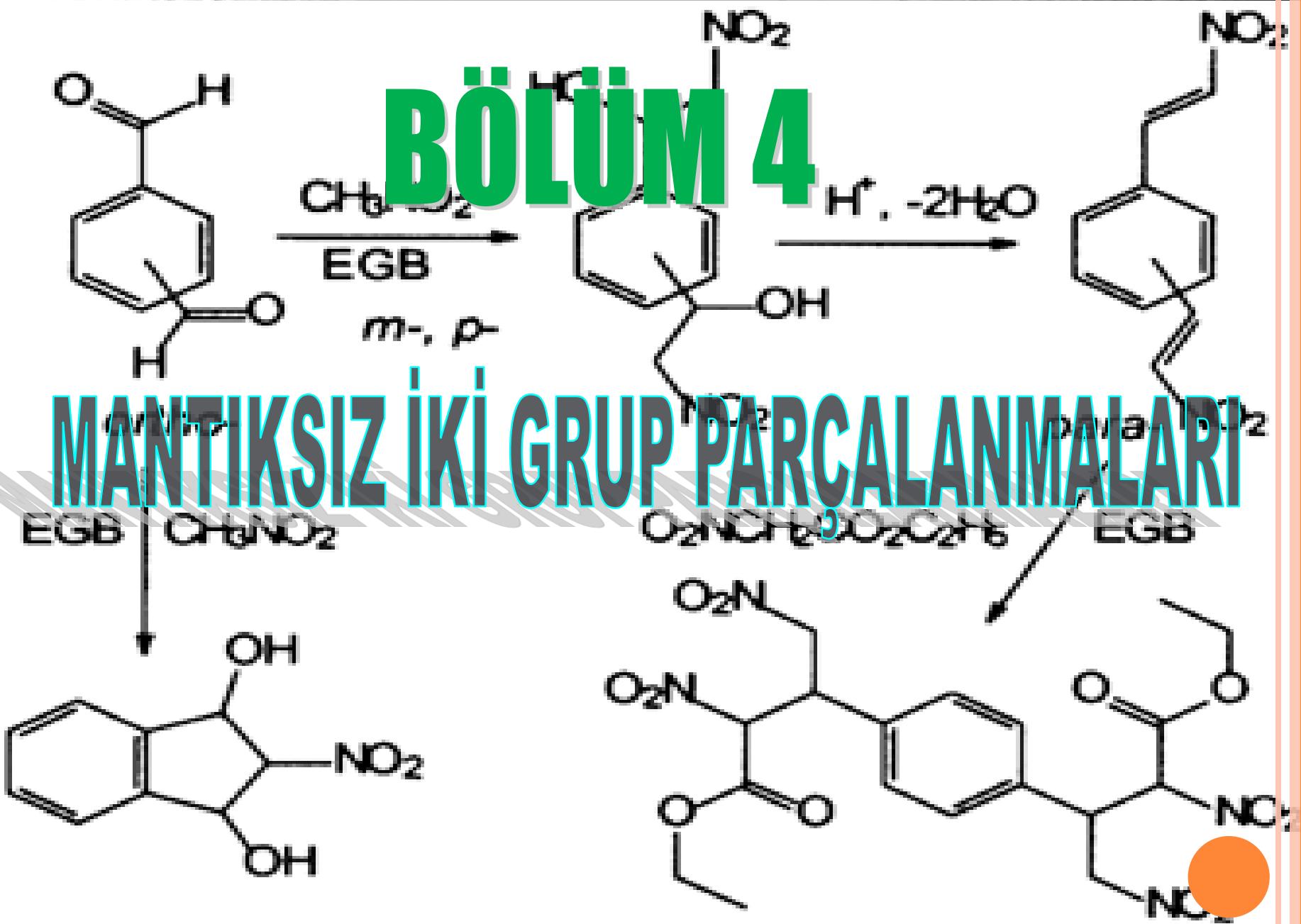


# BÖLÜM 4

## MANTIKSIZ İKİ GRUP PARCALANMALARI

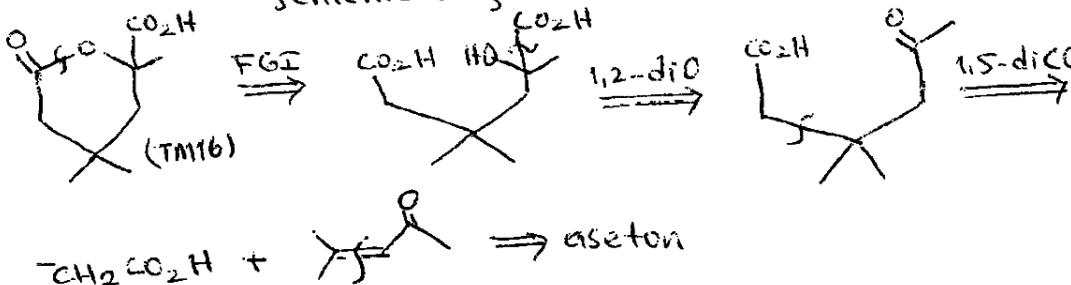
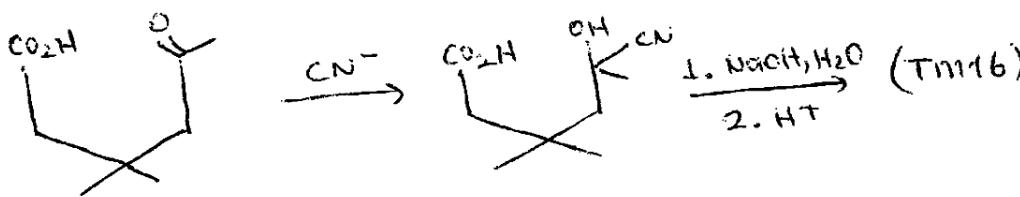
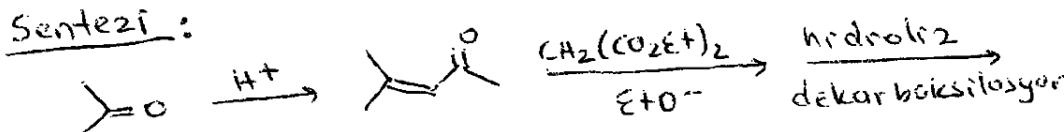


Scheme 3

(d) Problemler

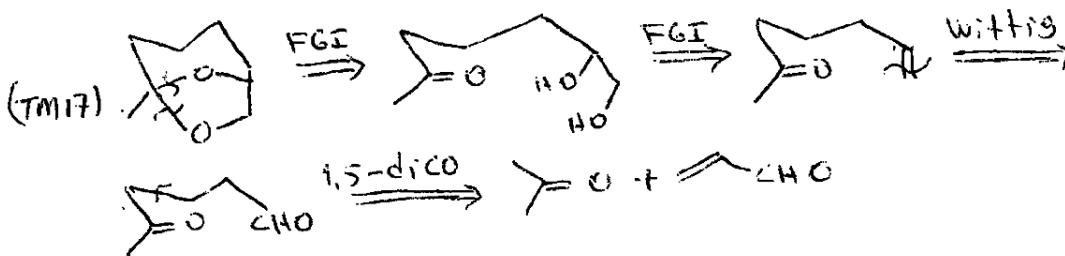
1. Aşağıdaki Lakton asidi (TM16) için bir sentez y\u0111ntemi

Analizi: Laktonun açılmasıyla, 1,2-, 1,5- ve 1,6-dioksi senteze ba\u0111antları ortaya çıkar.

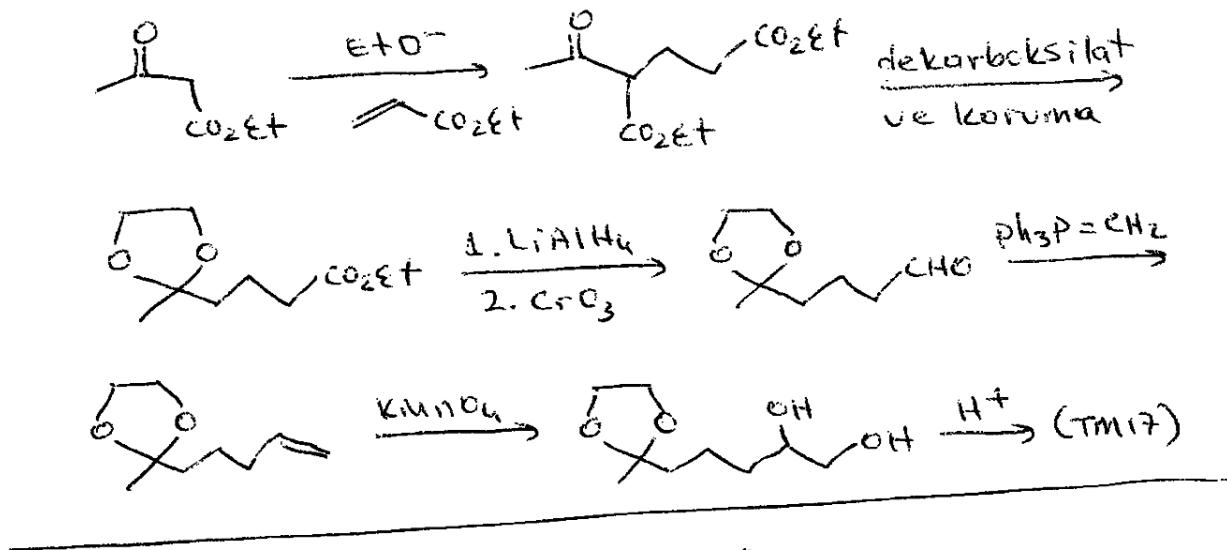
Sentezi:

2. (TM17) bilezi\u0111ının analiz ve sentezini yapınız.

Analizi: \u0131ncelikle, asetal funk\u0131yonlu grubu uzaklaştırılır.



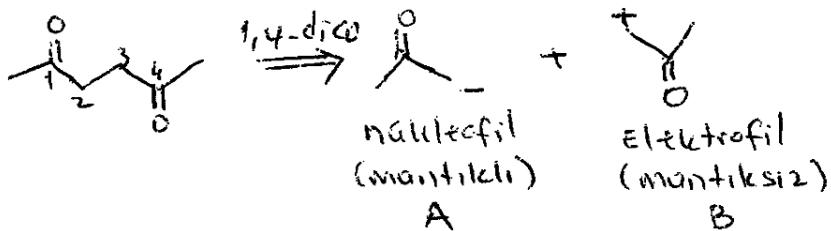
Sentezi: Wittig reaksiyonunu aldehit üzerinde yapınamayız, Keton ile etkileşmemesi için Keton grubunu korumalıyız. Bundan dolayı, aldehitte bir ester grubu bağlamalıyız.



## 2. 1,4-DİOKSİJENLEME MODELİ

### (a) 1,4-Dikarbonil Bileşikleri

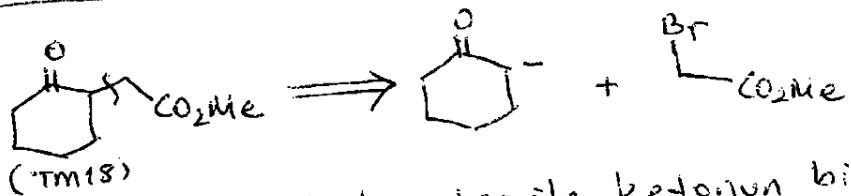
1,4-dikarbonil bileşiklerinin parçalanması sorusunda, mantıklı nükleofilik synthon (bir enolat anyonu) olurken, mantıksız elektrofilik synthon da ortaya çıkar



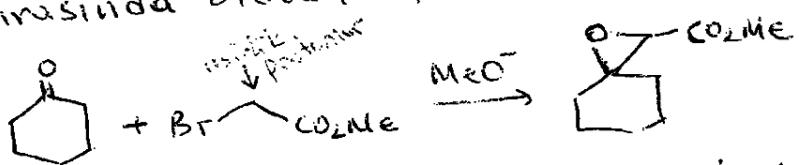
Bican, polaritesi giderilmiş bir keton türümüne ihtiyac duyulur, bunun için en ideal  $\alpha$ -halo karbonil bileşigidir.

Örnek 1 : LTM18) bileşığının analizi ve sentezi how  
ğneiderde bulununuz.

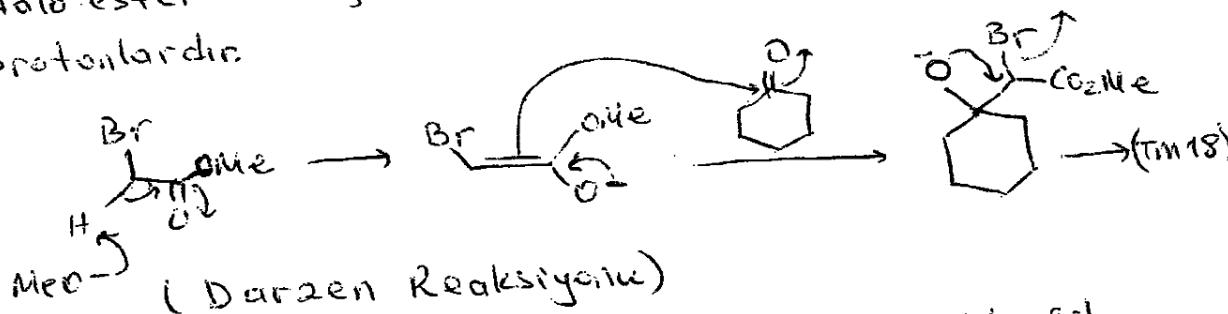
Analiz :



Sentezi :  $\alpha$ -halo ester ile ketonun birleştirilmesi sırasında ulduzlar farklı reaksiyonlar olur:



Halo ester bileşığının metilen protonları en oxidik protonlardır.

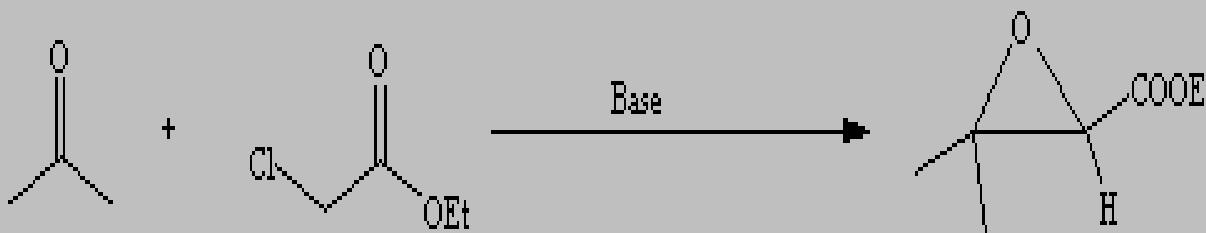


(Darzen Reaksiyonu)

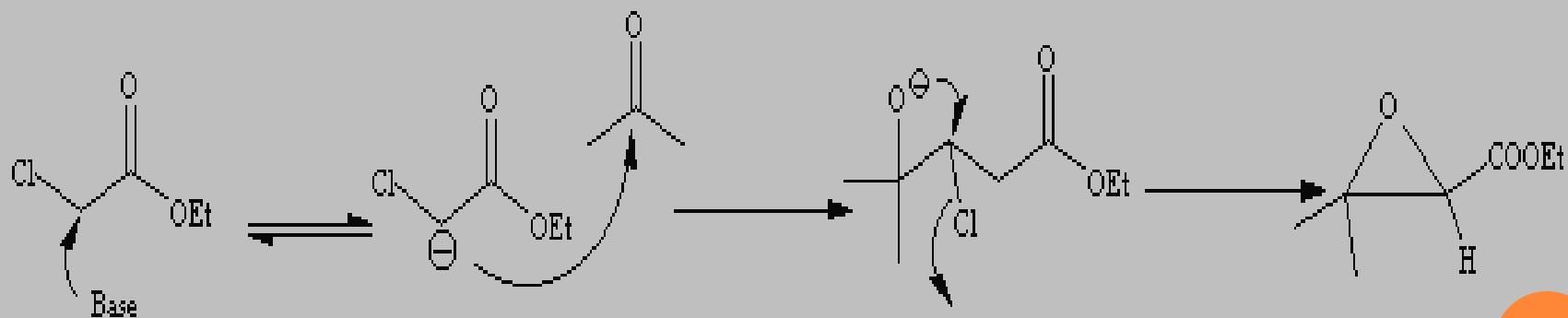
Burada, ikinci kondensasyonda ketonu nükleofil olarak kullanmak gereklidir. Bunu yapmak için en iyi yol,

## Darzen kondenzasyonu (reaksiyonu)

Formation of  $\alpha,\beta$ -epoxy esters by the condensation of aldehydes or ketones with esters of  $\alpha$ -haloacids.:

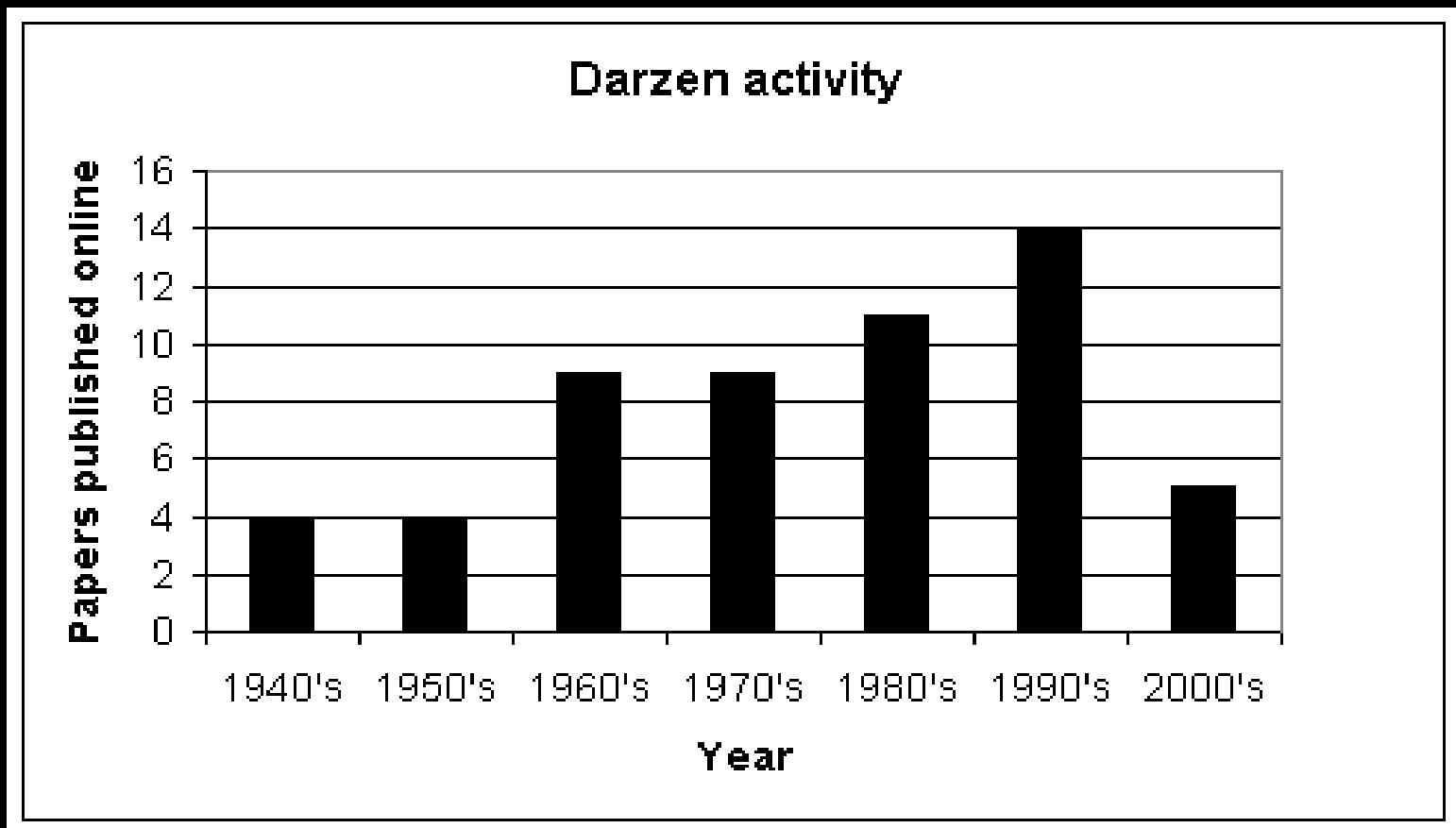


### Mekanizma



## Frequency of appearance:

This bar graph represents all of the online articles that were found to contain this specific name reaction in the title of the article. Tetrahedron letters, Tetrahedron, Synthetic letters, Synthesis, Journal of Organic Chemistry and Journal of the American Chemical Society are represented here. This table by no means represents the periodicity of the name reaction found in the literature.



## Recent academic references:

### Camphor-Based Bromo Ketones for the Asymmetric Darzens Reaction

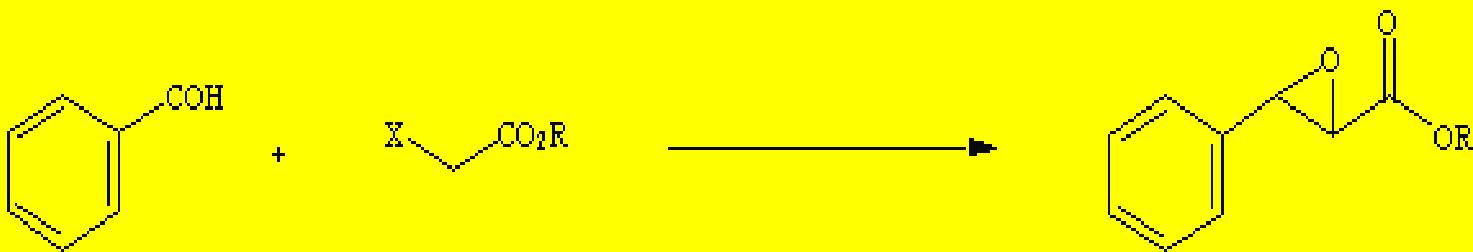
Palomo, C.; et al., *J. Org. Chem.*; **2000**; 65(26); 9007-9012.

### Inverted Diastereoselectivity in Asymmetric Aziridine Synthesis via Aza-Darzens Reaction of (2S)-N-Bromoacyl Camphorsultam

McLaren, A. B.; et al., *Org. Lett.*; **1999**; 1(9); 1339-1341.

### A Cyclic Transition State for the Darzen Reaction

Yliniemi, A.; et al., *J. Org. Chem.*; **1996**; 61(19); 6723-6726.



Transition state study

## Scope and Limitations:

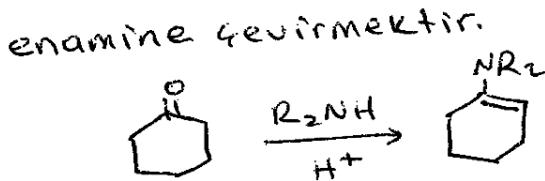
Good yields with aromatic aldehydes and ketones. A+B

Aliphatic aldehydes need the aid of LDA or LiN(SiMe<sub>3</sub>)<sub>2</sub> to 1st deprotonate the alpha halo ester to obtain high yields. A+B

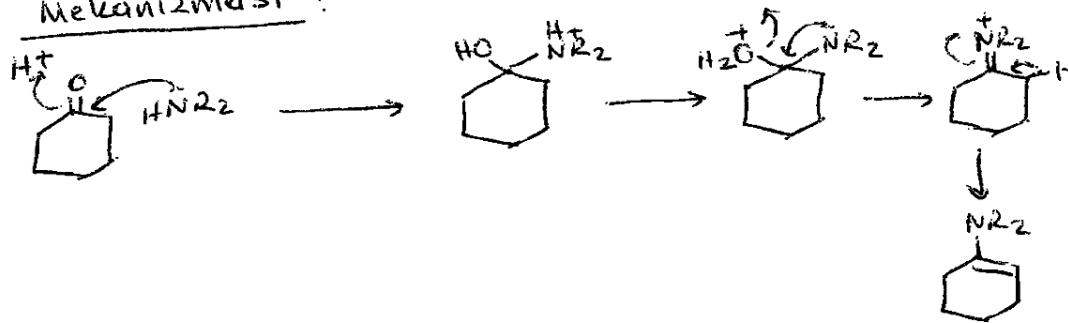
alpha-halo ketones, nitriles, sulphones and N,N-amides are also used for Darzen's condensation.  
A+B

Na ethoxide is often employed as a base. A

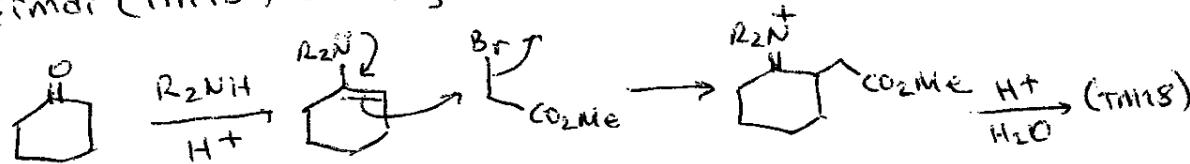
Reaction can also be catalyzed by an acid. A



Mekanizması :



Şimdi (TM18) bileşliğinin sentezi

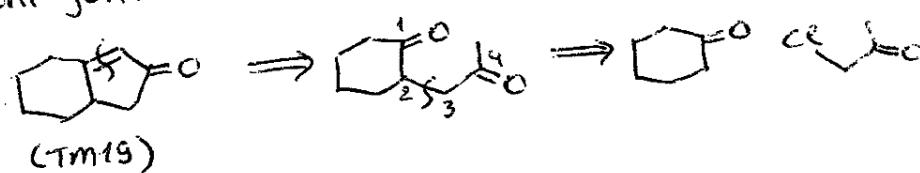


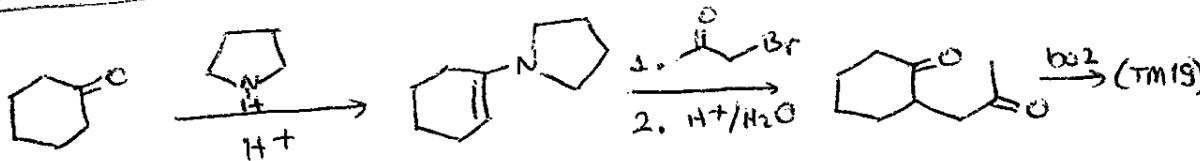
şeklinde tamamlanır.

Enamin, reaktif  $\alpha$ -karbonil halogenürüne karbonil grubunun kendisinden daha gele atak yapar.

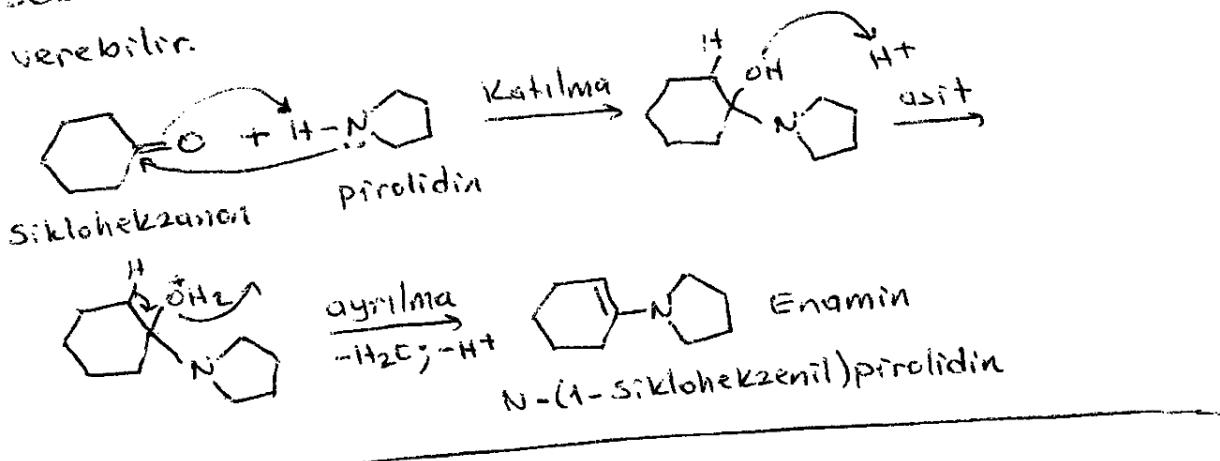
Örnek 2 : (TM19) bileşliğini nasıl sentezlersiniz?

Analizi :  $\alpha,\beta$ -deyimmiş keton parçaları ile birebir ve yeni yöntemde kullanacağımız 1,4-diketona sahip oluruz.



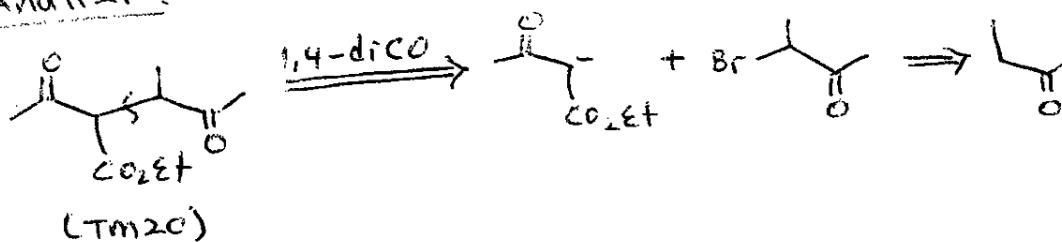
Sentezi:Enamin mekanizması

Sekonder aminler karbonil bileşikleriyle kondensasyon verebilir.

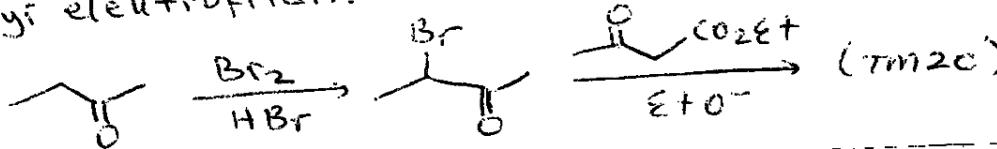


- Enaminitler her zaman gereklidir, bazen enol anyonunun fazla kendisi yeterince kararlıdır.

Örnek 2: (TM20) bileşигини nasıl yaparsınız?

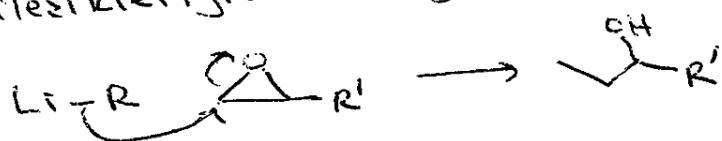
Analizi:

Sentezi: Bütanonun bromlanması (asit reride) istediğimiz izomeri verir. olusan  $\alpha$ -karbonlu halogenür iyi elektrofildir.



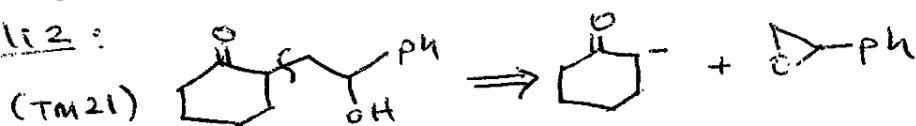
### (b) $\gamma$ -Hidroksi Karbonil Bilezikleri

$\alpha$ -halo karbonil bilezikleri,  $\text{C}=\text{O}$  synthonu için reaktif olarak kullanılmaktadır. Daha düşük yükseltme basamağında  $\text{C}=\text{O}^{\text{OH}}$  synthonu için reaktif genme basamağında  $\text{C}=\text{O}$  synthonu için reaktif olarak epoksitler kullanılır (Grignard ve organometalik bilezikleriyle reaksiyonlarında etkisi gibi).

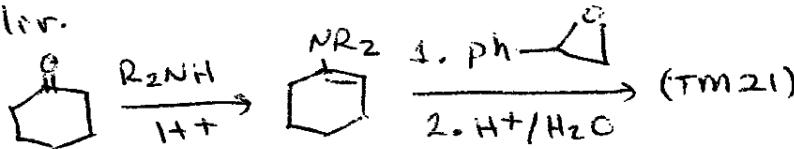


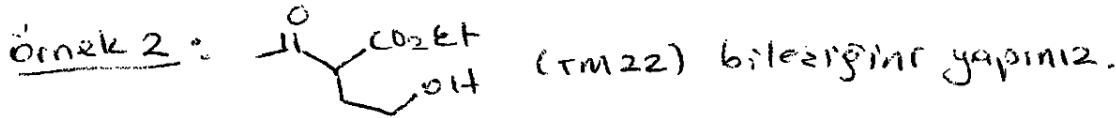
İnceleme 1: (TM21) aşağıda gösterilen  $\delta$ -hidroksi keton bileziğini analiz ederek bir sentez öneriniz.

Analiz:

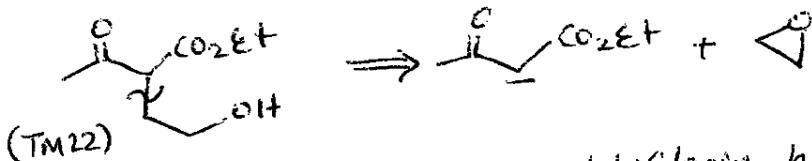


Sentezi: Enolat synthonu sağlamak için enamin kullanılabılır.

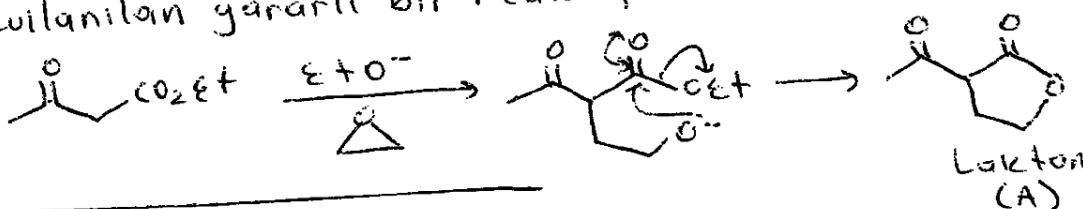




Analizi:

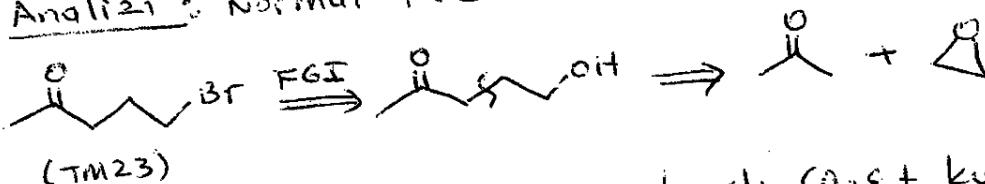


Sentezi: Aslında reaktiflerin birleştirilmesi (TM22)'ye verme 2. B-nin yerine Lakton (A) olusur. Bu lakton, planladığımız (TM22) bileşiginin bütün reaksiyonlarında kullanılan gararlı bir reaktiftir.

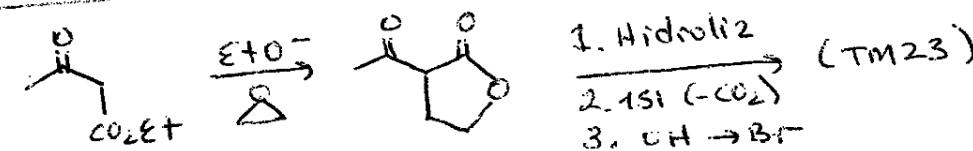


Örnek 3: Aşağıda görülen  $\delta$ -haloketon (TM23)'in nasıl yopersiniz?

Analizi: Normal FGI alkol verir.

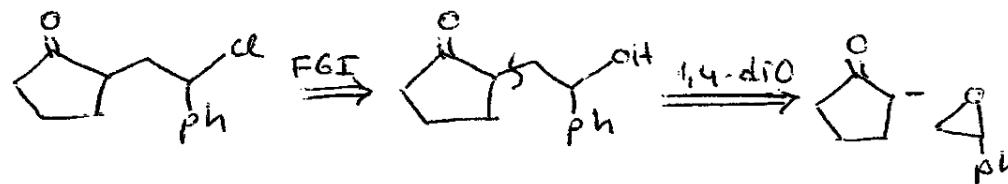


Sentezi: Aktiflectirici grup olarak  $\text{CO}_2\text{Et}$  kullanılır.

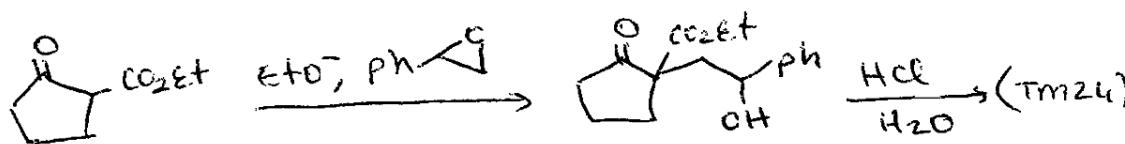


Örnek 4: Aşağıdaki  $\delta$ -halo ketonu (TM24) nasıl elde edersemiz?

Analizi:



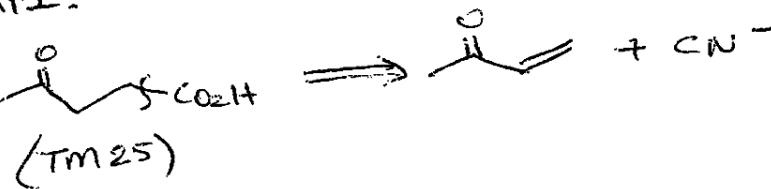
Sentezi: Başlangıç maddesinde aktifleştirmeli bir grup olmalıdır.



### (c) Diğer Mantıksız Synthonlar

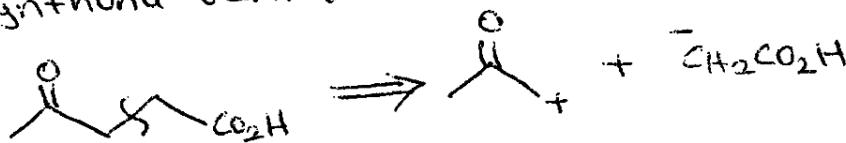
1,4-dikotsijenlenmiş bilesikleri elde etmek için hem mantıklı hem de mantıksız synthonlar kullanılmıştır.

Örnek 1: Aşağıdaki gibi bir  $\delta$ -keto asidi elde etmek için CN- iyonunu ( $\text{CO}_2\text{H}$  synthonu olarak) nasıl kullanırız.

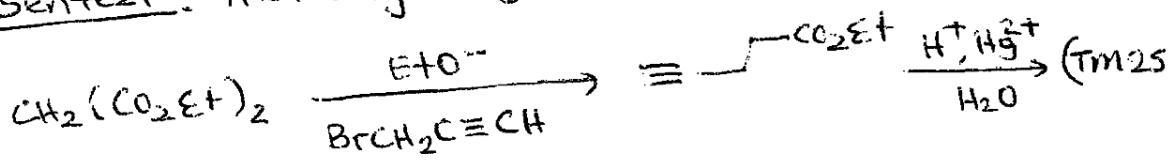


Örnek 2: Aynı asidi, propen-jil bromür ( $\text{Br}-\text{CH}_2-\text{C}\equiv\text{CH}$ ) (mantıksız bölüm) kullanarak nasıl yaparsınız?

Analizi: Asetilenler, keton vermek üzere hidratize edilebilmektedir böylece propargil bromür,  $\text{MeCOCH}_2\text{Br}$  synthonu verir:



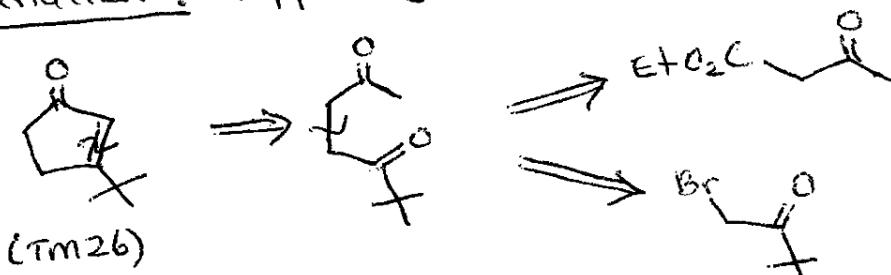
Sentezi: Aktivasyon gerekektir:



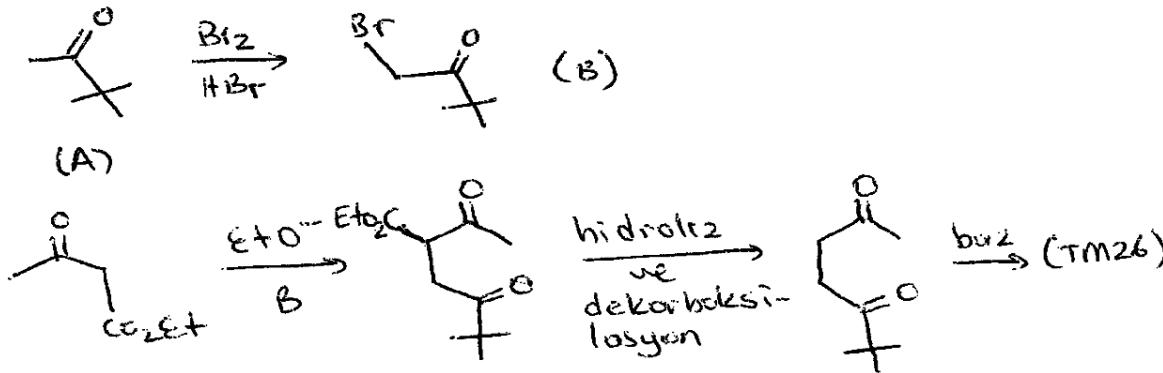
#### (d) Problemler ve Çözümleri

1. Doğada bulunan ve prostaglandin sentezinde önemli bir bileşik olan siklopentenonlardan aşağıdaki bileşik nasıl yaparsınız? (TM26)

Analizi:  $\alpha, \beta$ -doymamış karbeninden başlatabiliriz:

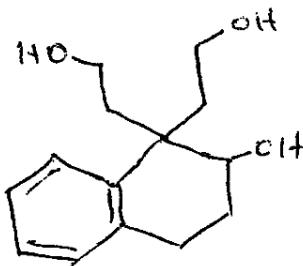


Sentezi: (A) ketonu pinakolon olursa ikin, pinakolon gevrilmesyle eide edilebilir:



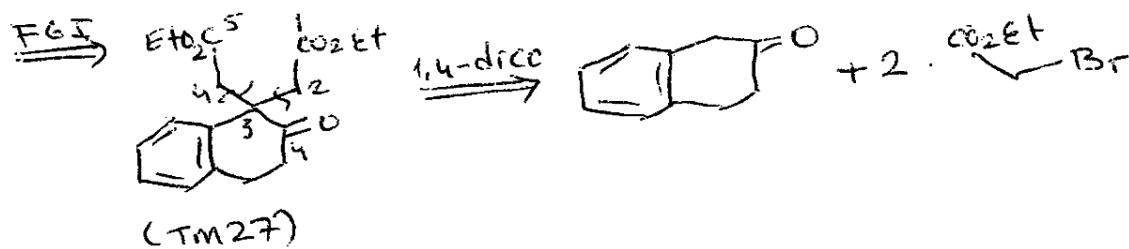
2. Aşağıdaki triol (TM27) 1,4-veya 1,5-dikisittenlenmiş bileşik olarak alınabilir. Aslında bunlardan birisi uygundur. Sentez rüsin bir öncesinde bulunurdu.

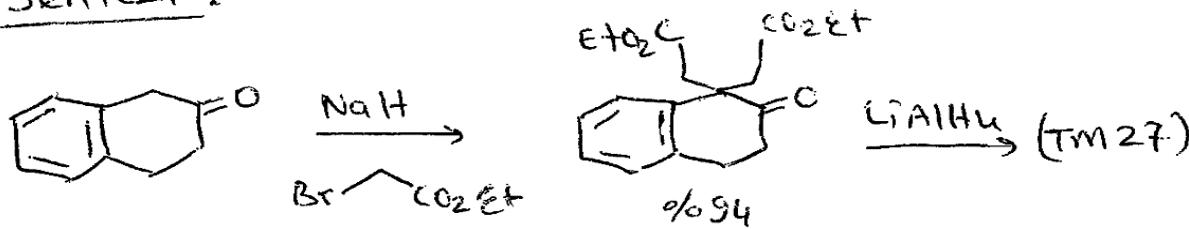
Analizi:



Bu üç OH grubuna karşı gelecek trikarbenil bileşiginin düzünmeliyiz.  $\text{CH}_2\text{OH}$  rüsin;  $\text{CHO}$  veya  $\text{CO}_2\text{Et}$  yapmamalıyız (FGI yapıılır). 1,5-paralelmasıyla, olusan öncüler rümdeler çift bağılar oda sıcaklığında kararsız olacağı rüsin, 1,5-trikarbenil paralelması icvulanılmaz.

İğinde kararsız olacağı rüsin, 1,5-trikarbenil paralelması icvulanılmaz.

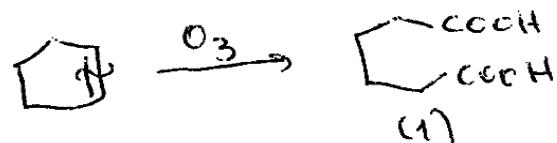


Sentezi:

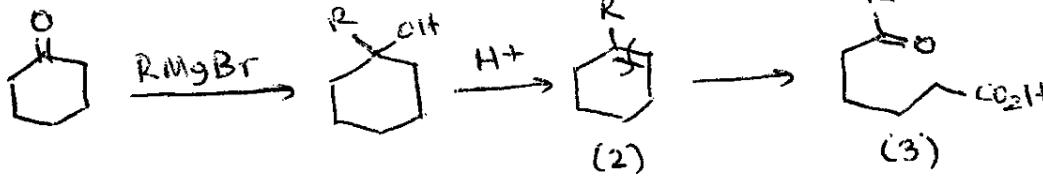
Güçlü maddesi olan keton, substitüte naffalinin indigen-mesi ile (J. Amer. Chem. Soc., 1950, 72, 3704) yapılabilir.

3. 1,6-DIKARBONİL BİLESİKLERİ

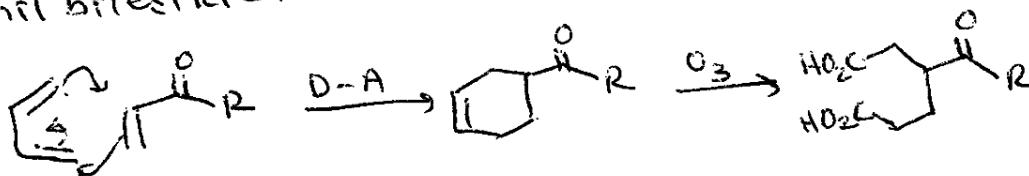
iki karbonil grubu olan bilesiklerin sentezinde bir takım problemler olmaktadır. Burada, yeniden birlesme (reconnection) 1,6-difunksiyonlu bilesiklerin sentezinde uygulanan genel bir stratejidir. Adipikasit (1)-sikloheksinden kolayca elde edilebilir:



1-geride substituent olan sikloheksenler (2), sikloheksanondan ve Grignard reaktiflerinden yapılabilir. Parvalanması keto asitleri (3) verir.



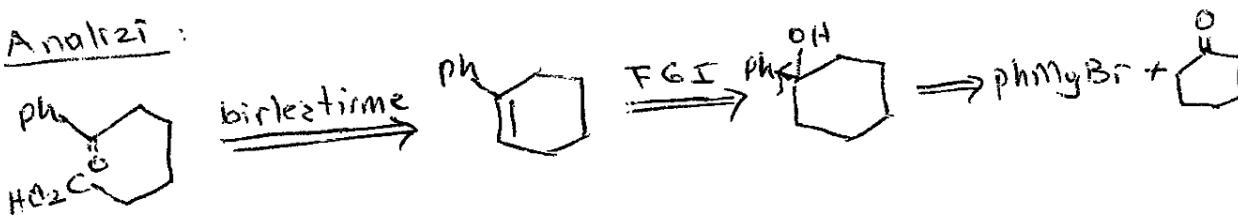
Siklohekzentenleri hazırlamak için en önemli yol, Drels-Alder reaksiyonu ve elde edilen ürünün parçalanması ile elazan 1,4- ve 1,5-dikarbonyl bilesiklerin 1,6-dikarbonyl bilesiklerinin sentezinde kullanılmıştır.



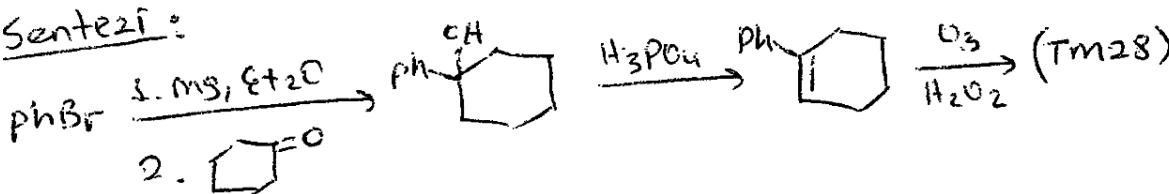
### Örnekler

1.  $\text{Ph}-\text{C}(=\text{O})-\text{CH}_2-\text{CH}_2-\text{CO}_2\text{Et}$  (Tm28) sentezini analiz ediniz.

### Analizi:

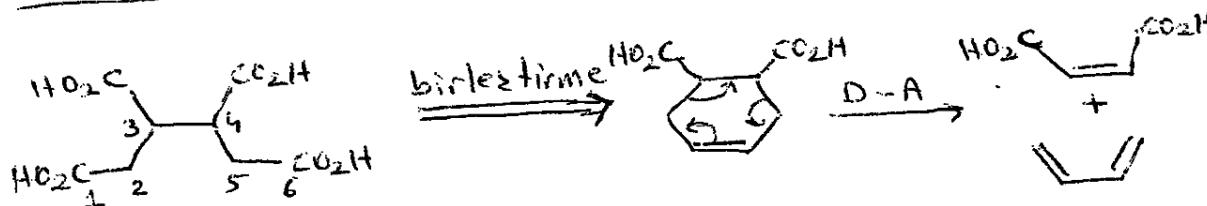


### Sentezi:

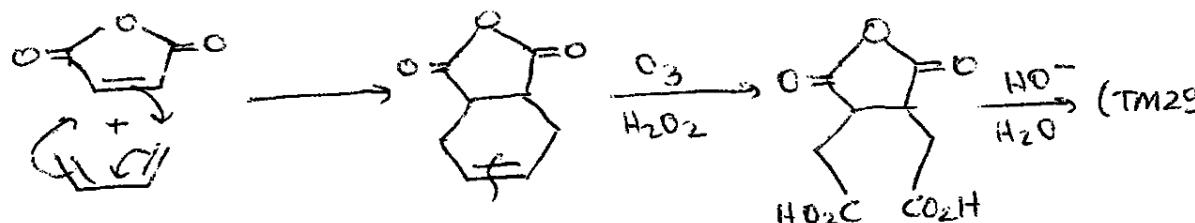


2. (TM29) bilesigini analiz ederek sentezini yapınız.

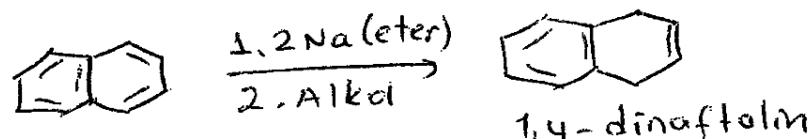
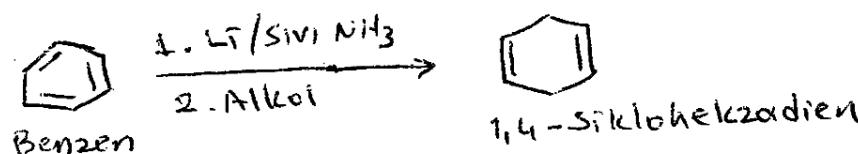
Analiz: Ençelikle, 1,6-dikarbonil bağlantısını seçiniz:



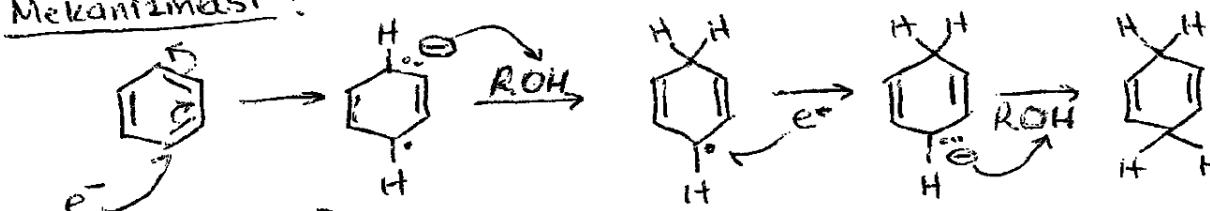
Sentezi: Molekül anhidrit en iyi reaktiftir



- Siklohekzenleri elde etmek için diper bir yöntem; benzen halkasının kısmi indirgememesi içeren "Birçok indirgemesidir!"

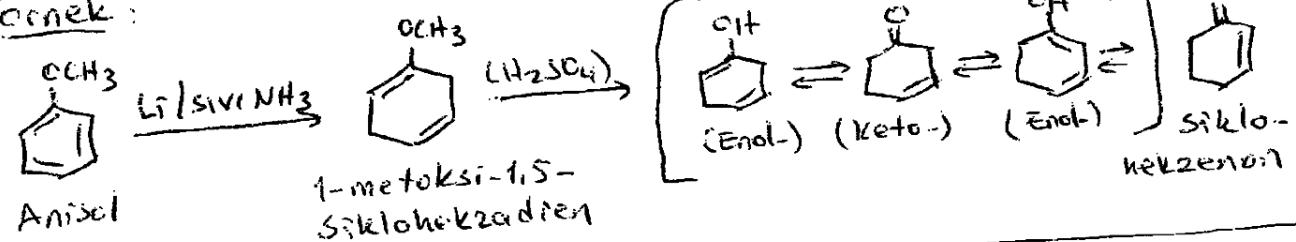


Reaksiyon, radical bir mekanizma üzerinden yürürlü

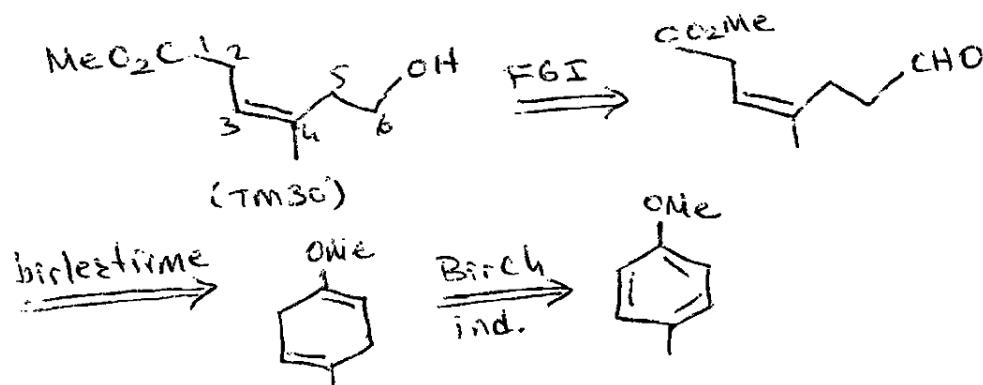
Mekanizması:

$[(Na(NiI_3)_x)^+ e^-]$  Salvatize.

Benzen halkasında, alkil, metoksi gibi elektron salıcı gruplar varsa reaksiyon yavaş olur ve hekzadienin çift bağı "2,5"-durumunda olazur. -COCH<sub>3</sub> gibi elektron çekici gruplar durumunda ise, reaksiyon hızlı olur ve çift bağı "2,4"-yerde meydana gelir.

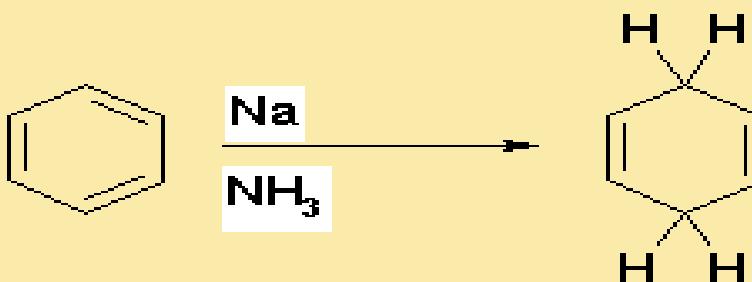
Örnek:

örnek 1 : (TM30) bileşüğünü analiz ediniz.



## Hatırlatma: *Birch indirgenmesi*

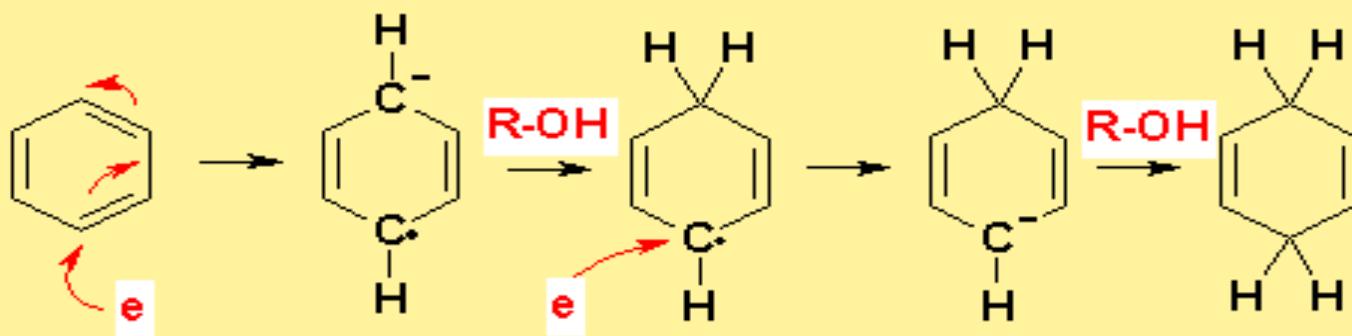
The Birch reduction is the organic reduction of aromatic rings with sodium in liquid ammonia to form 1,4-cyclohexadienes. The reaction was reported by the Australian chemist Arthur John Birch (1915–1995) in 1944.<sup>[1]</sup> <sup>[2]</sup> This reaction provides an alternative to catalytic hydrogenation, which usually reduces the aromatic ring all the way to a cyclohexane (after the initial reduction to a cyclohexadiene, catalytic reduction of the remaining (nonaromatic) double bonds is easier than the first reduction).



Lithium and potassium can substitute for sodium, and alcohol such as ethanol and tert-butanol can be used instead of ammonia.

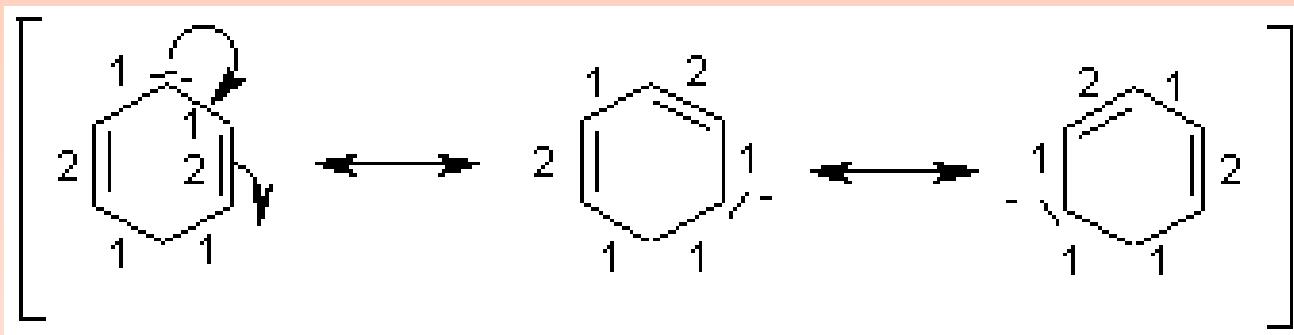
## Reaction mechanism

A solution of sodium in liquid ammonia consists of the electride salt  $[\text{Na}(\text{NH}_3)_x]^+ \text{e}^-$ , associated with the intense blue color of these solutions. The solvated electrons add to the aromatic ring to give a radical anion followed by the dianion. These carbanions deprotonate the ammonia to form the cyclohexadiene.

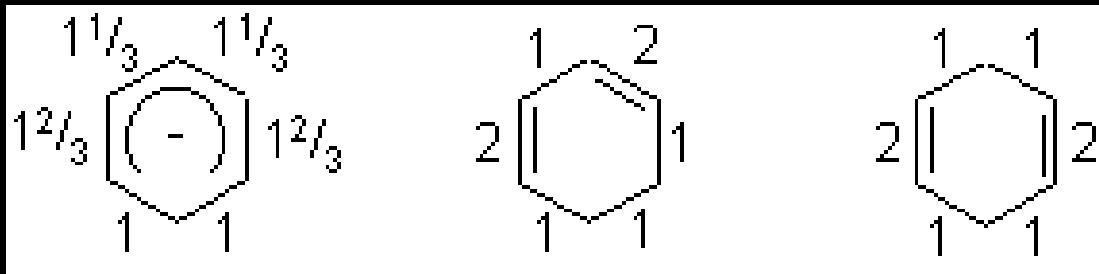


The question of why the 1,3-diene is not formed, even though it would be more stable through conjugation, can be rationalized with a simple mnemonic. When viewed in valence bond terms, electron-electron repulsions in the radical anion will preferentially have the nonbonding electrons separated as much as possible, in a 1,4-relationship.

This question can also be answered by considering the mesomeric structures of the dienyl carbanion

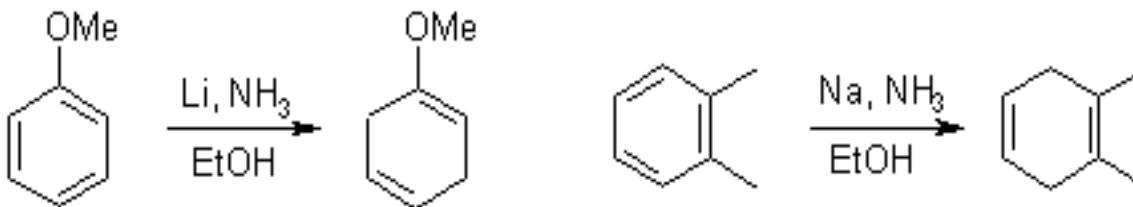


The numbers, which stand for the number of bonds, can be averaged and compared with the 1,3- and the 1,4-diene. The structure on the left is the average of all mesomers depicted above followed by 1,3 and 1,4-diene:

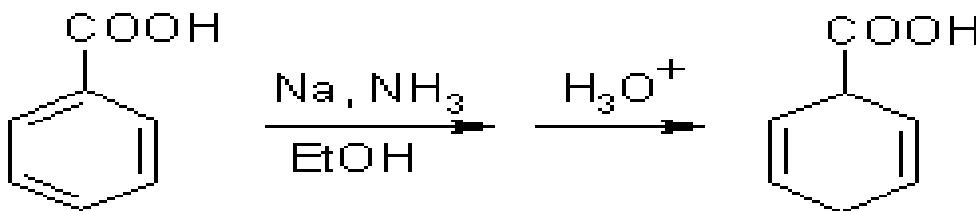


The difference between the dienyl carbanion and 1,3-diene in absolute numbers is 2, and between the dienyl carbanion and 1,4-diene is 4/3. The comparison with the least change in electron distribution will be preferred

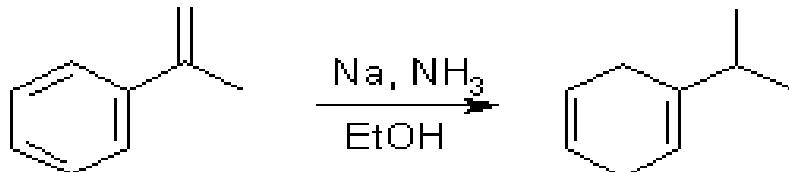
Reactions of arenes with +I- and +M-substituents lead to the products with the most highly substituted double bonds

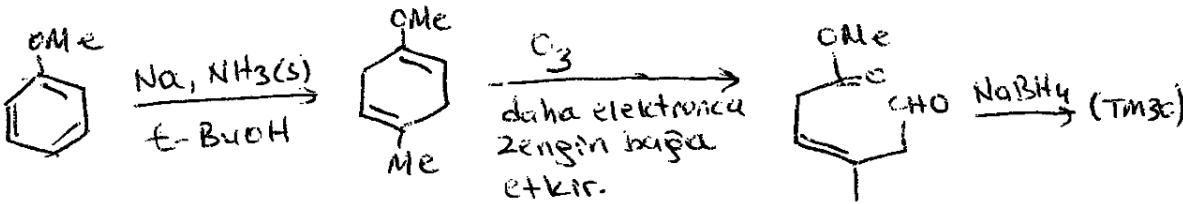
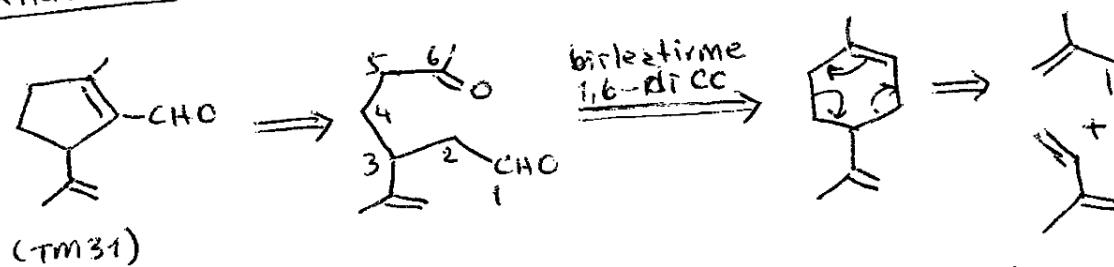
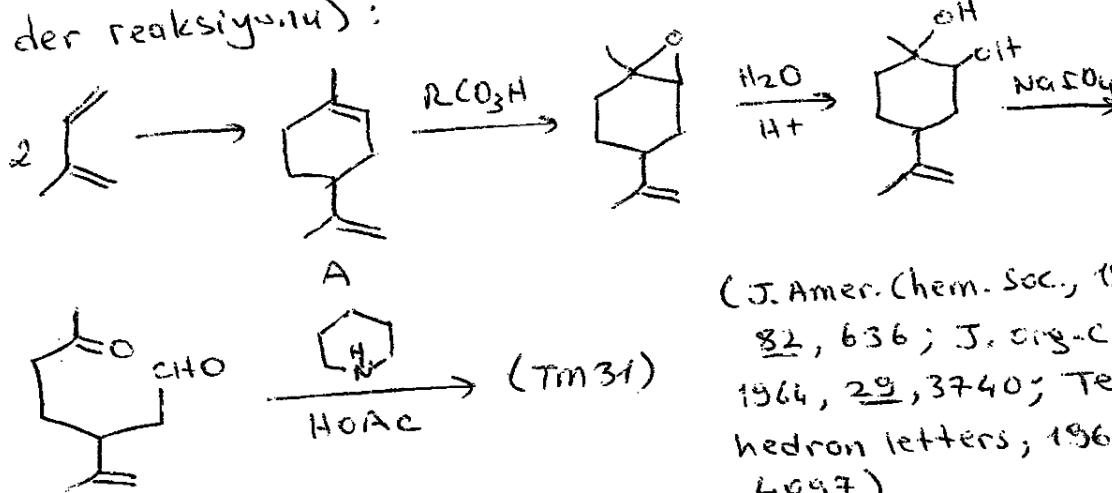


- The effect of electron-withdrawing substituents on the Birch Reduction varies. For example, the reaction of benzoic acid leads to 2,5-cyclohexadienecarboxylic acid, which can be rationalized on the basis of the carboxylic acid stabilizing an adjacent anion:



Alkene double bonds are only reduced if they are conjugated with the arene, and occasionally isolated terminal alkenes will be reduced.



Sentezi:Örnek 2: (TM31) bileşğini nasıl yaparsınız?Analizi: önce,  $\alpha, \beta$ -doymamış aldehit kullanılmalı:Sentezi: izoprenin, doğal olarak bulunan bir terpen olan (A) bileşğini vermek üzere dimerleşir (Diels-Alder reaksiyonu):

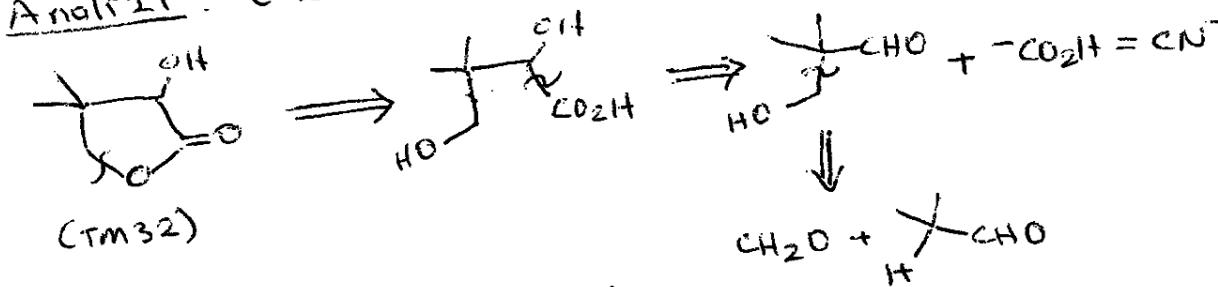
#### 4. LAKTONLARIN SENTEZİ

Şimdiye kadar edindiğimiz basit ikr-grup parçaları bilgi ve becerisyle, çoğu küçük moleküller için analiz ve sentez yöntemleri elde edebiliyoruz. Burada, bir seri problem üzerinde laktonların sentezini planlamaya çalışacağız.

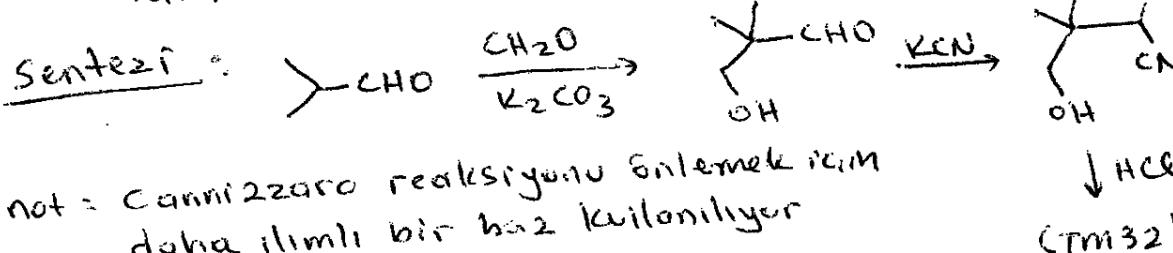
##### Örnekler

1. (TM32) bileşğinin (Khorana'nın Koenzim A sentezinde kullanılan bir aracının) sentez tasarımını yapınız (J. Amer. Chem. Soc., 1961, 83, 663).

Analizi: Önce lakton halkası açılır:

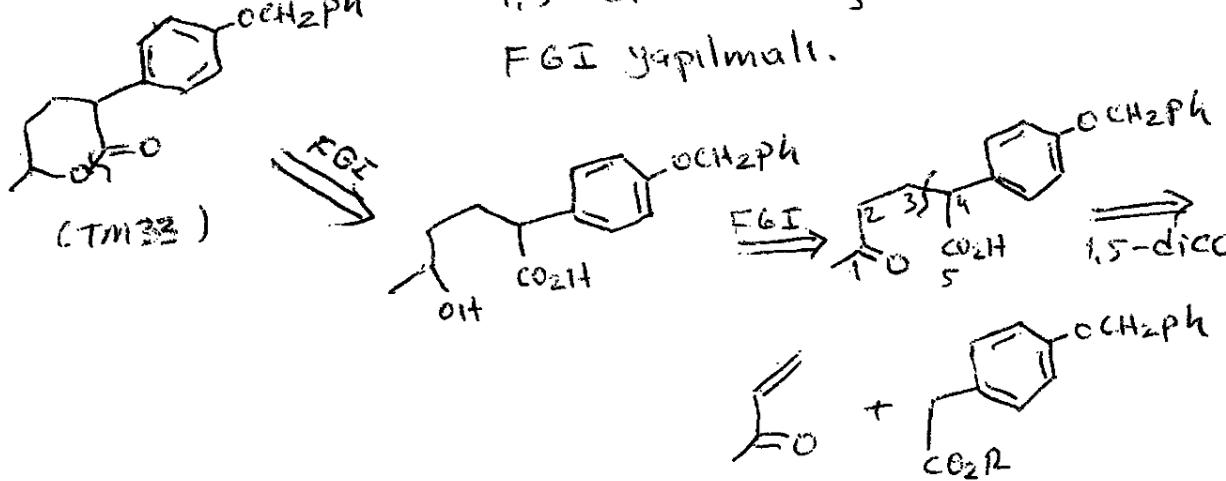


not:  $\text{CN}^-$  enjonusu,  $-\text{CO}_2\text{H}$  synthonu  
için reaktif olarak kullanılmaktadır.

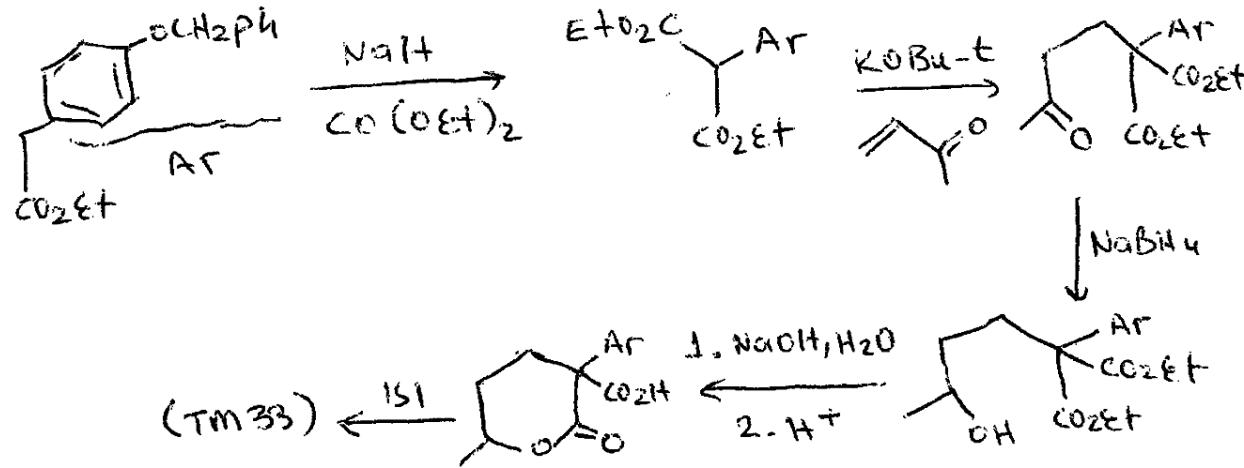


örnek 2: Cedren sentezinde bir ara ürün olan (TM33) bileşliğinin sentez tasarımını yapınız.

Analizi: Bileşikte, 1,5-dio iskeleti var, bundan dolaydı 1,5-dico bileşüğünü elde etmek için FGİ yapılmalıdır.

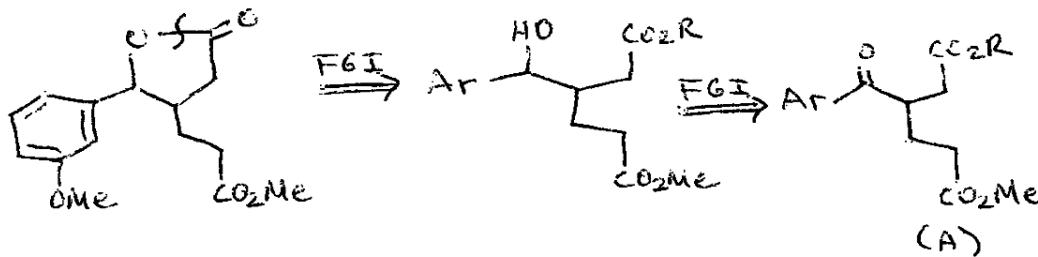


Sentezi: Michael reaksiyonu için aktiflectirici bir grup gereklidir.

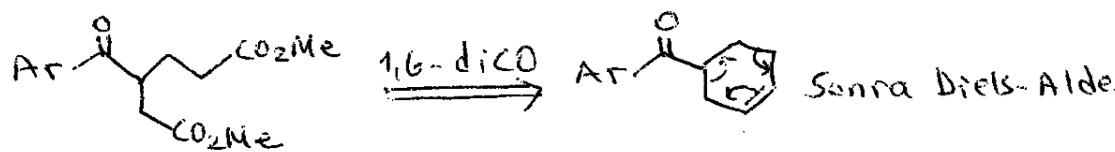


Örnek 3 : (TM34) bileşerinin (Woodward'in tetrasiklin sentezinde bir ara ürün) sentezi tasarımlını yapınız.

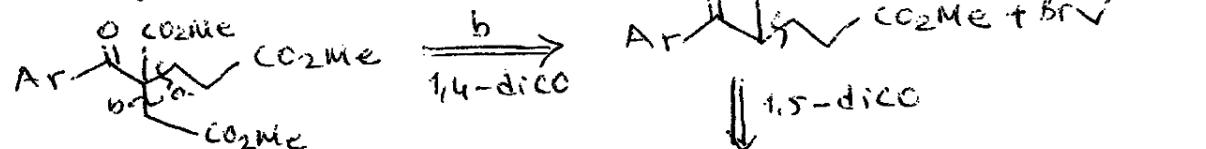
## Analiz:



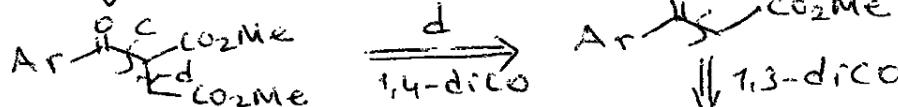
(A) bileşgi anahtar pozisyonundadır, fakat, 1,4-, 1,5- ve 1,6-dikarbonil bağlantılarını içermek. Bundan dolayı, farklı parçalanmalar olacaktır.



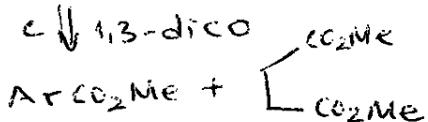
$\downarrow$  aktifleştirmeli  
grup eklenir



a ↓ 1.5-dico



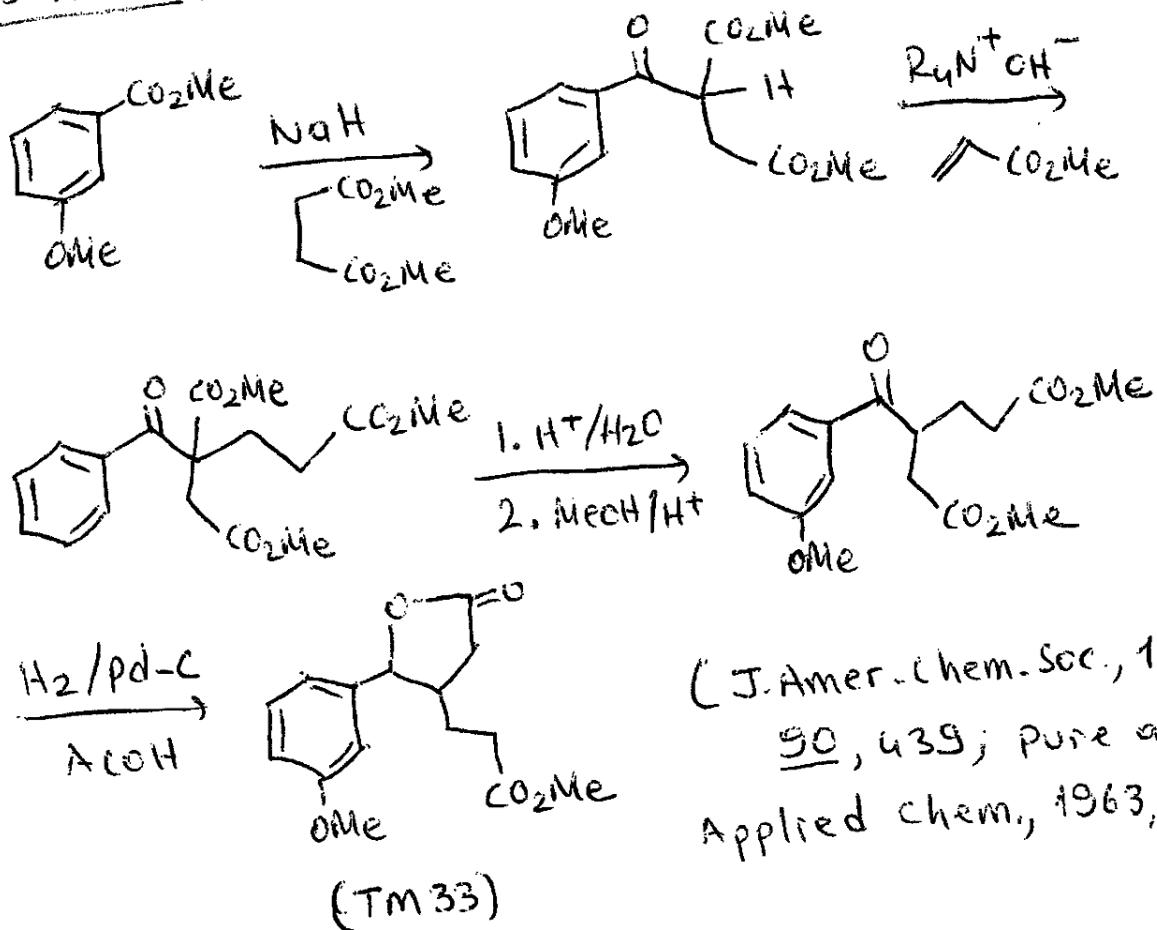
c. 11. 13-dico



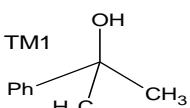
$$\text{ArCO}_2\text{Me} + \text{MeCO}_2\text{Me}$$

Woodward, bütün bu farklı yolların 1,6-dico bap-lantisi disinda, hepsini incelemis ve hepsinin basarili oldugunu gozlemisti. Ancak, sonunda  $\alpha$  ve  $\beta$ 'ye karzi gelen yollari secmisidir.

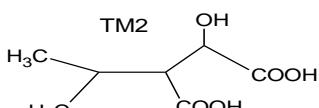
Sentezi:



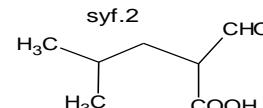
## Ek-1. Bölüm 4'de geçen bileşiklerin adlandırılması



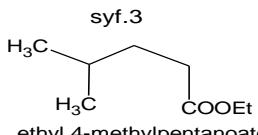
2-phenylpropan-2-ol



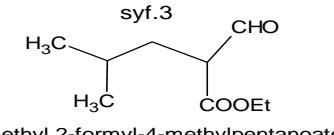
2-hydroxy-3-isopropylsuccinic acid



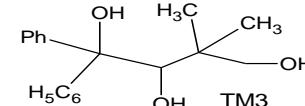
2-formyl-4-methylpentanoic acid



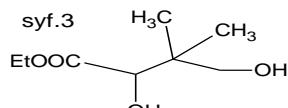
ethyl 4-methylpentanoate



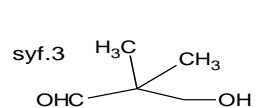
ethyl 2-formyl-4-methylpentanoate



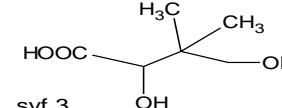
3,3-dimethyl-1,1-diphenylbutane-1,2,4-triol



ethyl 2,4-dihydroxy-3,3-dimethylbutanoate

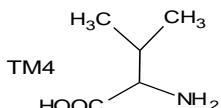


3-hydroxy-2,2-dimethylpropanal

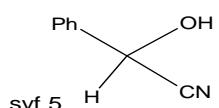


2,4-dihydroxy-3,3-dimethylbutanoic acid

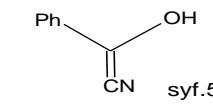
syf.3



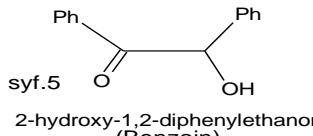
2-amino-3-methylbutanoic acid



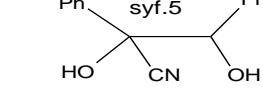
hydroxy(phenyl)acetonitrile



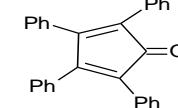
hydroxy(phenyl)acetonitrile



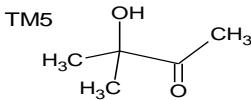
2-hydroxy-1,2-diphenylethanone (Benzoin)



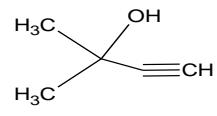
2,3-dihydroxy-2,3-diphenylpropanenitrile



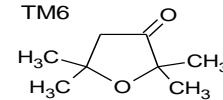
2,3,4,5-tetraphenylcyclopenta-2,4-dien-1-one



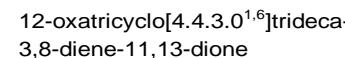
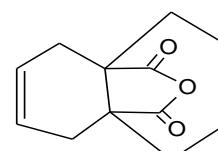
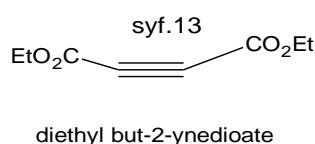
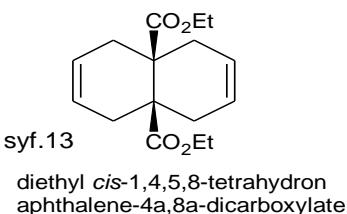
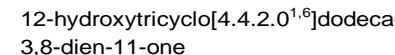
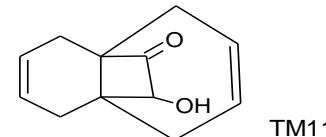
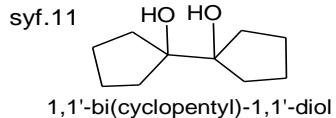
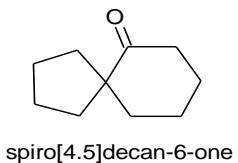
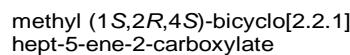
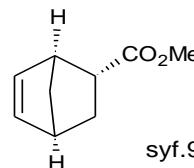
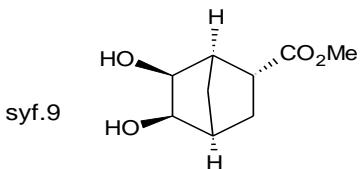
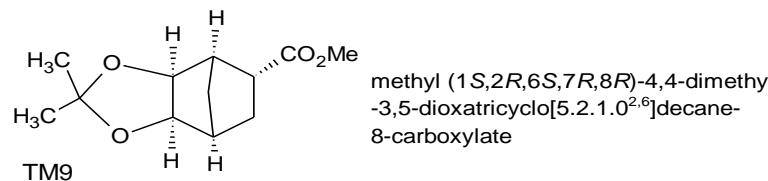
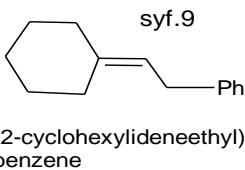
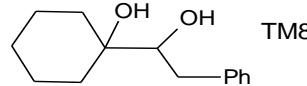
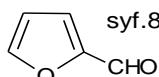
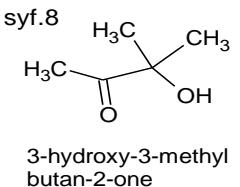
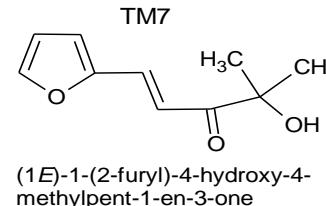
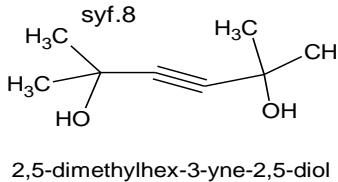
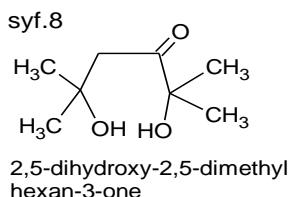
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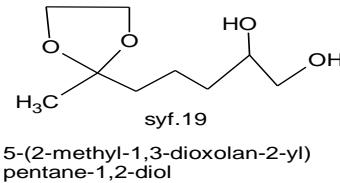
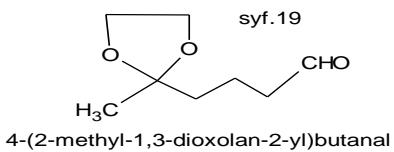
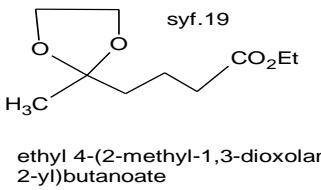
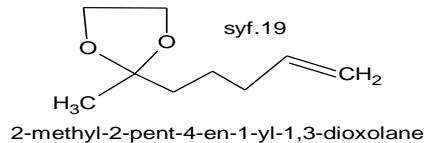
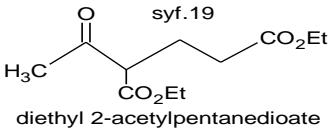
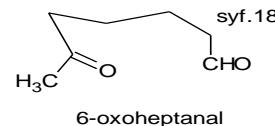
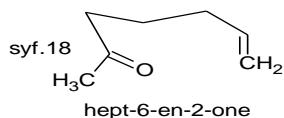
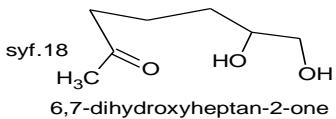
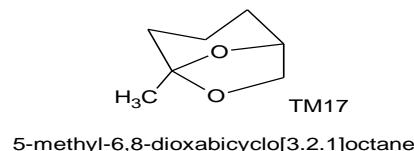
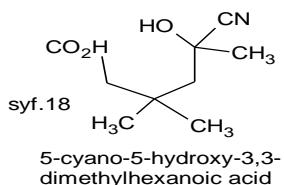
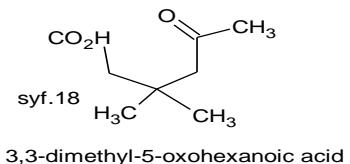
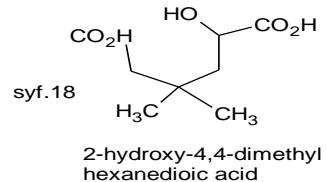
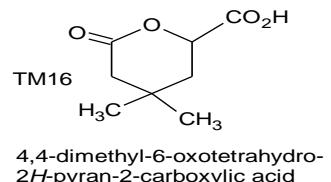
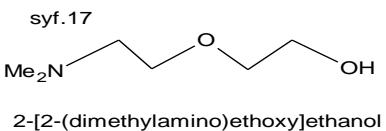
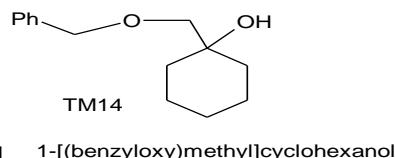
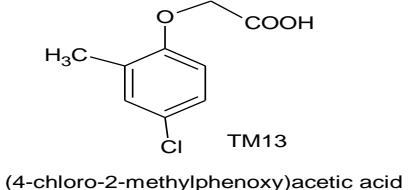
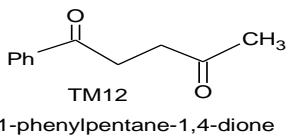


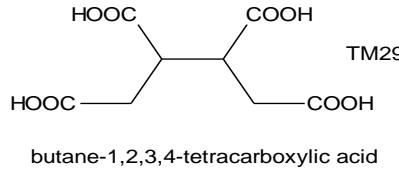
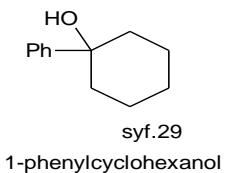
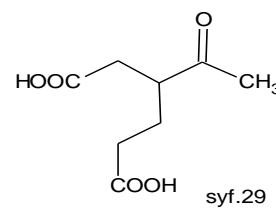
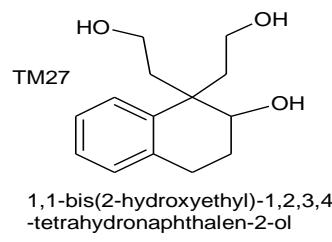
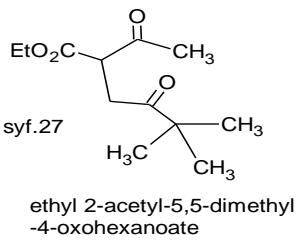
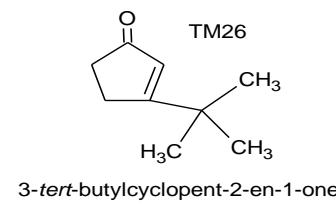
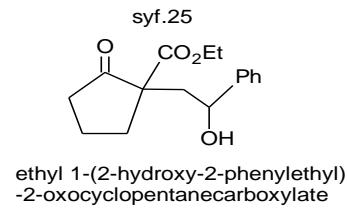
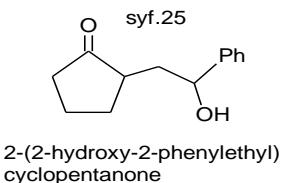
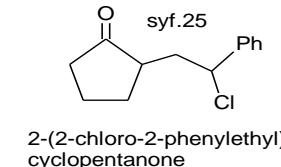
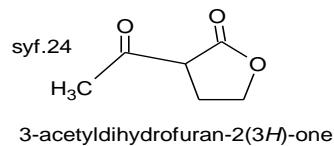
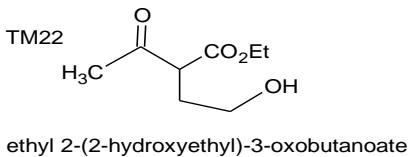
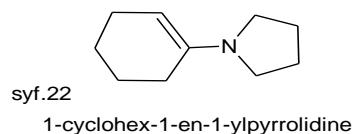
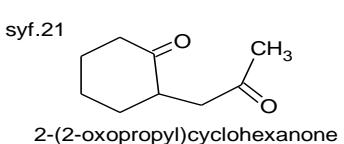
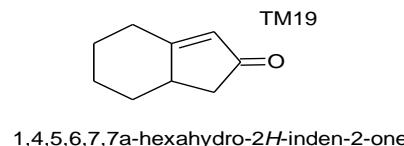
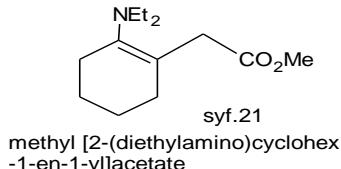
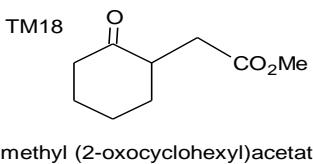
2-methylbut-3-yn-2-ol



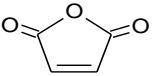
2,2,5,5-tetramethylidihydrofuran-3(2H)-one





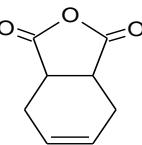


syf.30

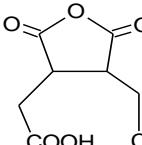


furan-2,5-dione

syf.30

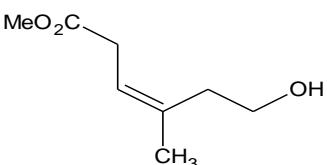


3a,4,7,7a-tetrahydro-2-benzofuran-1,3-dione

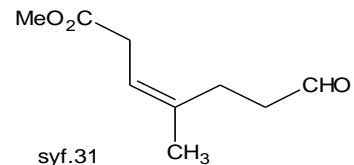


syf.30

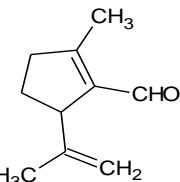
2,2'-(2,5-dioxotetrahydrofuran-3,4-diyl)diacetic acid

MeO<sub>2</sub>C

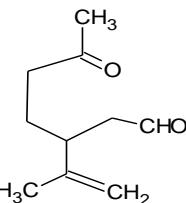
methyl (3Z)-6-hydroxy-4-methylhex-3-enoate

MeO<sub>2</sub>C

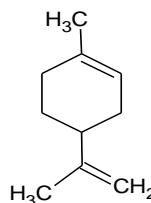
methyl (3Z)-4-methyl-7-oxohept-3-enoate



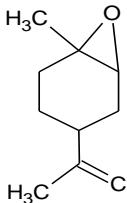
5-isopropenyl-2-methylcyclopent-1-ene-1-carbaldehyde



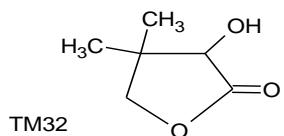
syf.32



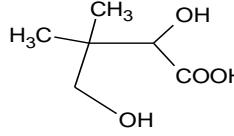
4-isopropenyl-1-methylcyclohexene



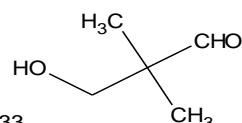
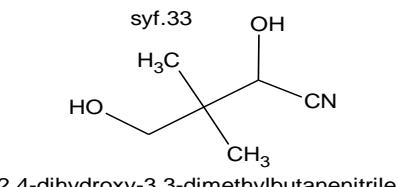
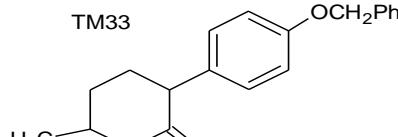
4-isopropenyl-1-methyl-7-oxabicyclo[4.1.0]heptane

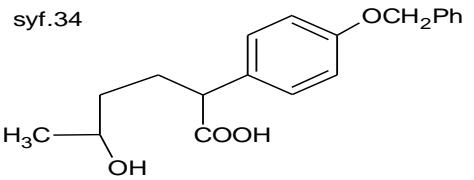
TM32  
3-hydroxy-4,4-dimethylidihydrofuran-2(3H)-one

syf.33

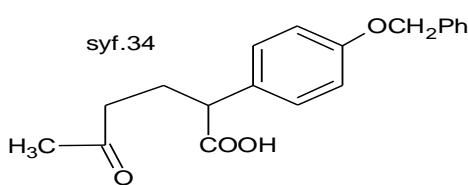


2,4-dihydroxy-3,3-dimethylbutanoic acid

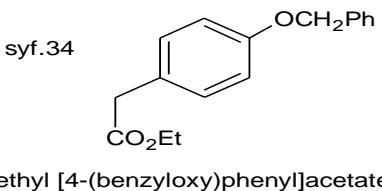
syf.33  
3-hydroxy-2,2-dimethylpropanalsyf.33  
2,4-dihydroxy-3,3-dimethylbutanenitrileTM33  
3-[4-(benzyloxy)phenyl]-6-methyltetrahydro-2H-pyran-2-one



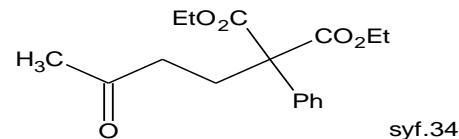
2-[4-(benzyloxy)phenyl]-5-hydroxyhexanoic acid



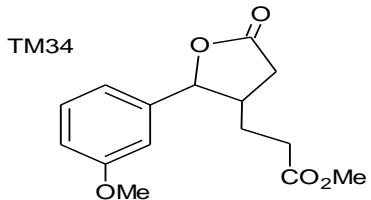
2-[4-(benzyloxy)phenyl]-5-oxohexanoic acid



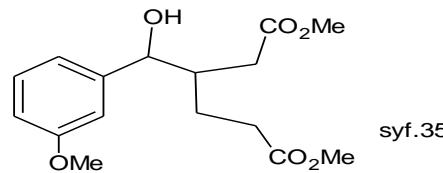
ethyl [4-(benzyloxy)phenyl]acetate



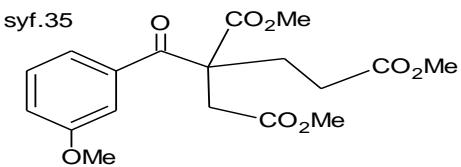
diethyl (3-oxobutyl)(phenyl)malonate



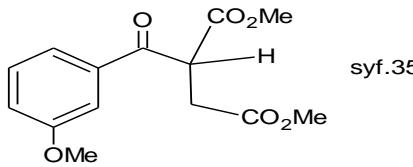
methyl 3-[2-(3-methoxyphenyl)-5-oxotetrahydrofuran-3-yl]propanoate



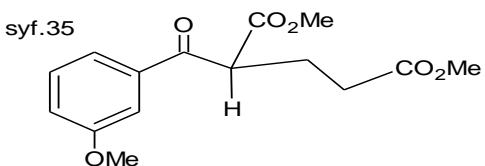
dimethyl 3-[hydroxy(3-methoxyphenyl)methyl]hexanedioate



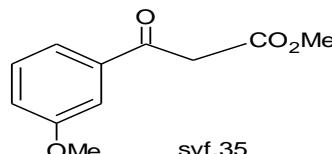
trimethyl 2-(3-methoxybenzoyl)butane-1,2,4-tricarboxylate



dimethyl 2-(3-methoxybenzoyl)succinate



dimethyl 2-(3-methoxybenzoyl)pentanedioate



methyl 3-(3-methoxyphenyl)-3-oxopropanoate