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A TITANOXYCYCLOPROPANE AS INTERMEDIATE IN A HIGHLY STEREOSELECTIVE HOMOALDOL TYPE ADDITION SYNTHESES OF CIS-SUBSTITUTED TETRAHYDROFURAN DERIVATIVES

Hans-Ulrich Reissig *)[a,b], Hiltrud Holzinger[b], and Gabriele Glomsda[a]

[a] Institut für Organische Chemie der Technischen Hochschule Darmstadt, Petersenstr. 22, D-6100 Darmstadt, FRG. - [b] Institut für Organische Chemie der Universität Würzburg, FRG.

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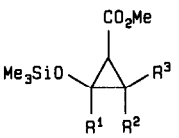
Summary: Reaction of methyl 2-siloxycyclopropanecarboxylate **4** with $TiCl_4$ provides the unique titanoxycyclopropane **10** whose structure could be elucidated by means of NMR-spectroscopy. Its additions to aldehydes and acetophenone occur with high stereoselectivity to afford homoaldol products like **6**. These intermediates can further be transformed to highly substituted tetrahydrofuran derivatives by activation with BF_3-OEt_2 and reaction with $HSiEt_3$ or silylated carbon nucleophiles, respectively. This substitution involves an oxocarbenium ion and proceeds with excellent diastereoselectivity.

Vicinally donor-acceptor-substituted cyclopropanes **1** are very valuable building blocks in organic synthesis[1]. The easily available[2] methyl 2-siloxycyclopropanecarboxylates **2** display special versatility to give after ring opening reactions a range of 1,4-difunctionalized compounds[1] which can often not be obtained by alternative methods with similar simplicity and flexibility regarding the substitution pattern.

1



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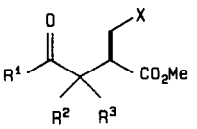


3

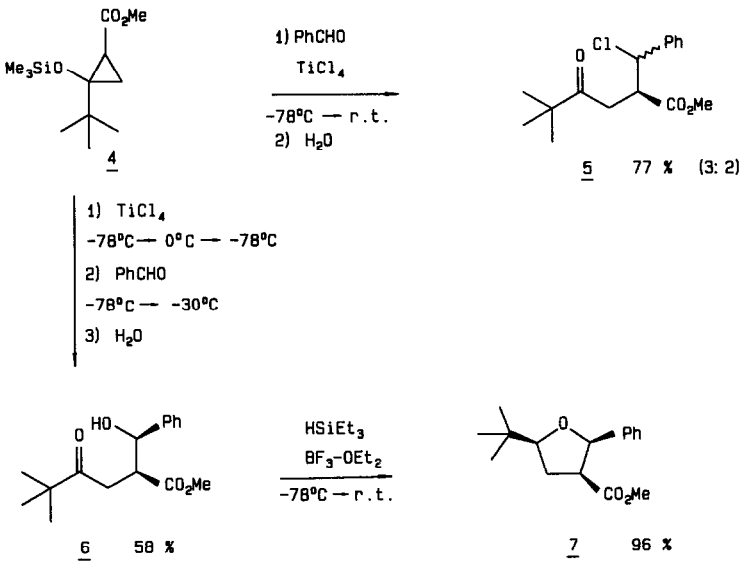
Of high synthetic and mechanistic interest are modes of ring cleavage with simultaneous formation of a new carbon-carbon bond to afford γ-oxocarboxylates of general structure **3**. In 1981 we reported on the possibility to realize this intention by reaction of siloxycyclopropanes **3** with carbonyl compounds under Lewis-acid promotion[3] allowing efficient preparation of a variety of substituted furan derivatives. A second method, using fluoride induced ring opening and subsequent trapping with carbon electrophiles, has also been discovered by us[4] und further explored by others[5]. With respect to the liberated carbonyl group these reactions can be classified as homoaldol type additions[6]. In this paper we want to disclose our results on the highly stereoselective reactions of cyclopropane **4** with aldehydes and acetophenone. Also, we will demonstrate that a titanoxycyclopropane **10** is formed as reactive species, which accounts for the stereoselectivity of the hydroxyalkylation process.

$TiCl_4$ promoted reaction of cyclopropane **4** with benzaldehyde

The reaction conditions successfully employed in the addition of **4** and of similar cyclopropanes to ketones[3] are not applicable if benzaldehyde is introduced as carbonyl component. Addition of **4** to a mixture of PhCHO / $TiCl_4$ at -78°C and warm up to room temperature does not provide primary adduct **6** (or its diastereomer). Instead, the chlorinated[7] compound **5** as a 3:2 mixture of two diastereomers is formed in good yield (scheme I). Apparently, during warm up the benzylic alcohol **6** is converted to **5** under the Lewis-acidic conditions. Since this substitution should proceed via an S_N1-mechanism, the ratio of diastereomers in **5** does not reflect the

stereochemistry of the addition step. On the other hand, experiments performed at -78°C afford only low quantities of 6 (16 %).

Scheme I



However, we could find proper conditions to synthesize 6 in reasonable yield. Warm up of a mixture of 4 and $TiCl_4$ to 0°C without benzaldehyde results in a striking color change of the solution from intensively wine red to pale ocher yellow; this color remains after cooling to -78°C. Subsequent reaction of benzaldehyde with this pretreated solution between -78°C and -30°C and aqueous work up give almost quantitatively crude primary adduct 6 as a single diastereomer with anti- or threo-configuration as depicted in scheme I. After recrystallization pure homoaldol adduct 6 is obtained in 58 % yield. There is no indication for formation of other stereoisomers.

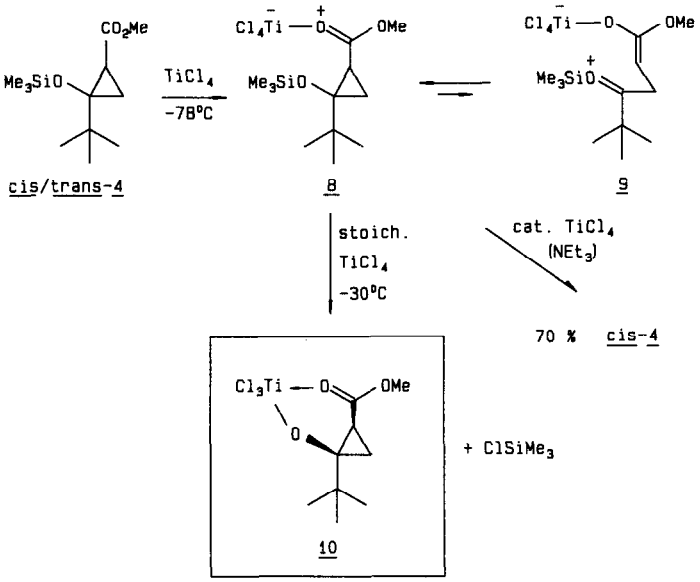
Determination of the stereochemistry of 6 is not easy, since it exists in solution as a mixture of the ring open form (≈ 75 %), as drawn in scheme I, and of the two cyclic hemiacetals (γ-lactols, ≈ 15 and 10 %). Therefore 6 is converted to tetrahydrofuran-3-carboxylate 7 by reduction with triethylsilane / BF_3-OEt_2[3a,3b]. This reaction - proceeding via the γ-lactol and the corresponding oxocarbenium ion derived thereof - gives only one stereoisomer, whose structure could be established by ^{1}H-NMR-spectroscopy. The extreme shift to high field of the CO_2Me signal (3.03 ppm) indicates cis-relation to the phenyl substituent. Further evidence for the cis-cis-stereochemistry in 7 is gained by NOE-effects, which unequivocally demonstrate cis-disposition of the t-butyl and phenyl group as well as that of 2-H, 3-H, and 5-H (see experimental).

Thus, two highly stereoselective reactions give tetrahydrofuran 7. The mechanism of the first step will be discussed below, whereas the attack of the silane reagent on the oxocarbenium ion trans to the two other ring substituents is to be expected in the light of former results[8]. An experiment employing crude 6 in the silane reduction provides 7 in 60 % overall yield with an isomeric purity of at least 95:5.

Structure of the intermediate and mechanistic discussion

With regard to the mechanism of the homoaldol addition step the following observations are of importance. Addition of catalytic amounts of $TiCl_4$ at -78°C in $CDCl_3$ or CH_2Cl_2 to a mixture of cis/trans-4 - as usually employed in all reactions - provides a wine red solution, just as observed above. Work up at 20°C by adding an excess of triethylamine allows isolation of pure cis-4 (70 % yield)[9]. As reported several years ago, this type of isomerization should proceed via an acyclic dipolar species 9, which is in equilibrium with the primary complex 8. Since the cis-trans ratio is mainly governed by steric effects, exclusive formation of the sterically more favourable cis-4 is not surprising[9]. The wine red color of these solutions might be attributed to the titanated ketene acetal moiety in 9[10]. However, we have so far not been able to obtain suitable NMR-spectra of these solutions.

Scheme II



Use of stoichiometric quantities of $TiCl_4$ and slow warm up induce the color change as mentioned to afford a pale ocher yellow, clear solution. The ^{1}H-NMR spectrum shows a singlet at 0.55 ppm for Me_3SiCl, whereas three protons appear as broad singlet at 2.35 ppm. The t-butyl and the OMe-group show signals at 1.18 and 4.07 ppm, respectively. A 400 MHz-NMR spectrum does not give further unambigous informations, since dynamic effects obviously cause severe signal broadening. However, the ^{13}C-NMR spectrum (fig. 1) unequivocally proves that a titanoxycyclopropane of structure 10 has been obtained. Other imaginable canditates, e.g. an acyclic ketene acetal or a C-titanated species, are excluded with certainty. Most intriguing are signals at 22.0 (d) and 21.3 (t) ppm with typical C-H coupling constants of 171 and 169 Hz, respectively, for cyclopropane carbons[11]. The spectrum of 10 is very similar to that of cis-4[12], with exception of a low field shift for CO_2Me (181.7, 56.9 ppm) and C-2 (92.4 ppm), indicating partial positive charges at these atoms.

The signal of the carbonyl group appears in a range which is typical for $TiCl_4$ complexes[12]. This effect as well as an IR-spectrum of a solution of **10** displaying a C=O frequency at 1680 cm^{-1} demonstrate a coordination of the ester group to titanium, which is only possible in the cis-isomer, as illustrated in the formula (scheme II). Evaporation of the solvent gives a yellow solid with an undefined melting point. A solution of this very moisture sensitive complex in $CDCl_3$ shows all ^{1}H-NMR signals but that of Me_3SiCl.

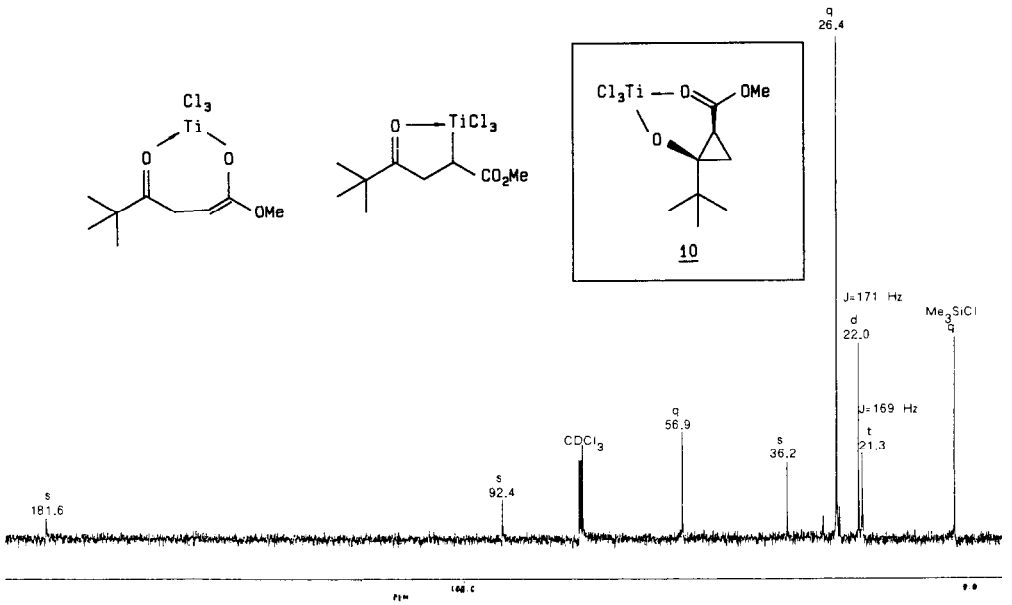
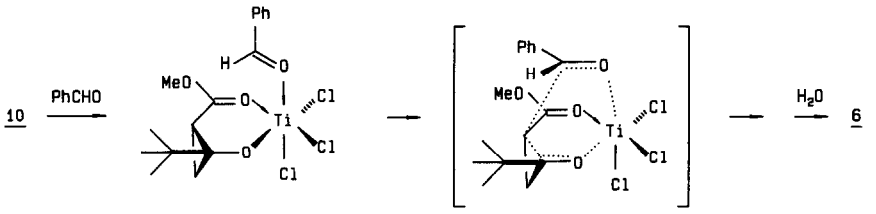


Fig. 1: ^{13}C-NMR spectrum of titanoxycyclopropane **10** ($CDCl_3$, 0°C, wide-band proton decoupled)

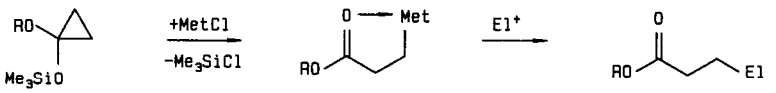
Therefore, all chemical and spectroscopic arguments demonstrate, that a titanoxycyclopropane **10** is formed during warm up and that this should be the species to react with carbonyl compounds. Only low concentrations of **10** are formed at -78°C and therefore reaction with carbonyl compounds is slow. However, warm up induces quantitative transformation **4** → **10**, which now can react with aldehydes without interference of chlorination at low temperature[13]. Interestingly only $TiCl_4$ brings about smooth homoaldol addition of **4**; Lewis-acids like $ZrCl_4$, $SnCl_4$, $SnCl_2$, BF_3-OEt_2, and $Me_3SiOSO_2CF_3$ could not been successfully applied for this process.

Is involvement of **10** compatible with the stereoselectivity observed? Actually, with this intermediate exclusive formation of **6** can be explained very well. Addition of benzaldehyde to **10** should give a hexacoordinated complex **11**. A yellow precipitate, which slowly dissolves during warm up, provides good evidence for this assumption. In the transition state **TS** the C-C bond forming interaction of the electrophilic aldehyde carbon with the nucleophilic C-1 of the cyclopropane occurs in the manner that the sterically less encumbered conformation with the phenyl group anti to the large t-butyl substituent is preferred. This approach via **TS** - as depicted in Scheme III - affords the adduct **6** with correct stereochemistry. The process also implies that cleavage of the C-1/C-2 cyclopropane bond and formation of the new carbon-carbon bond proceed under retention of configuration[14]. Examination of models reveals that reaction of an acyclic O-titanated ketene acetal species - possibly in equilibrium with **10** - should display less steric discrimination in the addition to the aldehyde[15].

Scheme III



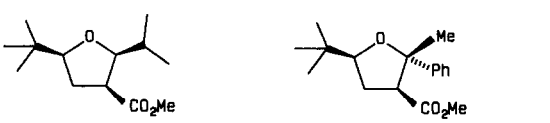
It is interesting to note, that a formally closely related homoaldol reaction - the $TiCl_4$ promoted addition of 1-alkoxy-1-trimethylsiloxycyclopropanes 12 to carbonyl compounds or other electrophiles[16] - proceeds through a structurally rather different intermediate. Nakamura, Kuwajima et al.[16] could demonstrate that a β-trichlorotitanium propionate 13 (Met = $TiCl_3$) is formed, which reacts to provide products 14. The C-titanated species adds onyl to rather reactive electrophiles, whereas the titanoxycyclopropane 10[17] even gives high yields with notoriously sluggish carbonyl compounds like benzophenone[3]. The ester function in 4 acts as the handle where the Lewis acid attacks and which finally stabilizes structure 10 by coordination to the metal center. On the other hand, 10 does not react with S_N2- or S_N1-active alkyl halides like allylbromide or t-butylchlorid.



12 13 14

Reactions of 4 with other carbonyl compounds

Reaction of 4 via 10 is not restricted to aromatic aldehydes. Analogously to synthesis of 7 isobutyric aldehyde affords cis-cis-tetrahydrofuran derivative 15 (selectivity ≈ 90 : 10) whose stereochemistry could also be established by means of NOE-effects. As an example for an unsymmetrical ketone acetophenone was employed to give compound 16 with the methyl group cis to the t-butyl and CO_2Me substituents. Strong NOE-effects between the t-Bu and Me group prove structure 16. Additional support for trans-disposition of the phenyl and the CO_2Me substituents is indicated by the low field shift of the OMe signal at 3.80 ppm. An isomer of 16 formed in ≈ 6 % very likely has cis-located ester and phenyl groups, as indicated by a singlet at 3.34 ppm in the ^{1}H-NMR spectrum. Apparently, in the transition state of this reaction the methyl group is recognized as smaller group as to compared to the flat phenyl substituent[18].



15 79 % (90: 10) 16 60 % (94: 6)

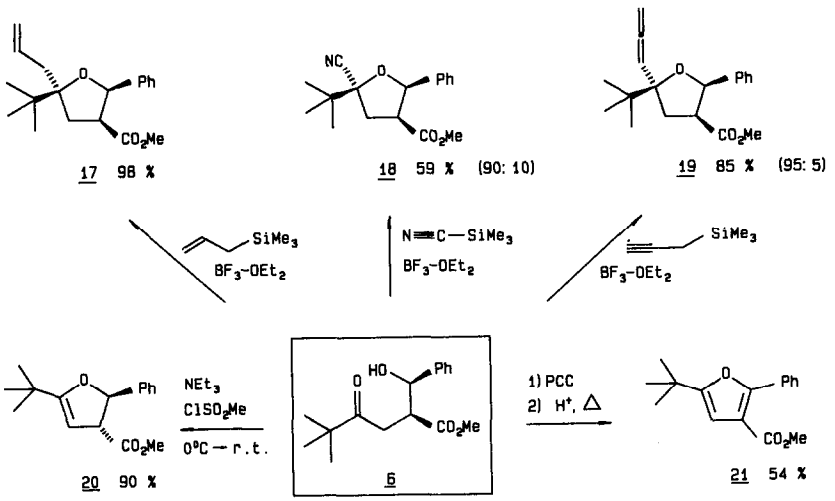
Although there are limitations, the reactions of siloxycyclopropanes 2 with ketones have already shown[3], that this type of hydroxyalkylation is not restricted to t-butyl substituted compound 4. Therefore a variety of highly substituted tetrahydrofuran-3-carboxylates, very

likely also bicyclic systems, should be attainable by this route employing activation with Lewis-acids[19]. An alternative concept - involving carbanion chemistry - has recently been published in full detail[8c].

Further transformations of primary adduct 6

Using the methods developed by us to combine γ-lactols with carbon nucleophiles[19], we could prepare tetrahydrofuran derivatives 17, 18, and 19, respectively. Activation of 6 with BF_3-OEt_2 in the presence of silylated nucleophiles like allyl trimethylsilane, cyano trimethylsilane, or propargyl trimethylsilane brings about the crucial C-C bond formation at C-5 with good to excellent stereoselectivity. Allylated compound 17 is formed isomerically pure (> 98 : 2), the allene derivative 19 is obtained with a stereoselectivity of at least 95 : 5, whereas the nitrile 18 is received as 90 : 10 mixture. The stereochemistry at C-5 is again governed by steric effects caused by substituents at C-2 and C-3[3b,19]. The stereochemical assignments are in full agreement with equilibration experiments (NaOMe / HOMe). From 17 a 60 : 40 mixture of C-3 epimers is obtained, whereas 18 provides three diastereomers in a ratio of 70 : 20 : 10 epimeric at C-3 and C-5 (see experimental for assignments).

Scheme IV



Dehydration of 6 with triethylamine / mesyl chloride gives methyl trans-dihydrofuran-3-carboxylate 20 as indicated by the low field appearance of the CO_2Me signal (3.76 ppm) in the ^1H-NMR spectrum and the vicinal coupling constant of 7 Hz of 2-H and 3-H[20]. Obviously, under the reaction conditions epimerization at C-3 to afford the thermodynamically more stable trans-20 has taken place. Finally, oxidation of 6 to a diketone with pyridinium chlorochromate and cyclization under acid catalysis gives trisubstituted furan derivative 21 in reasonable overall yield. Thus, all three oxidation levels of the furan system can be gained by one common precursor as demonstrated by synthesis of 7, 20, and 21, respectively, from the homoaldol adduct 6.

Conclusions

In this paper we could demonstrate that titanoxycyclopropane **10** is very likely the intermediate in a C-C-bond forming cyclopropane ring cleavage process. The addition to unsymmetrical carbonyl compounds and the subsequent elaboration of the primary products make available a variety of highly substituted tetrahydrofuran derivatives[21] in excellent diastereoselectivities and with good efficiency. Experiments performed with ketones[9] have already demonstrated that the C-C bond formation also occurs with other siloxycyclopropanes. Further investigations should prove whether the high stereoselectivity is restricted to cyclopropane **4** as starting material.

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Experimental

IR spectra were recorded on a Perkin-Elmer 1422 Ratio Recording, a Beckmann Acculab 4, or a Beckmann IR5a. - ^{1}H-NMR spectra: Varian T 60, Varian EM 360, Varian EM 390, Bruker WM 300, or Bruker WM 400 (internal reference TMS or $CHCl_3$). - ^{13}C-NMR spectra: Bruker WM 300, or Bruker WM 400 (internal reference $CDCl_3$). - Melting points: Kofler-Heiztischmikroskop apparatus (Reichert), corrected; SMP-20 (Büchi), uncorrected. - Boiling points of compounds obtained in small scale experiments refer to the temperature in a Büchi Kugelrohroven. - Radial chromatography was performed with a "Chromatotron" (Harrisson Research, Model 7924) using silica gel plates. All reactions were performed in flame dried reaction vessels under a slight pressure of dry nitrogen. Solvents and reagents were added by syringe. Dichloromethane was distilled from calcium hydride and stored over molecular sieves. $TiCl_4$ and BF_3-OEt_2 were distilled from calcium hydride. Carbonyl compounds were distilled before usage. All other commercially available starting materials were applied without further purification. Cyclopropane **4** was prepared according to lit. [2].

Methyl 5,5-Dimethyl-2(α-chlorobenzyl)hexanoate (**5**): To a solution of 0.742 g (7.00 mmol) of benzaldehyde in 10 ml of dichloromethane are added at -78°C 1.54 g (8.10 mmol) of $TiCl_4$. After 10 min 1.46 g (6.00 mmol) of siloxycyclopropane **4** are added dropwise to give a intensive wine red solution. Stirring is continued for 20 min at -78°C and for 4 h at room temp.; aqueous work up (10 ml H_2O, extraction with CH_2Cl_2), drying with $MgSO_4$ and evaporation give 1.85 g of crude **5**. Distillation (120-140°C/0.02 Torr) provides 1.38 g (77 %) of **5** as a very viscous colorless oil (ratio of diastereomers ≈ 3:2).

IR (CCl_4): ν = 3100-2800 cm^{-1} (C-H), 1730, 1705 (C=O). - ^{1}H-NMR ($CDCl_3$): δ = 7.35 (mc, 5H, Ph), 5.35, 5.15 (2d, J = 6.3 and 9.0 Hz, 0.4 and 0.6H, α-H), 3.73, 3.53 (2s, 1.8 and 1.2H, CO_2Me), 3.75-3.4, 3.3-2.3 (2m, 3H, 2-H, 3-H), 1.13, 1.02 (2s, 3.6 and 5.4H, t-Bu).

MS (70 eV): m/e = 260 (7 %, M - HCl), 57 (100 %).

$C_{16}H_{21}O_3Cl$ (296.8) Calcd. C 64.75 H 7.13 Found C 64.73 H 7.40

Methyl 5,5-Dimethyl-2(α-hydroxybenzyl)hexanoate (**6**): A solution of 1.22 g (5.00 mmol) of siloxycyclopropane **4** in 25 ml of CH_2Cl_2 is treated with 1.36 g (7.2 mmol) of $TiCl_4$ for 10 min at -78°C and for 30 min at room temp. to provide a homogeneous pale yellow solution. Addition of 0.69 g (6.50 mmol) of benzaldehyde results in formation of a yellow precipitate. Within 16 h this mixture is slowly warmed up to -30°C, then quenched with 15 ml of satd. aqueous NH_4F-solution and extracted thrice with 20 ml CH_2Cl_2. Drying ($MgSO_4$) and evaporation give 1.21 g (87 %) of crude crystalline **6**. Recrystallization from pentane afford 0.81 g (58 %) of **6** as

colorless needles (m.p. 98-100°C).

IR ($CHCl_3$): ν = 3700-3100 cm^{-1} (OH), 3100-2750 (C-H), 1725, 1705 (C=O). - IR (KBr): 3500 cm^{-1} (broad, OH), 3100-2750 (C-H), 1735, 1695 (C=O). - ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.4-7.2 (m, 5H, Ph), 5.98 (very broad, 1H, OH), 4.89 (d, J = 7.5 Hz, 1H, α-H), 3.64 (s, 3H, CO_2Me), 3.23 (dt, J = 5 and ≈ 8 Hz, 1H, 2-H), 2.80, 2.63 (AB-part of an ABX-system, J_{AB} = 18, J_{AX} = 8, J_{BX} = 5 Hz, 2H, 3-H), 1.04 (s, 9H, t-Bu); we assign other signals to two cyclic hemiacetal structures of 6, which are present in ≈ 15 and 10 % [e. g. 2 CO_2Me signals at δ = 3.14 and 3.05]. - ^{13}C-NMR ($CDCl_3$): δ = 213.5 (s, C=O), 174.5, 51.8 (s, q, CO_2Me), 141.3, 128.4, 127.9, 126.2 (s, 3d, Ph), 74.2 (d, 2-CH), 47.6 (d, C-2), 43.8, 26.2 (s, q, t-Bu), 35.9 (t, C-3).

$C_{16}H_{22}O_4$ (278.3) Calcd. C 69.05 H 7.96 Found C 68.67 H 7.99

Methyl c-5-tert-Butyl-c-2-phenyl-tetrahydrofuran-r-3-carboxylate (7): A solution of 0.278 g (1.00 mmol) of adduct 6 and 0.233 g (2.00 mmol) of triethylsilane in 10 ml of CH_2Cl_2 is treated with 0.28 g (2.0 mmol) of BF_3-OEt_2 for 40 min at -78°C and for 16 h at room temp. Work up with satd. aqueous $NaHCO_3$-solution, extraction with CH_2Cl_2, drying with $MgSO_4$, and evaporation afford 0.266 g of crude 7. Distillation (120°C/0.02 Torr) provides 0.252 g (96 %) of 7 as colorless crystals (m.p. 33-36.5°C).

IR (CCl_4): ν = 3100-2800 cm^{-1} (C-H), 1745 (CO_2Me). - ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.35-7.15 (m, 5H, Ph), 5.04 (d, J = 9 Hz, 1H, 2-H), 3.60 (dd, J = 5.5 and 10.5 Hz, 1H, 5-H), 3.36 (dt, J = 8 and 9 Hz, 1H, 3-H), 3.03 (s, 3H, CO_2Me), 2.25 (ddd, J = 8, 10.5, and 12.5 Hz, 1H, c-4-H), 1.94 (ddd, J = 5.5, 9, and 12.5 Hz, 1H, t-4-H), 1.06 (s, 9H, t-Bu).

NOE-experiments (300 MHz):

irradiation of	enhancement of the signal for
t-Bu	5-H, c-4-H, t-4-H (weak), Ph
2-H	Ph, 5-H, 3-H
5-H	2-H
3-H	t-4-H, 2-H

^{13}C-NMR ($CDCl_3$): δ = 172.6, 50.7 (s, q, CO_2Me), 140.0, 127.5, 127.4, 126.6 (s, 3d, Ph), 87.3, 86.6 (2d, C-2, C-5), 50.0 (d, C-3), 33.2, 26.0 (s, q, t-Bu), 29.7 (t, C-4).

$C_{16}H_{22}O_3$ (262.3) Calcd. C 73.54 H 8.10 Found C 73.66 H 8.66

One-pot-preparation of 7: Following the procedures above, one obtains from 0.488 g (2.00 mmol) of 4, 0.47 g (2.5 mmol) of $TiCl_4$, and 0.266 g (2.50 mmol) of benzaldehyde 0.485 g of crude 6. This is treated with 0.349 g (3.00 mmol) of $HSiEt_3$ and 0.42 g (3.0 mmol) of BF_3-OEt_2 to afford 314 mg (60 %) of 7 (b.p. 120-130°C/0.02 Torr), which is pure according to ^{1}H-NMR-spectroscopy.

Spectroscopic identification of titanoxycyclopropane 10: To a solution of 0.27 g (1.4 mmol) of $TiCl_4$ in 4 ml of dry $CDCl_3$ are added dropwise at -50°C 0.328 g (1.34 mmol) of siloxycyclopropane 4. The homogeneous mixture is warmed up to 0°C for 30 min and then cooled again to -50°C. From this solution 0.6 ml are transferred under nitrogen into the NMR-tube.

^{13}C-NMR ($CDCl_3$, 0°C): δ = 181.7, 56.9 (s, q, CO_2Me), 92.4 (s, C-2), 36.2, 26.4 (s, q, t-Bu), 22 (d, J = 171 Hz, C-1), 21.3 (t, J = 169 Hz, C-3), 3.2 (q, Me_3SiCl). ^{1}H-NMR ($CDCl_3$, room temp., 60 MHz): δ = 4.07 (s, 3H, CO_2Me), 2.35 (broad s, 3H, 1-H, 3-H), 1.18 (s, 9H, t-Bu), 0.55 (s, 9H, Me_3SiCl).

Dilution of this solution provides the sample for the IR-spectrum ($CDCl_3$): ν = 3020, 2980 cm^{-1} (sharp, C-H), 1680 (CO_2Me, shoulder at 1645).

Addition of pentane to the solution prepared above causes precipitation of 10 as pale yellow solid, which could be isolated by filtration (m.p. 90-100°C, decomposition).

Methyl c-5-tert-Butyl-c-2-isopropyl-tetrahydrofuran-r-3-carboxylate (15): Analogously to preparation of 6, 1.22 g (5.00 mmol) of siloxycyclopropane 4, 1.44 g (7.6 mmol) of $TiCl_4$, and 0.469 g (6.5 mmol) of isobutyric aldehyde in 25 ml of CH_2Cl_2 give 0.994 g (81 %) of crude primary

adduct. As applied for synthesis of 7, treatment of the crude product with 1.16 g (10.0 mmol) of triethylsilane and 1.42 g (10 mmol) of BF_3-OEt_2 in 20 ml of CH_2Cl_2 gives after the usual work up and careful distillation (60°C/0.02 Torr) 0.895 g (79 %) of 15 (purity ≈ 90 %). The sample for analysis is purified by chromatography (SiO_2, petrol ether/ethyl acetate = 8 : 2).
IR (CCl_4): ν = 3100-2800 cm^{-1} (C-H), 1740 (CO_2Me). - ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 3.66 (s, 3H, CO_2Me), 3.50 (t, J = 8 Hz, 1H, 2-H), 3.40 (t, J = 8.5 Hz, 1H, 5-H), 3.09 (q, J ≈ 8 Hz, 1 H, 3-H), 1.95 (t, J = 8 Hz, 2H, 4-H), 1.79 (oct, J ≈ 7 Hz, 1H, C<u>H</u>Me_2), 0.97, 0.88 (2d, J ≈ 7 Hz, 3H each, CH<u>Me</u>$_2$), 0.94 (s, 9H, t-Bu). The assignments are acertained by a COSY-spectrum.

NOE-experiment:

irradiation of	enhancement of the signal for
t-Bu + CH<u>Me</u>$_2$	5-H, 4-H, 2-H (weak), C<u>H</u>Me_2
C<u>H</u>Me_2	CH<u>Me</u>$_2$, 2-H
5-H	4-H, 3-H
4-H	3-H
3-H	5-H (weak), 4-H, 2-H
2-H	3-H, C<u>H</u>Me_2

Further signals in the ^{1}H-NMR-spectrum might be due to a stereoisomer of 15 (≈ 10 %): δ = 4.05 (dd, J ≈ 7 and 9 Hz), 3.69 (s, CO_2Me), 2.80, 2.58 (2t, J ≈ 7 Hz), 1.17 (s, t-Bu).
^{13}C-NMR ($CDCl_3$): δ = 174.2, 50.9 (s, q, CO_2Me), 86.2, 85,7 (2d, C-5, C-2), 46.2 (d, C-3), 32.9, 25.7 (s, q, t-Bu), 30.9 (t, C-4), 29.6, 19.4, 19.3 (d, 2q, $CHMe_2$).
$C_{13}H_{23}O_3$ (227.3) Calcd. C 68.69 H 10.20 Found C 68.05 H 10.84

Methyl c-5-tert-Butyl-c-2-methyl-t-2-phenyl-tetrahydrofuran-r-3-carboxylate (16): Analogously to synthesis of 6, 1.22 g (5.00 mmol) of siloxycyclopropane 4, 1.38 g (7.3 mmol) of $TiCl_4$, and 0.781 g (6.5 mmol) of acetophenone in 25 ml of CH_2Cl_2 provide 1.34 g (92 %) of crude primary adduct. This is treated analogously to preparation of 7 with 1.16 g (10.0 mmol) of triethylsilane and 1.42 g (10 mmol) of BF_3-OEt_2 in 20 ml of CH_2Cl_2. Usual work up and distillation (110°C/0.02 Torr) afford 0.835 g (60 %) of 16 as colorless very viscous liquid.
IR (CCl_4): ν = 3100-2800 cm^{-1} (C-H), 1740 (CO_2Me). - ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.6-7.5, 7.4-7.2 (2m, 5H, Ph), 3.80 (s, 3H, CO_2Me), 3.62 (dd, J = 4.5 and 11.5 Hz, 1H, 5-H), 3.38 (dd, J = 8.0 and 10.5 Hz, 1H, 3-H), 2.27 (q, J ≈ 11 Hz, 1H, c-4-H), 1.93 (ddd, J = 4.5, 8.0, and 12.0 Hz, 1H, t-4-H), 1.41 (s, 3H, 2-Me), 1.02 (s, 9H, t-Bu).

NOE-experiments (300 MHz):

irridiation of	enhancement of the signal for
t-Bu	5-H, c-4-H, t-4-H (weak)
2-Me	c-4-H
Ph	c-4-H, 5-H (weak)
5-H	t-4-H, Ph

Signals for a second isomer (≈ 6 %) show up at δ = 4.22 (t, J = 8 Hz, 5-H), 3.34 (s, CO_2Me), 1.72 (s, 2-Me), 0.99 (s, t-Bu).
^{13}C-NMR ($CDCl_3$): δ = 173.3, 51.8 (s, q, CO_2Me), 149.3, 128.2, 126.6, 124.8 (s, 3d, Ph), 85.6 (d, C-5), 84.3 (s, C-2), 55.2 (d, C-3), 33.0, 25.9 (s, q, t-Bu), 31.3 (t, C-4), 27.2 q (2-Me).
$C_{17}H_{24}O_3$ (276.4) Calcd. C 73.87 H 8.75 Found C 74.01 H 9.01

Methyl t-5-Allyl-c-5-tert-butyl-c-2-phenyl-tetrahydrofuran-r-3-carboxylate (17): Analogously to preparation of 7, 0.278 g (1.00 mmol) of 6, 0.228 g (2.00 mmol) of allyl trimethylsilane, and 0.28 g (2.0 mmol) of BF_3-OEt_2 in 5 ml of CH_2Cl_2 afford after distillation (150-160°C/0.02 Torr) 0.296 g (98 %) of 17 as colorless viscous liquid.
IR (CCl_4): ν = 3100-2800 cm^{-1} (C-H), 1740 (CO_2Me), 1670 (C=C). - ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.35-7.15 (m, 5H, Ph), 6.05, 5.15, 5.1 (3mc, 1H each, CH=CH_2), 5.34 (d, J = 10 Hz, 1H, 2-H), 3.54 (ddd, J = 8.5, 9.5, and 10 Hz, 1H, 3-H), 3.02 (s, 3H, CO_2Me), 2.64 (dd, J = 8.5 and 13 Hz, 1H, c-4-H), 2.45, 2.58 (AB-part of an ABX-system, J_{AB} = 15, J_{AX} = J_{BX} = 7 Hz, 1H each, 5-CH_2), 1.94 (dd, J = 9.5 and 13 Hz, 1H, t-4-H), 1.14 (s, 9H, t-Bu). - ^{13}C-NMR ($CDCl_3$): δ = 173.0, 50.9

(s, q, CO_2Me), 139.5, 127.6, 127.5, 127.0 (s, 3d, Ph), 136.1, 117.0 (d, t, $CH=CH_2$), 90.3 (s, C-5), 81.7 (d, C-2), 50.1 (d, C-3), 40.1, 34.1 (2t, 5-CH_2, C-4), 38.3, 26.5 (s, q, t-Bu).
$C_{19}H_{25}O_3$ (301.4) Calcd. C 75.72 H 8.36 Found C 75.88 H 8.29

Isomerization of 17 with sodium methoxide: Sodium (42 mg) is dissolved in 10 ml of dry methanol to give ≈ 1.8 mmol of sodium methoxide. Then 0.301 g (1.00 mmol) of **17** are stirred with this solution for 16 h at room temp.; work up with satd. aqueous NH_4Cl-solution and extraction with MeO-t-Bu provides after drying ($MgSO_4$) and distillation (150-170°C/0.02 Torr) 0.250 g (83 %) of a liquid, which is a 40 : 60 mixture of 17 and its C-3 epimer; NMR-data for methyl c-5-allyl-t-5-tert-butyl-t-2-phenyl-tetrahydrofuran-r-3-carboxylate: ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.4-7.15 (m, 5H, Ph), 6.05, 5.2, 5.05 (3mc, 1H each, $CH=CH_2$), 5.12 (d, J = 10 Hz, 1H, 2-H), 3.63 (s, 3H, CO_2Me), 2.88 (ddd, J = 9, 10, and 11 Hz, 3-H), 2.40, 2.30 (2dd, J = 11 and 13, J = 9 and 13 Hz, 1H each, 4-H), 2.58, 2.27 (AB of ABX, 5-CH_2), 1.06 (s, 9H, t-Bu). - ^{13}C-NMR ($CDCl_3$): δ = 173.1, 51.6 (s, q, CO_2Me), 140.5, 127-126 (s, 3d, Ph), 135.2, 118.3 (d, t, $CH=CH_2$), 88.9 (s, C-5), 83.2 (d, C-2), 53.5 (d, C-3), 41.2, 36.3 (2t, 5-CH_2, C-4), 38.6, 26.0 (s, q, t-Bu).

Methyl c(t)-5-tert-Butyl-t(c)-5-cyano-c-2-phenyl-tetrahydrofuran-r-3-carboxylate (18): Analogously to preparation of 7, 0.556 g (2.00 mmol) of 6, 0.396 g (4.00 mmol) of cyano trimethylsilane, and 0.57 g (4.0 mmol) of BF_3-OEt_2 in 10 ml of CH_2Cl_2 give after filtration of the crude product solution through a pad of Al_2O_3 and evaporation 0.338 g (59 %) of 18 as colorless crystals (m.p. 63-68°C). The product is a 90 : 10 mixture of two stereoisomers epimeric at C-5.
IR (CCl_4): ν = 3100-2800 cm^{-1} (C-H), 2250 (very weak, CN), 1740 (CO_2Me).
NMR-data for the major (90 %) isomer: ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.35-7.2 (m, 5H, Ph), 5.45 (d, J = 9 Hz, 1H, 2-H), 3.64 (dt, J = 8 and 9 Hz, 1H, 3-H), 3.05 (s, 3H, CO_2Me), 2.79, 2.37 (2dd, J = 8 and 13.5, J = 9 and 13.5 Hz, 1H each, 4-H), 1.24 (s, 9H, t-Bu). - ^{13}C-NMR ($CDCl_3$): δ = 171.5, 51.3 (s, q, CO_2Me), 136.7, 128.2, 127.9, 126.7 (s, 3d, Ph), 119.8 (s, CN), 87.3 (s, C-5), 82.6 (d, C-2), 48.6 (d, C-3), 36.5, 25.1 (s, q, t-Bu), 35.6 (t, C-4).
^{1}H-NMR-data ($CDCl_3$, 400 MHz) for the minor (10 %) isomer: δ = 5.34 (d, J = 7.5 Hz, 1H, 2-H), 3.50 (ddd, J = 4.0, 7.5, and 8.5 Hz, 1H, 3-H), 3.24 (s, 3H, CO_2Me), 2.85, 2.53 (2dd, J = 8.5 and 14, J = 4.0 and 14 Hz, 1H each, 3-H), 1.14 (s, 9H, t-Bu).
$C_{17}H_{21}O_3N$ (287.4) Calcd. C 71.05 H 7.37 N 4.88 Found C 71.34 H 7.49 N 4.46

Isomerization of 18 with sodium methoxide: Analogously to the isomerization, of 17 one obtains from the 90 : 10 mixture of 18, as prepared above, a mixture of three isomers in a ratio of ≈ 70 : 20 : 10 (m.p. 81-87°C). Significant ^{1}H-NMR-signals ($CDCl_3$, 400 MHz): Major (70 %) isomer: 5.29 (d, J = 9 Hz, 2-H), 3.60 (s, CO_2Me), 2.94 (ddd, J = 7.5, 9, and 10.5 Hz, 3-H), 1.16 (s, t-Bu); proposed stereochemistry: t-5-tert-butyl-c-5-cyano-t-2-phenyl-3-r-CO_2Me. - (20 %) Isomer: 5.46 (d, J = 9.5 Hz, 2-H), ≈ 3.65 (3-H), 3.05 (s, CO_2Me), 1.24 (s, t-Bu); proposed stereochemistry: c-5-tert-butyl-t-5-cyano-c-2-phenyl-r-3-CO_2Me. - Minor (10 %) isomer: 5.13 (d, J = 10 Hz, 2-H), 3.66 (s, CO_2Me), 3.41 (q, J ≈ 10 Hz, 3-H); proposed stereochemistry: c-5-tert-butyl-t-5-cyano-t-2-phenyl-r-3-CO_2Me. -
^{13}C-NMR ($CDCl_3$) of the major isomer: δ = 171.2, 52.2 (s, q, CO_2Me), 138.2, 128.5, 128.5, 126.1 (s, 3d, Ph), 120.1 (s, CN), 85.9 (s, C-5), 83.7 (d, C-2), 51.5 (d, C-3), 37.1 (t, C-4), 37.0, 24.7 (s, q, t-Bu). ^{13}C-NMR ($CDCl_3$) data of the (20 %) isomer are identical with the signals of the predominanting isomer before isomerization.

Methyl t-5-Allenyl-c-5-tert-butyl-c-2-phenyl-tetrahydrofuran-r-3-carboxylate (19): Analogously to synthesis of 7, 0.278 g (1.00 mmol) of 6, 0.224 g (2.00 mmol) of propargyl trimethylsilane and of 0.28 g (2.0 mmol) of BF_3-OEt_2 in 5 ml of CH_2Cl_2 provide after distillation (180°C/0.02 Torr) 0.254 g (85 %) of 19 as colorless viscous liquid.
IR (film): ν = 3100-2800 cm^{-1} (C-H), 1950 ($CH_2=C=CH$), 1740 (CO_2Me). - ^{1}H-NMR ($CDCl_3$): δ =

7.45-7.1 (m, 5H, Ph), 5.26, 4.84 (broad dt, d, J = 1.5 and 6, J = 6 Hz, 1H and 2H, CH=C=CH$_2$), 5.20 (d, J = 9.5 Hz, 1H, 2-H), 3.47 (q, J ≈ 9.0 Hz, 1H, 3-H), 3.05 (s, 3H, CO_2Me), 2.53 (ddd, J = 1.5, 8.5, and 12.5 Hz, 1H, c-4-H), 2.21 (dd, J = 9.0 and 12.5 Hz, 1H, t-4-H), 1.14 (s, 9H, t-Bu); a singlet at 3.62 ppm might be due to a second isomer (≈ 5 %).

$C_{19}H_{24}O_3$ (300.4) Calcd. C 75.97 H 8.05 Found C 75.23 H 8.34

Methyl 5-tert-Butyl-t-2-phenyl-2,3-dihydrofuran-r-3-carboxylate (20): A solution of 0.278 g (1.00 mmol) of 6, 0.202 g (2.00 mmol) of triethylamine, and 10 ml of CH_2Cl_2 is treated at 0°C with 0.229 g (2.00 mmol) of mesyl chloride. After 30 min at this temperature and further stirring for 30 min at room temp. 10 ml of H_2O are added. The mixture is extracted twice with CH_2Cl_2, the organic phase is washed with brine and dried with $MgSO_4$ to give after distillation (120-140°C/0.02 Torr) 0.234 g (90 %) of 20, which is pure according to ^{1}H-NMR spectroscopy, however, due to hydrolysis too sensitive for correct elemental analysis.

IR (CCl_4): ν = 3100-2800 cm^{-1} (C-H), 1730 (CO_2Me), 1640 (C=C). - ^{1}H-NMR ($CDCl_3$): δ = 7.33 (s, 5H, Ph), 5.83 (d, J = 7 Hz, 1H, 2-H), 4.63 (d, J = 2.5 Hz, 1H, 4-H), 3.76 (s, 3H, CO_2Me), 3.68 (dd, J = 2.5 and 7 Hz, 1H, 3-H), 1.22 (s, 9H, t-Bu).

Methyl 5-tert-Butyl-2-phenyl-furan-3-carboxylate (21): A suspension of 0.431 g (2.00 mmol) of pyridinium chlorochromate in 5 ml of CH_2Cl_2 is stirred with 0.278 g (1.00 mmol) of 6 for 16 h at room temp. Filtration (Al_2O_3) and distillation (140°C/0.02 Torr) provides 0.233 g (84 %) of methyl 2-benzoyl-5,5-dimethyl-4-oxohexanoate as colorless liquid. IR (CCl_4): ν = 1745, 1710, 1690 cm^{-1} (C=O). - ^{1}H-NMR ($CDCl_3$): δ = 8.2-7.9, 7.6-7.2 (2m, 5H, Ph), 4.93 (t, J = 7 Hz, 2-H), 3.65 (s, 3H, CO_2Me), 3.27 (d, J = 7 Hz, 1H, 3-H), 1.18 (s, 9H, t-Bu).

$C_{16}H_{20}O_4$ (276.3) Calcd. C 69.55 H 7.30 Found C 69.47 H 7.22

A solution of 0.180 g (0.65 mmol) of this diketone in 5 ml of toluene is refluxed for 4 h with 50 mg of TosOH and 2 g of molecular sieves. Addition of K_2CO_3, filtration and distillation (110°C/0.02 Torr) afford 0.091 g (54 %) of 21 as colorless liquid.

IR (film): ν = 1735 cm^{-1} (CO_2Me). - ^{1}H-NMR ($CDCl_3$): δ = 8.15-7.8, 7.6-7.3 (2m, 5H, Ph), 6.40 (s, 1H, 4-H), 3.82 (s, 3H, CO_2Me), 1.32 (s, t-Bu).

$C_{16}H_{18}O_3$ (258.3) Calcd. C 74.40 H 7.02 Found C 74.37 H 7.28

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