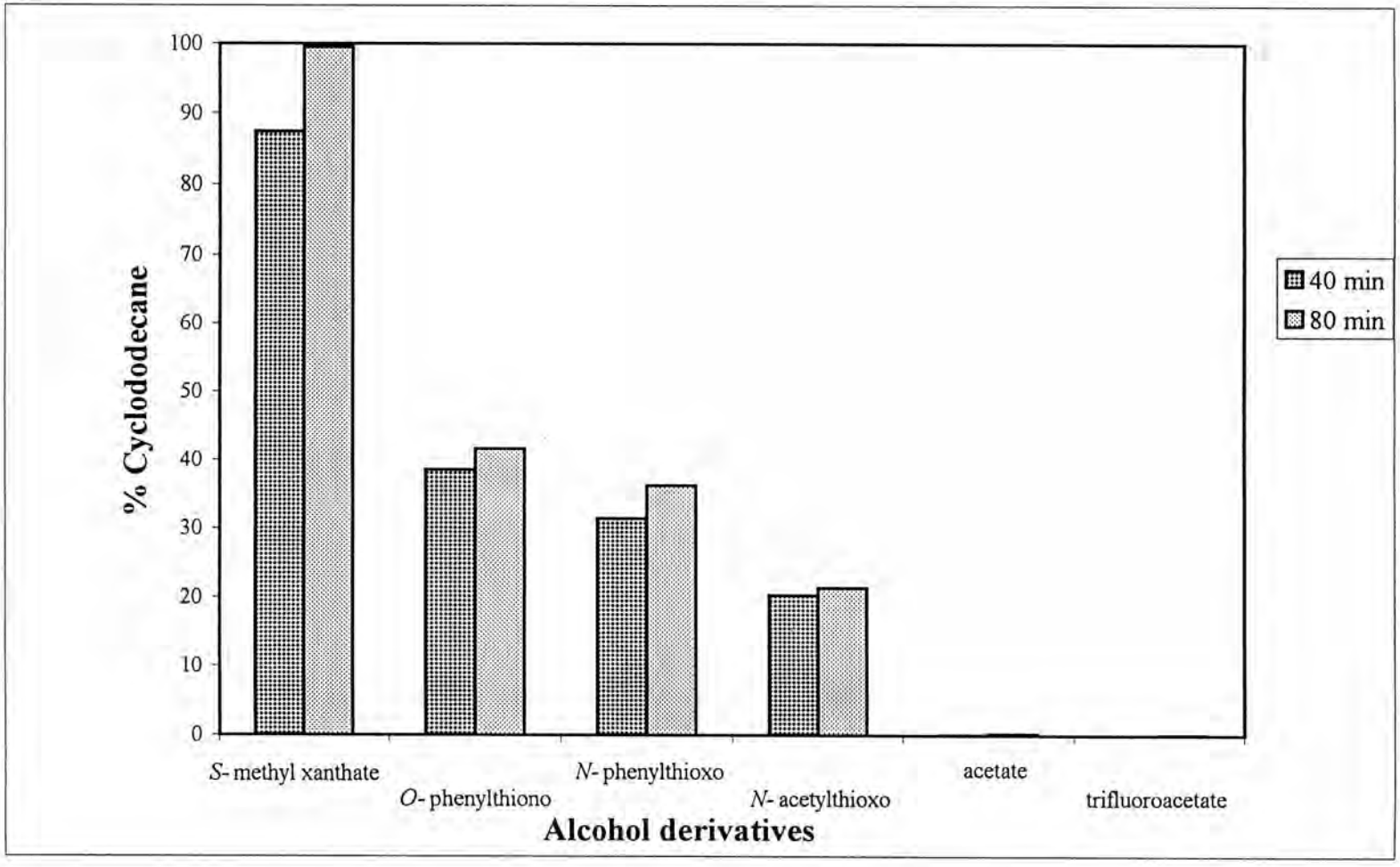
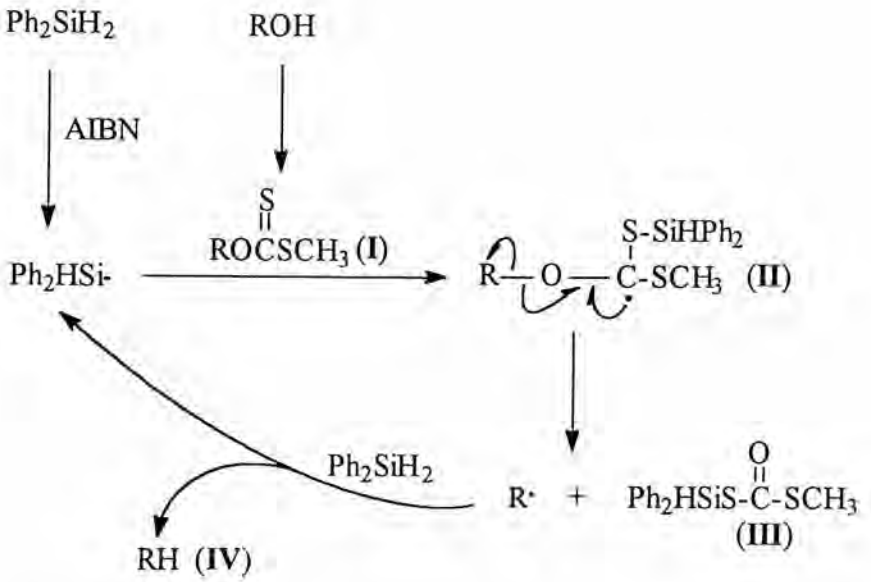


Figure 3.6 The effects of alcohol derivatives

It can be seen from Fig 3.6 that when using cyclododecyl *S*-methyl xanthate as a substrate, it afforded the highest yield of cyclododecane about three times or more compared with other thiocarbonyl derivatives. For cyclododecyl acetate and cyclododecyl trifluoroacetate, these two derivatives provided poor yield of deoxygenated product (about 0.3%). One of the main reasons is because a carbonyl oxygen is not suitable for radical deoxygenation, perhaps due to the high energy of C-O bond to be cleaved. Therefore many researches in this field have attempted to replace carbonyl oxygen by sulfur.[7] Based upon the results attained, reactivity of various alcohol derivatives can be ordered from highest reactivity as follows cyclododecyl *S*-methyl xanthate (**3a**), cyclododecyl *O'*-phenylthioxocarbamate (**6a**), cyclododecyl *N*-phenylthioxocarbamate (**5a**), cyclododecyl *N*-acetylthioxocarbamate (**4a**), cyclododecyl acetate (**7a**) and cyclododecyl trifluoroacetate (**8a**)

3.1.6 Mechanism of the Radical Deoxygenation of Cyclododecyl *S*-methyl xanthate

The mechanism operated for the deoxygenation reaction examined was believed to take place *via* the same route as that described by D. H. R. Barton and coworkers.[21] Radical reactions take place under neutral conditions, and therefore are ideally suited for application to sensitive polyfunctional compounds. Radical deoxygenation, *i.e.* the homolytic clevage can be realized according to Scheme 3.1 in which a suitable alcohol derivative (**I**) is converted to an intermediate radical (**II**), which fragments by β cleavage into an alkyl radical and a carbonyl compound (**III**). The alkyl radical further reacts with a hydrogen donor yielding the corresponding hydrocarbon (**IV**).



Scheme 3.1 The mechanism of the Barton-McCombie reaction of *S*-methyl xanthate derivative of alcohol using diphenylsilane as a chain carrier and AIBN as an initiator

3.2 Deoxygenation of Some Related Compounds

In order to apply previously developed standard conditions to deoxygenate other alcohols besides a model compound, some different alcohols were selected to examine.

3.2.1 2-adamantanol

2-Adamantanol was another secondary alcohol which was chosen to deoxygenate. It was initially transformed to methyl xanthate derivative in 76% yield. Then reduction of 2-adamantanyl *S*-methyl xanthate with diphenyl silane (Ph_2SiH_2) 2 equivalents in dry toluene was carried out at 100°C in the presence of catalytic amount 20 mol% (0.2 equivalent) of AIBN for 80 minutes. After work-up, the reaction mixture was analyzed by gas chromatograph. Adamantane as the desired product was attained only 11.76%. On an account of a low yield of deoxygenated product, it may imply that a chain carrier (Ph_2SiH_2) may not be enough in this particular case. Thereby, Ph_2SiH_2 3.75 and 5.0 equivalents (compared with a substrate) were tried. The results of using various amounts of Ph_2SiH_2 to deoxygenate 2-adamantanyl *S*-methyl xanthate are displayed in Table 3.9.

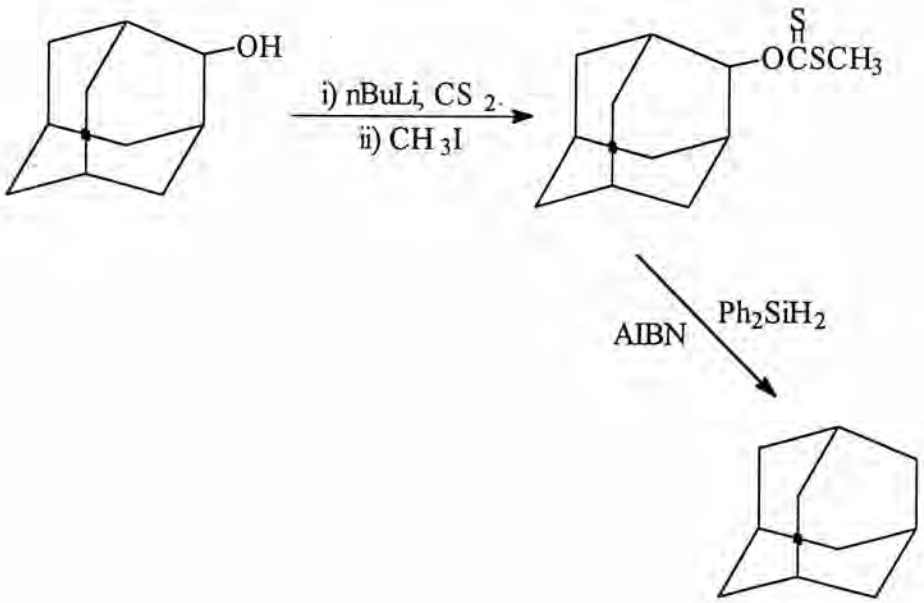


Table 3.9 Deoxygenation of 2-adamantanyl *S*-methyl xanthate

Diphenylsilane (mmol)	AIBN (mmol)	% adamantane
0.8	0.08	11.76
1.5	0.15	25.06
2.0	0.20	63.03

Reaction conditions : 2-adamantyl *S*-methyl xanthate (0.4 mmol), Ph_2SiH_2 (variable), AIBN (variable), toluene (4 mL)

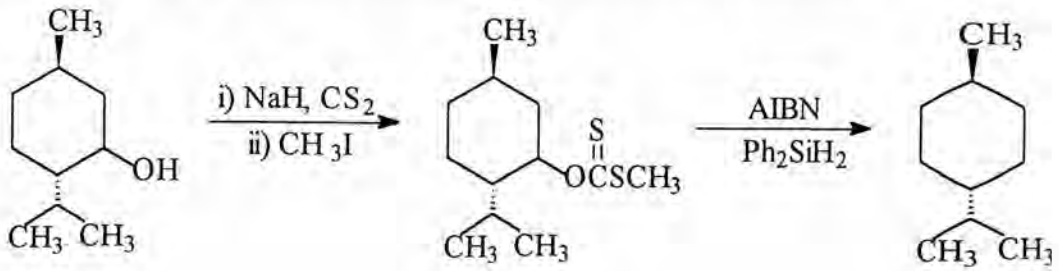
Reaction time : 80 minutes

It can obviously be seen from Table 3.9 that when both Ph_2SiH_2 and AIBN were doubly used, the amount of adamantane was increased by twice. Moreover, 63% of adamantane could be achieved when Ph_2SiH_2 (2.0 mmol) and AIBN (0.20 mmol) were employed.

3.2.2 menthol

Menthol was the next target that was chosen as another model to deoxygenate. To our best knowledge, there was no report on the preparation of mentyl *S*-methyl xanthate and the deoxygenation of this compound in chemical literature.

Deoxygenation reaction of menthol *via* methyl xanthate derivative was carried out. The structure of the xanthate derivative (**3c**) was well-characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. By using diphenylsilane (5 equivalents to a substrate) at 100°C in dry toluene and AIBN (0.2 equivalent) as an initiator, the reaction was completed within 120 minutes (followed by the disappearance of the substrate). After work up, the product was analyzed by gas chromatograph (74.36%), comparing with the isolated *trans*-1-methyl-4-isopropylcyclohexane.



It could be seen that for two instances of secondary alcohols selected, 2-adamantanol and menthol, the conditions needed for deoxygenation has to be carefully optimized in order to obtain the highest yield of the desired product.

3.2.3 octadecanol

In order to extend the conditions studied for deoxygenation of primary alcohols, octadecanol was selected as a model for a primary alcohol. By utilizing the same methodology as that for secondary alcohols, octadecanol was transformed to a better derivative. Two alcohol derivatives of octadecanol were octadecyl *S*-methyl xanthate (**3d**) and octadecyl *N*-acetylthioxocarbamate (**4d**). Both of them were attained in good yield and their structures were well-confirmed by IR, ^{1}H and ^{13}C NMR spectra.

$$C_{18}H_{37}OH \xrightarrow[\text{ii) } CH_3I]{\text{i) } n\text{BuLi, } CS_2} C_{18}H_{37}O\overset{\overset{S}{\|}}{C}SCH_3 \quad (69\%)$$

$$C_{18}H_{37}OH \xrightarrow[KSCN]{CH_3\overset{\overset{O}{\|}}{C}Cl} C_{18}H_{37}O\overset{\overset{S}{\|}}{C}N\overset{\overset{O}{\|}}{C}CH_3. \quad (63\%)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad H$$

Each derivative of octadecanol was deoxygenated under the same conditions as that used for deoxygenation of cyclododecanol, the product was quantified by the aids of gas chromatograph by using cyclohexanone as an internal standard. The results are presented in Table 3.10.

Table 3.10 Deoxygenation of octadecyl thiocarbonyl derivatives

Octadecyl derivatives	Octadecane (%)	
	at 40 minutes	at 80 minutes
S-methyl xanthate	3.04	3.59
N-acetylthioxocarbamate	1.91	2.10

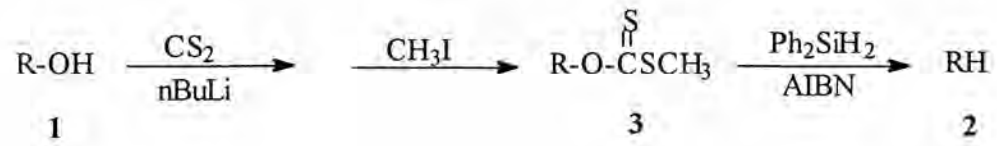
Reaction conditions : Octadecyl thiocarbonyl derivative (0.4 mmol), Ph_2SiH_2 (0.8 mmol), AIBN (0.08 mmol), toluene (4 mL)

The outcome of the reaction was not surprised. Generally, the deoxygenation of primary alcohol derivatives gives a lower yield than those of secondary alcohol derivatives under the same particular conditions. That is because the stability of primary radicals would be relatively lesser than that of the secondary radicals and made primary radicals have higher energy than secondary radicals. For this reason, thiocarbonyl of octadecanol derivatives gave trace deoxygenated product in this standard conditions. However, this experiment clearly revealed that this type of alcohol has also an ability to deoxygenate if it was treated under more suitable conditions.

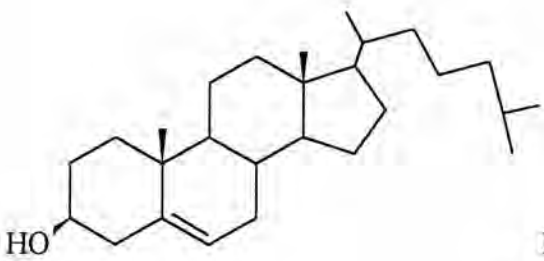
3.3 Application of Deoxygenation Reactions to Natural Products

Deoxygenation of aliphatic alcohols plays an important role in organic synthesis. That is because deoxygenated derivatives often exhibit a better biological activities than parent compounds.[39] The methods of removal hydroxy groups are therefore one of excellent techniques for enhancing the biological activity of natural occurring compounds. In this research, steroids and triterpenoids were selected as chemical models to deoxygenate under standard conditions explored.

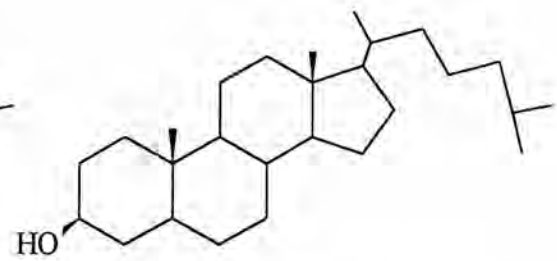
Two steroids and three triterpenoids as the structures shown in Fig 3.7 were selected. They were transformed into their *S*-methyl xanthate derivatives *via* the treatment of those compounds with CS_2 and CH_3I in the presence of suitable base. The corresponding methyl xanthates was obtained in good yield (66-79%) as presented in Table 3.11. A radical deoxygenation of all xanthate derivatives *via* Barton-McCombie method utilized alcohol derivatives 0.4 mmol, diphenylsilane (Ph_2SiH_2) as a chain carrier 2 mmol (5 equivalent) and AIBN as an initiator 0.08 mmol (0.2 equivalent) in dry toluene 3.0 mL was then performed. The reaction mixture were carried out at 100°C to afford the corresponding deoxygenated products in good to excellent yields at variable reaction time depending on the structures of substrate. The results of deoxygenation of some natural products are tabulated in Table 3.11. The structures of both methyl xanthates and the corresponding hydrocarbons were well-confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The general reaction scheme can illustrate as shown below.



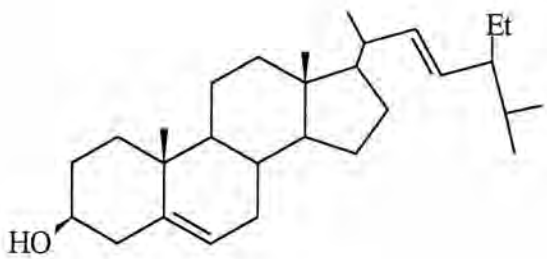
1 3 2



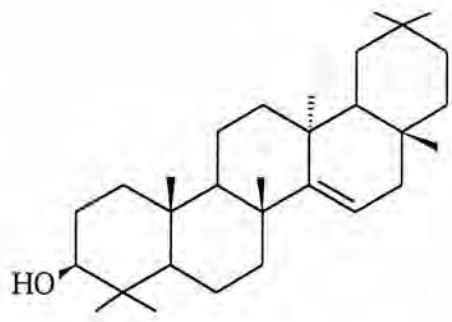
1e : cholesterol



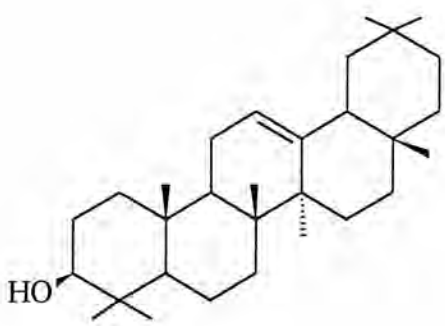
1f : cholestanol



1g : β-sitosterol



1h : taraxerol



1i : β-amyrin

Figure 3.7 Selected steroids and triterpenoids for deoxygenation

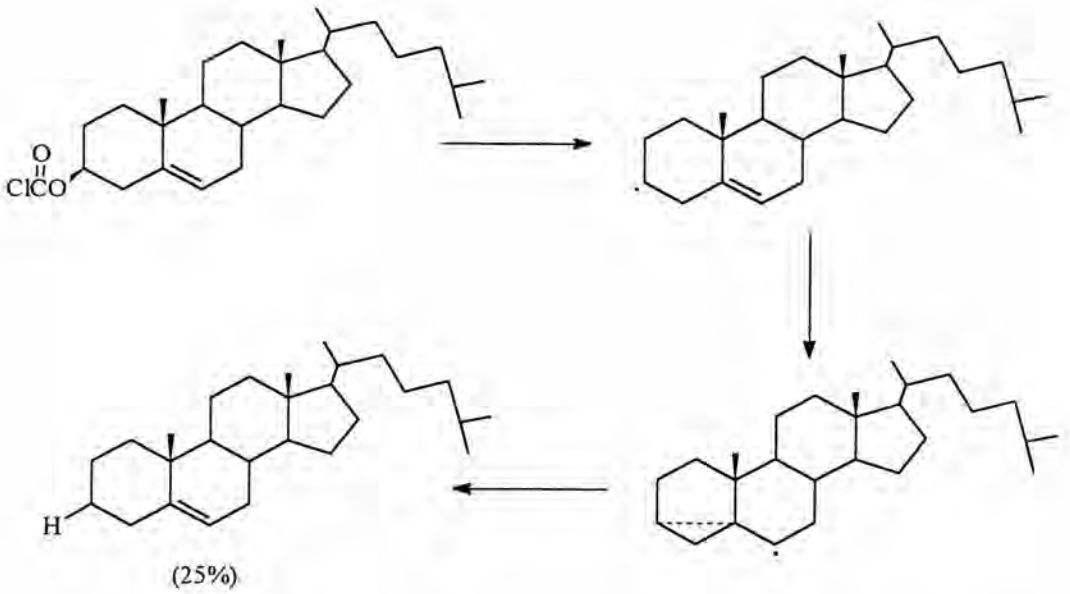
Table 3.11 The results of deoxygenation of some natural products

entry	R	% xanthate derivative	Deoxygenated reaction	
			Reaction time	% product [a]
1	Cholesteryl **(e)**	67.38	40 min.	61.97
2	Cholestanyl **(f)**	66.20	40 min.	54.71
3	β-sitosteryl **(g)**	69.73	215 min.	51.25
4	taraxeryl **(h)**	78.16	215 min.	94.15
5	β-amyryl **(i)**	67.41	240 min.	67.78

[a] isolated yield

Reaction conditions : *S*-methyl xanthate (0.4 mmol), Ph_2SiH_2 (2 mmol), AIBN (0.08 mmol), toluene (3.0 mL)

The results obtained from Table 3.11 clearly demonstrated that this deoxygenation reaction was comparably appropriate for removing the hydroxy group from natural products. The time required for the deoxygenation of cholesteryl *S*-methyl xanthate (**3e**) and cholestanyl *S*-methyl xanthate (**3f**) were shorter than that needed for other compounds. The isolated yields of these compounds were found to be relatively high (55-62%) compared with previous reports. For instance, R. A. Jackson and F. Malek reported that cholest-5-ene only 25% was obtained from the reduction of cholesteryl chloroformate, due to ring closure formation of the cholesteryl radical to give i-cholesteryl derivative.[19]



(25%)

It should also note at this point that a double bond functional group of steroids in position 5 and 6 of cholesterol is remained intact under this radical deoxygenation condition employed.

The fascinating result was attained from the deoxygenation of taraxerol *via* its methyl xanthate. Two derivatives of taraxerol namely taraxeryl *S*-methyl xanthate (**3h**) and taraxeryl *N*-phenylthioxocarbamate (**4h**) could be prepared in good yields, 78% and 76%, respectively. Both of them are new derivatives. Their structures are well-clarified by both spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR) and elemental analysis results. The deoxygenation reaction of both derivatives provided the desired product, taraxerene (**2h**) in excellent isolated yield. The results are summarized as shown in Table 3.12.

Table 3.12 The results of deoxygenation of taraxeryl derivatives

Derivative of taraxerol	% taraxeryl derivative	Deoxygenated reaction	
		Reaction time	% product [a]
S- methyl xanthate **(3h)**	78.16	215 min.	94.15
N-phenylthioxocarbamate **(4h)**	75.98	240 min.	92.73

[a] isolated yield

Reaction conditions : taraxeryl derivatives (0.4 mmol), Ph_2SiH_2 (2 mmol), AIBN (0.08 mmol), toluene (3 mL)

Comparing the results obtained from this experiment with that reported by Pasupati, it could clearly be seen that this present method was superior and gave more impressive results. To illustrate this, Pasupati used lithium and ethylamine to convert taraxerol to taraxerene (**2h**) *via* acetate derivative, giving only 50% yields.[40] The isolated product of taraxerene attained from this experiment either using taraxeryl *S*-methyl xanthate (**3h**) or taraxeryl *N*-phenylthioxocarbamate (**4h**) derivatives, all provided excellent yield of taraxerene (94 and 93% respectively).