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Cycloaddition Reactions of Ketene Diethyl Acetal toward the Synthesis of Cyclobutene Monomers

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Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

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Abstract—The [2+2]-cycloaddition reactions of ketene diethyl acetal with methyl acrylate and acrylonitrile were optimized. Highly efficient ketal cleavage to either 2-cyano-1-cyclobutanone or 2-methoxycarbonyl-1-cyclobutanone was achieved using formic acid. Among the numerous reduction methods attempted, only sodium cyanoborohydride in acidic medium led successfully to the corresponding alcohols, but isolation of the desired products was not achievable. We show that the anomalous cyclobutanone chemistry is due to the acidic α-proton and the electron-withdrawing substituent in the α-position. Substitution of the α-proton by a methyl group results in a turnaround back to textbook chemistry.

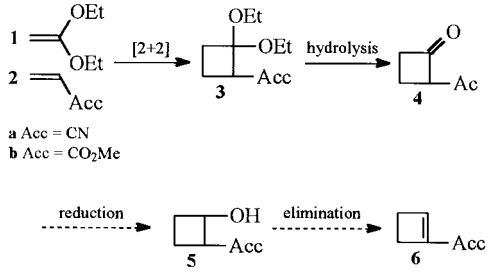
Introduction

Monomers containing the cyclobutane ring can be converted into interesting new polymers possessing novel physical properties such as high glass transition temperatures, high tensile strength and improved thermal stability.[1]

Hall and his collaborators have explored the bicyclobutane monomers thoroughly over a thirty-year period.[1] They showed that bicyclobutanes carrying electronegative substituents, such as cyano and carbomethoxy, at the bridgeheads were monomers which underwent ready free radical and anionic homo- and copolymerizations. The key intermediate in the syntheses of the various monomers investigated to date was 3-cyanocyclobutanone. This was synthesized by cycloaddition of allene and acrylonitrile, followed by oxidation, which is an inherently challenging synthesis too difficult for industrial applications. The consequent synthesis steps however were textbook chemistry and led to 1-cyanobicyclobutane in three steps: sodium borohydride reduction to an alcohol, replacement of the hydroxyl by chlorine using thionyl chloride and 1,3-elimination of hydrogen chloride by sodium hydride. The yields were high at every step. Other bicyclobutane monomers could be synthesized from 3-cyanocyclobutanone by standard organic reactions.

As mentioned, the properties of the resulting polymers were of substantial interest as regards to tensile, optical and piezoelectric properties. We were interested in synthesizing and comparing the analogous cyclobutene monomers. Gale and coworkers have already described the synthesis of 1-cyanocyclobutene. They carried out the photochemical head-to-head cyclodimerization of acrylonitrile at high temperatures, followed by dehydrocyanation over soda lime.[2] The dimerization yielded only about 4% of 1,2-dicyanocyclobutane, but more recently yields in the range of 50% have been reported.[3] The polymerization of 1-cyanocyclobutene has been investigated succinctly and interesting polymer properties were recorded. However, this synthesis is narrow in scope. Methyl 1-cyclobutenecarboxylate **6b** has also been synthesized previously in three steps with an overall yield of 45% starting from cyclobutanecarboxylic acid, which is available by a two-step synthesis in 52% overall.[4]

The recent availability of ketene diethyl acetal suggested an alternate route. The proposed economical four-step synthesis for cyclobutene monomers **6** is based on building the four-membered ring framework by [2+2]-cycloaddition of ketene diethyl acetal (**1**) as donor olefin and acrylonitrile (**2a**) or methyl acrylate (**2b**) as acceptor olefins (Scheme 1). Conia and Amice have reported the cycloaddition of this



Scheme 1.

Keywords: cycloaddition reaction; ketene diethyl acetal; cyclobutene monomers.

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acetal and the consequent hydrolysis to form 2-cyanocyclobutenone.[5] The same series of standard reactions described above, namely borohydride reduction, halogenation and base-induced elimination, should yield 1-cyanocyclobutene. These are the experiments we shall describe.

Background

Our original approach to build up the four-membered ring framework was based on [2+2]-cycloaddition of ethyl vinyl ether with acrylonitrile (**2a**) or methyl acrylate (**2b**). This reaction would proceed stepwise through a zwitterionic intermediate. We were unable to find such cycloadditions in the literature, and our own exploratory efforts were not encouraging. Since one electron-releasing alkoxy-substituent and one electron-withdrawing group in either of the reactants do not seem to stabilize the charges of the zwitterionic intermediate sufficiently, we tried to make the acceptor olefin more electron-deficient by complexing the cyano or ester group with Lewis acids. But instead of cycloaddition, the only reaction occurring in the presence of zinc chloride, lithium perchlorate or methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD), is oligomerization of ethyl vinyl ether.[6]

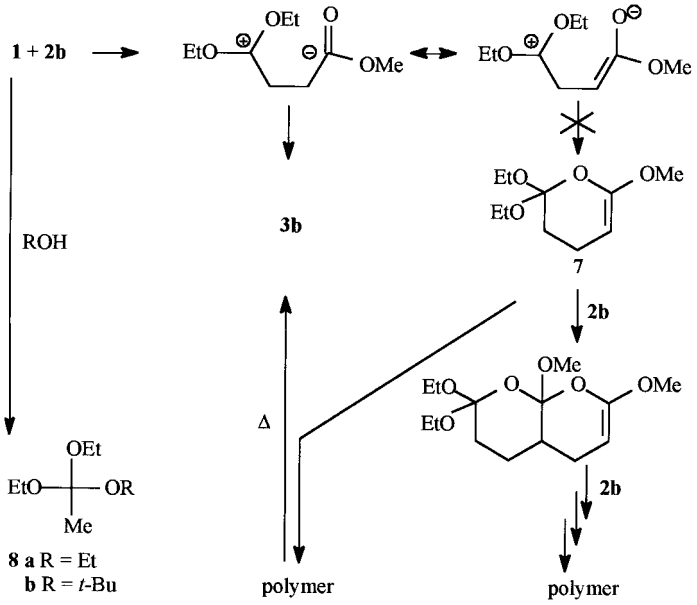
In view of these results and as mentioned in the Introduction, we decided that [2+2]-cycloaddition reactions using ketene acetals would be an appropriate first step in a seemingly simple synthesis scheme. In 1964, Brannock et al. reported the cycloaddition of ketene diethyl acetal and methyl acrylate to form **3b** in 63% yield by heating the starting materials in acetonitrile for eight days.[7] Conia and Amice, utilizing the same method, achieved a 60% yield of the same cyclobutane **3b** and 27% of the cycloadduct **3a** using acrylonitrile.[5] The cyclobutane ketals **3** were hydrolyzed by the French group with aqueous sulfuric acid to form cyclobutanones **4a** (71%) and **4b** (44%). Conia and Amice postulated a polymerization–depolymerization mechanism for cyclobutane formation.[5] This mechanism was based on the observation that the NMR spectra of the crude reaction mixtures did not show any characteristic signals of cyclobutanes **3**, and that the IR spectra of products derived from acrylonitrile were missing $\nu(C\equiv N)$ absorption. Even though the highly viscous crude products did not seem to contain cyclobutanes **3**, [2+2]-adducts could be isolated after fractional distillation or column chromatography. Conia and Amice proposed heterocyclization of a mesomeric zwitterion to give dihydropyran **7**, which can undergo subsequent polymerization with both methyl acrylate and itself, as shown in Scheme 2. Thermal degradation of the latter polymer would lead to cyclobutane **3b** by regression of the six-membered rings, although there was no experimental proof for the existence of a heterocyclic 1:1-adduct **7**. Very confusingly to our understanding, cyano ketal **3a** would be formed by the same mechanism. We would like to refute this reaction pathway.

Results and Discussion

[2+2]-Cycloaddition study: ketene diethyl acetal and mono-activated olefins

Two ketene acetals were investigated in this study, namely ketene diethyl acetal (**1**) and 2-methylene-1,3-dioxepane. The latter is known to be a highly reactive monomer in ring opening polymerizations[8] and indeed, no cyclobutanes are formed in the presence of **2a** and **2b**, only polymers of 2-methylene-1,3-dioxepane.

As a starting point, we tried to optimize the known [2+2]-cycloaddition reactions of ketene diethyl acetal with mono-activated olefins **2a** and **2b**. Our results on modifying the reaction conditions are summarized in Table 1. Entries 1 and 9 represent the reiteration of literature procedures, but with 20% of cyclobutane **3a** (lit.[5]: 27%) and 35% of **3b** (lit.[7]: 63%) the reported yields could not be reproduced. The crude products are indeed highly viscous mixtures, and big



Scheme 2.

Table 1. [2n+2]-Cycloadditions of ketene diethyl acetal (**1**) with acrylonitrile (**2a**) and methyl acrylate (**2b**)

Entry	Acceptor olefin	Molar equiv. of **1**	Solvent/Lewis acid	Inhibitors[a]	Yield of **3**[b] (%)
1	**2a**	1.0	CH_3CN[c]	–	20
2	**2a**	1.0	CH_3CN[c]	$N(i\text{-}Pr)_2Et$, sulfide[d]	13
3	**2a**	1.3	Neat[c]	$N(i\text{-}Pr)_2Et$, sulfide	15
4	**2a**	1.1	*tert*-BuOH[e]	DABCO, sulfide	16
5	**2a**	1.1	*tert*-BuOH[e]	–	23
6	**2a**	2.0	*tert*-BuOH[e]	–	62
7	**2a**	3.0	toluene/MAD[f]	–	47
8	**2a**	1.1	toluene/$(i\text{-}Bu)_2AlCl$[g]	$N(i\text{-}Pr)_2Et$	53
9	**2b**	1.0	CH_3CN[c]	–	35
10	**2b**	1.0	CH_3CN[c]	$N(i\text{-}Pr)_2Et$, sulfide	31
11	**2b**	1.0	CH_3CN[c]	DABCO, sulfide	44
12	**2b**	1.0	*tert*-BuOH[e]	Hydroquinone, sulfide	3
13	**2b**	1.1	*tert*-BuOH[e]	DABCO, sulfide	30
14	**2b**	2.0	*tert*-BuOH[e]	DABCO, sulfide	25
15	**2b**	1.1	*tert*-BuOH[e]	–	20
16	**2b**	2.0	*tert*-BuOH[e]	–	33
17	**2b**	3.0	toluene/MAD[f]	–	51
18	**2b**	1.1	toluene/$(i\text{-}Bu)_2AlCl$[g]	$N(i\text{-}Pr)_2Et$	29

[a] Inhibitors added in catalytic amounts of 0.04 molar equiv. Entries 8,18: 0.4 molar equiv. of inhibitor added (calcd for **2**).
[b] Isolated yields.
[c] 8 d at 82°C.
[d] Sulfide=3-*tert*-butyl-4-hydroxy-5-methylphenylsulfide.
[e] 3 d at 83°C under nitrogen atmosphere.
[f] 1 h at 20°C under nitrogen atmosphere. See Ref. 6.
[g] 1 h 20°C under nitrogen atmosphere. See Ref. 12.

amounts of oligomeric or polymeric material make it difficult to obtain meaningful spectra. But NMR, IR and GC/MS spectra do prove the presence of cyclobutanes **3** in the crude products. This becomes even more obvious after removing the high molecular weight fractions by precipitation with pentane (reactions of **2a**). Attempts to thermally depolymerize these isolated oligo-/polymers did not lead to cyclobutane **3a**. In our opinion and contrary to Conia, there is no need to suggest a different mechanism for cyclobutane formation but regular [2+2]-cycloaddition via zwitterionic tetramethylene intermediates, which is accompanied by polymerization of the starting materials.

In order to minimize this competitive side reaction, cationic inhibitors (*N,N*-diisopropylethylamine, DABCO) and free radical inhibitors (3-*tert*-butyl-4-hydroxy-5-methylphenylsulfide (sulfide), hydroquinone) were added to the reaction mixtures. The addition of inhibitor pair *N,N*-diisopropylethylamine/sulfide to reactions of **2a** (entries 2, 3) or **2b** (entry 10) lowers the amount of oligo-/polymeric material, but does not increase the yield of cyclobutanes **3a,b**. The system **2a**/acetonitrile/DABCO/sulfide affords a maximum yield of 44% **3b**. On replacing acetonitrile with *tert*-butanol[9] as another polar solvent to stabilize but not trap the zwitterionic intermediate (entries 4–6, 12–16), inhibition becomes less relevant, because oligo/polymerization itself no longer is an important side reaction. For example, adding pentane to the crude products derived from reactions of **2a** in *tert*-butanol does not precipitate high molecular weight material as it does for the corresponding acetonitrile reaction mixtures. Maximum yields of **3** in *tert*-butanol runs are 62% of **3a** and 33% of **3b**, which could be achieved without additional inhibitors using 2 molar equiv. of ketene acetal (entries 6,16).

The efficiency of using a double excess of **1** has its reason in another side reaction consuming ketene diethyl acetal, namely the formation of orthoesters **8**. These cycloadditions are accompanied by addition of ethanol to the ketene acetal double bond to give triethyl orthoformate (**8a**) in the range of 20–30%. In *tert*-butanol the amount of **8a** drops to about 10%, and *tert*-butyldiethyl orthoformate **8b** is generated in 40–60%. The addition of *tert*-butanol to **1** is an expected and well-understood reaction because as the solvent, this alcohol is present in the reaction mixture in high concentration. But there is no obvious explanation for the origin of ethanol giving rise to triethyl orthoformate. Two reference experiments were run in this respect. On the one hand, ketene diethyl acetal itself gives more than 20% of **8a**, if stirred at 80°C for eight days in bulk or dissolved in acetonitrile. On the other hand, isolated cycloadducts **3a**,**b** are stable under the above conditions and do not show any loss of ethanol as for example oxetane derivatives do, the [2+2]-adducts derived from ketene diethyl acetal and aldehydes.[10] Supported by these reference reactions, ethanol has its source in a compound arisen from ketene diethyl acetal itself. Our hypothesis concerning formation of **8a** is dimerization of **1** followed by splitting off ethanol. Such species would have a molecular weight of 186, and indeed, GC/MS spectra of crude products reveal compounds with molecular peaks for m/z=187 (MH^+).

The fact that [2+2]-cycloadditions of **1** and **2** are always accompanied by yield-decreasing side reactions such as oligo-/polymerization and orthoester formation might be due to a high activation barrier to formation of the tetramethylene intermediate in the rate-determining step. As in the ethyl vinyl ether case, we tried to lower this barrier and thus increase competitiveness of [2+2]-cycloadditions by Lewis acid catalysis (entries 7, 8, 17 and 18) and radical cation catalysis.[11] At ambient temperature and −78°C, commonly used Lewis acids such as zinc chloride and lithium perchlorate initiate homopolymerization of **1**, small amounts of triethyl orthoformate, and aliphatic as

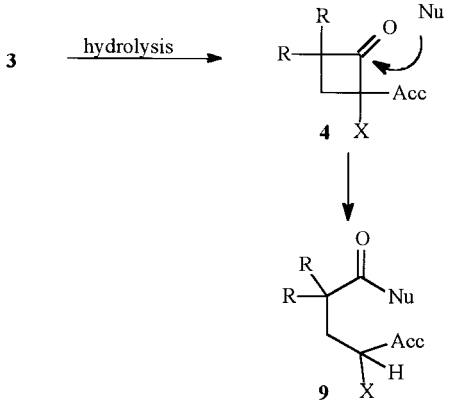
well as aromatic trimer of **1** are also formed.[12] Repeating a literature procedure for related cycloadditions, the use of MAD in toluene at 20°C affords 47% of **3a** (entry 7) and 51% of **3b** (entry 17).[6] Concerning methyl acrylate adduct **3b**, 51% is the highest yield ever achieved during this optimization study. But economically thinking, this method is not a very efficient one because of the expensive aluminum compound and huge amounts of solvent needed. In this respect, catalysis with diisobutylaluminum chloride in toluene at −20°C proves to be much more rational.[13] Unfortunately, the recently patented procedure only yields moderate amounts of cyclobutanes **3a** (entry 8; 53%) and **3b** (entry 18; 29%). Both MAD and diisobutylaluminum chloride completely suppress orthoester formation, which might be related to the low reaction temperatures. All attempts to apply radical cation catalysis to [2+2]-cycloadditions of **1** and **2** (Montmorillonite K10, K10-$FeCl_3$, $FeCl_3$, $(p\text{BrPh})_3N^{+}SbCl_6$) led to complex reaction mixtures with triethyl orthoformate being the only identifiable compound.[11]

In summary, we optimized the procedure of the [2+2]-cycloadditions of **1** and **2** for synthesizing **3a** and raised the yield from 27 to 62% by running the reaction in refluxing *tert*-butanol. We could not reproduce the literature yields of 63 and 60%, respectively, for **3b**, but adoption of the reported reaction conditions combined with deliberate addition of polymerization inhibitors represents a reasonable synthesis, leading to 44% of **3b**.[5,7]

Hydrolysis study or ants know how to do it

Although cyclobutanes **3** are formally nothing but diethyl ketals of 2-acceptor substituted ketones, hydrolysis of these compounds is not simply about removal of a protecting group. Besides Conia's work of 1974, there do not seem to be any literature references with respect to successful hydrolysis procedures for 2-acceptor cyclobutane ketals.[5] Brannock et al. were able to indirectly prove the formation of cyclobutanone **4b** by trapping it as its 2,4-dinitrophenylhydrazone.[7] Nevertheless glutaric acid was the only product isolated from hydrolysis reactions with methanolic hydrochloric acid. These observations already indicated that hydrolysis of **3** occurs, but cyclobutanones **4** readily undergo ring opening due to nucleophilic attack at the carbonyl carbon atom. According to Conia's and our findings, bond cleavage between C1 and C2 takes place on reaction with ethanol to give either glutaronitrile monoethylester **9a** or ethyl methyl glutarate **9b** (Scheme 3). Highly misleading, Conia and coworker reported that hydrolysis of **3** with 3 vol% aqueous sulfuric acid *permits cyclobutanone preparation without ring opening*, although they isolated only 44% of the desired ketone **4b**, along with 4% of **9b** and recovered 44% of **3b**.

We tested several hydrolyzing reagents of varying acidity to establish reaction conditions which suppress ring opening of cyclobutanones **4** and at the same time allow quantitative conversion of cyclobutane ketals **3**. In order to perform this screening efficiently, simple and quick detection methods concerning product formation and distribution, as well as unreacted starting materials were required. With **3b** as reactant, both IR and proton NMR spectroscopy were



	X	Acc	R	Nu
3, 4, 9a	H	CN	H	OEt
3, 4, 9b	H	COOMe	H	OEt
9c	H	COOMe, CN	H	OMe
9d	H	COOMe, CN	H	OH
4, 9e	Br	COOMe	Me	OH
9f	H	CN	H	piperidinyl, morpholinyl

Scheme 3.

successfully utilized for crude product examination. The characteristic cyclobutanone carbonyl absorption at about 1800 cm^{-1} generally serves as a very sensitive IR probe, whereas with **3b** especially, product distribution can be estimated by NMR because of one distinctive singlet for each

Table 2. Qualitative product distribution for hydrolyses of **3b**

Entry	Reagent	Solvent	Crude product[a]		
			4b	**3b**	**9b**
1	H_2SO_4 (3%)[b]	–	×	×	×[c]
2	HCl (18%)	THF[d]	–	–	×[c]
3	HCO_2H (88%)	–[d]	×	–	×
4	CF_3CO_2H	acetone/H_2O[d]	–	–	×
5	$(CF_3CO)O$	acetone/H_2O[d]	–	–	×
6	P_2O_5	–[e]	–	–	×[e]
7	Amberlyst-15	acetone/H_2O[d]	×	×	×
8	Al_2O_3 (ac)	ether (anh.)[d]	–	×	–
9	Al_2O_3 (ac)	ether (anh.)[f]	–	×	–
10	$BF_3{\cdot}Et_2O$/NaI	CH_3CN (anh.)[f]	tr.	–	×[e]
11	BBr_3/NaI	CH_3CN (anh.)[d]	tr.	–	×[e]
12	BBr_3/NaI	CH_3CN (anh.)[f]	–	–	×[e]
13	$TiCl_4$/LiI	ether (anh.)[d]	–	×	×[e]
14	$FeCl_3{\cdot}6H_2O$	CH_2Cl_2[d]	–	×	×[e]
15	$FeCl_3{\cdot}6H_2O$	CH_2Cl_2/acetone[d]	tr.	–	×[e]
16	$FeCl_3{\cdot}6H_2O/SiO_2$	$CHCl_3$[d]	–	×	×
17	Pyridinium tos.	acetone/H_2O[f]	tr.	×	×[e]
18	Steam distillation	H_2O[f]	–	×	–
19	PPh_3/CBr_4	CH_2Cl_2 (anh.)[d]	–	×	–
20	$PhOP(O)Cl_2$	C_6H_6 (anh.)[f]	tr.	–	×[e]
21	DDQ[g]	CH_3CN/H_2O[d]	–	×	–

[a] ×=Formation/recovery; –=No formation/recovery; tr. =Traces of **4b** (NMR: no discrete signals; IR: carbonyl absorption).
[b] See Ref. 5b.
[c] Formation of other, not further investigated products.
[d] Reaction at ambient temperature.
[e] Reaction at 150°C.
[f] Reaction under heating to reflux.
[g] DDQ=2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

methoxy group in **4b** (3.75 ppm), **3b** (3.70 ppm) and **9b** (3.67 ppm). Moreover, **3b** is easier to hydrolyze than **3a**.

The qualitative results are shown in Table 2. Tested hydrolysis reagents may be roughly divided into three groups: strongly acidic (entries 1–7), less acidic (entries 8–17) and neutral (entries 18–21). Concerning group 1, aqueous mineral and carboxylic acid hydrolysis is the most widespread method to induce ketal cleavage.[14] Deprotection of **3b** takes place with sulfuric acid (entry 1) as formerly stated by Conia. Formic acid (entry 3) leads to quantitative conversion of **3b** to a mixture of cyclobutanone **4b** and glutaric diester **9b**. Besides these protonic acids, only Amberlyst-15, a polystyrene based sulfonic acid cation exchange resin, induces cyclobutanone formation. Acidified aluminum oxide (entries 8-9), Lewis acids (entries 10–16) and pyridinium tosylate (entry 17) are characterized by lower acidity. Like Lewis acid $FeCl_3$, all reagents of group 2 are known to be more compatible with acid sensitive functional groups, and therefore might have offered milder conditions for successful hydrolysis of **3**. But none of these reagents leads to reasonable amounts of **4b**. Traces of cyclobutanone are only detectable in crude products of reactions with halogenide-assisted boron trifluoride or tribromide (entries 10 and 11), ferric chloride (entry 15) and pyridinium tosylate (entry 17). Moreover, **9b** is no longer the only side product, the NMR spectra reveal additional signals, which could not be assigned to specific structures. Neutral hydrolysis reagents of group 3 are even less efficient. Steam distillation (entry 18), triphenylphosphine/carbon tetrabromide (entry 19) and oxidative 2,3-dichloro-5,6-dicyano-*p*-quinone (entry 21) leave cyclobutanone ketal **3b** unchanged, and reaction with phenyl dichlorophosphate results in a very complex reaction mixture only containing traces of **4b**.

Worth mentioning is the importance of the work-up procedures. Although ketals **3** do not require anhydrous hydrolytic conditions, aqueous work-up like washing with saturated bicarbonate solution and/or brine (entries 10–15, 17) is not favorable. According to blank experiments, cyclobutanones **4** are not affected by sodium bicarbonate as a basic salt despite their extreme sensitivity toward bases. Instead, the low recovery of organic material from test experiments, perhaps from hydrolyses 10–15 and 17 as well, is due to considerable water solubility of **4**. Strong basic work-up with sodium hydroxide (entry 20) must definitely be avoided because of immediate ketone decomposition if formed at all. Most convenient and efficient procedures to remove hydrolyzing reagents are filtering off (entry 7) or simply evaporating as in case of formic acid.

On comparing successful hydrolyses (Table 3), only strong acidic reagents of group 1 are powerful enough to both remove the protecting group and provide reaction conditions for the isolation of cyclobutanones. Of those, formic acid offered the best approach toward higher yields of cyclobutanone **4b** with 59%, complete conversion of **3b** and 41% of glutaric diester **9b**. Relative percentages are estimated by means of crude product NMR spectra, and based on integration of the methyl ester proton signals. These results are also consistent for cyano ketal **3a**, only that formation of cyclobutanone **4a** is even more favored. Typical GC spectra show

Table 3. Successful hydrolyses of **3b** and relative yields

Entry	Reagent	Conditions[a]	Relative yields (%)[b]		
			4b	**3b**	**9b**
1a	H_2SO_4 (3%)	1 h, 0.2 molar equiv.	40	42	18
1b	H_2SO_4 (3%)	2 h, 0.2 molar equiv.	33	14	53
3	HCO_2H (88%)	1 h, 3.0 molar equiv.	59	0	41
7	Amberlyst-15	5 h	22	7	71

[a] All reactions at ambient temperature.
[b] Based on NMR signals of methyl ester protons (crude products) at: 3.75 ppm (**4b**); 3.70 ppm (**3b**); 3.67 ppm (**9b**).

crude product distributions in the range of 90–95% of **4a** and 5–10% of **9a**.

Additionally, we screened reaction conditions by varying temperature, reaction time, mole equivalents and water content of formic acid. To control the reaction, samples were taken regularly and examined by IR and NMR spectroscopy. It became very obvious that generation of **4b** requires milder conditions than **4a**, because of the lower stability of the former. Reaction temperatures above 40°C give rise to enhanced formation of **9b**, indicating the high tendency of **4b** to undergo ring opening. After one hour at 45°C only marginal amounts of **4b** are left, whereas **4a** is not as sensitive to temperature. Conversion of both ketals **3** proceeds unusually slowly when using 96% instead of 88% formic acid. Only deliberate addition of water to the reaction mixture facilitates complete conversion of **3**.

On the whole, 12 molar equiv. of 88% formic acid and a reaction temperature of 35–40°C work best for formation and stability of both **4a** and **4b**. In the case of carbomethoxy-substituted cyclobutane ketal **3b**, conversion to **4b** is complete after 1 h, while for the cyano-substituted cyclobutane ketal **3a** a reaction time of 20–24 h is needed. Maximum isolated yields are 51% of **4a** and 68% of **4b**. The colorless liquids are stable for months if stored at −20°C, but they start to turn viscous after a few days at room temperature. This observation is consistent with our findings, that distillation of **4** always goes along with considerable loss of substance and highly viscous residues, which might be due to aldol condensation and subsequent oligomerization reactions.

Attempted reduction or always trouble with alcohol

Obtaining cyclobutanols **5** should be easy by simply using sodium borohydride as a selective reducing agent for ketones. But contrary to our expectations, satisfactory reduction of 2-acceptor substituted cyclobutanones **4** did not occur.

In the very first reduction attempt, **4b** and sodium borohydride were combined in methanol at 0°C. Investigation of the reaction mixture by IR indicated the complete conversion of cyclobutanone **4b** by the disappearance of the carbonyl absorption at approximately 1800 cm^{-1} after 10 min. But the IR spectra of the crude product do not reveal a band for ν(OH) vibration, and the proton NMR indicate that the rather pure oil is a mixture of ethyl methyl glutarate (**9b**) and dimethyl glutarate (**9c**). The presence of **9b** is due

to the starting materials being a mixture of **4b** and **9b**, because they were generated in situ and used as the crude hydrolysis mixture immediately after evaporating formic acid. Formation of **9c** in approximately 70% yield (NMR) can be explained by an addition reaction of methanol to **4b** after ring opening. Moreover, 2-acceptor substituted cyclobutanones not only react with nucleophiles like methanol and ethanol (see hydrolyses). Even water causes hydrolytic ring cleavage to **9d** to a certain degree. This became obvious upon reaction of **4b** with sodium borohydride in water, which does not give the desired alcohol **5b,** but more than ten products of which **9d** is one (GC/MS). Formation of **9d** from cyclobutanone **4b** was also demonstrated by a simple test tube experiment in water. The anomalous sensitivity of cyclobutanones **4** towards nucleophiles and water has been previously demonstrated for **4e**, which was reported to open to glutarate **9e** in aqueous solution (Scheme 3).[15] Therefore, THF was selected as a more appropriate solvent. This time the cyclobutanone ν(C═O) absorption disappeared completely after 90 min.

Because NMR spectra are highly complex and not very meaningful in the sense of product characterization, acetylation with acetic anhydride was chosen as a work-up procedure. Neither IR, NMR nor GC/MS give any hint of an acetylated cyclobutanol. Thermal elimination of water from the putative **5b** to generate cyclobutene **6b** directly is not successful either. Further attempts to reduce cyclobutanones **4** with sodium borohydride/palladium chloride, sodium borohydride/moist alumina, zinc borohydride, sodium hydrosulfite and palladium on carbon/ammonium formate do not give the desired alcohols.[16]

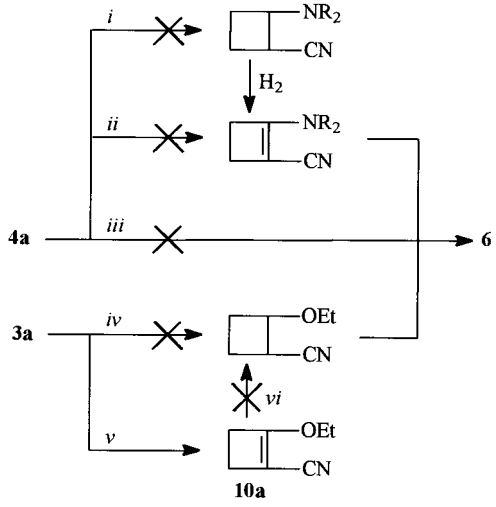
Finally, reaction with sodium cyanoborohydride in acidic conditions because of the hydride's stability at pH 4 facilitates cyclobutanol formation.[17] The pH level was controlled using bromocresol green as the indicator by dropwise addition of formic acid. Only a very small amount of highly viscous oil was isolated after work-up procedures from the reactions of both **4a** and **4b**. Complete conversion of **4** was only realized in the case of 2-cyanocyclobutanone **4a**. The IR, NMR and GC/MS spectra prove formation of cyclobutanols **5**. The crude products reveal strong ν(OH) IR absorptions at about 3450 cm^{-1}, and the proton NMR spectra show broad singlets at about 3.4 and 3.5 ppm, which fade after treatment with deuterium oxide. GC/MS spectra of the crude products **5a** define them as mixtures of ten and more compounds, two of which show fragment peaks for *m/z* of 69. The *m/z* peak at 69 corresponds to *cis*- and *trans*-cyclobutanol after splitting off ethylene (M^+28). The relative percentages of 10–20% isomeric **5a** can be increased to about 50% by pentane extraction of the byproducts and by Kugelrohr distillation to separate the product from the oligomeric material. The crude product mixture of **5b** consists of unreacted cyclobutanone, glutaric acid derivatives and about 30% of the desired alcohols. The desired product **5b** can be enriched to about 70% with the above mentioned purification procedures, but it could not be isolated. The same applies to cyclobutanol **5a**.

Although reduction finally occurred, poor conversion to the desired products, low selectivity and low recovery of organic materials prevent reaction with sodium cyanoborohydride from being a viable method for a satisfactory synthesis of cyclobutanols **5**.

Alternative routes toward cyclobutenes 6

Looking for a way out of this synthetic dead end, we tried alternative routes to obtain target cyclobutenes **6** starting from cyclobutanone **4a** and cyclobutane ketal **3a,** as shown in Scheme 4.

Enamine formation in the presence of Linde molecular sieves 13X (route *i*), as well as reductive amination with sodium cyanoborohydride (route *ii*) does not occur. Only mononitrile glutaric amides **9f** are formed by addition of either morpholine or piperidine to the keto carbon followed by ring opening (Scheme 3). Conversion of **4a** to glutaric amides ranged from 53 to 92%. Direct deoxygenation of **4a** with zinc and chlorotrimethylsilane leads to complex reaction mixtures exclusively (route *iii*), and treatment of **3a** with sodium cyanoborohydride and gaseous hydrochloric acid leaves **3a** unchanged instead of reductively cleaving the ketal (route *iv*). The only promising approach was base induced elimination of ethanol from **3a** by sodium bis(trimethylsilylamide) (TMSA) to give 43% of 1-cyano-2-ethoxycyclobutene (**10a**) (route *v*). But reduction of the tetrasubstituted, highly hindered double bond cannot be achieved by heterogeneous hydrogenation using various metal catalysts and solvents. In contrast, Gale and Cherkofsky reported quantitative hydrogenation of 1-cyano-2-methoxycyclobutene by palladium catalysis.[18] Presumably, exchanging methoxy for ethoxy as fourth substituent of the cyclobutene double bond dramatically enhances steric hindrance and prevents addition of hydrogen. In summary, none of the above alternatives turned out to be a viable route to cyclobutenes **6**.



Scheme 4. Reagents and conditions: (*i*) Linde molecular sieves 13X, ether, 9 d, 4°C, nitrogen atmosphere; (*ii*) $NaBH_3CN$, HCO_2H, THF, 4 d, r.t.; (*iii*) Zn, $ClSiMe_3$, ether, 3 d, r.t.; (*iv*) $NaBH_3CN$, HCl (g), THF, 15 min, 0°C; (*v*) TMSA, THF, 3 h, −78°C t r.t. (*vi*) (a) Pd/C (5%), H_2, ether, 3 d, r.t.; (b) PtO_2, H_2, ether, 20 h, r.t.; (c) PtO_2, H_2, HCl, ethanol, 20 h, r.t.; (d) PtO_2, H_2, CH_3CO_2H, 20 h, r.t.; (e) Pd/C, HCO_2NH_4, THF, 3 d, r.t.

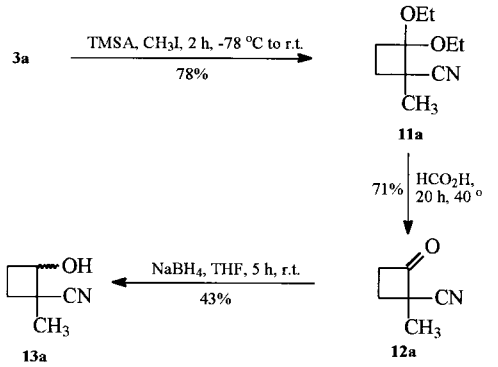
Properties of cyclobutanones 4 and their 2-methyl analogs

The 2-acceptor substituted cyclobutanones **4** not only show extreme sensitivity toward Brønsted bases and nucleophiles such as amines and alcohols, but even water initiates ring opening to glutaric acid derivatives. The corresponding 3-acceptor substituted cyclobutanones however, are readily transformed to cyclobutanols: they are stable, they do not undergo ring opening and all organic transformations typical for ketones can easily be accomplished.[1] Taking this and all our experimental results into account, the proton in 2-position somehow seems to be responsible for the anomalous chemistry of **4**.

Hasek and Martin reported ring cleavage reactions of 3-aminocyclobutanones due to protons α to the keto group.[19] Enolizable model compounds proved to be highly unstable and completely rearranged to acyclic aminovinyl ketones on distillation. These observations suggest electrocyclic ring-opening of 3-aminocyclobutenols as the corresponding enol form. That cyclobutanones were intermediately formed at all became evident by their characteristic carbonyl IR absorption. These cyclobutanones were not isolated, and thus no information about equilibrium concentrations of keto and enol form is available. However, it seems clear that their enol form dominates the chemistry of these compounds. Enolization is generally favored by a gain of conjugation energy.[20] Even though the cyano or ester substituents in cyclobutanones **4** can participate in a broad conjugated enol system, **4** predominantly exists in the keto form as revealed by the IR spectra. This corresponds to the fact that no electrocyclic ring opening of putative enols of **4** can be observed.

Since ring cleavage is not connected to keto–enol equilibria, substitution of the α-proton might give some hints as to whether this very proton actually destabilizes **4**. If substituted by an alkyl group, the electronic effects due to hyperconjugation should equalize the electron-withdrawing effect of the acceptor groups in 2-position, enhance stability and therefore suppress ring opening reactions. Acceptor substituents in **4** should be highly capable of stabilizing negative charges, and thus removal of the α-proton should cause generation of stable anionic species **4**, which can easily be alkylated. But generation of **4** with the help of sterically hindered bases like potassium *tert*-butoxide and TMSA can not be achieved. Reaction with potassium *tert*-butoxide leads to immediate oligo-/polymerization, whereas TMSA initiates decomposition. Even deprotonation of **4** in the presence of iodomethane or other methylating agents does not yield the 2-methyl analogs **12**.

Hence an indirect pathway was chosen to synthesize **12a** (Scheme 5). Starting with cyclobutane ketal **3a**, alkylation with iodomethane and TMSA affords 78% of **11a**. It was noticed that the experimental protocol is crucial during the base treatment with TMSA. The alkylating agent has to be present as the anion is generated, because otherwise elimination of ethoxide occurs to give cyclobutene **10a**. Hydrolysis of **11a** to methylated cyclobutanone **12a** with formic acid proceeds smoothly in 71% yield without even a trace of glutaric acid derivatives. Ketone **12a** can be



Scheme 5.

readily reduced with sodium borohydride to give 43% of an isomeric mixture of *cis*- and *trans*-cyclobutanol **13a**. All the above reactions and results are applicable to cyclobutane ketal **3b**.

On substituting the proton in the 2 position of cyclobutane ketal **3a** by a methyl group, the corresponding cyclobutanone no longer shows anomalous chemical behavior, since the hyperconjugative alkyl substituent seems to counteract the electron-withdrawing effect of the cyano group. Therefore, this push–pull substitution α to the keto group prevents cleavage reactions by stabilization of the four-membered ring and gives way to successful reduction to cyclobutanol **13a**.

Conclusions

We optimized [2+2]-cycloaddition reactions of ketene diethyl acetal and two mono-activated olefins by minimizing side reactions such as oligomerization, polymerization and orthoester formation. With *tert*-butanol as the solvent, yields of acrylonitrile adduct could be more than doubled. Literature yields of the corresponding methyl acrylate [2+2]-adduct were not reproducible in our hands, but deliberate addition of polymerization inhibitors gave reasonable results. As the result of a broad screening, highly efficient ketal cleavage with formic acid could be applied to both cycloadducts to give cyclobutanones in good yields, which were accompanied by minimum amounts of ring opened products. Conversion of these cyclobutanones to alcohols at last became possible on reduction in acidic medium with sodium cyanoborohydride, but isolation of the desired cyclobutanols was not achievable.

Evidently, we had to face the fact that synthesis of the target cyclobutene monomers by our proposed new and economical reaction pathway had turned into a dead end. The crucial point of this synthetic scheme can be found in the enormous tendency of 2-acceptor substituted cyclobutanones toward ring opening reactions under the influence of nucleophiles, bases and water. Although we were not able to gain access to cyclobutene monomers, we could show that anomalous cyclobutanone chemistry has its explanation in destabilization of the four-membered ring framework by an active proton and an electron-withdrawing substituent both in α-position to the keto group. Substitution of the α-proton

by a methyl group results in a turnaround back to textbook chemistry, with organic transformations no longer being ruled by nucleophile initiated ring cleavage to glutaric acid derivatives.

Experimental

General methods

NMR spectra were recorded at ambient temperature on a Varian Gemini 200. IR spectra were obtained on a Nicolet Impact 410 infrared spectrometer. Mass spectrometry low-resolution data (EI) were recorded on a HP 5988 A GC/MS system. All high-resolution mass spectra including fast atom bombardment (FAB) with high and low resolution were taken on a JEOL HX 110 A sector instrument. Elemental Analyses were performed by Desert Analytics, Tucson, AZ. Acrylonitrile and methyl acrylate were purified prior to use by filtering through a column with basic aluminum oxide.

1-Cyano-2,2-diethoxycyclobutane (3a): Method A.[9] Similar to a procedure described for related cycloadditions, ketene diethyl acetal (**1**) (88 mL, 0.6 mol) and acrylonitrile (**2a**) (20 mL, 0.3 mol) were heated to reflux in *tert*-butanol (150 mL) and under nitrogen atmosphere for 3 days. Evaporation of the solvent under reduced pressure and subsequent fractionation over a 10 cm Vigreux column (bp 87–89°C, 3 mmHg; lit.[5]: bp 78–80°C, 3 mmHg) afforded 31.5 g of **3a** (62%; lit.[5]: 27%). ^{1}H NMR ($CDCl_3$) δ 3.62–3.35 (4 H, m), 3.20–3.11 (1 H, m), 2.43–1.93 (4 H, m), 1.27 (3 H, t, J=7.1 Hz), 1.20 (3 H, t, J=7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 118.4, 100.2, 57.0, 56.9, 33.5, 31.1, 17.6, 14.8, 14.7. IR (neat) 2241 cm^{-1}. MS (EI) *m/z* (rel intensity) 141 (M^+28, 12). HRMS (EI) Calcd for $C_9H_{15}NO_2$ (M^+): 169.1103; Found: 169.1098.

Synthesis of **3a** under Lewis acid catalysis could be achieved according to described procedures for related [2+2]-cycloadditions. **Method B**:[6] Reaction of **1** (1.10 mL, 7.5 mmol) and **2a** (0.16 mL, 2.5 mmol) with in situ prepared MAD in toluene (35 mL) gave 0.2 g of **3a** (47%) after Kugelrohr distillation. **Method C**:[13] Reaction of **1** (16.0 mL, 0.11 mol) and **2a** (6.6 mL, 0.10 mol) in toluene (200 mL) in the presence of diisobutylaluminum chloride (21.5 mL, 0.11 mol) afforded 8.9 g of **3a** (53%) after Kugelrohr distillation.

1-Methoxycarbonyl-2,2-diethoxycyclobutane (3b). Method A:[5] Compound **3b** was prepared similarly to published procedures. Olefins **1** (44 mL, 0.3 mol) and **2b** (27 mL, 0.3 mol) were refluxed in acetonitrile (150 mL) for 8 days in the presence of DABCO and 3-*tert*-butyl-4-hydroxy-5-methylphenylsulfide as inhibitors (0.04 mol equiv. each). After the removal of solvent and volatiles under reduced pressure, fractional distillation of the highly viscous crude product over a 10 cm Vigreux column (bp 113°C, 10 mmHg; lit.[5]: bp 101–102°C, 20 mmHg) provided 27 g of **3b** (44%; lit.[5]: 63%). ^{1}H NMR ($CDCl_3$) δ 3.70 (3 H, s), 3.65–3.23 (5 H, m), 2.41–1.78 (4 H, m), 1.33 (3 H, t, J=7.1 Hz), 1.21 (3 H, t, J=7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 171.3, 102.0, 56.8, 56.3, 51.4, 49.1, 30.5, 14.9, 14.2. IR (neat) 1746 cm^{-1}. MS (EI) *m/z* (rel intensity) 174 (M^+−28, 8). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.10; H, 9.04. **Method B:**[6] MAD-catalyzed cycloaddition of **1** (1.10 mL, 7.5 mmol) and **2** (0.23 mL, 2.5 mmol) gave 0.26 g of **3b** (51%) after Kugelrohr distillation. **Method C:**[13] Reaction of **1** (16.0 mL, 0.11 mol) and **2** (9.0 mL, 0.10 mol) in the presence of diisobutylaluminum chloride (21.5 mL, 0.11 mol) in toluene (200 mL) afforded 5.9 g of pure **3b** (29%) after Kugelrohr distillation.

2-Cyano-1-cyclobutanone (4a). A mixture of cyclobutane ketal **3a** (3.00 g, 0.018 mol) and 88% formic acid (12.80 g, 0.216 mol) was kept at 35–40°C for 24 h. The volatiles were removed in vacuo and byproduct **9a** was extracted with several small portions of pentane. Kugelrohr distillation (0.1 mmHg) of the orange oil yielded 0.87 g (51%) of **4a**. ^{1}H NMR ($CDCl_3$) δ 4.25–4.09 (1 H, m), 3.55–3.20 (2 H, m), 2.24–2.64 (2 H, m). ^{13}C NMR ($CDCl_3$) δ 193.7, 114.7, 48.1, 45.8, 15.8. IR (neat) 2242, 1803 cm^{-1}. MS (EI) *m/z* (rel intensity) 95 (M^+, 1), 67 (M^+−28, 100). HRMS (EI) Calcd for C_5H_5NO (M^+): 95.0371. Found: 95.0356.

Attempted reduction of 4a with sodium cyanoborohydride. Sodium cyanoborohydride (0.47 g, 7.5 mmol) was added to a solution of cyclobutanone **4a** (1.43 g, 15.0 mmol) and traces of bromocresol green in THF (20 mL). The slowly changing color of the mixture from yellow to dark green, due to the presence of bromocresol green, was restored by dropwise addition of formic acid. After stirring at room temperature for 20 h, brine was added to the yellow suspension (10 mL) followed by extraction with ether (4×10 mL). The ethereal layers were dried over $MgSO_4$ and evaporated under reduced pressure to give little orange oil. The crude product contained more than 12 compounds (GC/MS) of which two with a total of 13% showed *m/z*=69, according to [M^+−28]-fragment peaks of isomeric alcohols **5a**. Removal of ring-opened compounds by extraction with pentane and Kugelrohr distillation afforded marginal amounts of a colorless liquid, consisting of six different compounds. The relative percentage of isomeric alcohols **5a** was increased to 54%, but the little recovery of organic material did not allow isolation of **5a**. ^{1}H NMR ($CDCl_3$) δ 3.5 (br s, disappears after treatment with D_2O). IR (neat) 3430, 2241 cm^{-1}.

2-Methoxycarbonyl-1-cyclobutanone (4b). Cyclobutane ketal **3b** (5.0 g, 0.025 mol) was reacted with 12 equiv. 88% formic acid (15.7 g, 0.300 mol) at 40°C for 1 h. Evaporation of the reaction mixture under reduced pressure followed by repeated extraction of byproduct **9b** with small portions of pentane and Kugelrohr distillation (0.1 mmHg) of the remaining oil gave 2.2 g (68%) of **4b**. ^{1}H NMR ($CDCl_3$) δ 4.24 (1 H, dd, J=9.9, 7.3 Hz), 3.75 (3 H, s), 3.25–3.16 (2 H, m), 2.55–2.17 (2 H, m). ^{13}C NMR ($CDCl_3$) δ 199.8, 167.1, 64.1, 52.2, 46.8, 13.3. IR (neat) 1796, 1733 cm^{-1}. MS (EI) *m/z* (rel intensity) 100 (M^+−28, 44). HRMS (EI) Calcd for $C_6H_8O_3$ (M^+): 128.0473. Found: 128.0466.

Attempted reduction of 4b with sodium cyanoborohydride. According to the attempted reduction of **4a**, little yellow oil was isolated after working-up the reaction mixture of **4b** (1.43 g, 11 mmol) and sodium cyanoborohydride (0.35 g, 5.5 mmol). It consisted of 36% unreacted

cyclobutanone **4b**, 32% glutaric diester **9b** and 32% isomeric **5b** (GC/MS). Although relative amounts of **5b** could be increased to 72% (see above), isolation was not possible. ^{1}H NMR ($CDCl_3$) δ 3.4 (br s, disappears after treatment with D_2O). IR (neat) 3461, 1728 cm^{-1}.

1-Cyano-2-ethoxycyclobutene (10a). Over a dropping funnel, a solution of cyclobutane ketal **3a** (8.1 g, 0.048 mol) in THF (20 mL) was added to a 1 M solution of sodium bis(trimethylsilyl)amide in THF (50 mL, 0.050 mol) at 78°C. The reaction mixture was stirred for 1 h at 78°C, for an additional hour at room temperature and quenched with water. The layers were separated, the aqueous slurry saturated with sodium chloride and extracted with ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and the ether stripped off in vacuo. Subsequent Kugelrohr distillation (0.1 mmHg) afforded 2.5 g (43%) of **10a**. ^{1}H NMR ($CDCl_3$) δ 4.29 (2 H, q, J=7.1 Hz), 2.60 (2 H, t, J=3.3 Hz), 2.36 (2 H, t, J=3.3 Hz), 1.39 (3 H, t, J=7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 164.2, 115.0, 77.5, 66.4, 30.8, 21.2, 14.3. IR (neat) 2202, 1641 cm^{-1}. MS (EI) *m/z* (rel intensity) 123 (M^+, 25), 95 (M^+-28, 25). HRMS (EI) Calcd for C_7H_9NO (M^+): 123.0689. Found: 123.0684.

1-Cyano-1-methyl-2,2-diethoxycyclobutane (11a). Over a period of 20 min, a 1 M solution of sodium bis(trimethylsilyl)amide in THF (50 mL, 0.05 mol) was added dropwise to a −78°C cold mixture of **3a** (8.3 g, 0.049 mol) and iodomethane (3.2 mL, 0.052 mol) in THF (20 mL). After stirring for 1 h at −78°C, the suspension was allowed to warm up to room temperature and stirred for an additional hour. Water was added, and the layers were separated. The aqueous slurry was saturated with sodium chloride and extracted with ether (3×20 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. Removal of the ether in vacuo followed by Kugelrohr distillation (0.1 mmHg) gave 6.5 g (78%) of **11a** as a colorless liquid. ^{1}H NMR ($CDCl_3$) δ 3.52–3.34 (4 H, m), 2.32–1.55 (4 H, m), 1.48 (3 H, s), 1.27 (3 H, t, J=6.9 Hz), 1.20 (3 H, t, J=6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 122.3, 100.8, 57.5, 57.4, 41.5, 28.9, 26.0, 19.7, 14.9, 14.7. IR (neat) 2236 cm^{-1}. MS (EI) *m/z* (rel intensity) 155 (M^+-28, 4). HRMS (FAB) Calcd for $C_{10}H_{18}NO_2$ (MH^+): 184.1338. Found: 184.1346.

2-Cyano-2-methyl-1-cyclobutanone (12a). Hydrolysis of methylated cyclobutane ketal **11a** (5.5 g, 0.030 mol) could be achieved on reaction with 12 equiv. 88% formic acid (19.2 g, 0.360 mol). After 20 h at 40°C, the resulting mixture was concentrated under reduced pressure, and the residue purified by Kugelrohr distillation (0.1 mmHg) to give 2.3 g (71%) of **12a**. ^{1}H NMR ($CDCl_3$) δ 3.46–3.37 (2 H, m), 2.68–2.53 (1 H, m), 2.19–2.04 (1 H, m). ^{13}C NMR ($CDCl_3$) δ 197.7, 118.1, 53.8, 45.6, 24.2, 19.8. IR (neat) 2235, 1800 cm^{-1}. MS (EI) *m/z* (rel intensity) 109 (M^+, 1), 81 (M^+-28, 70). HRMS (EI) Calcd for C_6H_7NO (M^+): 109.0528. Found: 109.0527.

2-Cyano-2-methyl-1-cyclobutanol (13a). A solution of methylated cyclobutanone **12a** (1.0 g, 0.010 mol) and sodium borohydride (0.2 g, 0.005 mol) in THF (25 mL) was stirred on a water bath at 25°C. After 5 h, the mixture was acidified to pH 4–6 by addition of formic acid, concentrated and extracted with ether (6×5 mL). The ether layers were washed with a saturated aqueous solution of sodium bicarbonate, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Kugelrohr distillation (0.1 mmHg) of the residue afforded 0.5 g (43%) of an isomeric mixture of **13a**. ^{1}H NMR ($CDCl_3$) δ 4.58–4.47/4.03–3.90 (1 H, m, 2 isomers), 4.12 (1 H, br s, disappears after treatment with D_2O), 2.41–1.23 (4 H, m), 1.47/1.44 (3 H, s, 2 isomers). ^{13}C NMR ($CDCl_3$) δ 124.0/122.5, 72.3/69.3, 42.7/36.1, 28.4/27.7/24.8/24.7, 22.4/16.2. IR (neat) 3430, 2235 cm^{-1}. MS (EI) *m/z* (rel intensity) 112 (MH^+, 1), 83 (M^+-28, 8). HRMS (EI) Calcd for C_6H_9NO (M^+): 111.0684. Found: 111.0695.

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