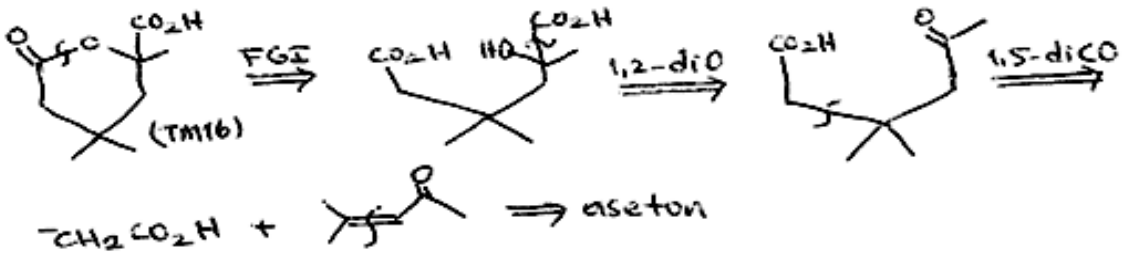
MANTIKSIZ İKİ GRUP PARÇALANMALARI

BÖLÜM 4

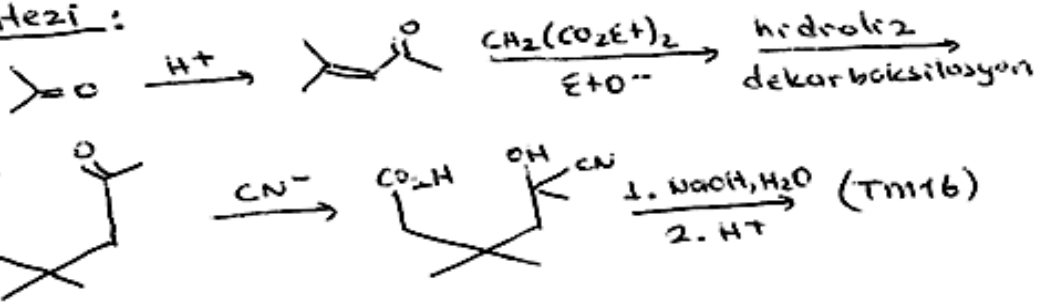
(d) Problemler

1. Aşağıdaki Lakton asidi (TM16) için bir sentez yöntemi

Analizi: laktonun açılmasıyla, 1,2-, 1,5- ve 1,6-dioksi fonksiyonlu bağlantıları ortaya çıkar.

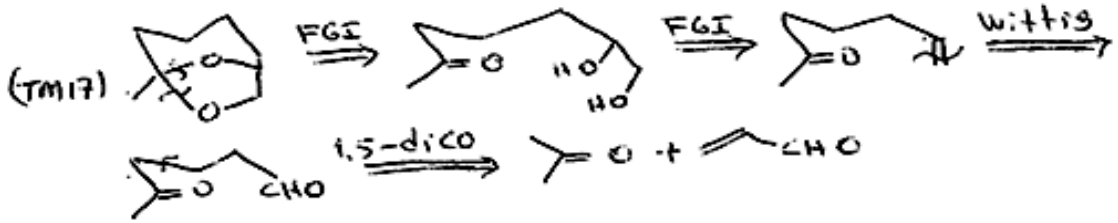


Sentezi:

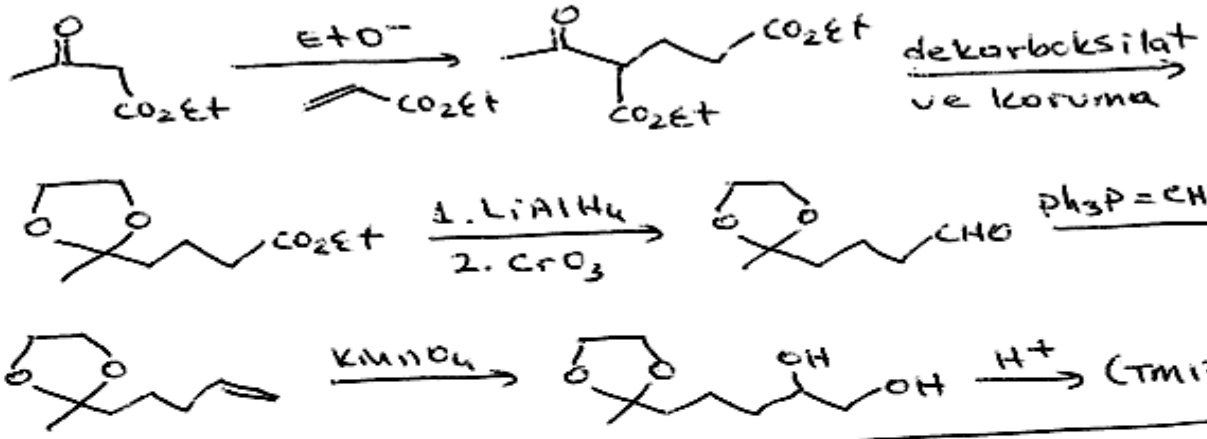


2. (TM17) bileşiğinin analiz ve sentezini yapınız.

Analizi: öncelikle, asetal (oksisiyonlu grubu uzaklaştırılır.



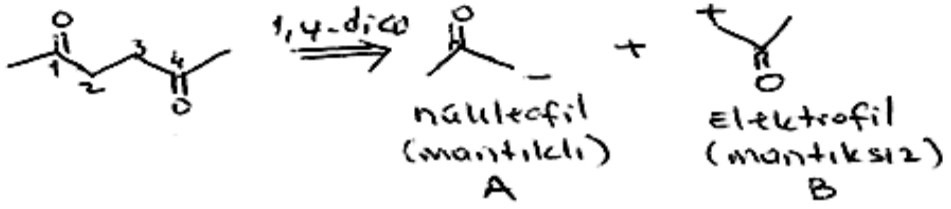
Sentezi: wittig reaksiyonunu aldehit üzerinde yapmalıyız, keton ile etkileşmemesi için keton grubunu korumalıyız. Bundan dolayı, aldehite bir ester grubu bağlamalıyız.



2. 1,4-DİOKSİJENLEME MODELİ

(a) 1,4-Dikarbonil Bileşikleri

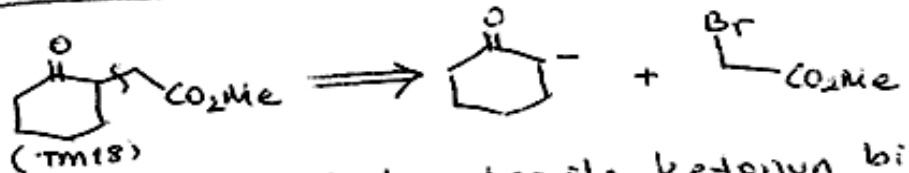
1,4-dikarbonil bileşiklerinin parçalanması sonucunda, mantıklı nükleofilik synthon (bir enolat anyonu) oluşurken, mantıksız elektrofilik synthon da ortaya çıkar.



B için, polaritesi giderilmiş bir keton türevine ihtiyaç duyulur, bunun için en ideali α-halo karbonil bileşiğidir.

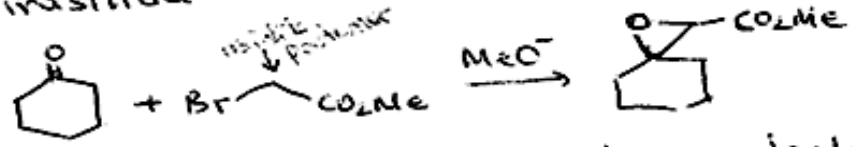
Örnek 1 : LTM18) bileşiğinin analiz ve sentezi için öneride bulununuz.

Analiz :

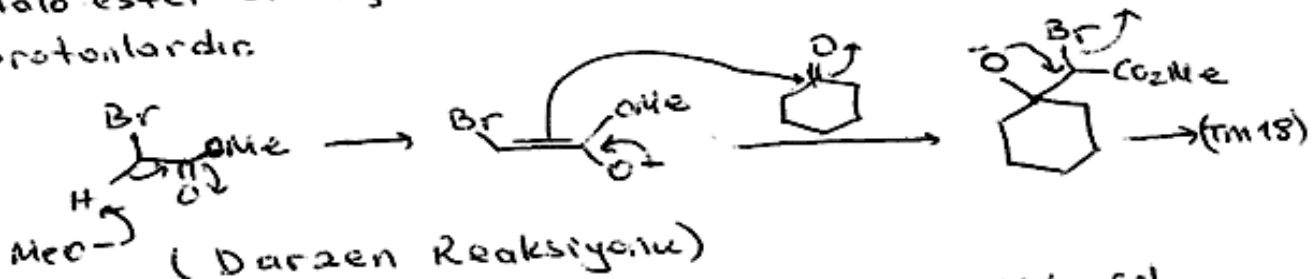


(TM18)

Sentezi : α-halo ester ile ketonun birleştirilmesi sırasında oldukça farklı reaksiyonlar olur:



Halo ester bileşiğinin metilen protonları en asidik protonlardır.

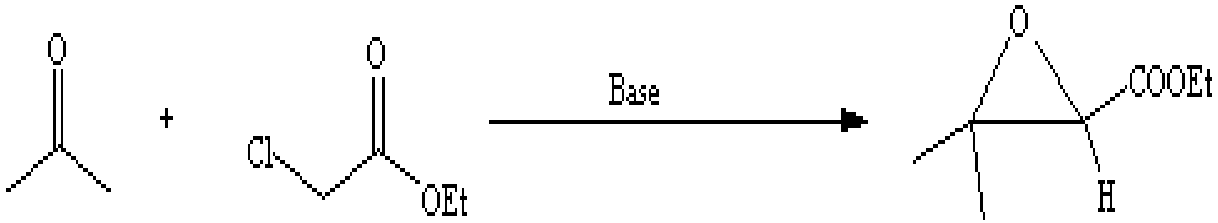


(Darzen Reaksiyonu)

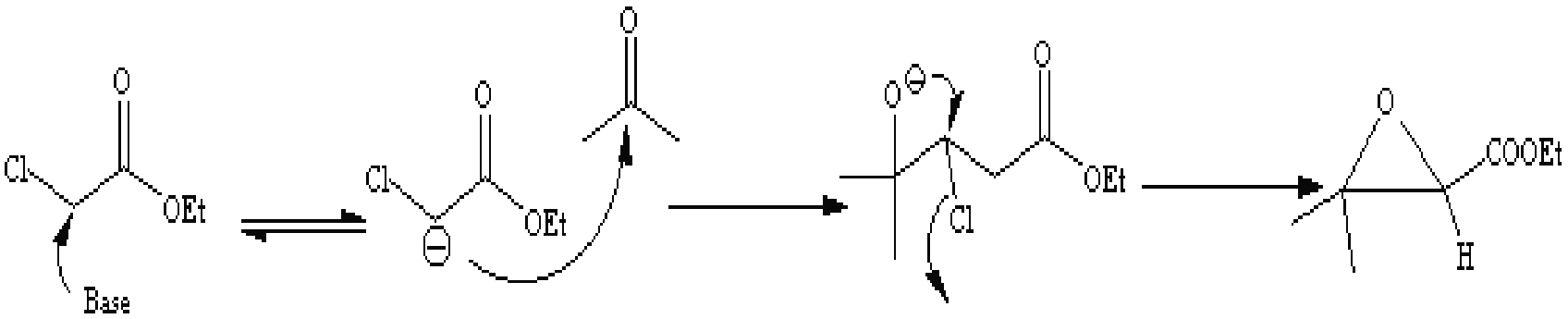
Burada, 1'lik kondenzasyonda ketonu nükleofil olarak kullanmak gerekir. Bunu yapmak için en iyi yol,

Darzen kondenzasyonu (reaksiyonu)

Aldehit veya ketonların alfa-haloasit esterleriyle kondensasyonu ile a,ß-epoksi esterlerinin oluşumu

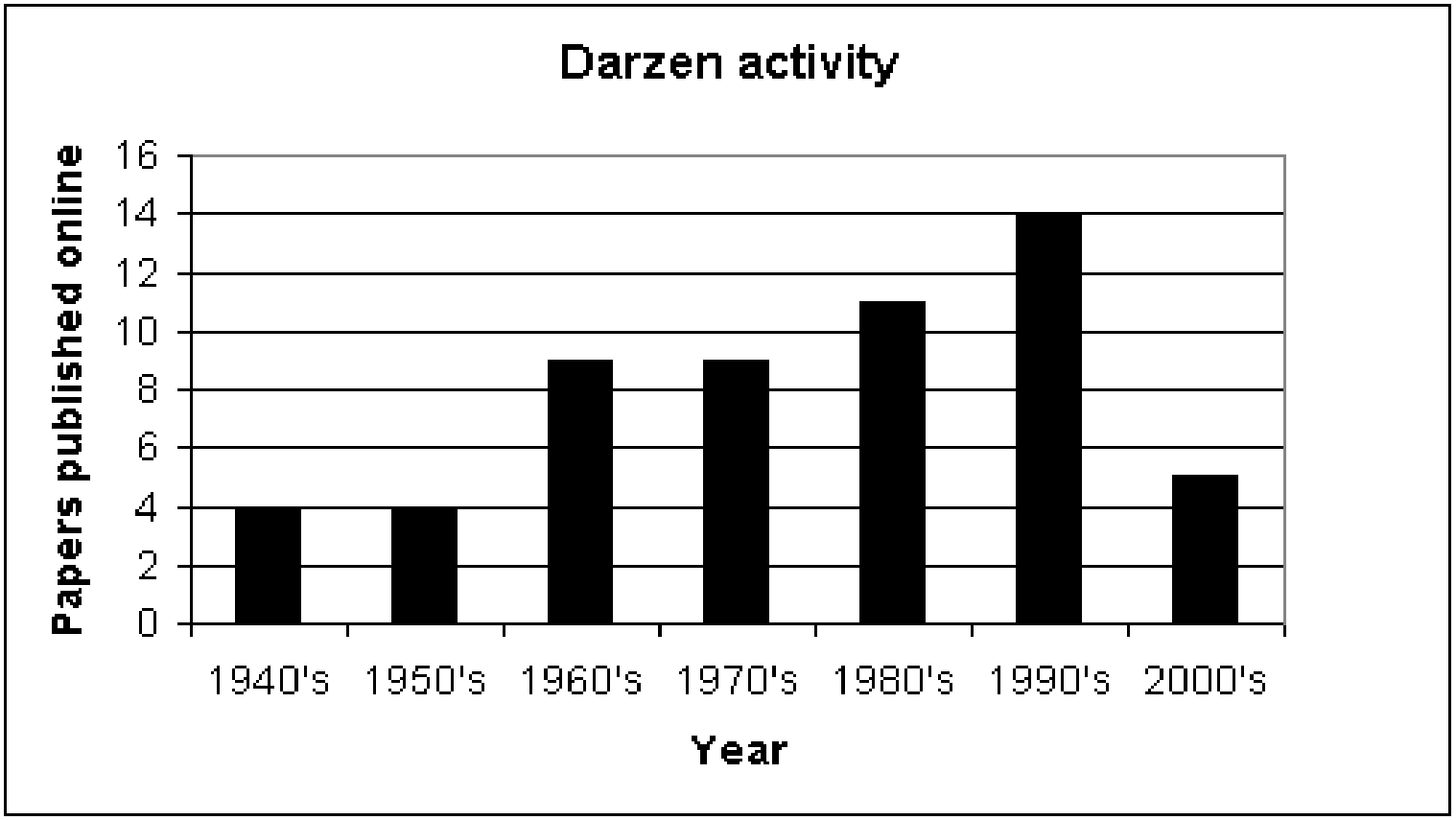


Mekanizma



Görünüm sıklığı:

Bu çubuk grafik, makalenin başlığında bu belirli isim reaksiyonunu içeren tüm çevrimiçi makaleleri göstermektedir. Yer aldığı dergilere, Tetrahedron letters, Tetrahedron, Synthetic letters, Synthesis, Journal of Organic Chemistry and Journal of the American Chemical Society gibi dergiler örnek verilebilir.



Kapsam ve Sınırlamalar:

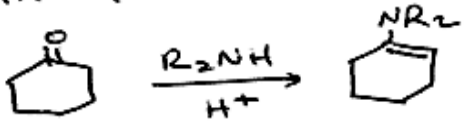
Aromatik aldehitler ve ketonlarla verim yüksektir.

Alifatik aldehitler, yüksek verimler elde etmek için alfa halo esterinden proton ayrılması gerekmektedir, bunun için LDA veya $LiN(SiMe_3)_2$'nin yardımına ihtiyaç duyar.

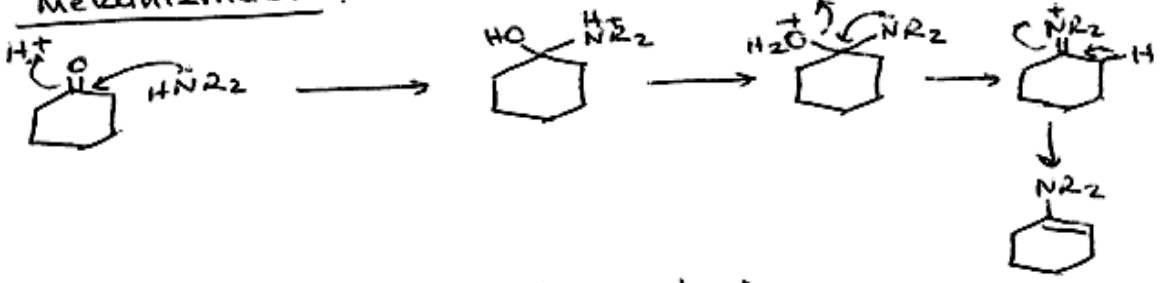
Alfa-halo ketonlar, nitriller, sülfonlar ve N,N-amitler de Darzen kondenzasyonunda kullanılmaktadır

Sodyum etoksit, genellikle baz olarak kullanılır. Reaksiyon ayrıca bir asit tarafından da katalizlenebilir.

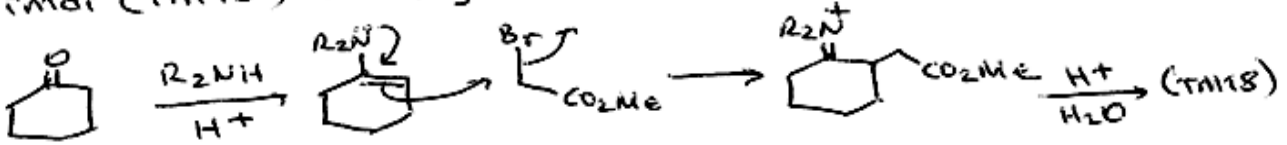
enamine çevirmektir.



Mekanizması :



Şimdi (TM18) bileşiğinin sentezi

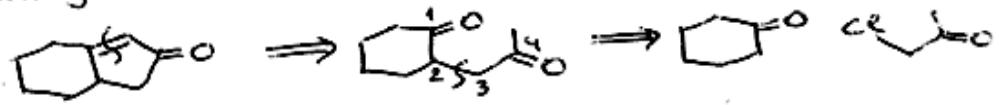


şeklinde tamamlanır.

Enamin, reaktif α-karbonil haleojenürüne karbonil grubunun kendisinden daha çok atak yapar.

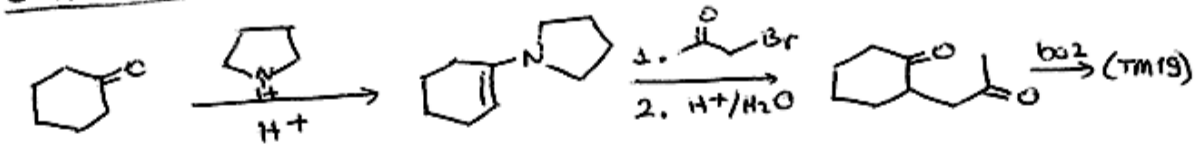
Örnek 2 : (TM19) bileşiğini nasıl sentezlersiniz?

Analizi : α,β-doymamış keton parçalanarak başlanır ve yeni yöntemde kullanacağımız 1,4-diketona sahip oluruz.



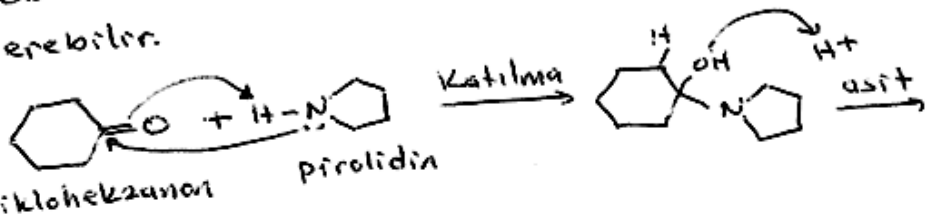
(TM19)

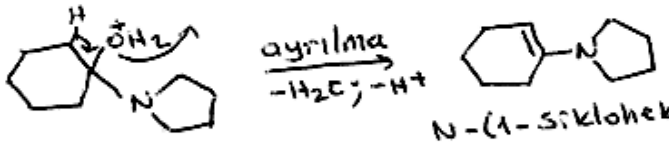
Sentezi :



Enamin mekanizması

Sekonder aminler karbonil bileşikleriyle kondenzasyon verebilir.

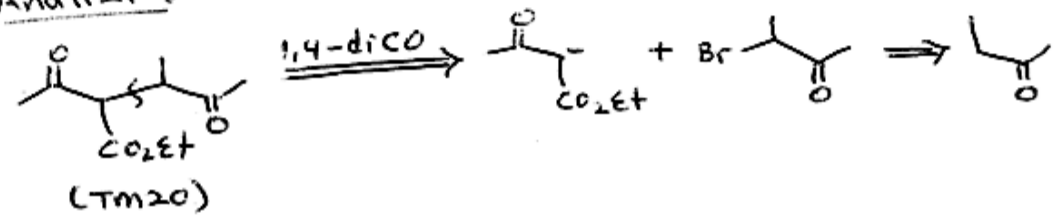




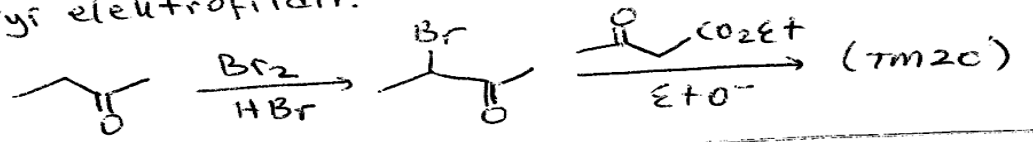
- Enaminler her zaman gerekli değildir, bazen enolat anyonunun bizzat kendisi yeterince kararlıdır.

Örnek 1 : (TM20) bileşiğini nasıl yaparsınız?

Analizi :

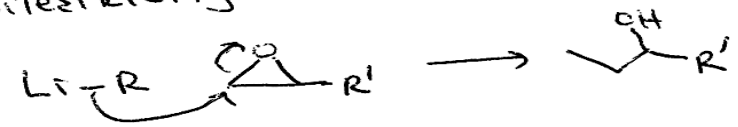


Sentezi: Bütanonun bromlanması (asit içinde) istediğimiz izomeri verir. oluşan α-karbonil haleşenür iyi elektrofildir.



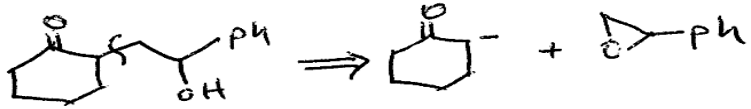
(b) γ-Hidroksi Karbonil Bileşikleri

α-halo karbonil bileşikleri, $\overset{+}{C}-\overset{O}{\overset{\|}{C}}$ synthonu için reaktif olarak kullanılmaktadır. Daha düşük yükseltgenme basamağında $\overset{+}{C}-\overset{OH}{C}$ synthonu için reaktif olarak epoksitler kullanılır (Grignard ve organolityum bileşikleriyle reaksiyonlarında olduğu gibi).

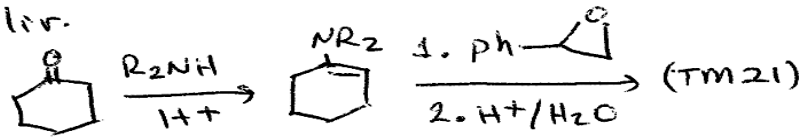


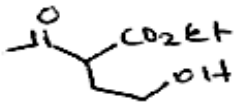
Örnek 1: (TM21) aşağıda gösterilen γ-hidroksi keton bileşiğini analiz ederek bir sentez öneriniz.

Analiz:

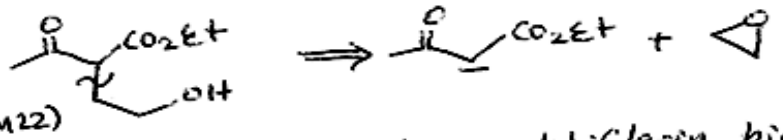
(TM21) 

Sentezi: Enolat synthonu sağlamak için enamin kullanılabilir.



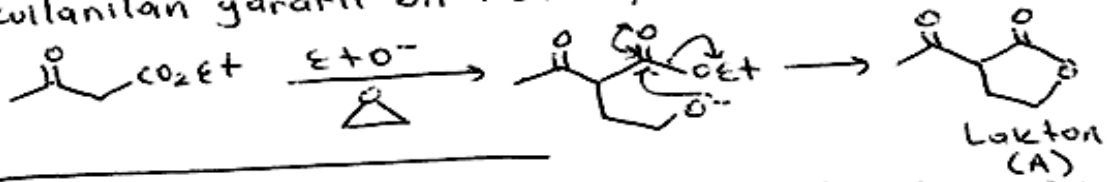
Örnek 2:  (TM22) bileşiğini yapınız.

Analiz:



(TM22)

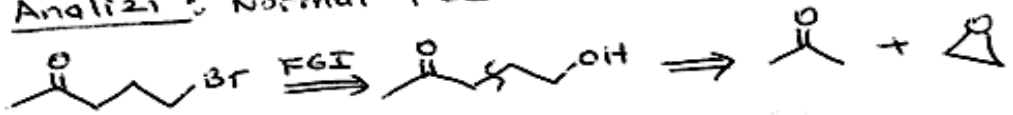
Sentezi: Aslında reaktiflerin birleştirilmesi (TM22)'yi vermez. Bunun yerine Lakton (A) oluşur. Bu lakton, planladığımız (TM22) bileşiğinin bütün reaksiyonlarında kullanılan yararlı bir reaktiftir.



Lakton (A)

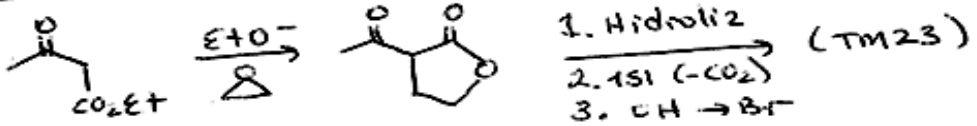
Örnek 3: Aşağıda görülen γ-haloketon (TM23)'ü nasıl yaparsınız?

Analizi: Normal FGI alkol verir.



(TM23)

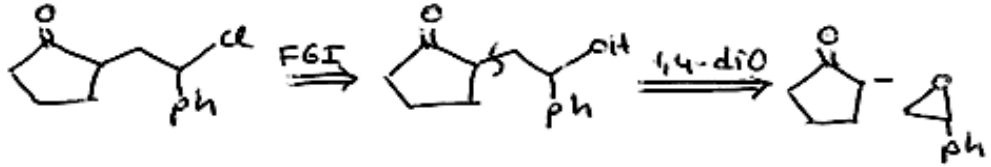
Sentezi: Aktifleştirici grup olarak CO_2Et kullanılır.



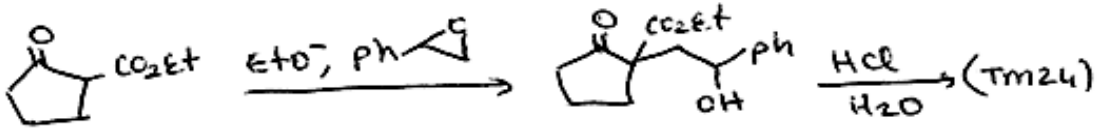
(TM23)

Örnek 4: Aşağıdaki γ-halo ketonu (TM24) nasıl elde edersiniz?

Analiz:



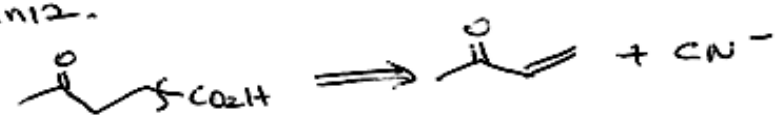
Sentezi: Başlangıç maddesinde aktifleştirici bir grup olmalıdır.



(c) Diğer Mantıksız Synthonlar

1,4-dioksijenlenmiş bileşikleri elde etmek için hem mantıklı hem de mantıksız synthonlar kullanılmıştır.

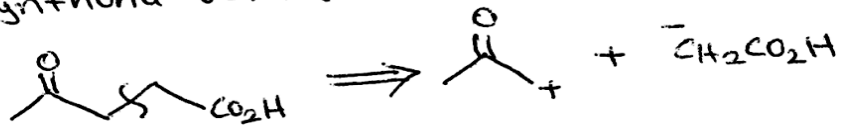
Örnek 1: Aşağıdaki gibi bir γ-keto asidi elde etmek için CN^- iyonunu ($^-CO_2H$ synthonu olarak) nasıl kullanırsınız.



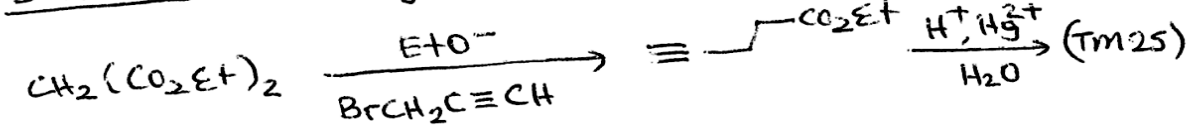
(TM25)

Örnek 2: Aynı asidi, propargil bromür ($BrCH_2C{\equiv}CH$) (mantıksız bölüm) kullanarak nasıl yaparsınız?

Analizi: Asetilenler, keton vermek üzere hidratize edilebilmektedir böylece propargil bromür, $MeCOCH_2^+$ Synthonu verir:



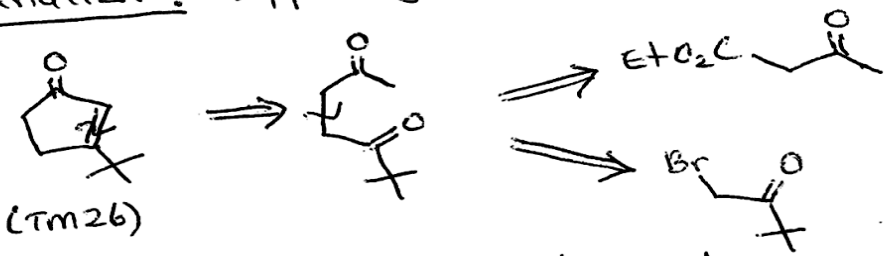
Sentezi: Aktivasyon gerekecektir:



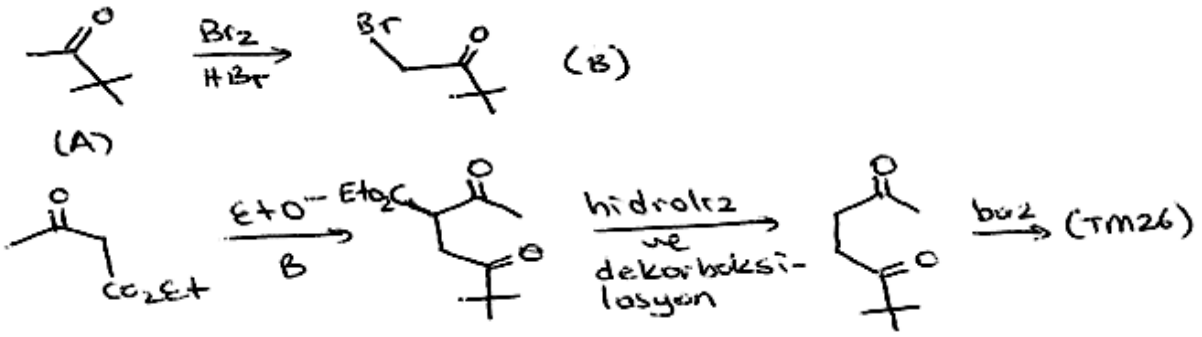
(d) Problemler ve çözümleri

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

Analizi: α,β-doymamış karbonilden başlamalıyız:

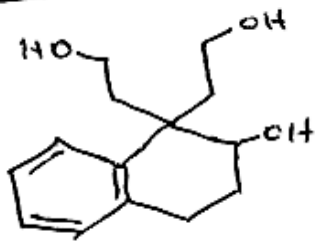


Sentezi: (A) ketone pinokolon olduğu için, pinokolon çevrilmesiyle elde edilebilir:

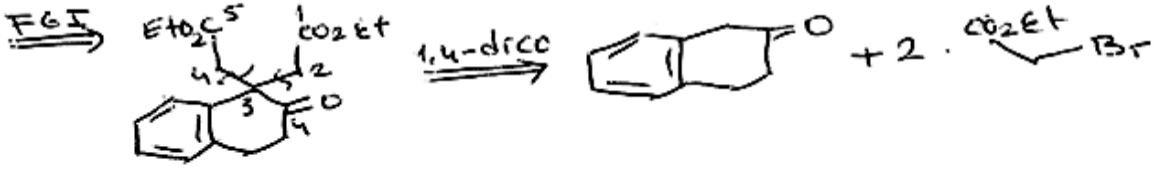


2. Aşağıdaki triol (TM27) 1,4-veya 1,5-dioksijenlenmiş bileşik olarak alınabilir. Aslında bunlardan biriyle uygundur. Sentezi için bir öneride bulunuyoruz.

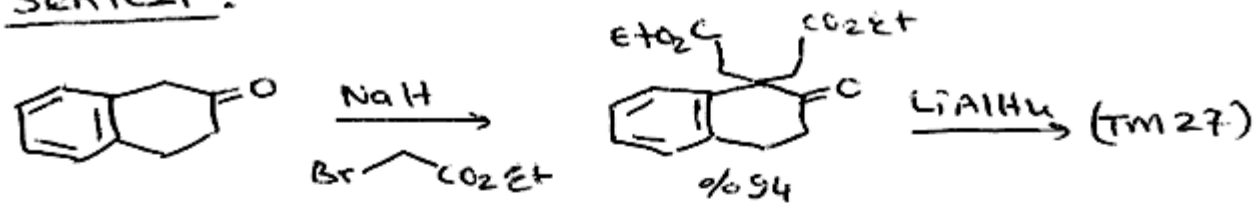
Analizi:



Bu üç OH- grubuna karşı gelen trikarbonil bileşiğini düşünmeliyiz. CH_2OH için; CHO veya CO_2Et yazmalıyız (FGI yapılır). 1,5- parçalanmasıyla, oluşan öncüler üzerindeki çift bağlar oda sıcaklığında kararsız olacağı için, 1,5-dikarbonil parçalanması kullanılmaz.



Sentezi:



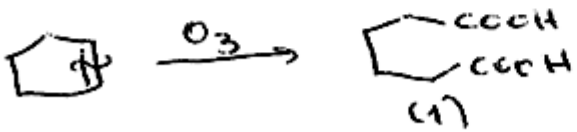
Giriş maddesi olan keton, sübstitüe naftalinin indirgenmesi ile (J. Amer. Chem. Soc., 1950, 72, 3704) yapılabilir.

---

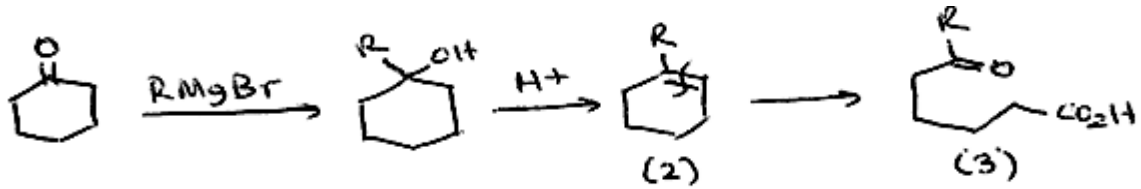
3. 1,6-DİKARBONİL BİLEŞİKLERİ

İki karbonil grubu olan bileşiklerin sentezinde bir takım problemler olacaktır. Burada, yeniden birleştirme (reconnection) 1,6-difonksiyonlu bileşiklerin sentezinde uygulanan genel bir strajedidir.

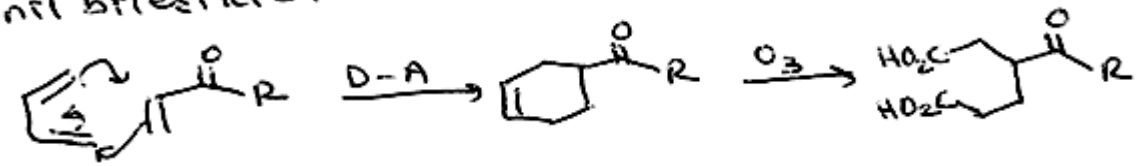
Adipik asit (1) siklohekzenden kolayca elde edilebilir:



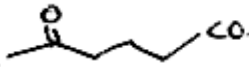
1-yerinde sübstitüent olan siklohekzenler (2), siklohekzanondan ve Grignard reaktiflerinden yapılabilir. parçalanması keto asitleri (3) verir.



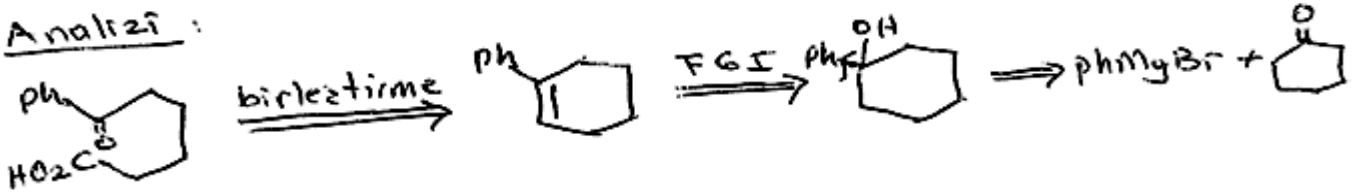
Sikloheksenleri hazırlamak için en önemli yol, Diels-Alder reaksiyonu ve elde edilen ürünün parçalanması ile oluşan 1,4- ve 1,5-dikarbonil bileşiklerinin 1,6-dikarbonil bileşiklerinin sentezinde kullanılmasıdır.



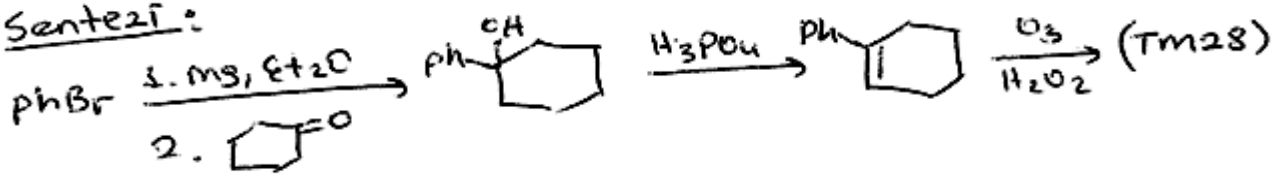
Örnekler

1.  (TM28) sentezini analiz ediniz.

Analizi:

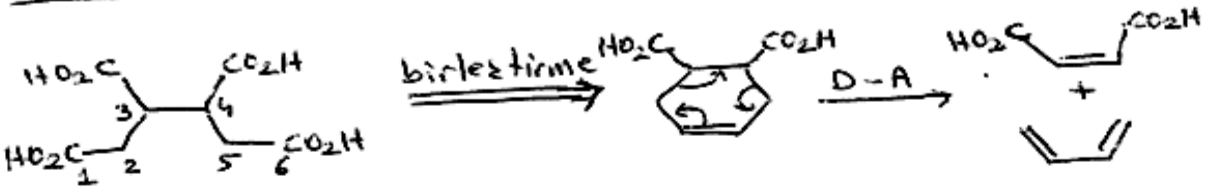


Sentezi:

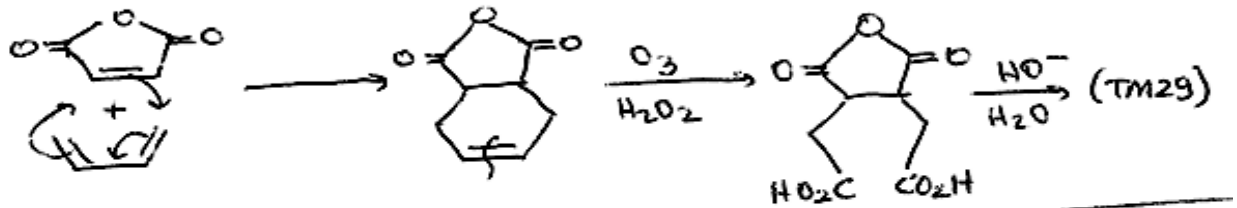


2. (TM29) bileşiğini analiz ederek sentezini yapınız.

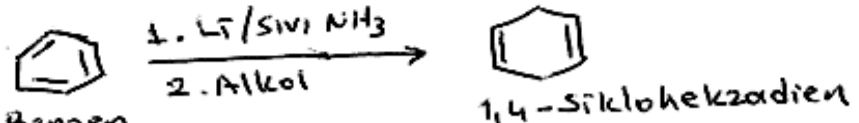
Analiz: Öncelikle, 1,6-dikarbonil bağlantısını seçiniz:

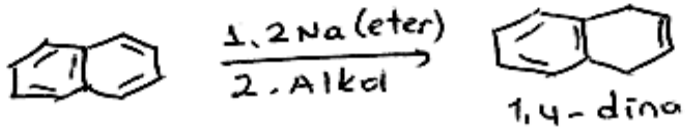


Sentezi: Maleik anhidrit en iyi reaktiftir



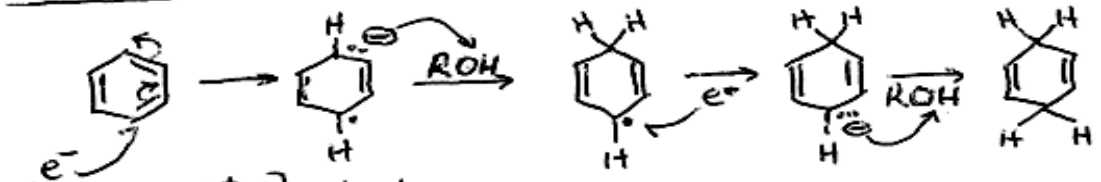
- Siklohekzenleri elde etmek için diğer bir yöntem; benzen halkasının kısmi indirgenmesini içeren "Birch indirgemesidir"





Reaksiyon, radikal bir mekanizma üzerinden yürür:

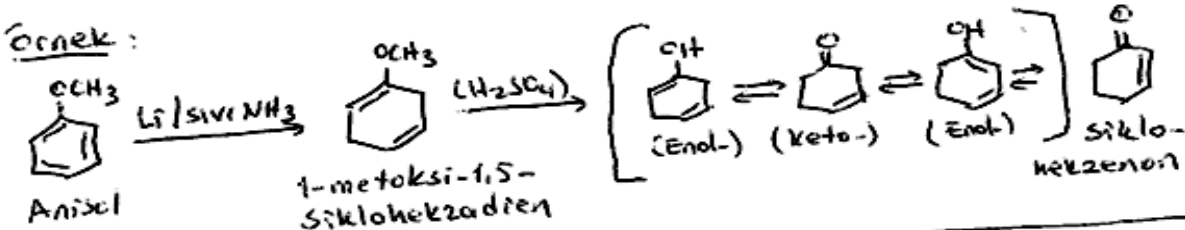
Mekanizması :



$[(Na(NH_3)_x)^+ e^-]$ solvatize.

Benzen halkasında, alkil, metoksi gibi elektron salıcı gruplar varsa reaksiyon yavaş olur ve hekzadienin çift bağları "2,5"- durumunda oluşur. -COCH gibi elektron çekici gruplar durumunda ise, reaksiyon hızlı olur ve çift bağlar "2,4-" yerinde meydana gelir.

Örnek :

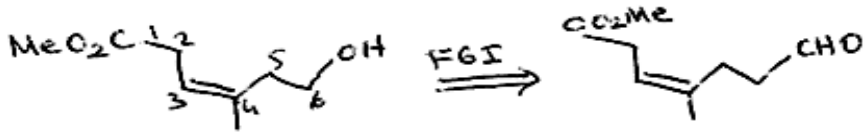


Anisol

1-metoksi-1,5-Siklohekzadien

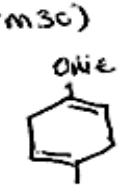
Siklo-hekzenon

Örnek 1 : (TM30) bileşiğini analiz ediniz.

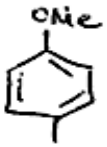


(TM30)

birleştirme

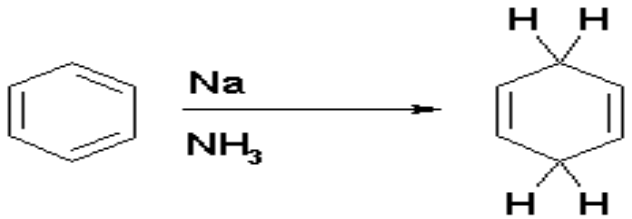


Birch ind.



Hatırlatma: *Birch indirgenmesi*

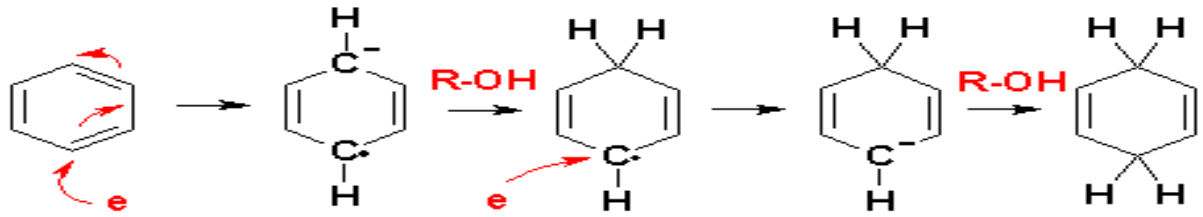
Birch indirgemesi, 1,4-siklohekzadienleri oluşturmak için sıvı amonyakta sodyum ile aromatik halkanın indirgenmesidir. Reaksiyon, Avustralyalı kimyager Arthur John Birch (1915–1995) tarafından 1944'te gerçekleştirilmiştir. Bu reaksiyon, genellikle bir aromatik halkayı siklohekzana kadar indirgeyen katalitik hidrojenlemeye alternatif bir yöntemdir.



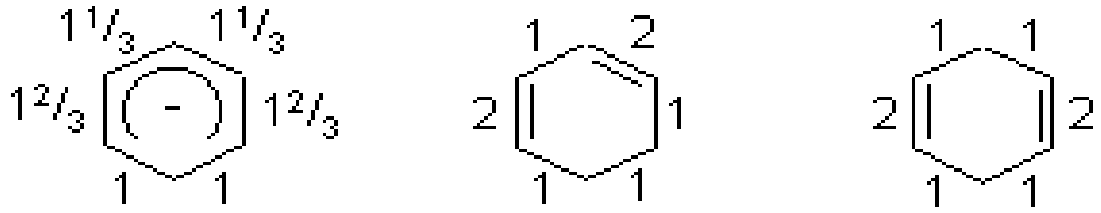
Sodyum yerine lityum ve potasyum, amonyak yerine ise etanol ve t-bütanol gibi alkoller kullanılabilir.

Reaksiyon Mekanizması

Sıvı amonyakta sodyum çözeltisi, bu çözeltilerin yoğun mavi rengiyle ilişkili olan elektrolit tuzu $[Na(NH_3)_x]^+$ e^-'den oluşur. Çözünen elektronların aromatik halkaya atağı sonucunda, radikal bir anyon ve ardından dianyon oluşur. Bu karbanyonlar alkolden proton alarak siklohekzadieni oluşturur.

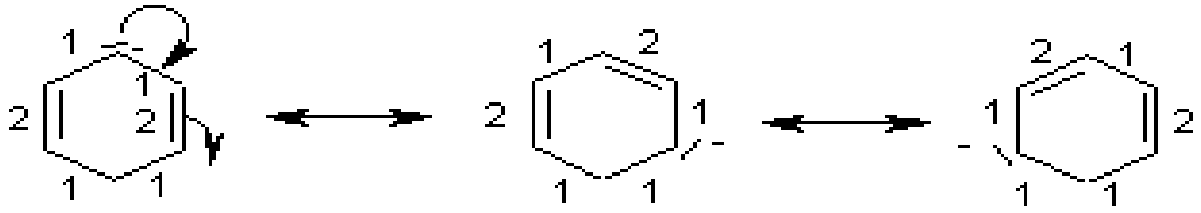


1,3-dienin niçin oluşmadığı sorusu, konjugasyon yoluyla daha kararlı olmasına rağmen, radikal anyondaki elektron-elektron itmeleri, tercihen, 1,4-ilişkisinde, bağlanmayan elektronların mümkün olduğunca ayrılmasını sağlayacaktır. Bu soru, dienil karbanyonunun, mezomerik yapıları dikkate alınarak da yanıtlanabilir.

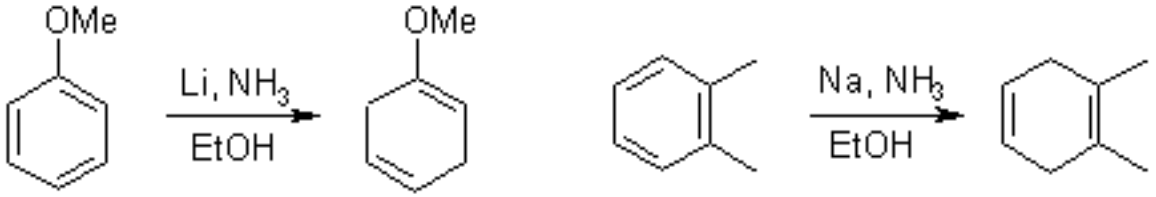


Bağ sayısını temsil eden sayılar, ortalama alınabilir ve 1,3- ve 1,4-diene ile karşılaştırılabilir. Soldaki yapı, yukarıda gösterilen tüm mezomerlerin ortalamasıdır ve ardından 1,3 ve 1,4-dien gelir:

Dienil karbanyon ile 1,3-dien arasındaki mutlak sayılardaki fark 2'dir ve dienil karbanyon ile 1,4-dien arasındaki fark 4/3'tür. Elektron dağılımında en az değişime sahip olan karşılaştırma tercih edilecektir

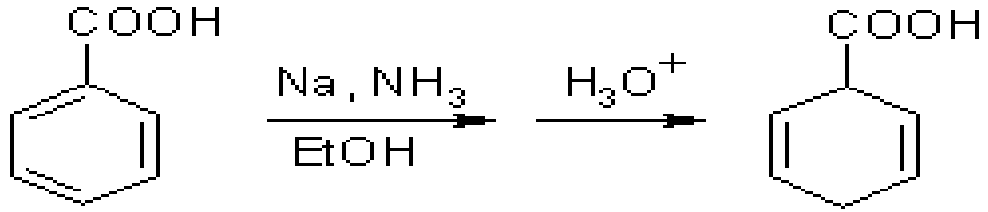


Arenlerin +I- ve +M- türden sübstitüentlerle reaksiyonları en yüksek oranda sübstitüe edilmiş çift bağlara sahip ürünlere yol açar

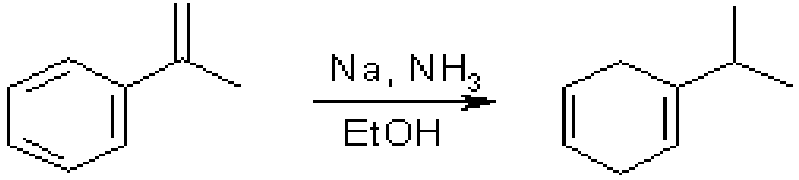


:

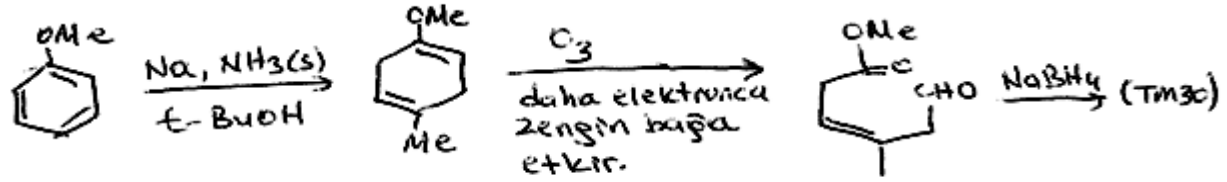
Elektron çeken sübstitüentlerin, Birch inidirgenmesi üzerindeki etkisi değişir. Örneğin, benzoik asidin reaksiyonu, karboksilik asitin bitişik bir anyonu kararlı kılması, siklohekza-2,5-dienoik aside yol açar:



Alken çift bağları, yalnızca arenle konjuge olduğunda indirgenir ve bazen izole uç alkenler de indirgenir.

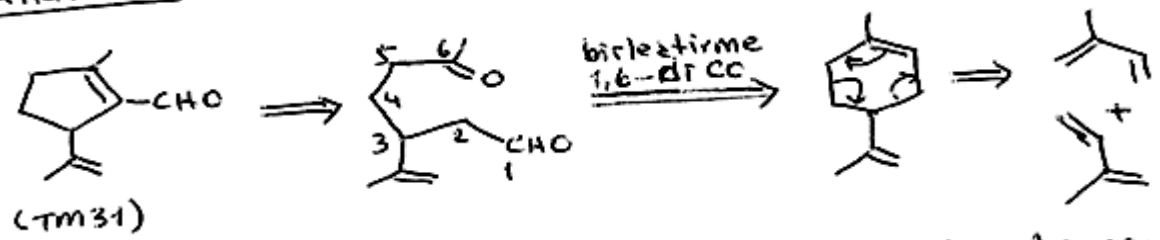


Sentezi:

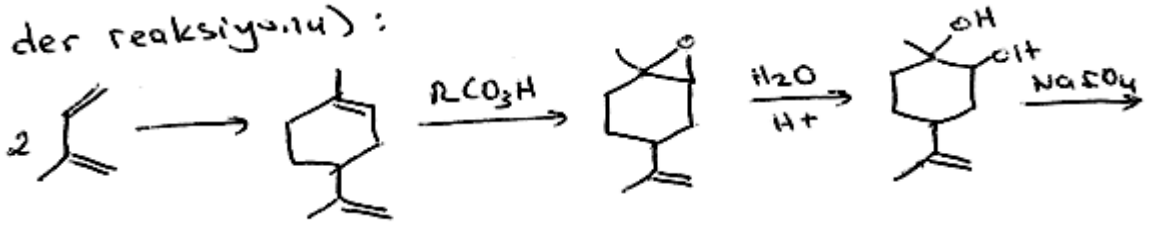


Örnek 2: (TM31) bileşiğini nasıl yaparsınız?

Analizi: önce, α,β-doymamış aldehit kullanılmalı:



Sentezi: İzoprenin, doğal olarak bulunan bir terpen olan (A) bileşiğini vermek üzere dimerleşir (Diels-Alder reaksiyonu):



(J. Amer. Chem. Soc., 1960, 82, 636; J. Org-Chem., 1964, 29, 3740; Tetrahedron letters, 1965, 4097)

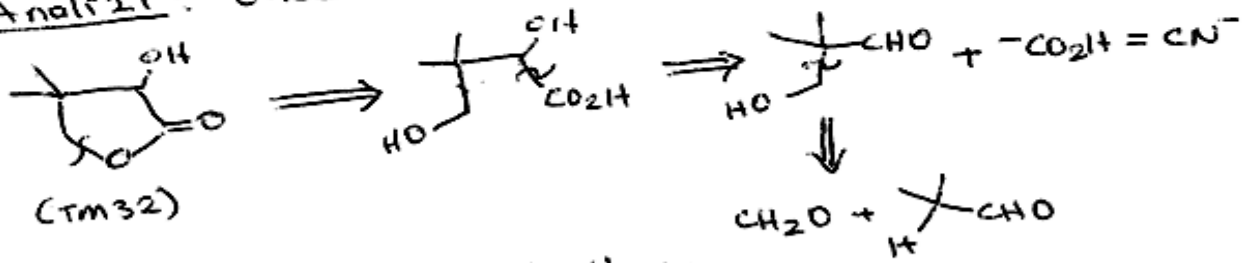
4. LAKTONLARIN SENTEZİ

Şimdiye kadar edindiğimiz basit iki-grup parçalanmaları bilgi ve becerisiyle, çoğu küçük moleküller için analiz ve sentez yöntemleri önerebiliriz. Burada, bir seri problem üzerinde laktonların sentezini planlamaya çalışacağız.

Örnekler

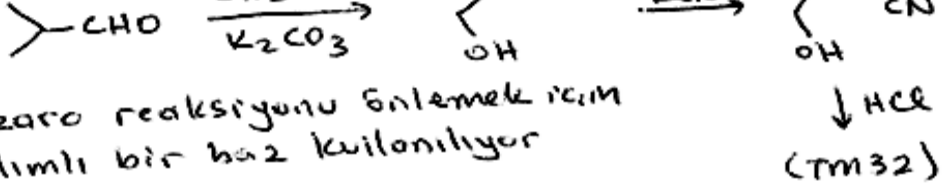
1. (TM32) bileşiğinin (Khorana'nın koenzim A sentezinde kullanılan bir ara ürün) sentez tasarımını yapınız (J. Amer. Chem. Soc., 1961, 83, 663).

Analizi: önce lakton halkası açılır:



not: CN^- anyonu, $-CO_2H$ synthonu için reaktif olarak kullanılmaktadır.

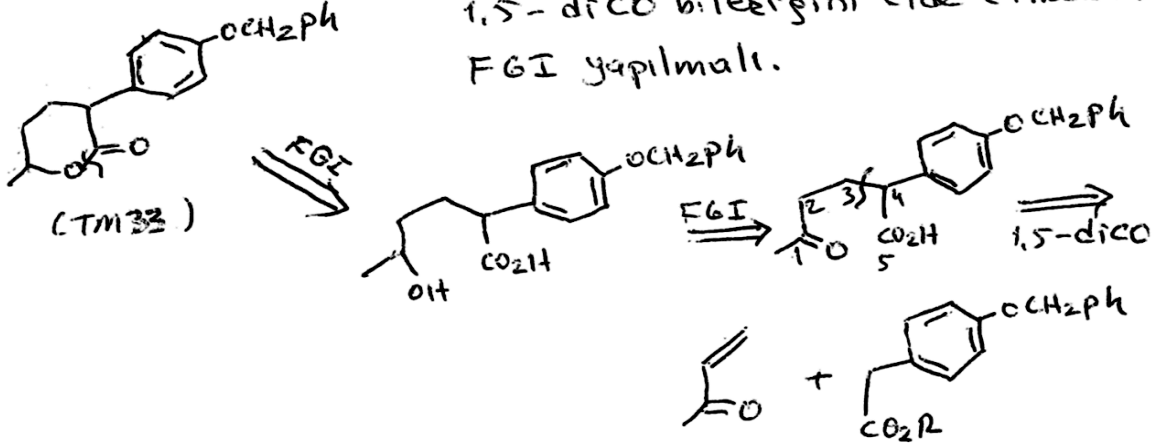
Sentezi:



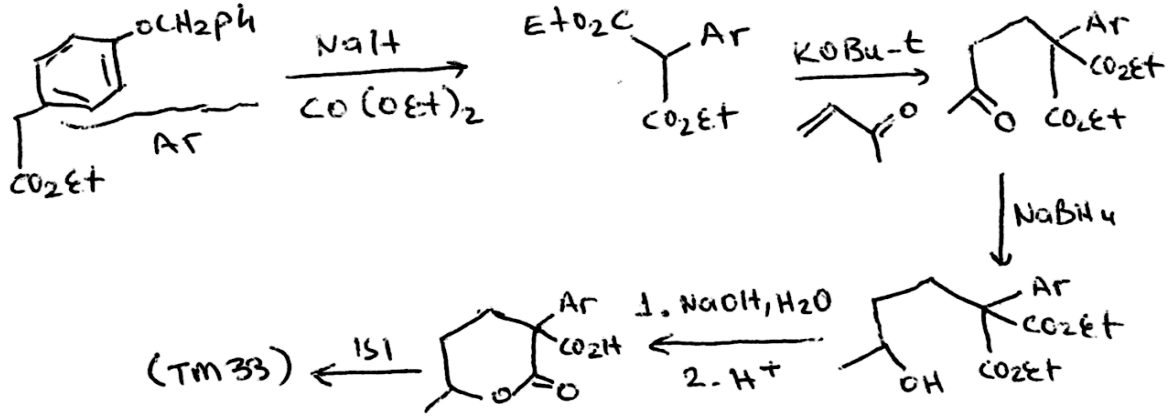
not: Cannizzaro reaksiyonu önlemek için daha ılımlı bir baz kullanılıyor

Örnek 2: Cedren sentezinde bir ara ürün olan (TM33) bileşiğinin sentez tasarımını yapınız.

Analizi: Bileşikte, 1,5-diO iskeleti var, bundan dolayı 1,5-diCO bileşiğini elde etmek için FGI yapılmalı.

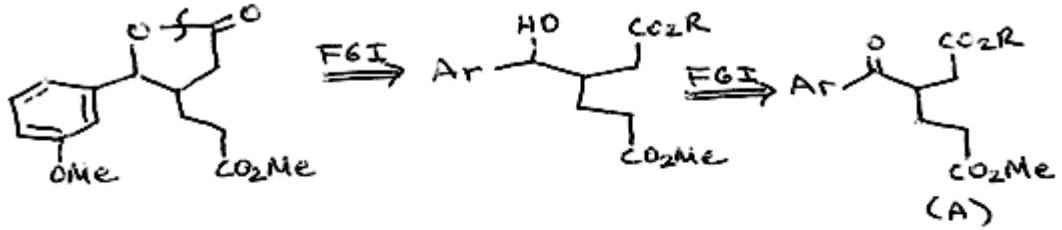


Sentezi: Michael reaksiyonu için aktifleştirici bir grup gereklidir.

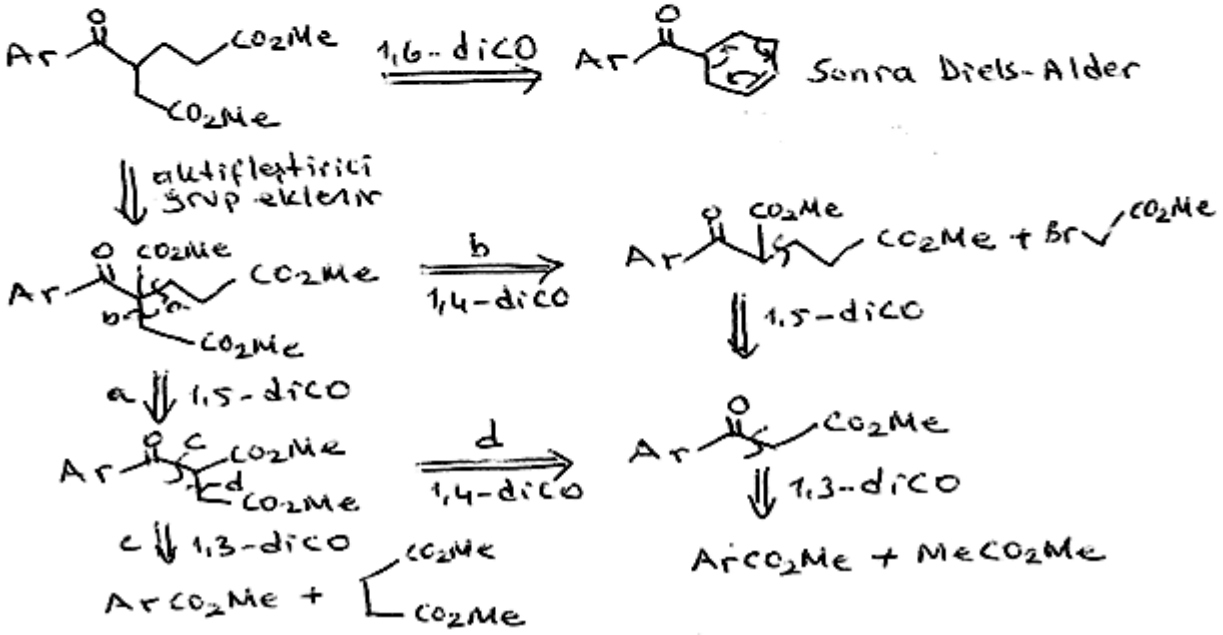


Örnek 3 : (TM34) bileşiğinin (Woodward'ın tetrasiklin sentezinde bir ara ürün) sentez tasarımını yapınız.

Analiz :

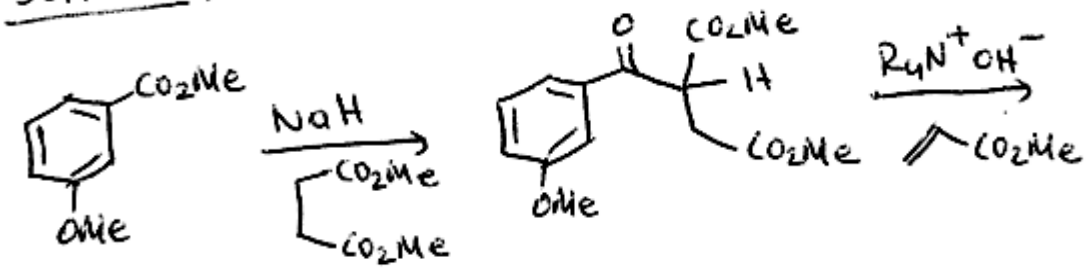


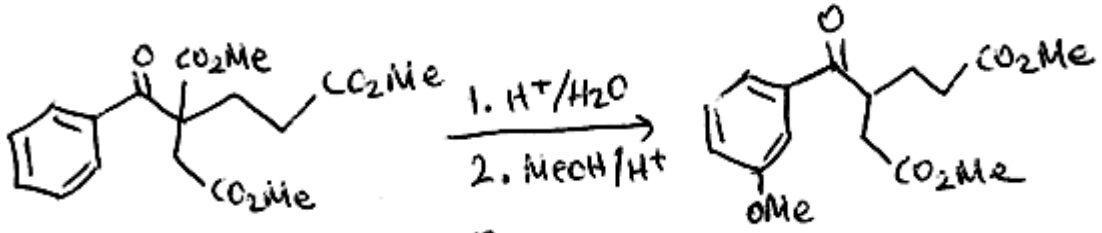
(A) bileşiği anahtar pozisyonundadır, çünkü, 1,4-, 1,5-, ve 1,6-dikarbonil bağlantılarını içerir. Bundan dolayı, farklı parçalanmalar olacaktır :

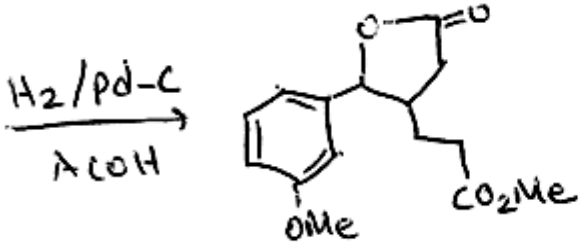


Woodward, bütün bu farklı yolların 1,6-dico bağlantısı dışında, hepsini incelemiş ve hepsinin başarılı olduğunu gözlemiştir. Ancak, sonunda ⊆ ve ⊆'ye karşı gelen yolları seçmiştir.

Sentezi:



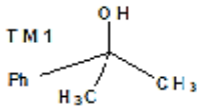




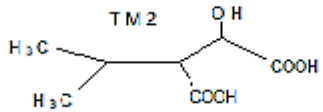
(TM33)

(J. Amer. Chem. Soc., 1968, 90, 439; Pure and Applied Chem., 1963, 6, 651).

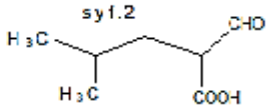
Ek-1. Bölüm 4'de geçen bileşiklerin adlandırılması



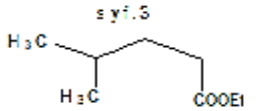
2-phenylpropan-2-ol



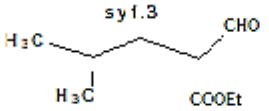
2-hydroxy-3-isopropylsuccinic acid



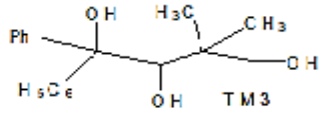
2-formyl-4-methylpentanoic acid



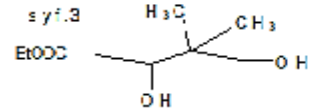
ethyl 4-methylpentanoate



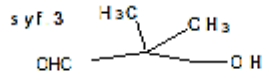
ethyl 2-formyl-4-methylpentanoate



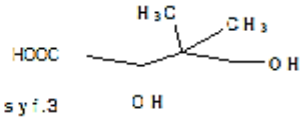
3,3-dimethyl-1,1-diphenylbutane-1,2,4-triol



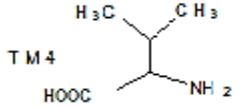
ethyl 2,4-dihydroxy-3,3-dimethylbutanoate



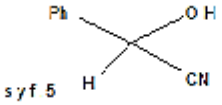
3-hydroxy-2,2-dimethylpropanal



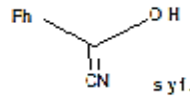
2,4-dihydroxy-3,3-dimethylbutanoic acid



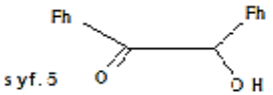
2-amino-3-methylbutanoic acid



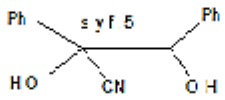
hydroxy(phenyl)acetonitrile



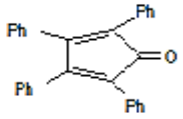
hydroxy(phenyl)acetonitrile



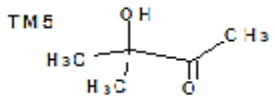
2-hydroxy-1,2-diphenylethanone (Benzoin)



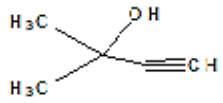
2,3-dihydroxy-2,3-diphenylpropanenitrile



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

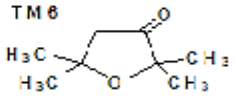


3-hydroxy-3-methylbutan-2-one



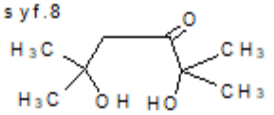
2-methylbut-3-yn-2-ol

syf.7



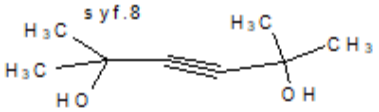
2,2,5,5-tetramethyldihydrofuran-3(2H)-one

syf.8



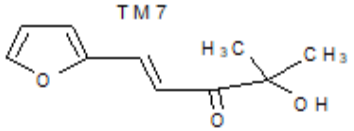
2,5-dihydroxy-2,5-dimethylhexan-3-one

syf.8



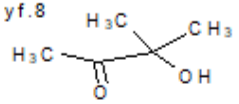
2,5-dimethylhex-3-yne-2,5-diol

TM7



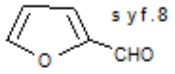
(1*E*)-1-(2-furyl)-4-hydroxy-4-methylpent-1-en-3-one

syf.8

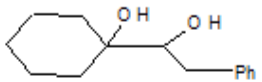


3-hydroxy-3-methylbutan-2-one

syf.8

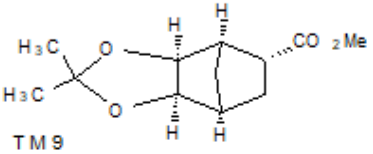


2-furaldehyde



TM8

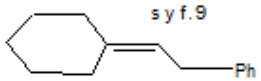
1-(1-hydroxy-2-phenylethyl)cyclohexanol



TM9

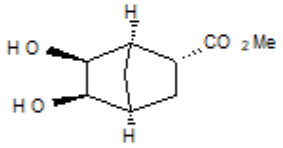
methyl (1*S*,2*R*,6*S*,7*R*,8*R*)-4,4-dimethyl-3,5-dioxatricyclo[5.2.1.$0^{2,6}$]decane-8-carboxylate

syf.9

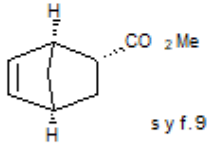


(2-cyclohexylideneethyl)benzene

syf.9

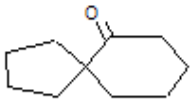


methyl (1*R*,2*R*,4*S*,5*R*,6*S*)-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxylate



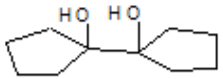
syf.9

methyl (1*S*,2*R*,4*S*)-bicyclo[2.2.1]hept-5-ene-2-carboxylate

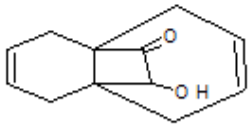


spiro[4.5]decan-6-one

syf.11

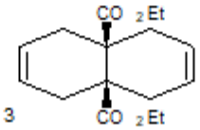


1,1'-bi(cyclopentyl)-1,1'-diol



TM11

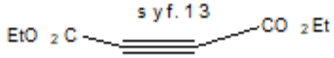
12-hydroxytricyclo[4.4.2.$0^{1,6}$]dodeca-3,8-dien-11-one



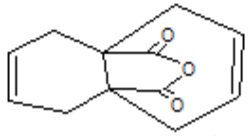
syf.13

diethyl *cis*-1,4,5,8-tetrahydronaphthalene-4a,8a-dicarboxylate

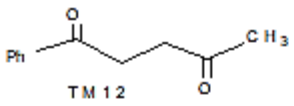
syf.13



diethyl but-2-ynedioate

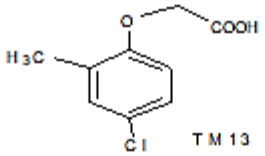


12-oxatricyclo[4.4.3.$0^{1,6}$]trideca-3,8-diene-11,13-dione



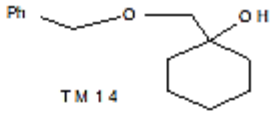
TM 12

1-phenylpentane-1,4-dione



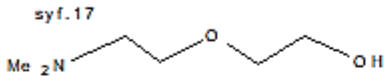
TM 13

(4-chloro-2-methylphenoxy)acetic acid

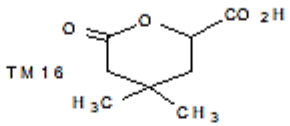


TM 14

1-[(benzyloxy)methyl]cyclohexanol

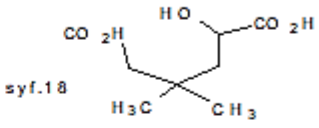


2-[2-(dimethylamino)ethoxy]ethanol

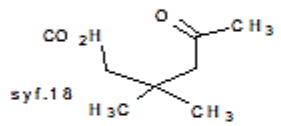


TM 16

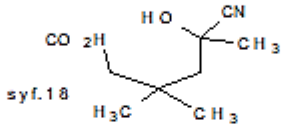
4,4-dimethyl-6-oxotetrahydro-2*H*-pyran-2-carboxylic acid



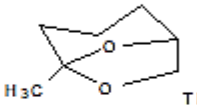
2-hydroxy-4,4-dimethyl hexanedioic acid



3,3-dimethyl-5-oxohexanoic acid

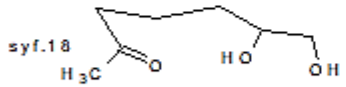


5-cyano-5-hydroxy-3,3-dimethylhexanoic acid

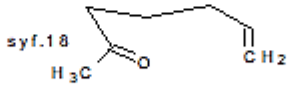


TM 17

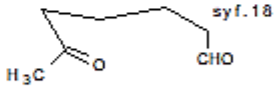
5-methyl-6,8-dioxabicyclo[3.2.1]octane



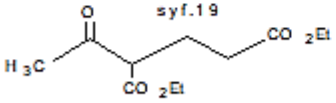
6,7-dihydroxyheptan-2-one



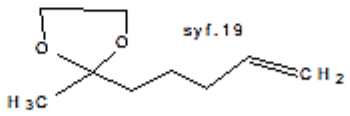
hept-6-en-2-one



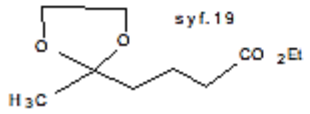
6-oxoheptanal



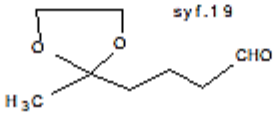
diethyl 2-acetylpentanedioate



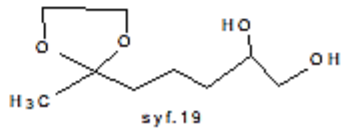
2-methyl-2-pent-4-en-1-yl-1,3-dioxolane



ethyl 4-(2-methyl-1,3-dioxolan-2-yl)butanoate

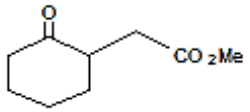


4-(2-methyl-1,3-dioxolan-2-yl)butanal

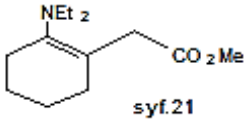


5-(2-methyl-1,3-dioxolan-2-yl) pentane-1,2-diol

TM 18



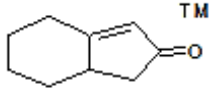
methyl (2-oxocyclohexyl)acetate



syf.21

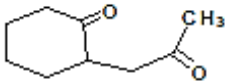
methyl [2-(diethylamino)cyclohex-1-en-1-yl]acetate

TM 19

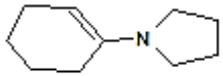


1,4,5,6,7,7a-hexahydro-2*H*-inden-2-one

syf.21

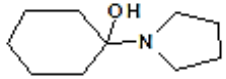


2-(2-oxopropyl)cyclohexanone



syf.22

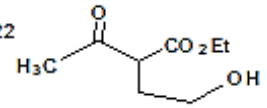
1-cyclohex-1-en-1-ylpyrrolidine



syf.22

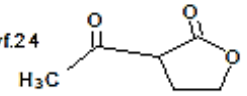
1-pyrrolidin-1-ylcyclohexanol

TM 22

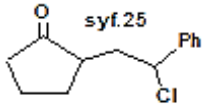


ethyl 2-(2-hydroxyethyl)-3-oxobutanoate

syf.24



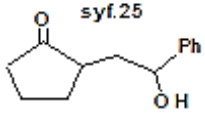
3-acetyldihydrofuran-2(3*H*)-one



syf.25

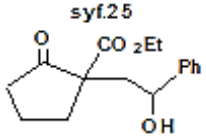
2-(2-chloro-2-phenylethyl)cyclopentanone

syf.25



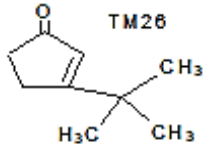
2-(2-hydroxy-2-phenylethyl)cyclopentanone

syf.25

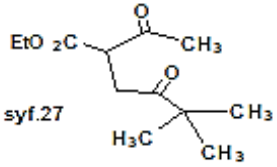


ethyl 1-(2-hydroxy-2-phenylethyl)-2-oxocyclopentanecarboxylate

TM26



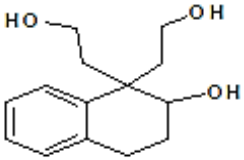
3-*tert*-butylcyclopent-2-en-1-one



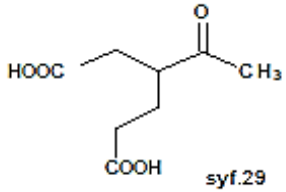
syf.27

ethyl 2-acetyl-5,5-dimethyl-4-oxohexanoate

TM27

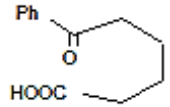


1,1-bis(2-hydroxyethyl)-1,2,3,4-tetrahydronaphthalen-2-ol



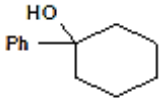
syf.29

3-acetylhexanedioic acid



syf.29

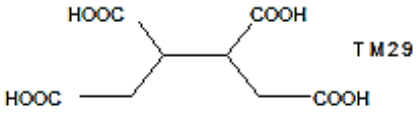
6-oxo-6-phenylhexanoic acid



syf.29

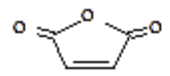
1-phenylcyclohexanol

TM29

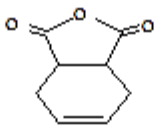


butane-1,2,3,4-tetracarboxylic acid

syf.30

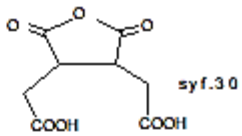


furan-2,5-dione



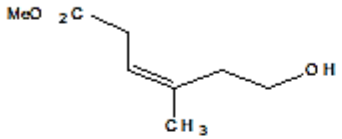
syf.30

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

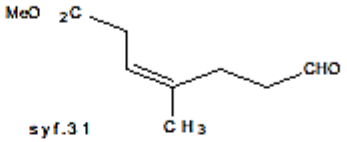


syf.30

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

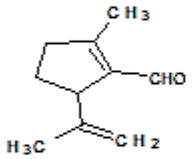


methyl (3Z)-6-hydroxy-4-methylhex-3-enoate

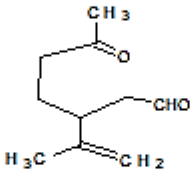


syf.31

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

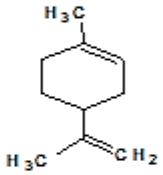


5-isopropenyl-2-methylcyclopent-1-ene-1-carbaldehyde

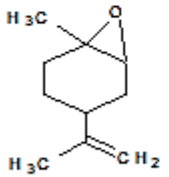


syf.32

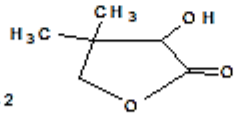
3-isopropenyl-6-oxoheptanal



4-isopropenyl-1-methylcyclohexene



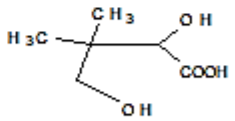
4-isopropenyl-1-methyl-7-oxabicyclo[4.1.0]heptane



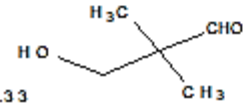
TM32

3-hydroxy-4,4-dimethyldihydrofuran-2(3*H*)-one

syf.33



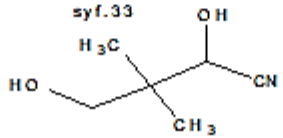
2,4-dihydroxy-3,3-dimethylbutanoic acid



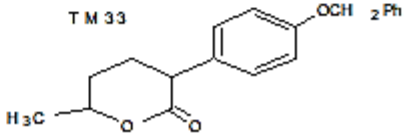
syf.33

3-hydroxy-2,2-dimethylpropanal

syf.33

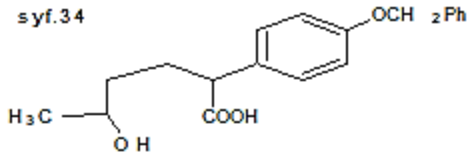


2,4-dihydroxy-3,3-dimethylbutanenitrile

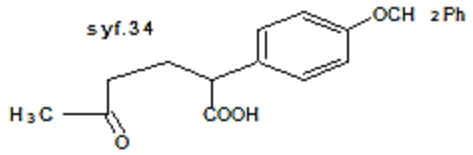


TM33

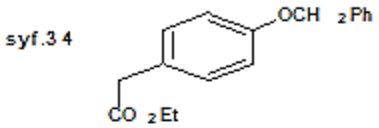
3-[4-(benzyloxy)phenyl]-6-methyltetrahydro-2*H*-pyran-2-one



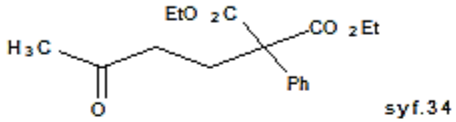
2-[4-(benzyloxy)phenyl]-5-hydroxyhexanoic acid



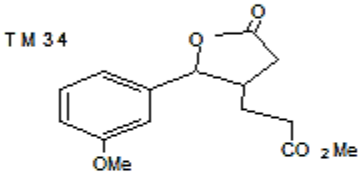
2-[4-(benzyloxy)phenyl]-5-oxohexanoic acid



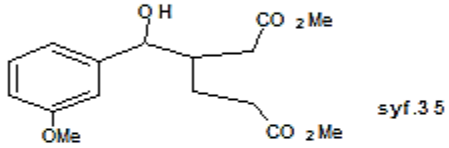
ethyl [4-(benzyloxy)phenyl]acetate



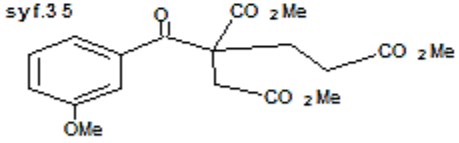
diethyl (3-oxobutyl)(phenyl)malonate



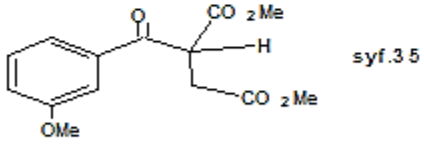
methyl 3-[2-(3-methoxyphenyl)-5-oxotetrahydrofuran-3-yl]propanoate



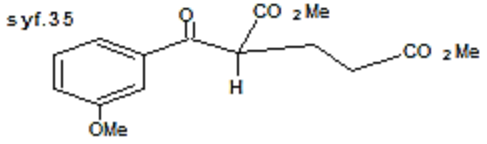
dimethyl 3-[hydroxy(3-methoxyphenyl)methyl]hexanedioate



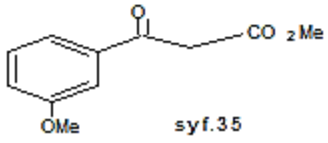
trimethyl 2-(3-methoxybenzoyl)butane-1,2,4-tricarboxylate



dimethyl 2-(3-methoxybenzoyl)succinate



dimethyl 2-(3-methoxybenzoyl)pentanedioate



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

BÖLÜM SONU