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On the Mechanism and Kinetics of Radical Reactions of Epoxyketones and Epoxynitriles Induced by Titanocene Chloride

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The reactions of a series of epoxynitriles and epoxyketones induced by titanocene chloride have been studied. The kinetics of the decyanogenation of β , γ -epoxynitriles with Ti(III) corresponds to a radical reaction ($k_{25} \approx 10^6 \text{ s}^{-1}$), as demonstrated by competition experiments with H-transfer from 1,4-cyclohexadiene (1,4-CHD) or PhSH or conjugate addition to acrylonitrile. The 5-*exo* cyclization onto nitrile induced by Ti(III) is a radical reaction ($k_{25} \approx 10^7 \text{ s}^{-1}$) as seen in competition experiments with H-transfer from PhSH or the titanocene—water complex. The iminyl or alkoxyl radicals generated by 5-*exo* cyclization onto nitriles or ketones only undergo a reduction with Ti(III). This reaction overwhelms any alternative process, such as tandem cyclization onto alkenes or β -scission. Iminyl radicals generated by 4-*exo* cyclizations onto nitriles undergo reduction with Ti(III) and β -scission in a ratio of 60:40 when the α -substituent is COOR. In nearly all the reactions studied, the role of Ti(III) is triple: a radical initiator (homolytic cleavage of oxirane), a Lewis acid (coordination to CN or C=O), and a terminator (reduction of iminyl or alkoxyl radicals).

Introduction

Intramolecular additions of radicals to polar multiple bonds such as a carbonyl group or a cyano group are unfavorable processes,¹ the former due to reversibility and the latter to slowness. Despite these drawbacks, radical cyclization to polar multiple bonds might be successful if the alkoxyl or iminyl radical intermediate can be effectively trapped² and the cyano group can be activated. Radical cyclization onto nitriles has been reported to be an enigmatic reaction.³ It is known that 5-*exo*trig cyclization onto nitrile is a slow process, at the limit of the synthetic usefulness,⁴ while 6-*exo* and 7-*exo* processes have received little attention.^{1e,2c} We have not found examples of 4-*exo* cyclization onto nitriles except when the radicals are generated with Ti(III).^{5a} Cyclic iminyl radicals generated with Bu₃SnH could undergo reduction, β -scission, or tandem cyclization onto alkenes, depending on the nature of the α -substituents (Scheme 1).^{3a} β -Scission is favored by ring strain⁶ and

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SCHEME 2. Reversibility in Radical Cyclization onto Carbonyl Groups



the formation of stabilized radicals (X = attractor group).⁷ Tandem reactions onto alkenes are faster than reduction with Bu_3SnH .^{3a,8}

The intramolecular addition of radicals generated with Bu₃-SnH to aldehydes has been established for 5-*exo* and 6-*exo* ring closures.² Examples of radical cyclizations onto ketones by this method are rare, due to faster β -scission. To avoid reversibility in the radical cyclization onto aldehydes, and especially onto ketones, a method based on the fast trapping of the intermediate alkoxyl radicals with reagents such as triethylborane has been devised (Scheme 2). A 5-*exo*-trig cyclization onto ketone has been achieved with triethylborane in the presence of oxygen. Good yields of cyclopentanols need a large excess of BEt₃/O₂. This reagent is claimed to act as a Lewis acid, a radical initiator, and a terminator.^{2b} However, no other size cycles have been obtained by this method.

We have recently reported high yield methods for the synthesis of cyclobutanones to cycloheptanones from epoxynitriles^{5a} and cyclopropanols to cyclohexanols from epoxyaldehydes and epoxyketones, with titanocene chloride as reagent.^{5b-d} It is well-known that Ti(III) promotes the homolytic cleavage of a epoxide

SCHEME 3. CN Elimination



SCHEME 4. Hypothetical Heterolytic Pathways



SCHEME 5. Base-Catalyzed Elimination

 $\begin{array}{c} H \\ I \\ R - CH - CH_2 \\ L \\ CN \\ CN \end{array} \xrightarrow{B^{\Theta}} R - CH - CH_2 \\ CN \\ CN \\ CN \end{array} \xrightarrow{B^{\Theta}} R - CH = CH^{+ \Theta} CN$

to a carbon radical,⁹ but we are unaware of the actual role of Ti(III) in these reactions. Below we compare the behavior of Cp_2TiCl with that reported for Bu_3SnH . The kinetics, mechanism, and synthetic usefulness of reactions induced by titanocene chloride on a series of epoxyketones and epoxynitriles are explored, and some interesting new reactions have been uncovered.

Results and Discussion

The first reaction to be studied was the reported reaction of the epoxynitrile **1** with Cp₂TiCl, which affords exclusively the allylic alcohol **2** instead of the desired cyclopropanone (Scheme 3).^{5a}

The reaction takes place in two steps. The initial step of this reaction is based on the well-documented titanocene-mediated opening of epoxides⁹ such as **1** to give the radical **3**, which could further react following two pathways. The heterolytic way should be discarded due to the following: the attack of a second equivalent of the titanium reagent to the tertiary radical **3** to give the reduction product **4** is very improbable, due to steric factors (Scheme 4). The behavior of Cp₂TiCl is comparable to that of bulky bases with tertiary alkyl halides.¹⁰

In the event of the intermediate **4** being formed, it would evolve in three ways to afford deoxygenation, decyanogenation,

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SCHEME 6. Homolytic Pathway











or dehydrogenation products. The deoxygenation pathway has mainly been observed for secondary radicals.^{9a}

The elimination of $^-$ CN would be the least likely. From previous work with base-catalyzed elimination, it is known that the cyano group is a very poor leaving group (Scheme 5).¹¹ For the depicted reaction, only 2% alkene was obtained after 117 h.

The dehydrogenation pathway would not be feasible because the s-alkyl complexes of the electron-poor transition metals (Ti, Zr), such as **4**, in high formal oxidation states, show a low tendency to be eliminated as hydride complexes to give alkenes.¹²

SCHEME 9. Radical Competition Cyclization versus Additions



SCHEME 10. Mechanistic Pathway for Radical Cyclization of 9 with Ti(III)



Following the homolytic pathway, the radical **3** would evolve in two directions: the well-known β -hydrogen elimination^{5b,10a,b} and the unknown β -cyano elimination^{5a} (Scheme 6).

The kinetics of the decyanogenation corresponds, as will be seen, to a radical reaction. The following experiments should demonstrate that the homolytic decyanogenation would be the real reaction pathway (Scheme 7). First, when we treated 1 with Cp₂TiCl (2.5 equiv) in the presence of 1,4-CHD (10 equiv), two products were obtained, 2 and 7, in a 93:7 ratio. The decyanogenation compound 2 was the main product. This result indicated that the elimination of CN is almost 13 times faster than the hydrogen atom transfer from 1,4-CHD ($k_{50} = 2 \times 10^5$ $M^{-1} s^{-1}$).¹³ Second, when we treated **1** with Cp₂TiCl (2.5 equiv) in the presence of methylacrylate (10 equiv), two products were obtained, 2 and 8, in a 70:30 ratio. The major product was the allylic alcohol 2, resulting from the decyanogenation. The minor product 8 was the result of an intermolecular radical addition^{9a} followed by a Thorpe-type cyclization and radical reduction. This result showed that elimination of CN is twice as fast as the radical addition to an activated alkene ($k_{20} = 1.1 \times 10^6$ $M^{-1} s^{-1}$).¹⁴

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FIGURE 1. Titanocene complex with water or methanol.



SCHEME 12. Reaction of 16 with Ti(III)



A third experiment with the epoxynitrile **1** was performed, adding PhSH (10 equiv) to the reaction with Cp₂TiCl (2.5 equiv). This time only the reduction product **7** was obtained after the reaction of radical **3** with thiophenol hydrogen ($k_{20} =$ $9 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$).¹⁵ The former two reactions showed the rate constant for the decyanogenation to be close to $k_{25} = 2.5 \times 10^6 \text{ s}^{-1}$, which is coherent with the result obtained for the reaction with added PhSH.¹⁵ The reaction of **1** with Cp₂TiCl was not altered by the presence of methanol or phenol. SCHEME 13. Reaction of 23 with Ti(III)



In light of these results, the decyanogenation of epoxynitrile 1 to give 2 could be explained in terms of two homolytic cleavages aided by coordination of Cp₂TiCl to nitrile, as shown in Scheme 8, and indicate that Cp₂TiCl acts as not only a radical initiator but also a Lewis acid and radical terminator.¹⁶

The second process to be studied was the reaction of epoxynitrile **9** with Cp_2TiCl in THF, which gave only the cyclic hydroxyketone **10** after further hydrolysis.^{5a} We have assumed a radical mechanism to explain this reaction. Here our aim is to test this hypothesis by carrying out several experiments (Scheme 9).

First, we observed that at least 2 equiv of Cp₂TiCl was necessary for the reaction to be completed. Only one-third of conversion was reached using 1 equiv of Cp₂TiCl. These results are consistent with the formation of a titanium-coordinated nitrile, ClCp₂Ti···NC-R, in which the nitrile group is an efficient radical acceptor as compared with the noncoordinated nitrile.^{16,17} The titanium–nitrile complex would also explain the increased rate of radical cyclization when compared with that promoted by Bu₃SnH in halonitriles.¹⁸ The yield and conversion were independent of the addition order: reagent over substrate or vice versa.

For a better understanding of the kinetic of the cyclization, we repeated the reaction using five additives. When PhSH (10 equiv) was added to the reaction of **2** with Cp₂TiCl, a mixture of hydroxyketone **10** and hydroxynitrile **11** in a 56:44 ratio was obtained. It is known that the rate constant for the reaction of radicals with PhSH is $k_{20} = 9 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$.¹⁵ This result shows that the cyclization and hydrogen transfer from PhSH rate are almost equal. This means that the rate constant for 5-*exo* radical cyclization onto nitrile is around $k_{25} = 9 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, which is farther away from that reported for the 5-cyanobutyl radical, $k_{25} = 4 \times 10^3 \text{ s}^{-1}$.¹⁸ This shows that titanocene accelerates the cyclization through a titanium-coordinated nitrile

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SCHEME 14. Reaction of 29 with Ti(III)



 $ClCp_2Ti$ ···NC $-R^{17a}$ with a LUMO level lower than the uncoordinated nitrile **9** (Scheme 10). The cyclization gave an iminyl radical coordinated to Ti(III) **14**,¹⁶ which further evolved to afford the N-Ti bond, as in **15**.

The addition of 1,4-CHD did not alter the result obtained without it. It is clear that cyclization is much faster than hydrogen transfer. The same happened when methyl acrylate was the additive.

Recently, water has been introduced as a source of hydrogen atoms in radical chemistry mediated by Ti(III).^{10a} When water (10 equiv) was added to the reaction between 9 + Ti(III), a mixture of **10** and **11** was obtained in a 78:22 ratio, but conversion of the epoxide was 50%. An aqua complex such as that shown in Figure 1 has been proposed^{10a} to explain the transfer of hydrogen atoms to radicals. This means that the reagent is partly consumed in this reaction. When methanol was added to the reaction, only **10** was obtained, but conversion was only 50%. The methanol seems to complex the Ti(III) (Figure 1) and inhibit the reaction with the epoxide but does not transfer atomic hydrogen as in the case of water.

To corroborate the role of Cp₂TiCl in the radical cyclization onto nitriles, we examined the reaction of precursors with electron-withdrawing α -substituents. Reported examples of radicals generated from nitrile halides with Bu₃SnH indicate that only translocation products are obtained, due to stabilization of intermediate radicals (Scheme 11).³

In our case, from 16, no translocation product 22 was obtained, only the cyclization product 20 (94%) (Scheme 12). This means that the reaction proceeds through the titanium-coordinated nitrile 17, following with titanium-coordinated iminyl radical 18 and finally the imine Ti(IV) derivative 19, which after hydrolysis and tautomerization gives the amino nitrile 20. The reaction of the iminyl radical 18 with the coordinated Ti(III) is faster than translocation to 21.

The translocations are favored not only by the stabilization of radicals but also by ring strain. All the reported examples of cyclobutyliminyl radical intermediates evolve to nitriles by β -fission.¹⁹ We found that the major product from the reaction of epoxydinitrile **23** with Ti(III) was the enaminonitrile **26** (75%), which arose by tautomerization of the initial imine Ti-(IV) **25** after hydrolysis (Scheme 13). The minor compound was the translocation product **28** (3%). In this case, the results





are best rationalized in terms of the cyclobutane ring strain, which competes, although to a low extent, with the reduction of the coordinated iminyl radical **24**.

Our next insight into the kinetics and mechanisms of radical reactions came from a tandem radical reaction involving cyclization onto nitriles to yield intermediate iminyl radicals followed by cyclization of the iminyl radicals onto alkenes. This kind of tandem reaction has been attempted from unsaturated dinitrile halides, with the translocation compound as the only reaction product.^{3a} In our case, from 29, two products were obtained: the cyclization diastereomeric mixture 32 in 62% yield, and the translocation diastereomeric mixture 34 in 30% yield (Scheme 14). No direct 6-exo cyclization onto the C=C double bond nor tandem cyclization takes place. The translocation product would not be expected if the earlier epoxydinitrile 16 were taken as reference. We attribute the difference in behavior to the very crowded environment of the nitrogen iminyl radical in the intermediate 30, which is partly decoordinated from Ti(III).

The substitution of a CN attractor group by a hydrogen group in the model dinitrile **29** would facilitate the tandem reaction against translocation, as has been reported.^{3a} In our case, the mononitrile compound **35** afforded only the diastereomeric cyclization mixture onto nitrile **36** (88%); neither the tandem product nor the translocation product was obtained (Scheme 15).

To check whether the radical generated by a translocation, which is conjugated to the nitrile group as in **41**, reacted faster with Ti(III) than with the C=C bond in a 5-*exo* cyclization, we assayed a model involving the unsaturated epoxydinitrile **37** (Scheme 16). The unsaturated chain is longer than that of the model **29** and permits the 5-*exo* cyclization of the radical **41**. The reaction of **37** with Ti(III) afforded a diastereomeric mixture of the cyclization product onto nitrile **40** as the major product (62%) and the translocation compound **42** as the minor product (31%). No product derived from the 5-*exo* or 6-*endo* cyclization of the conjugated radical **41** with Ti(III) was faster.

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SCHEME 16. Reaction of 37 with Ti(III)



SCHEME 17. Reaction of 43 with Ti(III)



In a previous work,^{5b} we observed that radical cyclization of epoxyketones with Ti(III) is inhibited by PhSH but not by MeOH or PhOH. In the present work, we performed the reaction of **43** with Ti(III), adding 1,4-CHD. The result was the same as that without 1,4-CHD (Scheme 17).^{5b} A mixture of diastereomeric diols **46** (86%) was the only product obtained. In light of this result, the rate constant for the cyclization of a tertiary radical onto C=O would be situated between $k_{20} = 9 \times 10^7$ M⁻¹s⁻¹ (ref 15) and $k_{50} = 2 \times 10^5$ M⁻¹ s⁻¹ (ref 13).

An interesting step in the radical cyclization is the fate of the alkoxyl radical **45**. It has been suggested that these highly electrophilic radicals abstract hydrogen from the solvent THF (Scheme 18).²⁰ If this hypothesis were correct, the tetrahydro-furanyl radical could be trapped by aldehydes, as has been shown recently by Yoshimitsu et al.²¹

The addition of 4-methoxybenzaldehyde to the reaction of epoxyketone **43** with Ti(III) in THF did not produce the expected α -substituted tetrahydrofuran-2-methanol, but unaltered aldehyde.

Another experiment to determine the evolution of the alkoxyl radical was carried out with the unsaturated epoxyketone **47**

SCHEME 18. Hydrogen Abstraction by Alkoxyl Radical and Aldehyde Trap







with the aim of trapping the alkoxyl radical **49** through a 5-*exo* cyclization process onto a C=C bond to **52** (Scheme 19). The rate constant for this type of cyclization is around $k = (4 \pm 2) \times 10^8 \text{ s}^{-1}$.²² The reaction of epoxyketone **47** with Ti(III) only afforded the diol **51** as a diastereomeric mixture (83%). No hydroxyether **53** was found. These results could be explained, as with the nitriles, in terms of a titanium-coordinated carbonyl

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ClCp₂Ti···O=CR₂, as in **48** in which the carbonyl group is an efficient radical acceptor.^{16,17} The reaction of **47** with Ti(III) must proceed through similar intermediates as seen in Scheme 10. The reaction of the alkoxyl radical with Ti(III) is faster than (a) intramolecular addition to the C=C bond, (b) abstraction of hydrogen from THF ($k = 10^7 \text{ M}^{-1} \text{ s}^{-1}$),²³ or (c) β -scission ($k_{25} = 9.1 \times 10^7 \text{ s}^{-1}$).^{18b}

Previously, we have seen (Scheme 14) that the iminyltitanium radical complex undergoes β -scission when the environment of the N-Ti bond is very crowded and if the radical formed after the fission is stabilized by an attractor group. Regarding this issue, we investigated the behavior of some analogue alkoxyl radicals.^{3b} Treatment of epoxyketoester 54 with Ti(III) gave a diastereomeric mixture of diol esters 57 (65%) (Scheme 20). No translocation product, such as 59, was obtained from the reaction of 54 with Cp2TiCl, but only the cyclization product resulting from radical alkoxyl trapping with Ti(III). In this case, the R–O•••••Ti(III) coordination must be stronger than R-CN••••Ti(III).17a The PM3 semiempirical calculations developed by Itoh et al. suggest that the unpaired spin is localized on the titanium center in the complex Cp₂PhTi···NC-CH₃, whereas the unpaired spin is almost completely transferred to the carbonyl carbon from the titanium center in the complex PhCp₂Ti····O=C(CH₃)₂.¹⁷

To force the cleavage of the alkoxyl radical intermediate, we tackled the cyclization of epoxyketoester **60**, which must occur through the highly strained cyclobutane intermediate **61** (Scheme 21). The reaction of **60** with Cp₂TiCl gave a diol ester **63** (35%) and a diastereomeric mixture of hydroxyketoesters **65** (21%). The acyclic product **65** is the result of the radical **61** β -scission.

The syntheses of the epoxides whose radical reactions have been studied in the present work are described in the Supporting Information.

Conclusion

The results above show that the kinetics of CN elimination induced by Cp₂TiCl in β , γ -epoxynitriles is in the range expected for a radical reaction. Epoxynitriles and epoxyketones cyclizations induced by titanocene chloride are mediated radical processes.

SCHEME 21. Reaction of Epoxide 60 with Ti(III)



The role of titanocene chloride, substantial in this kind of process, is to promote the homolytic regioselective cleavage of oxirane rings and also to complex the cyano and carbonyl groups. The complexation facilitates radical cyclization by making accessible a low-lying LUMO level of complex. Finally, the titanocene chloride acts as a radical terminator.

The rate of iminyl or alkoxyl radical reductions with titanocene chloride is much faster than radical cyclization or the β -scission reaction. Only cyclobutane alkoxyl or iminyl radicals gave some β -scissions.

Experimental Section

General Methods. Melting points are uncorrected. ¹H NMR spectra were measured at either 200 or 400 MHz, and ¹³C NMR were measured at 50 or 100 MHz in CDCl₃ and referenced to TMS (¹H) or solvent (¹³C), except where indicated otherwise. IR spectra were recorded for neat samples on NaCl plates, unless otherwise noted. Standard mass spectrometry data were acquired by using GC-MS system in EI mode with a maximum m/z range of 600. When required, all solvents and reagents were purified by standard techniques: tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone ketyl and degassed before use. Dimethylformamide (DMF) was dried over CaH₂, distilled under reduced pressure, and degassed before use. All reactions were conducted under a positive pressure of argon, utilizing standard benchtop techniques for the handling of air-sensitive materials. Chromatographic separations were carried out under pressure on silica gel using flash column techniques on Merck silica gel 60 (0.040-0.063 mm). Yields reported are for chromatographically pure isolated products unless otherwise mentioned.

General Procedure 1 (GP 1). Reaction of Epoxides with Cp₂TiCl. A mixture of Cp₂TiCl₂ (2.50 mmol) and Zn (7.50 equiv) in strictly deoxygenated THF (4 mL) was stirred at room temperature until the red solution turned green. In a separate flask, the epoxy compound (1 mmol) was dissolved in strictly deoxygenated THF (20 mL). The green Ti(III) solution was slowly added via cannula to the epoxide solution. After 30 min, an excess of saturated NaH₂PO₃ was added, and the mixture was stirred for 20 min. The product was extracted into ether, and the combined organic layers were washed with saturated NaHCO₃ and brine, dried (Na₂SO₄), and filtered. After removal of the solvent, the crude product was purified by flash chromatography.

Reaction of 1 with Cp₂TiCl. According to GP 1, reaction of 1 (200 mg, 1.10 mmol) with Cp₂TiCl followed by flash chromatography (hexane/diethyl ether 85:15) furnished 2-methylnon-1-en-3-ol 2 (111 mg, 65%), as a colorless oil: IR, ν 3370, 1653, 1030

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(c) Busfield, W. K.; Grice, I. D.; Jenkins, I. D. J. Chem. Soc., Perkin Trans. 2 1994, 1079–1086.

cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (3H, t, J = 7 Hz), 1.2–1.6 (10H, m), 1.72 (3H, s), 4.05 (1H, t, J = 6.5 Hz), 4.83 (1H, s), 4.93 (1H, s) ppm; ¹³C NMR (CDCl₃) δ 13.9 (CH₃), 17.4 (CH₃), 22.5 (CH₂), 25.4 (CH₂), 29.1 (CH₂), 31.7 (CH₂), 34.9 (CH₂), 75.9 (CH), 110.8 (CH₂), 147.6 (C) ppm; MS EI, m/z (relative intensity) 156 (M⁺, 3), 99 (11), 94 (12), 86 (18), 71 (100), 55 (20); HRMS (ESI) 157.1566 (M⁺ + H, C₁₀H₂₁O), calcd 157.1587. Anal. Calcd for C₁₀H₂₀O: C, 76.86; H, 12.90. Found; C, 76.91; H, 12.96.

Reaction of 1 with Cp2TiCl/1,4-CHD. According to GP 1, reaction of 1 (70 mg, 0.39 mmol) with Cp2TiCl and 1,4-CHD (312 mg, 3.90 mmol) followed by flash chromatography (hexane/diethyl ether 85:15) furnished 2 (38 mg, 63%) and a 1:1 mixture of diastereoisomeric 4-hydroxy-3-methyldecanonitrile 7 (3.5 mg, 5%), as a viscous oil: IR, v 3488, 2248, 1028, cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (6H, t, J = 6.6 Hz), 1.02 (3H, d, J = 6.8 Hz), 1.09 (3H, d, J = 6.8 Hz)*, 1.2–1.5 (20H, m), 1.84 (1H, m)*, 1.94 (1H, m), 2.30 (1H, dd, $J_1 = 7.6$ Hz, $J_2 = 16.1$ Hz), 2.48 (3H, m), 3.45 (1H, m)*, 3.64 (1H, m) ppm; ¹³C NMR (CDCl₃) δ 12.9 (CH₃), 14.0 (2CH₃), 16.4 (CH₃)*, 20.3 (CH₂)*, 21.4 (CH₂), 22.52 (2CH₂), 25.3 (CH₂)*, 25.9 (CH₂), 29.1 (2CH₂), 31.7 (2CH₂), 34.2 (CH), 34.5 (CH₂)*, 35.6 (CH), 36.1 (CH)*, 73.0 (CH), 74.2 (CH)*, 119.4 (C) 120.1 (C)* ppm; MS EI, m/z (relative intensity) 138 (M⁺ - 45, 1), 96 (24), 68 (100), 55 (20); HRMS (ESI) 206.1532 (M^+ + Na, C₁₁H₂₁NONa), calcd 206.1520.

Reaction of 1 with Cp₂TiCl/Methyl Acrylate. According to GP 1, reaction of 1 (50 mg, 0.28 mmol) with Cp₂TiCl and methyl acrylate (240 mg, 2.80 mmol) followed by flash chromatography (hexane/diethyl ether 85:15) furnished 2 (29 mg, 67%) and two diastereoisomers of methyl 2-amino-4-(1-hydroxy-hepthyl)-4-methylcyclopent-1-enecarboxylate 8: less polar isomer (11 mg, 16%), more polar isomer (12 mg, 16%).

Data for less polar isomer: IR, ν 3451, 3360, 1735, 1668 cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (3H, t, J = 6.6 Hz), 1.06 (3H, m), 1.2– 1.7 (10H, m), 1.98 (2H, d, J = 16.5 Hz), 2.23 (1H, d, J = 14.0Hz), 2.55 (1H, d, J = 14.0 Hz), 2.66 (1H, d, J = 16.5 Hz), 3.49 (1H, m), 3.68 (3H, s) ppm; ¹³C NMR (CDCl₃) δ 14.0 (CH₃), 22.5 (CH₂), 23.4 (CH₃), 26.7 (CH₂), 29.2 (CH₂), 31.8 (CH₂), 32.4 (CH₂), 39.9 (CH₂), 43.4 (C), 44.8 (CH₂), 50.2 (CH₃), 78.8 (CH), 93.4 (C), 159.9 (C), 168.3 (C) ppm; MS EI, m/z (relative intensity) 269 (M⁺, 7), 154 (100), 122 (36), 115 (90), 94 (37), 83 (25), 67 (20), 55 (65); HRMS (ESI) 292.1883 (M⁺ + Na, C₁₅H₂₇NO₃Na), calcd 292.1888. Anal. Calcd for C₁₅H₂₇NO₃: C, 66.88; H, 10.10; N, 5.20. Found: C, 66.69; H, 10.19; N, 5.34.

Data for more polar isomer: IR, ν 3458, 3380, 1739, 1669 cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (3H, t, J = 6.6 Hz), 1.03 (3H, m), 1.2– 1.7 (10H, m), 2.10 (1H, d, J = 16.5 Hz), 2.17 (1H, d, J = 13.7Hz), 2.46 (1H, d, J = 13.7 Hz), 2.69 (1H, d, J = 16.5 Hz), 3.49 (1H, m), 3.68 (3H, s) ppm; ¹³C NMR (CDCl₃) δ 14.0 (CH₃), 22.1 (CH₃), 22.5 (CH₂), 26.7 (CH₂), 29.2 (CH₂), 31.7 (CH₂), 32.4 (CH₂), 40.5 (CH₂), 43.5 (C), 45.7 (CH₂), 50.2 (CH₃), 78.8 (CH), 93.2 (C), 159.9 (C), 168.3 (C) ppm; MS EI, m/z (relative intensity) 269 (M⁺, 4), 154 (53), 122 (26), 115 (100), 94 (25), 83 (27), 67 (13), 55 (38); HRMS (ESI) 292.1881 (M⁺ + Na, C₁₅H₂₇NO₃Na), calcd 292.1888. Anal. Calcd for C₁₅H₂₇NO₃: C, 66.88; H, 10.10; N, 5.20. Found: C, 66.71; H, 10.16; N, 5.22.

Reaction of 1 with Cp₂TiCl/PhSH. According to GP 1, reaction of **1** (80 mg, 0.44 mmol) with Cp₂TiCl and PhSH (404 mg, 4.40 mmol) followed by flash chromatography (hexane/diethyl ether 85: 15) furnished **7** (75 mg, 93%), as a 1:1 mixture of diastereoisomers.

Reaction of 9 with Cp₂TiCl. According to GP 1, reaction of **9** (125 mg, 1.0 mmol) with Cp₂TiCl followed by flash chromatography (hexane/diethyl ether 50:50) furnished 2-(hydroxymethyl)-2-methylcyclopentanone **10** (102 mg, 80%), as a colorless oil: IR, ν 3445, 1732 cm⁻¹; ¹H NMR (CDCl₃) δ 0.98 (3H, s), 1.6–2.4 (6H, m), 3.42 (1H, d, J = 10.9 Hz), 3.58 (1H, d, J = 10.9 Hz) ppm; ¹³C NMR (CDCl₃) δ 18.74 (CH₂), 19.2 (CH₃), 33.05 (CH₂), 38.3 (CH₂), 50.2 (C), 66.9 (CH₂), 224.3 (C) ppm; MS EI, *m/z* (relative intensity) 128 (M⁺, 9), 82 (27), 69 (89), 57 (100); HRMS (ESI) 129.0905 (M⁺ + H, $C_7H_{13}O_2$), calcd 129.0910. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.83; H, 9.41.

Reaction of 9 with Cp₂TiCl/PhSH. According to GP 1, reaction of **9** (40 mg, 0.32 mmol) with Cp₂TiCl and PhSH (352 mg, 3.20 mmol) followed by flash chromatography (hexane/diethyl ether 50: 50) furnished **10** (22 mg, 56%) and 6-hydroxy-5-methylhexanenitrile **11** (18 mg, 44%), as a viscous oil: IR, ν 3409, 2248, 1047 cm⁻¹; ¹H NMR (CDCl₃) δ 0.94 (3H, d, J = 6.5 Hz), 1.20 (2H, m), 1.5–1.8 (3H, m), 2.35 (2H, t, J = 6.7 Hz), 3.48 (2H, d, J = 5.3 Hz) ppm; ¹³C NMR (CDCl₃) δ 16.2 (CH₃), 17.3 (CH₂), 22.9 (CH₂), 32.2 (CH₂), 35.0 (CH), 67.6 (CH₂), 119.5 (C) ppm; MS EI, *m/z* (relative intensity) 96 (M⁺ – 31, 44), 82 (51), 69 (86), 54 (100); HRMS (ESI) 150.0734 (M⁺ + Na, C₇H₁₃NONa), calcd 150.0734. Anal. Calcd for C₇H₁₃NO: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.23; H, 10.36; N, 11.13.

Reaction of 9 with Cp₂TiCl/1,4-CHD. According to GP 1, reaction of **9** (40 mg, 0.32 mmol) with Cp₂TiCl and 1,4-CHD (256 mg, 3.20 mmol) followed by flash chromatography (hexane/diethyl ether 50:50) furnished **10** (38 mg, 95%)

Reaction of 9 with Cp₂TiCl/Methyl Acrylate. According to GP 1, reaction of **9** (100 mg, 0.80 mmol) with Cp₂TiCl and methyl acrylate (688 mg, 8.0 mmol) followed by flash chromatography (hexane/diethyl ether 50:50) furnished **10** (77 mg, 75%).

Reaction of 9 with Cp₂TiCl/H₂O. According to GP 1, reaction of **9** (40 mg, 0.32 mmol) with Cp₂TiCl and H₂O (58 mg, 3.2 mmol) followed by flash chromatography (hexane/diethyl ether 50:50) furnished **10** (16 mg, 39%) and **11** (4.5 mg, 11%).

Reaction of 9 with Cp₂TiCl/MeOH. According to GP 1, reaction of **9** (50 mg, 0.40 mmol) with Cp₂TiCl and MeOH (128 mg, 4.0 mmol) followed by flash chromatography (hexane/diethyl ether 50:50) furnished **10** (24 mg, 50%).

Reaction of 16 with Cp₂TiCl. According to GP 1, reaction of **16** (100 mg, 0.66 mmol) with Cp₂TiCl followed by flash chromatography (hexane/ethyl acetate 30:70) furnished 2-amino-3-hydroxy-3-methylcyclopent-1-enecarbonitrile **20** (94 mg, 94%), as a colorless oil: IR, ν 3363, 2179, 1614, 1052 cm⁻¹; ¹H NMR (CDCl₃) δ 1.20 (3H, s), 1.65 (2H, m), 2.45 (2H, m), 3.53 (1H, d, J = 10.4 Hz), 3.62 (1H, d, J = 10.4 Hz) ppm; ¹³C NMR (CDCl₃) δ 20.5 (CH₃), 27.5 (CH₂), 33.5 (CH₂), 49.3 (C), 69.3 (CH₂), 73.1 (C), 118.8 (C), 166.9 (C); HRMS (ESI) 175.0857 (M⁺ + Na, C₈H₁₂N₂ONa), calcd 175.0847. Anal. Calcd for C₈H₁₂N₂O: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.25; H, 7.91; N, 18.49.

Reaction of 23 with Cp₂TiCl. According to GP 1, reaction of **23** (80 mg, 0.58 mmol) with Cp₂TiCl followed by flash chromatography (hexane/diethyl ether 75:25) furnished 2-(hydroxymethyl)-2-methylpentanedinitrile **28** (2 mg, 3%), as a colorless oil: IR, ν 3429, 2220, 1057 cm⁻¹; ¹H NMR (CDCl₃) δ 1.38 (3H, s), 1.90 (1H, m), 2.20 (1H, m), 2.62 (2H, m), 3.63 (1H, d, J = 11.0 Hz), 3.74 (1H, d, J = 11.0 Hz) ppm; ¹³C NMR (CDCl₃) δ 13.4 (CH₂), 20.7 (CH₃), 31.6 (CH₂), 39.0 (C), 67.3 (CH₂), 118.4 (C), 121.3 (C) ppm; HRMS (ESI) 161.0693 (M⁺ + Na, C₇H₁₀N₂ONa), calcd 161.0690. Anal. Calcd for C₇H₁₀N₂O: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.88; H, 7.32; N, 20.22.

2-Amino-3-hydroxymethyl-3-methylcyclobut-1-enecarbonitrile **26** (60 mg, 75%) was obtained as a colorless oil: IR, ν 3442, 2249, 1093 cm⁻¹; ¹H NMR (CDCl₃) δ 1.60 (3H, s), 1.68 (1H, d, J = 5.3Hz), 1.79 (1H, d, J = 5.3 Hz), 4.20 (1H, d, J = 9.6 Hz), 4.30 (1H, d, J = 9.6 Hz) ppm; ¹³C NMR (CDCl₃) δ 15.2 (CH₃), 26.4 (CH₂), 35.6 (C), 72.3 (CH₂), 77.6 (C), 114.0 (C), 168.7 (C) ppm; MS EI, m/z (relative intensity) 136 (M⁺ - 2, 6), 122 (13), 93 (23), 80 (87), 66 (25), 52 (100); HRMS (ESI) 161.0684 (M⁺ + Na, C₇H₁₀N₂-ONa), calcd 161.0690. Anal. Calcd for C₇H₁₀N₂O: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.69; H, 7.39; N, 20.21.

Reaction of 29 with Cp₂TiCl. According to GP 1, reaction of **29** (100 mg, 0.57 mmol) with Cp₂TiCl followed by flash chromatography (hexane/ethyl acetate 60:40) furnished a mixture of isomers of 1-allyl-3-(hydroxymethyl)-3-methyl-2-oxocyclopentanecarbonitrile **32** (61 mg, 62%), in a ratio of 1.5:1, as a viscous liquid: IR, ν 3480, 2242, 1755 cm⁻¹; ¹H NMR (CDCl₃) δ 1.06 (3H, s)*, 1.13

(3H, s), 1.80–2.60 (12H, m), 3.44 (1H, d, J = 10.5 Hz), 3.52 (1H, d, J = 10.7 Hz)*, 3.73 (1H, d, J = 10.7 Hz)*, 3.76 (1H, d, J = 10.5 Hz), 5.22 (2H, d, J = 15.3 Hz), 5.25 (2H, d, J = 24.1 Hz), 5.80 (2H, m) ppm; ¹³C NMR (CDCl₃) δ 19.8 (CH₃)*, 20.7 (CH₃), 29.2 (CH₂), 29.9 (CH₂), 30.1 (CH₂)*, 30.2 (CH₂)*, 36.7 (CH₂), 38.6 (CH₂)*, 48.3 (C), 49.3 (C)*, 51.3 (C)*, 51.4 (C), 66.6 (CH₂), 67.6 (CH₂)*, 118.5 (C)*, 119.2 (C), 120.7 (CH₂), 120.9 (CH₂)*, 130.6 (CH)*, 130.7 (CH), 212.9 (C) 213.2 (C)* ppm; MS EI, *m*/*z* (relative intensity) 192 (M⁺ – 1, 3), 150 (14), 136 (16), 122 (19), 94 (32), 67 (26), 57 (100); HRMS (ESI) 194.1132 (M⁺ + H, C₁₁H₁₆-NO₂), calcd 194.1176. Anal. Calcd for C₁₁H₁₅NO₂: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.42; H, 7.84; N, 7.28.

A mixture of isomers of 5-allyl-2-(hydroxymethyl)-2-methylhexanedinitrile **34** (30 mg, 30%) was obtained in a ratio 1.5:1, as a viscous liquid: IR, ν 3455, 2242, 1060 cm⁻¹; ¹H NMR (CDCl₃) δ 1.34 (3H, s), 1.36 (3H, s), 1.75–2.10 (8H, m), 2.40 (4H, m), 2.66 (2H, m), 3.63 (4H, m), 5.20 (1H, d, J = 11.3 Hz), 5.22 (1H, d, J = 16.6 Hz), 5.81 (2H, m) ppm; ¹³C NMR (CDCl₃) δ 20.5 (CH₃)*, 21.0 (CH₃), 26.9 (CH₂)*, 27.1 (CH₂), 31.4 (CH), 31.5 (CH)*, 33.0 (CH₂), 33.1 (CH₂)*, 35.9 (CH₂)*, 36.1 (CH₂), 39.1 (C)*, 39.2 (C), 67.5 (CH₂)*, 67.9 (CH₂), 119.3 (2CH₂), 120.8 (2C), 122.4 (2C), 132.4 (2CH) ppm; MS EI, m/z (relative intensity) 177 (M⁺ – 15, 3), 175 (12), 161 (31), 147 (49), 134 (40), 122 (19), 108 (17), 94 (62), 81 (89), 68 (100), 54 (92); HRMS (ESI) 193.1375 (M⁺ + H, C₁₁H₁₇N₂O), calcd 193.1336. Anal. Calcd for C₁₁H₁₆N₂O: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.97; H, 8.32; N, 14.53.

Reaction of 35 with Cp₂TiCl. According to GP 1, reaction of **35** (120 mg, 0.73 mmol) with Cp₂TiCl followed by flash chromatography (hexane/diethyl ether 70:30) furnished 5-allyl-2-(hydroxymethyl)-2-methylcyclopentanone **36**, major isomer (58 mg, 48%) and minor isomer (49 mg, 40%).

Data for major isomer, as a viscous liquid: IR, ν 3444, 1730 cm⁻¹; ¹H NMR (CDCl₃) δ 1.09 (3H, s), 1.65 (2H, m), 2.07 (3H, m), 2.41 (2H, m), 3.47 (1H, d, J = 10.8 Hz), 3.55 (1H, d, J = 10.8 Hz), 5.02 (1H, d, J = 7.6 Hz), 5.07 (1H, d, J = 13.0 Hz), 5.74 (1H, m) ppm; ¹³C NMR (CDCl₃) δ 20.3 (CH₃), 25.0 (CH₂), 31.6 (CH₂), 33.7 (CH₂), 47.9 (CH), 50.1 (C), 67.1 (CH₂), 116.6 (CH₂), 135.6 (CH), 224.3 (C) ppm; MS EI, m/z (relative intensity) 168 (M⁺, 5), 122 (14), 107 (12), 100 (23), 81 (53), 67 (100), 57 (96); HRMS (ESI) 169.1245 (M⁺ + H, C₁₀H₁₇O₂), calcd 169.1223. Anal. Calcd for C₁₀H₁₆O₂: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.53.

Data for minor isomer, as a viscous liquid: IR, ν 3444, 1737 cm⁻¹; ¹H NMR (CDCl₃) δ 0.98 (3H, s), 1.64 (2H, m), 1.96 (1H, m), 2.12 (2H, m), 2.26 (1H, m), 2.50 (1H, m), 3.48 (1H, d, J = 10.8 Hz), 3.65 (1H, d, J = 10.8 Hz), 5.02 (1H, d, J = 9.2 Hz), 5.06 (1H, d, J = 12.3 Hz), 5.73 (1H, m) ppm; ¹³C NMR (CDCl₃) δ 18.9 (CH₃), 24.9 (CH₂), 30.7 (CH₂), 34.1 (CH₂), 49.6 (CH), 50.5 (C), 67.4 (CH₂), 116.5 (CH₂), 135.5 (CH), 224.0 (C) ppm; MS EI, m/z (relative intensity) 168 (M⁺, 5), 122 (17), 107 (12), 100 (30), 81 (49), 67 (100), 57 (96); HRMS (ESI) 169.1228 (M⁺ + H, C₁₀H₁₇O₂), calcd 169.1223. Anal. Calcd for C₁₀H₁₆O₂: C, 71.39; H, 9.59. Found: C, 71.35; H, 9.57.

Reaction of 37 with Cp₂TiCl. According to GP 1, reaction of **37** (100 mg, 0.47 mmol) with Cp₂TiCl followed by flash chromatography (70:30 hexane/ethyl acetate) furnished 3-(hydroxymethyl)-3-methyl-2-oxo-1-(pent-4-enyl)cyclopentanecarbonitrile 40 (64 mg, 62%), as a mixture of isomers in a ratio of 2:1: IR, ν 3487, 3078, 2242, 1748 cm⁻¹; ¹H NMR (CDCl₃) δ 1.09 (3H, s)*, 1.15 (3H, s), 1.50-2.50 (20H, m), 3.46 (1H, d, J = 10.5 Hz), 3.55 (1H, d, J =10.7 Hz, $3.75 (1\text{H}, \text{d}, J = 10.7 \text{ Hz})^*$, 3.78 (1H, d, J = 10.5 Hz), 5.04 (4H, m), 5.78 (2H, m) ppm; ¹³C NMR (CDCl₃) δ 20.1 (CH₃)*, 20.9 (CH₃), 24.0 (CH₂), 24.2 (CH₂)*, 29.6 (CH₂), 30.2 (CH₂)*, 31.0 (CH₂), 31.2 (CH₂)*, 32.2 (CH₂), 33.1 (CH₂), 33.1 (CH₂)*, 34.1 (CH₂)*, 48.6 (C), 49.7 (C)*, 51.1 (C)*, 51.2 (C), 67.0 (CH₂), 67.7 (CH₂)*, 115.4 (CH₂), 115.6 (CH₂)*, 118.6 (C)*, 119.4 (C), 137.2 (CH)*, 137.3 (CH), 213.3 (C) 213.71 (C)* ppm; MS EI, m/z (relative intensity) 206 (M^+ – 15, 2), 154 (40), 122 (19), 110 (18), 94 (25), 80 (23), 72 (39), 57 (100); HRMS (ESI) 222.1456 (M⁺ +

H, $C_{13}H_{20}NO_2$), calcd 222.1483. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.67; H, 8.64; N, 6.34.

2-(Hydroxymethyl)-2-methyl-5-(pent-4-enyl)hexanedinitrile **42** (32 mg, 31%) was obtained as a mixture of isomers in a ratio of 1:1: IR, ν 3461, 2242, 1644, 1073 cm⁻¹; ¹H NMR (CDCl₃) δ 1.35 (3H, s), 1.36 (3H, s), 1.50–2.20 (12H, m), 2.58 (2H, m), 3.64 (4H, m), 5.00 (2H, d, J = 9.2 Hz), 5.03 (2H, d, J = 17.2 Hz), 5.78 (2H, m) ppm; ¹³C NMR (CDCl₃) δ 20.5 (CH₃), 21.0 (CH₃), 26.2 (2CH₂), 27.5 (CH₂), 27.7 (CH₂), 31.2 (CH₂), 31.3 (CH₂), 31.5 (CH), 31.6 (CH), 32.9 (2CH₂), 33.1 (CH₂), 33.2 (CH₂), 39.1 (C), 39.3 (C), 67.6 (CH₂), 68.0 (CH₂), 115.4 (2CH₂), 121.3 (2C), 122.4 (2C), 137.4 (2CH) ppm; MS EI, *m/z* (relative intensity) 205 (M⁺ – 15, 3), 190 (3), 189 (12), 175 (16), 161 (20), 134 (14), 122 (74), 109 (85), 94 (95), 81 (63), 69 (100), 54 (97); HRMS (ESI) 221.1693 (M⁺ + H, C₁₃H₂₁N₂O), calcd 221.1649. Anal. Calcd for C₁₃H₂₀N₂O: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.77; H, 9.21; N, 12.79.

Reaction of 43 with Cp₂TiCl. According to GP 1, reaction of **43** (200 mg, 1.41 mmol) with Cp₂TiCl followed by flash chromatography (hexane/ethyl acetate 70:30) furnished 1,2,2-trimethylcy-clopentane-1,3-diol **46**, minor isomer (75 mg, 37%), major isomer (99 mg, 49%).

Data for minor isomer, colorless oil: IR, ν 3381, 1036 cm⁻¹; ¹H NMR (CDCl₃) δ 0.76 (3H, s), 1.03 (3H, s), 1.14 (3H, s), 1.88 (3H, m), 2.09 (1H, m), 2.96 (1H, br s), 3.73 (1H, d, J = 5.9 Hz) ppm; ¹³C NMR (CDCl₃) δ 15.8 (CH₃), 21.5 (CH₃), 23.8 (CH₃), 30.7 (CH₂), 37.8 (CH₂), 48.2 (C), 82.8 (CH), 83.3 (C) ppm; MS EI, m/z (relative intensity) 126 (M⁺ – 18, 14), 111 (59), 93 (71), 69 (80), 55 (89), 43 (100); HRMS (ESI) 167.1053 (M⁺ + Na, C₈H₁₆O₂Na), calcd 167.1047. Anal. Calcd for C₈H₁₆O₂: C, 66.63; H, 11.18. Found: C, 66.87; H, 11.07.

Data for major isomer, white solid: mp 85–89 °C; IR, ν 3391, 1055 cm⁻¹; ¹H NMR (CDCl₃) δ 0.77 (3H, s), 0.95 (3H, s), 1.17 (3H, s), 1.4–2.2 (5H, m), 4.17 (1H, t, J = 8.5 Hz) ppm; ¹³C NMR (CDCl₃) δ 17.4 (CH₃), 18.8 (CH₃), 23.3 (CH₃), 29.0 (CH₂), 35.9 (CH₂), 47.3 (C), 79.4 (CH), 81.7 (C) ppm; MS EI, m/z (relative intensity) 126 (M⁺ – 18, 13), 108 (92), 93 (40), 83 (39), 71 (100), 55 (55); HRMS (ESI) 167.1043 (M⁺ + Na, C₈H₁₆O₂Na), calcd 167.1047. Anal. Calcd for C₈H₁₆O₂: C, 66.63; H, 11.18. Found: C, 66.98; H, 11.13.

Reaction of 47 with Cp₂TiCl. According to GP 1, reaction of **47** (150 mg, 0.82 mmol) with Cp₂TiCl followed by flash chromatography (hexane/ethyl acetate 70:30) furnished of 1-but-3-enyl-2,2-dimethylcyclopentane-1,3-diol **51**, minor isomer (30 mg, 20%) and major isomer (96 mg, 63%)

Data for minor isomer, colorless oil: ¹H NMR (CDCl₃) δ 0.79 (3H, s), 1.07 (3H, s), 1.48 (1H, m), 1.61 (1H, s), 1.81 (2H, m), 1.97 (1H, m), 2.12 (2H, m), 2.31 (1H, m), 3.75 (1H, br s), 4.96 (1H, d, J = 10 Hz), 5.05 (1H, d, J = 16.2 Hz), 5.87 (1H, m) ppm; ¹³C NMR (CDCl₃) δ 16.0 (CH₃), 23.7 (CH₃), 28.4 (CH₂), 30.8 (CH₂), 34.4 (CH₂), 35.6 (CH₂), 48.8 (C), 83.5 (CH), 85.4 (C), 114.4 (CH₂), 139.3 (C) ppm; HRMS (ESI) 207.1345 (M⁺ + Na, C₁₁H₂₀O₂-Na), calcd 207.1355. Anal. Calcd for C₁₁H₂₀O₂: C, 71.70; H, 10.94. Found: C, 71.87; H, 10.96.

Data for major isomer, white solid: mp 88–89 °C; ¹H NMR (CDCl₃) δ 0.78 (3H, s), 1.09 (3H, s), 1.2–1.7 (4H, m), 1.84 (1H, m), 2.12 (2H, m), 2.21 (1H, m), 4.20 (1H, dd, J = 8.2 Hz, $J_1 = 8.3$ Hz), 4.96 (1H, d, $J_2 = 10.1$ Hz), 5.04 (1H, d, J = 17.2 Hz), 5.86 (1H, m) ppm; ¹³C NMR (CDCl₃) δ 16.9 (CH₃), 18.8 (CH₃), 27.80 (CH₂), 28.7 (CH₂), 33.5 (CH₂), 35.2 (CH₂), 47.8 (C), 79.3 (CH), 83.5 (C), 114.5 (CH₂), 139.2 (C) ppm; HRMS (ESI) 207.1318 (M⁺ + Na, C₁₁H₂₀O₂Na), calcd 207.1355. Anal. Calcd for C₁₁H₂₀O₂: C, 71.70; H, 10.94. Found: C, 71.63; H, 11.07.

Reaction of 54 with Cp₂TiCl. According to GP 1, reaction of **51** (125 mg, 0.55 mmol) with Cp₂TiCl followed by flash chromatography (hexane/diethyl ether 60:40) furnished a diastereomeric mixture of ethyl 2-hydroxy-3-hydroxymethyl-1,2,3-trimethylcyclopentanecarboxylate **57** (82 mg, 65%) in a ratio of 7:3, as a viscous liquid: IR, ν 3426, 1720, 1033 cm⁻¹; ¹H NMR (CDCl₃) δ (major) 0.88 (3H, s), 1.19 (3H, s), 1.24 (3H, t, J = 7.0 Hz), 1.24 (3H, s),

1.4–2.4 (4H, m), 3.53 (2H, br s), 4.16 (2H, m); (minor) 0.99 (3H, s)*, 1.16 (3H, s)*, 1.24 (3H, t, $J = 7.0 \text{ Hz})^*$, 1.24 (3H, s)*, 1.4– 2.4 (4H, m)*, 3.92 (2H, br s)*, 4.16 (2H, m, $J = 7.0 \text{ Hz})^*$ ppm; ¹³C NMR (CDCl₃) δ (major) 14.0 (CH₃), 20.2 (CH₃), 22.5 (CH₃), 22.8 (CH₃), 32.5 (CH₂), 32.8 (CH₂), 48.6 (C), 57.7 (C), 60.4 (CH₂), 69.5 (CH₂), 85.8 (C), 176.5 (C); (minor) 13.5 (CH₃)*, 14.0 (CH₃)*, 14.7 (CH₃)*, 17.2 (CH₃)*, 33.8 (CH₂)*, 34.3 (CH₂)*, 45.5 (C)*, 55.6 (C)*, 60.4 (CH₂)*, 77.6 (CH₂)*, 78.61 (C)*, 176.5 (C)* ppm; MS EI, *m*/*z* (relative intensity) 166 (M⁺ – 64, 1), 141 (20), 125 (22), 116 (50), 98 (48), 85 (93), 69 (100), 57 (99); HRMS (EI) 253.1399 (M⁺ + Na, C₁₂H₂₂O₄Na), calcd 253.1410. Anal. Calcd for C₁₂H₂₂O₄: C, 62.58; H, 9.63. Found: C, 62.88; H, 9.69.

Reaction of 60 with Cp2TiCl. According to GP1, reaction of 60 (90 mg, 0.43 mmol) with Cp₂TiCl followed by flash chromatography (hexane/ethyl acetate 40:60) furnished a diastereomeric mixture of ethyl 4-hydroxymethyl-2,4-dimethyl-5-oxohexanoate 65 (19 mg, 21%) in a ratio 12:1, as a viscous liquid: ^{1}H NMR (CDCl₃) δ 1.11 (3H, s), 1.13 (3H, s), 1.18 (6H, d, J = 7.0 Hz), 1.26 (3H, t, J = 7.1 Hz), 1.27 (3H, t, J = 7.1 Hz), 1.58 (4H, m), 2.15 (3H, s), 2.19 (3H, s), 2.48 (2H, m), 3.4–3.6 (4H, m), 4.17 (4H, m) ppm; ^{13}C NMR (CDCl₃) δ 14.0 (CH₃), 14.2 (CH₃), 19.4 (CH₃), 19.6 (CH₃), 19.9 (CH₃), 20.2 (CH₃), 22.7 (CH₃), 26.0 (CH₃), 33.5 (CH₂), 35.4 (CH), 35.7 (CH), 38.0 (CH₂), 43.0 (C), 49.6 (C), 60.4 (CH₂), 60.7 (CH₂), 67.3 (CH₂), 69.2 (CH₂), 177.1 (C), 177.2 (C), 213.5 (C), 213.7 (C) ppm; MS (EI, m/z) 186 (M⁺ - 30, 1), 140 (8), 102 (10), 83 (100), 69 (25), 56 (52); HRMS (ESI) 239.1276 (M^+ + Na, C₁₁H₂₀O₄Na), calcd 239.1259. Anal. Calcd for C₁₁H₂₀O₄: C, 61.09; H, 9.32. Found: C, 61.34; H, 9.16.

Ethyl 2-hydroxy-3-hydroxymethyl-1,2,3-trimethylcyclobutanecarboxylate **63** (32 mg, 35%) was obtained as a viscous oil: IR, ν 3414, 1707, 1027 cm⁻¹; ¹H NMR (CDCl₃) δ 1.26 (3H, t, J = 7.2Hz), 1.28 (3H, s), 1.33 (3H, s), 1.44 (3H, s), 2.24 (1H, s), 2.27 (1H, s), 3,41 (1H, d, J = 10.8 Hz), 3.61 (1H, d, J = 10.8 Hz), 4.14 (2H, q, J = 7.2 Hz) ppm; ¹³C NMR (CDCl₃) δ 14.2 (CH₃), 19.4 (CH₃), 20.6 (CH₃), 21.4 (CH₃), 33.5 (CH₂), 43.5 (C), 49.6 (C), 60.4 (CH₂), 68.6 (CH₂), 76.2 (C), 175.71 (C) ppm; MS (EI, m/z) 141-(M⁺ - 75, 10), 102 (20), 83 (100), 69 (22), 56 (56); HRMS (ESI) 239.1264 (M⁺ + Na, C₁₁H₂₀O₄Na), calcd 239.1254. Anal. Calcd for C₁₁H₂₀O₄: C, 61.09; H, 9.32. Found: C, 61.23; H, 9.35.

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Supporting Information Available: Preparation and characterization of epoxides, and NMR spectra of compounds **2**, **7**, **8**, **10**, **11**, **20**, **26**, **28**, **32**, **34**, **36**, **40**, **42**, **51**, **57**, **63**, and **65**. This material is available free of charge via the Internet at http://pubs.acs.org. JO701497E