79. Studies Directed Towards the Biosynthesis of the C_7N Unit of Rifamycin B: A New Synthesis of Quinic Acid from Shikimic Acid

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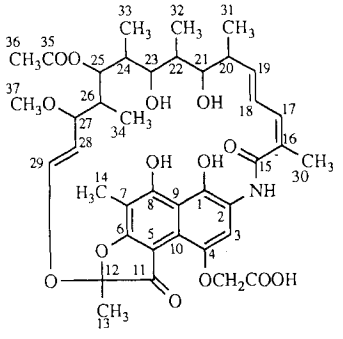
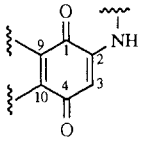
The synthesis of quinic acid (**4**) *via* epoxide **13**, starting from shikimic acid (**5**), is described (*Scheme 1*). Treatment of **13** with thiophenol yielded not only **17**, but also the γ-lactones **18** and **19** as result of migration of silyl groups within a *cis*- and *trans*-diol system. The conversion provides a direct stereoselective epoxidation of a shikimic-acid derivative as well as an alternative pathway for the preparation of **4**. A shorter approach *via* the disilylated epoxide **22** was unsuccessful because the γ-lactone **25** was obtained in place of the desired α-hydroxy ester **24** (*Scheme 2*).

Introduction. – The rifamycins belong to the class of antibiotics known as the ansamycins. Although all ansamycins have been tested for their antibacterial, antiviral, and antitumor activity, the only substances suitable for pharmaceutical application were members of the rifamycin family [1] [2]. Subsequently, most of the biosynthetic and fermentation studies have dealt with this family of antibiotics.

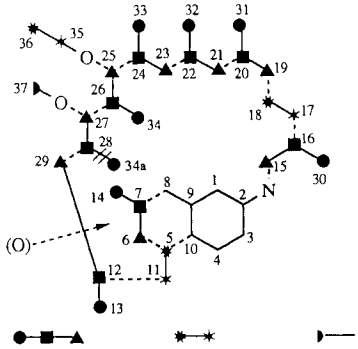
Although rifamycin B (**1**) is the chief fermentation product obtained from cultures of *Nocardia mediterranei*, biosynthetic studies were conducted using the simpler rifamycin S (**2**). Incorporation experiments with ^{14}C- or ^{3}H-labelled precursors followed by chemical degradation, or using ^{13}C-precursors combined with ^{13}C-NMR spectroscopy established that the ansa ring of rifamycins is constructed from eight propionate and three acetate units as well as one Me group, originating from L-methionine, and the so-called seven-carbon amino unit (C_7N) of as yet uncertain origin [3] [4], consisting of C(1), C(2), C(3), C(4), C(8), C(9), and C(10) acting as initiator. Incorporation studies with rifamycin



Rifamycin B (**1**)



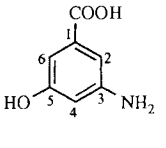
Rifamycin S (**2**)



CH_3CH_2COOH CH_3COOH CH_3-S-Methionine

and D-[1-^{13}C]glucose and D-[1-^{13}C]glycerate led to the hypothesis that the C_7N unit of rifamycin S (**2**) was derived from an intermediate of the shikimic-acid pathway [5]. However, incorporation attempts with [U-^{14}C]shikimate were unable to substantiate this statement in that [^{14}C]shikimate was found neither in the ansa chain nor in the C_7N unit of rifamycin S (**2**) [3].

Independently from *Kibby et al.* [6], *Ghisalba* and coworkers [7] [8] were able to identify the direct precursor of the C_7N unit as 3-amino-5-hydroxybenzoic acid (**3**). In an attempt to identify the precursor of **3**, an incorporation experiment using ^{14}C-labelled quinic acid (**4**) with the double-mutant *N. mediterranei* P14, which excretes shikimic acid (**5**) and an earlier precursor of rifamycin B (**1**), identified as P8/1-OG (**6**) [9], was conducted by *Gygax* [10]. Identification of the radioactive products on TLC allowed the recognition of quinic acid (**4**), shikimic acid (**5**), 3,*O*-didehydroshikimic acid (**7**), and a product with an R_f value very similar to that of product P8/1-OG (**6**). The results of this experiments suggested that the biosynthesis of **3** most likely occurs *via* a cyclic intermediate, which is then transaminated to **3**. It was necessary to confirm this result with further incorporation experiments using isotopically labelled quinic acid (**4**).



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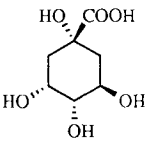

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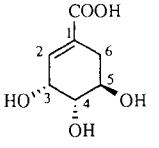

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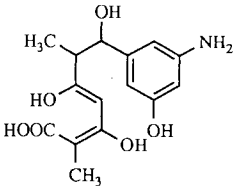

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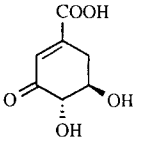

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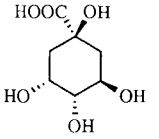

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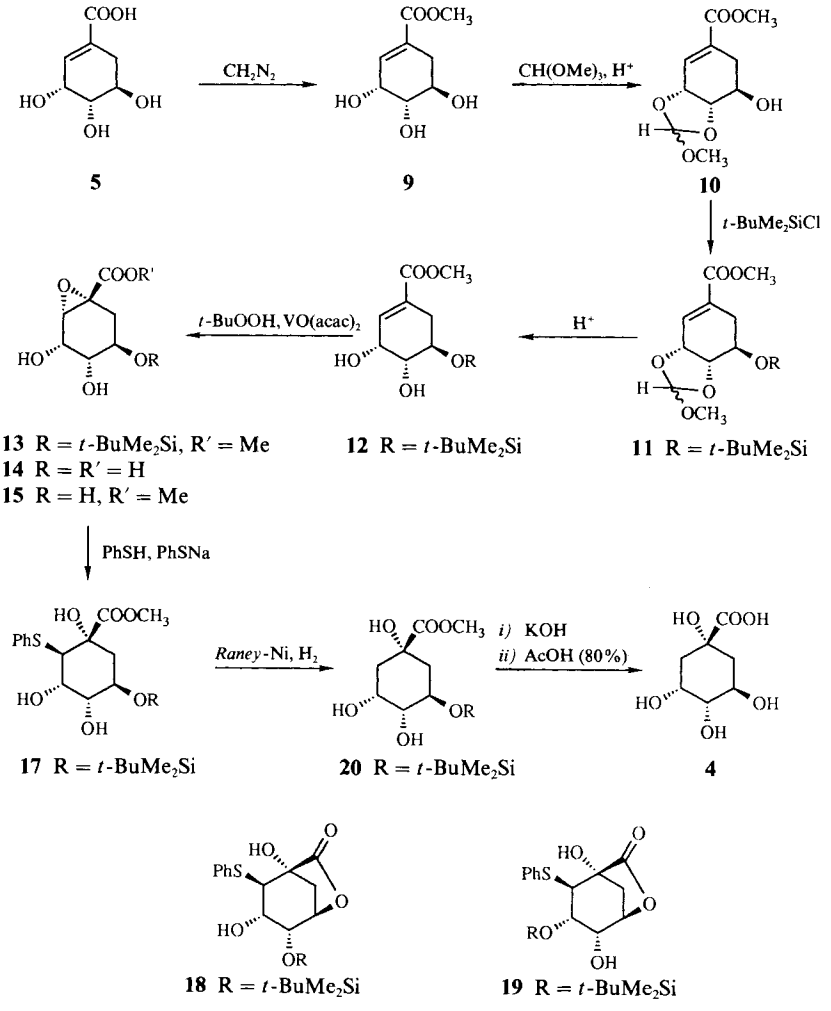
It was our intention to transform [^{14}C]shikimic acid which is commercially available, into [^{14}C]quinic acid. *Grewe* and *Lorenzen* reported the conversion of shikimic acid (**5**) into quinic acid (**4**) *via* the dibromo derivative using a solid-phase bromination [11]. Treatment of the dibromo derivative with Ag_2CO_3 in aqueous solution afforded 2-bromoquinic acid, as its lactone, which was transformed into quinic acid (**4**) by catalytic hydrogenation, with an overall yield of *ca.* 50%. Despite this publication, we decided to design a new, more economic synthetic route in view of the future synthesis of radioactive compounds.

The 1-OH group in quinic acid (**4**) could be introduced *via* an epoxy group at C(1) and C(2) of shikimic acid (**5**). *Grewe* and *Lorenzen* reported that under carefully controlled basic conditions, the dibromo derivative of shikimic acid delivered the 1,2-epoxy derivative in *ca.* 60% yield [11]. *Sprinson* and coworkers disclosed [12] that shikimic acid (**5**) and

derivatives of shikimic acid could not be epoxidized with 3-chloroperbenzoic acid or with H_2O_2 and sodium tungstate. They concluded that the double bond of shikimic acid (**5**) was insufficiently reactive towards addition reactions. *Campbell et al.* [13] reacted 5-epishikimic acid and potassium peroxide with [18]crown-6 ether and isolated the free carboxylic acid as well as the 1,2-epoxy derivative in 50 and 1.7% yield, respectively.

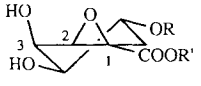
Results. – Owing to the allylic OH group at C(3) of shikimic acid (**5**), the *Sharpless* epoxidation should be favored, in which an allylic alcohol reacts with *tert*-butyl hydroperoxide (*t*-BuOOH) and a vanadium catalyst to give the epoxide *cis* to the OH group with high stereoselectivity [14]. Since homoallylic alcohols are also capable of demonstrating this *cis*-directing effect, the 5-OH group of shikimic acid (**5**) was protected in order to prevent the formation of the epoxide *cis* to the 5-OH group and ultimately of epiquinic acid (**8**).

Scheme 1

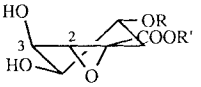


In order to selectively protect the 5-OH group in shikimic acid (**5**), the *cis*-orientated OH groups on C(3) and C(4) were initially protected by an acid-sensitive orthoformate group [15], after esterification with diazomethane (→ **9** → **10** (yield 83%); see *Scheme 1*). The 5-OH group of **10** was subsequently protected as its (*tert*-butyl)dimethylsilyl ether (→ **11**, 88% yield) according to [16] and the orthoformate group removed [15] to give crystalline **12** in 70% yield. The low yield indicated that the acid-labile silyloxy group was partially hydrolyzed during treatment with weak acid; this was later confirmed by the isolation of the H_2O-soluble methyl shikimate (**9**). Treatment of **12** with *t*-BuOOH in CH_2Cl_2 in the presence of vanadium diacetate catalyst according to *Sharpless* and *Michaelson* [17] gave epoxy derivative **13** (81% yield, after purification).

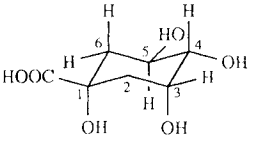
Sprinson and coworkers previously reported [12] the ^{1}H-NMR data (220 and 100 MHz) for (2*S*)-1,2-anhydro-2-hydroxyquinic acid (**14**) and for methyl (2*S*)-1,2-anhydro-2-hydroxyquinate (**15**) in a mixture of D_2O, (D_6)acetone, and (D_5)pyridine: the coupling constant J(2,3) was 4.0 and 3.5 Hz, respectively, and the *dd* of H–C(2) arose from an additional long-range coupling with the equatorial H–C(6). According to *Sprinson*, **14** occupies the energetically preferred half-chair **14a** with an axial OH–C(3) and equatorial OH–C(4) and OH–C(5). It was expected that **13** with its voluminous equatorial *t*-$BuMe_2Si$ group would also be present in this energetically favored conformation. However, the relatively small J(2,3) of 2.4 Hz in the ^{1}H-NMR spectrum of **13** corresponds to a dihedral angle of *ca.* 20° between H–C(2) and H–C(3). The epoxidation product of **12** could be a mixture of the two diastereoisomers **13** and **16**. However, in the undesired **16**, the analogous dihedral angle is 60° (*Dreiding* model), and the *Karplus* equation [18] suggests a larger J(2,3) for **13** (epoxy group *cis* to 3-OH) than for the *trans*-configurated **16**.



14a R = R′ = H
13 R = *t*-$BuMe_2Si$, R′ = Me



16 R′ = Me
R = *t*-$BuMe_2Si$



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Nucleophilic attack on C(2) of **13** by thiophenol/sodium thiophenolate in DMSO resulted in the formation of **17**. The regioselective attack was confirmed by the ^{13}C-NMR spectrum. In the case of attack on C(1), its signal at 78.1 ppm would be shifted to higher field by 10–20 ppm (O more electronegative than S) [19]. Occasionally, in addition to **17**, two further products were obtained which were assigned the structures **18** and **19** (^{1}H-NMR; IR: 1795 cm^{-1} (γ-lactone), no ester CO) and probably are due to traces of H_2O in DMSO. Numerous literature examples of *t*-$BuMe_2Si$ transfer not only in *cis*-1,2-diols but also in *trans*-1,2-diols [20] [21] substantiate the migration of the *t*-$BuMe_2Si$ group to the 4-OH (**13** → **18**) or 3-OH (**13** → **19**) group. The isolation of **18** and **19** supported further the configurational assignment of epoxide **13** (COOMe *cis* to 5-OH).

The orthogonal arrangement of the axial H–C(5) and H–C(6) in **18** and **19** was confirmed by the lack of coupling between these two protons. Only geminal coupling was observed for H_{ax}–C(6), in contrast to H_{eq}–C(6) which displayed in addition also vicinal coupling with H–C(5) as well as, in the case of **19**, a long-range coupling with H–C(4). The large J(2,3) of *ca.* 10.5 Hz was easily explained by the *trans*-diaxial orientation of H–C(2) and H–C(3). The fact that H–C(3) of **18** appeared as a *ddd* which collapsed to a *dd* after exchange with D_2O allowed the differentiation of **18** (H–C(4) geminal to SiO) and **19** (H–C(3) geminal to SiO).

The phenylthio group of **17** was removed by reduction with *Raney*-Ni and H_2 at 4.5 atm (*Scheme 1*). All attempts to increase the yield of **20** from *ca.* 70% by variation of the solvent, the ratio **17**/*Raney*-Ni, or the pressure (1 and 4.5 atm) failed. Finally, the two

protecting groups were removed by treatment with aqueous KOH/THF solution, yielding quinic acid (**4**) quantitatively (after ion exchange), in an overall yield of 21–25% from shikimic acid (**5**). The identity of the ^{1}H- and ^{13}C-NMR spectra of the synthesized quinic acid (**4**) with authentic material is a further confirmation that the epoxidation of the 5-silyloxy methyl ester **12** had given quinic acid (**4**) and not epiquinic acid (**8**).

A detailed NMR study published by *Corse* and coworkers in 1966 [22] and later confirmed by *Haslam* and *Turner* in 1971 [23] showed that quinic acid (**4**) in solution is in the expected chair conformation with the COOH group equatorially orientated. H–C(3), H–C(4), and H–C(5) of our synthetic sample **4** exhibited resonances between 3.39 and 4.09 ppm. The *dd* at 3.39 ppm was unequivocally assigned to H–C(4) which coupled with H–C(5) and H–C(3). The fact that H–C(4) and H–C(5) display a dihedral angle of 180° explained the large coupling constant of *ca.* 9.1 Hz; the smaller one of *ca.* 3.2 Hz was a result of the synclinal conformation (axial/equatorial) between H–C(4) and H–C(3). As in the case of other substances in this series, the two protons on C(6) appeared as a *dd* at 1.86 and 2.12 ppm. The resonance at 1.86 ppm could be assigned, as a result of its large coupling constant of *ca.* 11.0 Hz corresponding to a *trans*-diaxial orientation, to H_{ax}–C(6). Although no symmetry axis is present for the two protons at C(2), and although they are magnetically nonequivalent, they appeared, surprisingly, as a *d*. They displayed magnetic equivalence with an identical J of 2.4 Hz to H–C(3).

In the ^{13}C-NMR of **4**, the signals for the appropriate 6 C-atoms were observed. In **4**, both 1-OH and 3-OH are 1,3-diaxially orientated, so that C(5) should experience an upfield shift of *ca.* 5 ppm. As a result, the signal at 68.11 ppm could be unequivocally assigned to C(5). According to the chemical-shift theory, C(6) appeared at lower field than C(2) (42.5 and 38.5 ppm, resp.) [24].

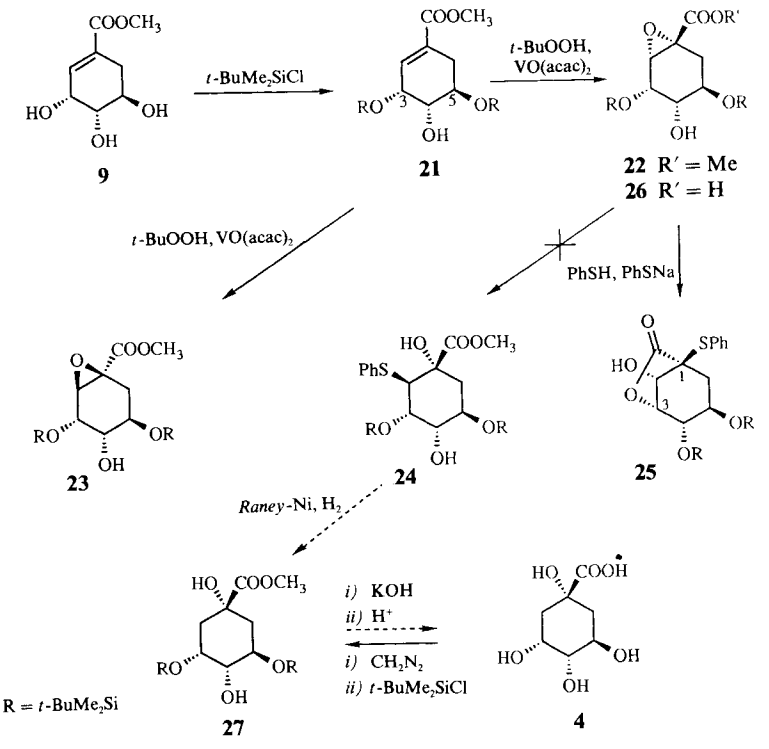
In an attempt to shorten the synthetic route, the *Sharpless* epoxidation was conducted using methyl shikimate (**9**) in either CH_2Cl_2 or in AcOEt. Both resulted in low yields. A further attempt in AcOEt, followed by *in situ* opening of the epoxide with thiophenol lead to a multitude of products. The epoxidation was repeated in AcOEt, the reaction solution concentrated directly and the product purified to deliver two diastereoisomers in *ca.* 35% yield.

Because of the unsatisfactory results obtained in the epoxidation of methyl shikimate (**9**), another shorter synthetic concept was designed (*Scheme 2*). The OH groups at C(3) and C(5) were protected by silylation with *t*-BuMe$_2$SiCl according to *Desmaele* and *Tanier* [25] to furnish **21** (78%), and subsequent treatment of **21** with *t*-BuOOH and VO(acac)$_2$ provided epoxy derivatives **22** (*cis* to 4-OH) and **23** (*trans* to 4-OH) in 87 and 7% yield, respectively. But all attempts to prepare **24** from **22** failed. Instead, γ-lactone **25** was obtained in 45% yield. The formation of **25** was accounted for by the migration of the *t*-BuMe$_2$Si group from 3-OH to 4-OH, as described above for **18** and **19**.

In the ^{1}H-NMR of **22**, H–C(2) appeared at 3.52 ppm as a *dd*, through coupling with H–C(3) (J = 2.5 Hz) and long-range coupling with H–C(6). As in the case of the monosilylated **13** (see above), the disilylated **22** should occupy the energetically preferred half-chair with the axial *t*-BuMe$_2$SiO group at C(3) and the equatorial one at C(5). Indeed, a comparison of the ^{1}H-NMR spectra of **13** and **22** indicated only negligible differences in the chemical shifts and coupling constants. The fact that J(2,3) was smaller for the undesired **23** than for the correct diastereoisomer **22** was in agreement with the predictions of the *Karplus* equation [18]. As a result of the attack on C(1) instead of C(2) in **22**, the configuration at C(1) of **25** is inverted (*cf.* epiquinic acid), so that the free 4-OH group could form a δ-lactone between C(1) and C(4). But the ^{1}H-NMR spectrum suggested a γ-lactone between C(1) and C(3). The lack of coupling between H–C(2) and H–C(3) of **25** indicated that these protons are positioned orthogonal to one another. A small coupling constant for H–C(3) (4.60 ppm) of *ca.* 1.1 Hz, *i.e.* J(3,4), correlates well with the angle of 67°. The large coupling constant of *ca.* 10.9 Hz was explained by the fact that H_{ax}–C(6) lies *trans*-diaxial to H–C(5).

Due to the unexpected attack of the thiophenolate at C(1) instead of C(2) of the disilylated epoxy derivative **22**, the epoxide opening was attempted using different hydride reagents. Treatment of **22** or its free acid **26** with $NaBH_4$ in EtOH or H_2O, $LiBH_4$ in

Scheme 2



THF, $LiAlH(t\text{-}BuO)_3$) in THF or with $LiBH(Et)_3$/*Super Hydride* (*Aldrich*) did not yield the expected compound **27** or its free acid, as indicated by TLC analysis. Thus, the synthesis according to *Scheme 1* was utilized for the conversion of [U-^{14}C]shikimic acid to [U-^{14}C]quinic acid as described in a subsequent paper.

Considering length and overall yield, the new synthetic route offers little advantage for the conversion of shikimic acid (**5**) into quinic acid (**4**) in comparison to the method first published in 1953 by *Grewe* and *Lorenzen* [11]. However, it presents the first possibility for the direct stereoselective epoxidation of a shikimic-acid derivative with acceptable yields, completely in contrast to the unsuccessful attempts reported by *Sprinson* and coworkers [12] or by *Campbell et al.* [13].

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Experimental Part

General. Shikimic acid (**5**) and quinic acid (**4**) were purchased from *Fluka*. H_2O- and air-sensitive reactions were carried out under inert gas (N_2, Ar). THF was freshly distilled over Na-K alloy; CH_2Cl_2 was dried over aluminium oxide and stored over molecular sieves (4 Å). All org. extracts were dried (Na_2SO_4) and evaporated below 40°. TLC: silica gel *60 F_{254}* (*Merck*). Column chromatography (CC): silica gel (60–200 μm, *Chemische Fabrik Uetikon*). M.p.: *Kofler* block; corrected. $[\alpha]_D$: *Perkin-Elmer-141* polarimeter. IR spectra (cm^{-1}): *Perkin-Elmer-781* IR spectrometer. NMR: *Varian-EM-360* (^1H, 60 MHz), *Varian-EM-390* (^1H, 90 MHz), *Bruker-WH-90-FT* (^1H, 90 MHz; ^{13}C, 22.63 MHz), and *Varian-VXR-400* spectrometer (^1H, 400 MHz; ^{13}C, 101 MHz, correlation of the signals was accomplished by BB and APT experiments); chemical shifts in ppm relative to internal TMS; digital resolution for the coupling constants (J), ±0.2 Hz/point. MS: *VG-70-250* spectrometer (Cl with NH_3), m/z values with relative intensities (%) in parentheses.

*Methyl (3*R,*4*S,*5*R*)-3,4,5-Trihydroxycyclohex-1-ene-1-carboxylate* (**9**) [15]. To a colorless soln. of shikimic acid (**5**; 4.00 g, 22.99 mmol) in abs. MeOH (100 ml) was added dropwise at −15 to −20° [26] an Et_2O soln. of diazomethane until the pale yellow color persisted. After evaporation followed by the addition of AcOEt, colorless **9** precipitated. A probe for anal. purposes was recrystallized from AcOEt. M.p. 115–116° ([27] [28]: 115–116.5°). $[\alpha]_D^{22} = -132.9$ ($c = 1.4$, EtOH; [27] [28]: $[\alpha]_D^{20} = -125$ ($c = 1.8$, EtOH)). IR (KBr): 3340 (OH), 2960, 2910, 1725 (α,β-unsat. ketone), 1660 (C=C). ^1H-NMR (400 MHz, CD_3OD): 2.20 (*ABX*, $J = 18.2, 5.4, 1.7, 1.7$, H_{ax}–C(6)); 2.69 (*ABX*, $J = 18.2, 4.9, 1.9, 1.9$, H_{eq}–C(6)); 3.68 (*dd*, $J = 4.2, 7.2$, H–C(4)); 3.74 (*s*, $COOCH_3$); 3.99 (*ddd*, $J = 7.2, 5.2, 5.2$, H–C(5)); 4.36 (*m*, H–C(3)); 6.78 (*ddd*, $J = 1.8, 1.9, 3.6$, H–C(2)). ^{13}C-NMR (101 MHz): 31.5 (C(6)); 52.4 ($COOCH_3$); 67.2 (C(5)); 68.3 (C(4)); 72.6 (C(3)); 130.2 (C(1)); 139.0 (C(2)); 168.7 (C(7)). CI-MS: 206 (100.0, $[M + NH_4]^+$), 188 (10.3, $[M]^+$). EI-MS (70 eV): 156 (16.6), 138 (13.3), 129 (31.6, $[M - COOCH_3]^+$), 111 (17.5), 97 (100.0), 81 (16.9), 69 (43.9), 60 (30.1), 53 (23.7), 41 (38.3).

*Methyl (3*R,*4*S,*5*R*)-5-Hydroxy-3,4-[(methoxymethylene)dioxy]cyclohex-1-ene-1-carboxylate* (**10**) [15]. To a stirred suspension of **9** (500 mg, 2.66 mmol) in CH_2Cl_2 (10 ml) at r.t.was added first trimethyl orthoformate (0.72 ml, 6.56 mmol) followed by TsOH (35 mg, 0.18 mmol). After 1.5 h stirring, the clear soln. was cooled to 0° and excess Na_2CO_3 (solid) was added. The suspension was diluted with 150 ml of AcOEt (prewashed with sat. Na_2CO_3 soln.) and washed with sat. Na_2CO_3 soln. (5 × 40 ml), H_2O (3 × 40 ml), and brine (2 × 40 ml). The aq. phase was washed with AcOEt (150 ml), the combined org. phase dried and evaporated, and the resulting yellow oil (100%) submitted to CC (20–60% AcOEt/hexane): 509 mg (83%) of a colorless oil, mixture of diastereoisomers **10**. IR (film): 3490 (OH), 2960, 2850, 1725 (α,β-unsat. ketone), 1660 (C=C), 1440 (C–O), 1260 (C–O, ester), 1075 (C–O). ^1H-NMR (90 MHz, $CDCl_3$): 2.30 (*ABX*, $J = 17.5$, H_{ax}–C(6)); 2.79 (*ABX*, $J = 17.5$, H_{eq}–C(6)); 3.30, 3.36 (2*s*, 2 CH_3O); 3.78 (*s*, $COOCH_3$); 3.93 (*dd*, $J = 6.6, 4.7$, H–C(4)); 4.24 (*m*, H–C(5)); 4.87 (*m*, H–C(3)); 5.77, 5.82 (2*s*, 2 OCH); 6.90 (br. *s*, H–C(2)). ^{13}C-NMR (22.63 MHz): 29.3, 29.5 (C(6)); 51.8, 52.1 ($COOCH_3$); 68.1 (C(5)); 71.7, 72.6 (C(4)); 77.7, 77.9 (C(3)); 115.6, 116.8 (C(9)); 130.5, 131.4 (C(1)); 132.8, 133.8 (C(2)); 166.5, 166.7 ($COOCH_3$); $CHOCH_3$ could not be correctly identified. CI-MS: 248 (0.4, $[M + NH_4]^+$), 231 (0.2, $[M + H]^+$), 199 (100.0, $[M - CH_3O]^+$), 171 (6.4, $[M - COOCH_3]^+$), 188 (3.2, $[M + 2H - CHOCH_3]^+$). EI-MS (70 eV): 199 (31.3, $[M - CH_3O]^+$), 171 (4.7, $[M - COOCH_3]^+$), 167 (11.8), 153 (17.7, $[M - COOCH_3 - H_2O]^+$), 138 (66.6, $[HOOCC_6H_4OH]^+$), 124 (17.8), 111 (49.6), 110 (100.0), 93 (43.9), 82 (64.3), 81 (53.7), 59 (49.2, $[COOCH_3]^+$), 53 (65.3).

*Methyl (3*R,*4*R,*5*R*)-5-[(*tert*-Butyl)dimethylsilyloxy]-3,4-[(methoxymethylene)dioxy]cyclohex-1-ene-1-carboxylate* (**11**). According to [16], a soln. of **10** (612 mg, 2.66 mmol) in DMF (12 ml), Et_3N (890 μl, 6.39 mmol), *t*-$BuMe_2SiCl$ (881 mg, 5.85 mmol), and 4-(dimethylamino)pyridine (215 mg, 1.76 mmol) were stirred at r.t. After 6 h, the pale yellow soln. was cooled to 0° and quenched with H_2O (10 ml). The mixture was extracted with AcOEt (150 ml), the extract washed with H_2O (6 × 40 ml) and sat. NH_4Cl soln. (40 ml), the aq. phase washed with AcOEt (2 × 150 ml), and the combined org. phase dried and evaporated: 807 mg (88%) of a yellow oil, mixture of diastereoisomers **11**. IR (film): 2940, 2860, 1725 (α,β-unsat. ketone), 1660 (C=C), 1435, 1250 (C–O, ester), 1075 (C–O). ^1H-NMR (90 MHz, $CDCl_3$): 0.04, 0.07 (2*s*, 2 Me_2Si); 0.84 (*s*, *t*-BuSi); 2.41 (*ABX*, $J = 6.6, 4.1, 1.0$, CH_2(6)); 3.24, 3.32 (2*s*, 2 CH_3O); 3.74 (*s*, $COOCH_3$); 3.94 (*m*, H–C(4)); 4.19 (*m*, H–C(5)); 4.79 (*m*, H–C(3)); 5.68, 5.76 (2*s*, 2 $CH(OCH_3)$); 6.83 (*dd*, $J = 1.7, 3.5$, H–C(2)). ^{13}C-NMR (22.63 MHz): −4.8 ($(CH_3)_2Si$); 18.1 ($(CH_3)_3CSi$); 25.8 ($(CH_3)_3CSi$); 29.4, 29.9 (C(6)); 51.7 ($COOCH_3$); 52.0 ($CHOCH_3$); 68.5, 68.7 (C(5)); 71.9, 72.1 (C(4)); 77.0, 77.5 (C(3)); 115.6, 116.7 ($CHOCH_3$); 129.5, 130.8 (C(1)); 132.7, 133.9 (C(2)); 166.6, 166.8 ($COOCH_3$). CI-MS: 379 (2.5, $[M + NH_4 + NH_3]^+$), 362 (35.9, $[M + NH_4]^+$), 347 (16.8, $[M + NH_4 - CH_3]^+$), 330 (71.9, $[M + NH_4 - CH_3OH]^+$), 313 (100.0, $[M - CH_3O]^+$). EI-MS (70 eV): 313 (6.3, $[M - CH_3O]^+$), 287 (35.5, $[M - (CH_3)_3C]^+$), 269 (2.6, $[M - OSi(CH_3)_2H]^+$), 227 (100.0, $[M - OSi(CH_3)_2H - CH_2OC]^+$), 195 (39.5), 167 (43.0), 89 (49.0), 75 (48.0, $[OSi(CH_3)_2H]^+$), 73 (54.4, $[OC(CH_3)_3]^+$), 59 (17.8, $[COOCH_3]^+$).

*Methyl (3R,4R,5R)-5-[(*tert*-Butyl)dimethylsilyloxy]-3,4-dihydroxycyclohex-1-ene-1-carboxylate* (**12**). According to [15], a soln. of **11** (198 mg, 0.57 mmol) in MeOH/H_2O/HCl 100:1.0:0.1 (5 ml) was stirred for 15 min. The reaction was then quenched by the addition of sat. aq. $NaHCO_3$ soln. (1 ml). The resulting milky soln. was treated with excess $NaHCO_3$ (solid) to complete the hydrolysis of the intermediate orthoformates. The suspension was then diluted with AcOEt (75 ml) and the org. phase washed with H_2O until neutral (3 × 20 ml, 3 × 10 ml) and with brine (25 ml). Drying and evaporation of the org. phase gave **12** (122 mg, 70%) as a colorless solid that was used without further purification. An anal. sample was obtained by dissolution in CH_2Cl_2 and hexane and evaporation, followed by recrystallization of the powdery solid from hexane and AcOEt. M.p. 98.5–100°. $[\alpha]_D^{22} = -74.3$ ($c = 1.01$, AcOEt). IR (film): 3270 (OH), 2955, 2930, 2905, 2895, 2860, 1715 (α,β-unsat. ketone), 1660 (C=C), 1250, 1095, 835. ^{1}H-NMR (400 MHz, CD_3OD): 0.09 (*s*, MeSi); 0.10 (*s*, MeSi); 0.88 (*s*, *t*-BuSi); 2.20 (*ABX*, $J = 19.0, 3.3, 1.6$, H_{eq}–C(6)); 2.59 (*ABX*, $J = 18.2, 4.1, 2.3$, H_{ax}–C(6)); 3.73 (*s*, $COOCH_3$); 3.75 (*m*, H–C(4)); 4.13 (*ddd*, $J = 5.7, 3.8, 3.8$, H–C(5)); 4.40 (*s*, broadned by coupling with H–C(6), H–C(3)); 6.75 (br. *s*, H–C(2)). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.08 (*s*, Me_2Si); 0.86 (*s*, *t*-BuSi); 2.17 (*ABX*, $J = 17.9, 6.7, 2.1, 1.4$, H_{eq}–C(6)); 2.55 (br. *s*, 2 OH); 2.71 (*ABX*, $J = 17.9, 5.0, 1.5$, H_{ax}–C(6)); 3.64 (*dd*, $J = 4.2, 8.0$, H–C(4)); 3.73 (*s*, $COOCH_3$); 4.03 (*ddd*, $J = 5.0, 6.7, 7.9$, H–C(5)); 4.46 (*dd*, $J = 4.1, 4.1$, H–C(3)); 6.81 (*m*, H–C(2)). ^{13}C-NMR (22.63 MHz, $CDCl_3$): −4.80 (MeSi); −4.5 (MeSi); 18.0 ($(CH_3)_3CSi$); 25.8 ($(CH_3)_3CSi$); 31.8 (C(6)); 51.9 ($COOCH_3$); 66.1 (C(4)); 68.4 (C(5)); 72.3 (C(3)); 130.2 (C(1)); 136.2 (C(2)); 166.9 ($COOCH_3$). CI-MS: 320 (25.9, $[M + NH_4]^+$), 302 (11.0, $[M]^+$), 285 (95.9, $[M - OH]^+$), 188 (12.1, $[M + H - Si(CH_3)_2C(CH_3)_3)]^+$). EI-MS (70 eV): 285 (0.8, $[M - OH]^+$), 245 (5.7, $[M - (CH_3)_3C]^+$), 227 (100.0, $[M - OSi(CH_3)_2H]^+$), 195 (30.6), 167 (28.9), 89 (23.7), 75 (81.4, $[OSi(CH_3)_2H]^+$), 73 (44.4, $[OC(CH_3)_3]^+$), 59 (19.8, $[COOCH_3]^+$). Anal. calc. for $C_{14}H_{26}O_5Si$ (302.45): C 55.60, H 8.67; found: C 55.41, H 9.01.

*Methyl (1R,2S,3S,4S,5R)-5-[(*tert*-Butyl)dimethylsilyloxy]-1,2-epoxy-3,4-dihydroxycyclohexane-1-carboxylate* (**13**) [29]. To a soln. of **12** (105 mg, 0.35 mmol) in CH_2Cl_2 (6 ml) under Ar was added $VO(acac)_2$ (4.9 mg, 0.018 mmol) in one portion (→pale green soln.). The mixture was stirred 5 min at 0°, and 3.0M *t*-BuOOH in toluene (810 µl, 2.43 mmol) was added dropwise within 10 min (darkening of the soln.). The red-brown mixture was slowly warmed to r.t., stirred for 24 h, and then cooled to 0°. The excess of *t*-BuOOH was quenched with an 15% aq. Na_2SO_3 soln. After 1 h stirring, the lemon-yellow soln. gave a negative reaction with acidified I_2/starch paper (*no t*-BuOOH left). The soln. was extracted with $CHCl_3$ (5 × 60 ml) and washed with H_2O (3 × 30 ml) and with brine (30 ml). Combining the org. phases, drying, evaporation, and CC (20–40% AcOEt/hexane) afforded 97 mg (88%) of **13** as pale yellow oil which slowly crystallized upon standing. Recrystallization from hexane gave 90 mg (81%) of **13**. M.p. 45.5–46.5°. $[\alpha]_D^{23} = -44.3$ ($c = 0.99$, AcOEt). IR (film): 3460 (OH), 3000 (CH, epoxy), 2950, 2930, 2855, 1740 (C=O, ester), 1275 (C–O, epoxy), 1255, 1100, 1075, 870, 835. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.05 (*s*, MeSi); 0.08 (*s*, MeSi); 0.85 (*s*, *t*-BuSi); 2.31 (*ABX*, $J = 16.0, 4.1, 0.7$, H_{eq}–C(6)); 2.48 (br. *s*, OH); 2.55 (*ABX*, $J = 15.8, 3.4$, H_{ax}–C(6)); 2.75 (br. *s*, OH); 3.66 (br. *s*, H–C(4))[1]; 3.70 (*dd*, $J = 2.5, 1.2$, H–C(2)); 3.76 (*s*, $COOCH_3$); 4.06 (*ddd*, $J = 5.7, 3.9, 3.9$, H–C(5)); 4.26 (br. *s*, H–C(3))[2]. ^{13}C-NMR (101 MHz): −5.0 (MeSi); −4.9 (MeSi); 17.9 ($(CH_3)_3CSi$); 25.6 ($(CH_3)_3CSi$); 28.7 (C(6)); 53.0 ($COOCH_3$); 58.7 (C(1)); 61.3 (C(2)); 64.4 (C(3)); 68.1 (C(5)); 72.0 (C(4)); 169.4 ($COOCH_3$). CI-MS: 336 (100.0, $[M + NH_4]^+$), 319 (15.1, $[M + H]^+$), 318 (12.6, $[M]^+$). EI-MS (70 eV): 261 (30.7), 243 (3.1), 211 (11.1), 201 (5.1), 183 (19.5), 166 (14.8), 155 (10.0), 145 (4.7), 137 (6.0), 129 (12.0), 113 (12.8), 109 (10.3), 103 (5.5), 89 (14.5), 81 (8.2), 75 (100.0, $[OSi(CH_3)_2H]^+$), 73 (51.6, $[OC(CH_3)_3]^+$), 59 (25.0, $[COOCH_3]^+$). Anal. calc. for $C_{14}H_{26}O_6Si$ (318.45): C 52.81, H 8.23; found: C 51.53, H 8.34.

*Methyl (1S,2R,3S,4R,5R)-5-[(*tert*-Butyl)dimethylsilyloxy]-3,4-dihydroxy-2-(phenylthio)cyclohexane-1-carboxylate* (**17**), *(1S,2R,3S,4R,5R)-4-[(*tert*-Butyl)dimethylsilyloxy]-1,3-dihydroxy-2-(phenylthio)-6-oxabicyclo[3.2.1]octan-7-one* (**18**), *and (1S,2R,3S,4S,5R)-3-[(*tert*-Butyl)dimethylsilyloxy]-1,4-dihydroxy-2-(phenylthio)-6-oxabicyclo[3.2.1]octan-7-one* (**19**). To a stirred soln. of **13** (644 mg, 20.2 mmol) in DMSO (30 ml) was added thiophenol (465 µl, 4.55 mmol) followed by sodium thiophenolate (503 mg, 3.81 mmol). After 20 h stirring at r.t., the mixture was extracted with $CHCl_3$ (6 × 100 ml), the extract washed with H_2O (2 × 50 ml) and brine (50 ml), dried, and evaporated, and the crude product further purified by CC ($CHCl_3$ or AcOEt/hexane) to yield an oil which solidified upon addition of MeOH: 732 mg (84%) of **17** as a colorless precipitate. A probe for anal. purposes was recrystallized from MeOH. M.p. 117.5–121°. $[\alpha]_D^{23} = -1.1$ ($c = 1.57$, AcOEt). IR (KBr): 3450–3180 (OH), 3050 (arom. CH), 2950, 2930, 2895, 2850, 1735 (C=O, ester), 1580 (arom. C=C). ^{1}H-NMR (400 MHz, $CDCl_3$; int. standard CH_2Cl_2, 5.32 ppm): 0.12 (MeSi); 0.13 (MeSi); 0.92 (*t*-BuSi); 2.25 (*d*, $J = 5.6$, H_{ax}–C(6), H_{eq}–C(6)); 2.66 (*d*, $J = 2.9$, OH–C(4)); 3.38 (br. *s*, OH); 3.64 (*d*, $J = 6.3$, H–C(2)); 3.73 (*s*, $COOCH_3$); 3.98 (*dd*, $J = 3.2, 6.5$, H–C(4)); 4.11 (*dt*, $J = 6.4, 6.1$, H–C(5)); 4.38 (*dd*, $J = 6.5, 3.3$, H–C(3)); 7.27–7.50 (*m*, C_6H_5). ^{13}C-NMR (101 MHz): −4.9 (MeSi); −4.6 (MeSi); 18.1 ($(CH_3)_3CSi$); 25.8 ($(CH_3)_3CSi$); 38.3 (C(6)); 52.4

[1]) Br. *s* after exchange with D_2O.

[2]) *dd*, $J = 2.6, 4.4$, after exchange with D_2O.

($COOCH_3$); 57.1 (C(2)); 68.8 (C(5)); 72.5 (C(3), C(4)); 78.1 (C(1)); 127.5 (C_p); 129.2, 131.3 ($C_{m,o}$); 135.3 (C_{ipso}); 172.2 ($COOCH_3$). CI-MS: 446 (2.4, $[M + NH_4]^+$), 429 (32.5, $[M + H]^+$), 411 (100.0, $[M - OH]^+$). EI-MS (70 eV): 428 (1.4, $[M]^+$), 371 (32.0, $[M - (CH_3)_3C]^+$), 353 (41.9, $[M - OSi(CH_3)_2H]^+$), 335 (14.1), 293 (6.3), 275 (3.9), 243 (14.8), 225 (16.4), 205 (10.4), 183 (16.4), 167 (6.8), 147 (49.8), 109 (20.4, $[C_6H_5S]^+$), 89 (11.1), 75 (100.0, $[OSi(CH_3)_2H]^+$), 73 (68.1, $[OC(CH_3)_3]^+$), 59 (16.3, $[COOCH_3]^+$).

The reaction of **13** with thiophenol and sodium thiophenolate in DMSO yielded occasionally two side products which were spectroscopically identified as **18** and **19**.

Data of **18**: $[\alpha]_D^{22} = +3.6$ ($c = 1.32$, MeOH). IR (film): 3490 (OH), 3060 (arom. CH), 2950, 2930, 2860, 1795 (C=O, γ-lactone), 1565 (arom. C=C), 1360, 1255, 1090. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.14 (*s*, MeSi); 0.17 (*s*, MeSi); 0.91 (*s*, *t*-BuSi); 2.54 (*d*, $J = 8.7$, OH–C(3)); 2.55 (*dd*, $J = 11.9$, 5.2, H_{eq}–C(6)); 2.59 (*d*, $J = 11.2$, H_{ax}–C(6)); 3.27 (*d*, $J = 10.7$, H–C(2)); 3.69 (*ddd*, $J = 10.6$, 4.6, 8.6, H–C(3)); 3.87 (*s*, OH); 4.27 (*dd*, $J = 4.6$, 4.6, H–C(4)); 4.62 (*dd*, $J = 5.0$, 5.0, H–C(5)); 7.27–7.60 (*m*, C_6H_5). ^{13}C-NMR (101 MHz): –4.8 (MeSi); –4.7 (MeSi); 18.1 ($(CH_3)_3CSi$); 25.7 ($(CH_3)_3CSi$); 35.9 (C(6)); 62.3 (C(2)); 68.5 (C(5))[3]; 70.9 (C(3))[3]; 72.8 (C(1)); 75.5 (C(4))[3]; 127.9 (C_p); 129.2, 132.6 ($C_{m,o}$); 133.9 (C_{ipso}); 174.8 ($COOCH_3$). CI-MS: 453 (0.1, $[M + (CH_3)_3C]^+$), 414 (100.0, $[M + NH_4]^+$), 398 (10.9, $[M + NH_4 - H_2O]^+$), 397 (7.7, $[M + H]^+$), 339 (4.2, $[M - (CH_3)_3C]^+$), 265 (4.3, $[M - OSi(CH_3)_2C(CH_3)_3]^+$). EI-MS (70 eV): 396 (0.02, $[M]^+$), 339 (17.4, $[M - (CH_3)_3C]^+$), 209 (37.1), 109 (17.3), 75 (100.0, $[OSi(CH_3)_2H]^+$), 73 (70.8, $[OC(CH_3)_3]^+$).

Data of **19**: IR (film): 3490 (OH), 3060 (arom. CH), 2950, 2930, 2890, 2855, 1795 (C=O, γ-lactone), 1590 (arom. C=C), 1360, 1250, 1100. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.18 (MeSi); 0.19 (MeSi); 0.91 (*t*-BuSi); 2.57 (*ddd*, $J = 12.1$, 5.9, 0.8, H_{eq}–C(6)); 2.69 (*d*, $J = 12.1$, H_{ax}–C(6)); 3.00 (*s*, OH); 3.44 (*d*, $J = 10.4$, H–C(2)); 3.78 (*dd*, $J = 10.3$, 4.5, H–C(3)); 3.82 (*s*, OH); 4.13 (*dd*, $J = 4.6$, 4.6, H–C(4)); 4.85 (*dd*, $J = 5.3$, 5.3, H–C(5)); 7.21–7.49 (*m*, C_6H_5). ^{13}C-NMR (101 MHz): –4.7 (MeSi); –4.3 (MeSi); 18.0 ($(CH_3)_3CSi$); 25.8 ($(CH_3)_3CSi$); 35.6 (C(6)); 61.7 (C(2)); 68.0 (C(5))[3]; 72.7 (C(3))[3]; 72.8 (C(1)); 75.2 (C(4))[3]; 127.1 (C_p); 129.2, 130.3 ($C_{m,o}$); 135.8 (C_{ipso}); 175.1 ($COOCH_3$). CI-MS: 453 (0.07, $[M + (CH_3)_3C]^+$), 414 (100.0, $[M + NH_4]^+$), 398 (8.3, $[M + NH_4 - H_2O]^+$), 397 (2.5, $[M + H]^+$), 339 (14.4, $[M - (CH_3)_3C]^+$), 265 (44.2, $[M - OSi(CH_3)_2C(CH_3)_3]^+$). EI-MS (70 eV): 339 (59.1, $[M - (CH_3)_3C]^+$), 219 (37.1), 109 (20.1, $[C_6H_5S]^+$), 75 (100.0, $[OSi(CH_3)_2H]^+$), 73 (76.4, $[OC(CH_3)_3]^+$).

*Methyl (1S,3R,4R,5R)-3-[(*tert*-Butyl)dimethylsilyloxy]-1,4,5-trihydroxycyclohexane-1-carboxylate* (**20**). To a suspension of Ni-Al aloy (1.0 g) in H_2O (10 ml) at 0° was slowly added NaOH (1.8 g). After 30 min at 60°, the aq. phase was decanted and the remaining black Ni powder washed with H_2O (10 × 20 ml) followed by MeOH (5 × 10 ml) and AcOEt (5 × 10 ml). Then, **17** (100 mg, 0.23 mmol) was added to the freshly prepared *Raney*-Ni *W-2* [30] [31] suspended in AcOEt (10 ml), and the mixture was saturated with H_2 under 4.5 atm and shaken overnight. The catalyst was filtered through *Celite* and the residue washed with boiling AcOEt (500 ml) followed by boiling MeOH (500 ml). Evaporation of the org. phase followed by CC (0–2.5% MeOH/$CHCl_3$) yielded 54 mg (72%) of pure **20** that slowly crystallized. M.p. 81–87°. $[\alpha]_D^{23} = -34.9$ ($c = 0.78$, AcOEt). IR (film): 3430 (OH), 2950, 2930, 2890, 2855, 1740 (C=O, ester), 1250, 1100, 835. ^{1}H-NMR (400 MHz, CD_3OD): 0.08 (*s*, MeSi); 0.09 (*s*, MeSi); 0.88 (*s*, *t*-BuSi); 1.87 (*ABX*, $J = 13.0$, 8.4, H_{eq}–C(6)); 1.97 (*ABX*, $J = 13.4$, 3.8, 1.0, H_{eq}–C(2)); 2.06 (*ABX*, $J = 13.5$, 6.5, H_{ax}–C(2)); 2.16 (*ABX*, $J = 13.1$, 3.7, H_{ax}–C(6)); 3.51 (*dd*, $J = 3.1$, 6.2, H–C(4)); 3.70 (*s*, $COOCH_3$); 4.04 (*ddd*, $J = 6.3$, 6.3, 3.8, H–C(3)); 4.10 (*ddd*, $J = 3.5$, 3.5, 8.1, H–C(5)). ^{13}C-NMR (101 MHz): –4.71 (MeSi); –4.66 (MeSi); 19.0 ($(CH_3)_3CSi$); 26.4 ($(CH_3)_3CSi$); 38.0 (C(6)); 40.6 (C(2)); 52.7 ($COOCH_3$); 69.4 (C(3)); 71.2 (C(5)); 74.6 (C(4)); 75.5 (C(1)); 175.7 ($COOCH_3$). CI-MS: 338 (15.7, $[M + NH_4]^+$), 321 (100.0, $[M + H]^+$). EI-MS (70 eV): 263 (7.8, $[M - (CH_3)_3C]^+$), 245 (2.3, $[M - OSi(CH_3)_2H]^+$), 227 (75.4, $[M - OSi(CH_3)_2H - H_2O]^+$), 209 (4.0, $[M - OSi(CH_3)_2H - 2H_2O]^+$), 185 (22.9), 167 (21.6), 143 (17.6), 129 (12.6), 111 (17.2), 89 (10.8), 75 (100.0, $[OSi(CH_3)_2H]^+$), 73 (46.3 $[OC(CH_3)_3]^+$), 59 (18.0, $[COOCH_3]^+$).

(1R,3R,4S,5R)-1,3,4,5-Tetrahydroxycyclohexane-1-carboxylic Acid (**4**) [32]. To a stirred soln. of **20** (144 mg, 0.45 mmol) in THF (4 ml) was added KOH (38 mg, 0.68 mmol) in H_2O (1 ml). The resulting pale yellow soln. was stirred for 1 h before adding 80% AcOH/H_2O (5 ml). After 15 h stirring at r.t., the mixture was evaporated, the resulting oil dissolved in MeOH (1.2 ml), and Et_3N (1.2 ml) added dropwise (→precipitation of a light-beige solid). After evaporation, the precipitate was dissolved in several drops of H_2O, loaded onto an *Amberlite IR-120* column (2 cm × 16.5 cm), and eluted with H_2O (100 ml). The cloudy eluate was evaporated, and traces of H_2O were removed azeotropically with abs. EtOH: 92 mg of crude material. Recrystallization from EtOH yielded 78 mg (90%) of pure **4** [33]. M.p. 169.5–172.5°. $[\alpha]_D^{23} = -40.7$ ($c = 2.04$, H_2O). CD: 200–500; (+)-*Cotton* effect [33]. IR (KBr): 3520 (OH, free), 3400 (OH), 3340 (OH), 2970, 2920, 2800–2510 (OH, acid), 1685 (C=O, acid), 1450, 1295, 1270, 1225, 1135, 1080, 1065, 1055, 975. ^{1}H-NMR (400 MHz, CD_3OD): 1.86 (*ABX*, $J = 13.2$, 10.9, H_{ax}–C(6)); 2.05 (*d*, $J = 3.0$, CH_2(2)); 2.12 (*ABX*, $J = 13.3$, 4.5, 1.7, H_{eq}–C(6)); 3.39 (*dd*, $J = 3.1$, 9.0, H–C(4)); 3.99 (*ddd*, $J = 9.2$, 4.7,

[3]) Assignments may be reversed.

10.7, H–C(5)); 4.09 (*dd*, J = 3.4, 3.4, H–C(3)). ^{13}C-NMR (101 MHz): 38.5 (C(2)); 42.5 (C(6)); 68.1 (C(5)); 72.0 (C(3)); 76.9 (C(1)); 77.1 (C(4)); 177.7 (COOH). CI-MS: 210 (100.0, $[M + NH_4]^+$), 192 (63.8, $[M]^+$). EI-MS (70 eV): 147 (7.2, $[M - COOH]^+$), 129 (5.1, $[M - COOH - H_2O]^+$), 118 (18.5), 111 (24.9, $[M - COOH - 2H_2O]^+$), 100 (9.6), 89 (11.8), 83 (12.3), 73 (11.6), 69 (19.7), 60 (65.5), 57 (48.2).

An authentic sample **4** from (*Fluka*) displayed the following data: M.p. 169.5–175.5°. $[\alpha]_D^{22} = -43.4$ (c = 2.01, H_2O). CD: 200–500 nm; (+)-*Cotton* effect [33]. ^{1}H-NMR (400 MHz, CD_3OD): 1.86 (*ABX*, J = 13.2, 11.0, H_{ax}–C(6)); 2.05 (*d*, J = 2.9, CH_2(2)); 2.12 (*ABX*, J = 13.3, 4.6, 1.6, H_{eq}–C(6)); 3.39 (*dd*, J = 3.2, 9.1, H–C(4)); 3.99 (*ddd*, J = 9.1, 10.9, 4.6, H–C(5)); 4.09 (*dd*, J = 3.4, 3.4, H–C(3)). ^{13}C-NMR (101 MHz): 38.5 (C(2)); 42.4 (C(6)); 68.1 (C(5)); 72.0 (C(3)); 76.9 (C(1)); 77.1 (C(4)); 177.6 (COOH).

*Methyl (3*R*,4*R*,5*R*)-3,5-Bis[(*tert*-butyl)dimethylsilyloxy]-4-hydroxycyclohex-1-ene-1-carboxylate* (**21**). According to [25], a soln. of **9** (200 mg, 1.06 mmol) in DMF (4 ml), Et_3N (370 µl, 2.65 mmol), *t*-$BuMe_2SiCl$ (337 mg, 2.24 mmol), and 4-(dimethylamino)pyridine (65 mg; 0.53 mmol) were stirred for 4 h at 0°. To the pale yellow soln. was added H_2O (5 ml) followed by Et_2O (150 ml). The org. phase was then washed with H_2O (3 × 50 ml) and sat. NH_4Cl soln. (3 × 50 ml), the aq. layer washed with Et_2O (2 × 150 ml), the combined extract dried and evaporated, and the yellow oil submitted to CC (10% AcOEt/hexane): 324 mg (78%) of **21**, which slowly crystallized upon standing. M.p. 39–43.5°. $[\alpha]_D^{21} = -68.7$ (c = 0.53, MeOH); ([25]: $[\alpha]_D^{25} = -66.5$ (c = 1, MeOH)). IR (film): 3670 (OH, free), 2950, 2930, 2890, 2860, 1725 (α,β-unsat. ketone), 1655 (C=C), 1255, 1095, 900, 835, 775. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.07 (*s*, Me_2Si); 0.08 (*s*, Me_2Si); 0.87 (*s*, 2*t*-BuSi); 2.18 (*ABX*, J = 18.3, 6.5, 2.1, 1.1, H–C(6)); 2.81 (*ABX*, J = 18.3, 5.3, 1.5, H–C(6)); 3.62 (*dd*, J = 3.5, 7.8, H–C(4)); 3.73 (*s*, $COOCH_3$); 4.07 (*ddd*, J = 7.7, 6.3, 6.3, H–C(5)); 4.36 (*dd*, J = 3.8, 3.8, H–C(3)); 6.73 (*ddd*, J = 4.1, 1.9, 1.9, H–C(2)). ^{13}C-NMR (101 MHz): −4.8 (MeSi); −4.5 (MeSi); −4.12 (MeSi); −4.17 (MeSi); 18.2 ($2(CH_3)_3CSi$); 25.88 ($(CH_3)_3CSi$); 25.93 ($(CH_3)_3CSi$); 31.3 (C(6)); 51.9 ($COOCH_3$); 67.3 (C(4))[3]; 67.7 (C(5))[3]; 74.1 (C(3)); 128.8 (C(1)); 138.3 (C(2)); 167.1 ($COOCH_3$). CI-MS: 473 (0.2, $[M + C(CH_3)_3]^+$), 434 (1.7, $[M + NH_4]^+$), 417 (2.4, $[M + H]^+$), 359 (3.2, $[M - (CH_3)_3C]^+$), 285 (100.0, $[M - OSi(CH_3)_2C(CH_3)_3]^+$). EI-MS (70 eV): 359 (9.1, $[M - (CH_3)_3C]^+$), 227 (100.0, $[M - OSi(CH_3)_2 - Si(CH_3)_2C(CH_3)_3]^+$), 195 (25.7), 167 (16.0), 89 (12.8), 75 (29.2, $[OSi(CH_3)_2H]^+$), 73 (47.5, $[OC(CH_3)_3]^+$), 59 (5.3, $[COOCH_3]^+$).

*Methyl (1*R*,2*S*,3*S*,4*S*,5*R*)-3,5-Bis[(*tert*-butyl)dimethylsilyloxy]-1,2-epoxy-4-hydroxycyclohexane-1-carboxylate* (**22**) *and Methyl (1*S*,2*R*,3*S*,4*S*,5*R*)-3,5-Bis[(*tert*-butyl)dimethylsilyloxy]-1,2-epoxy-4-hydroxycyclohexane-1-carboxylate* (**23**). To a soln. of **21** (302 mg, 0.72 mmol) in CH_2Cl_2 (10 ml) at r.t. under Ar was added $VO(acac)_2$ (3.3 mg, 0.012 mmol). After 5 min stirring, 3.0M *t*-BuOOH in toluene (1.7 ml) was added dropwise within 10 min and refluxed for 18 h. The yellow-orange soln. was cooled to 0° and the excess of *t*-BuOOH destroyed with 15% aq. Na_2SO_3 soln. (6 ml; negative reaction with acidified I_2/starch paper). The soln. was extracted with CH_2Cl_2 (5 × 50 ml), the extract washed with H_2O (2 × 50 ml) and brine (2 × 50 ml), dried, and evaporated, and the yellow oil purified by CC (10% AcOEt/hexane): 272 mg (87%) of **22** and 21 mg (7%) of **23**.

Data of **22**: M.p. 44.5–47.5°. $[\alpha]_D^{22} = -48.9$ (c = 0.55, MeOH). IR (film): 3570 (OH), 2965, 2930, 2890, 2860, 1745 (C=O, ester), 1255, 1100. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.08 (*s*, MeSi); 0.11 (*s*, MeSi); 0.16 (*s*, MeSi); 0.18 (*s*, MeSi); 0.89 (*s*, *t*-BuSi); 0.96 (*s*, *t*-BuSi); 2.31 (*ABX*, J = 15.7, 3.7, H_{ax}–C(6)); 2.56 (*ABX*, J = 15.8, 2.9, 0.6, H_{eq}–C(6)); 2.62 (*d*, J = 5.6, OH–C(4); on decoupling at 3.67→br. *s*); 3.52 (*dd*, J = 2.5, 1.2, H–C(2); on decoupling at 4.37→*d*, J = 0.7); 3.67 (*ddd*, J = 4.6, 4.6, 4.6, H–C(4)); 3.78 (*s*, $COOCH_3$); 4.12 (*ddd*, J = 5.1, 3.3, 3.3, H–C(5)); 4.37 (*dd*, J = 2.5, 4.6, H–C(3)). ^{13}C-NMR (101 MHz): −5.1 (MeSi); −5.0 (MeSi); −4.9 (MeSi); −4.7 (MeSi); 17.9 ($(CH_3)_3CSi$); 18.2 ($(CH_3)_3CSi$); 25.6 ($(CH_3)_3CSi$); 25.8 ($(CH_3)_3CSi$); 27.9 (C(6)); 52.8 ($COOCH_3$); 57.7 (C(1)); 60.6 (C(2)); 66.1 (C(3)); 69.0 (C(5)); 71.5 (C(4)); 170.2 ($COOCH_3$). CI-MS: 489 (3.6, $[M + (CH_3)_3C]^+$), 450 (66.6, $[M + NH_4]^+$), 433 (21.4, $[M + H]^+$). EI-MS (70 eV): 375 (31.9, $[M - (CH_3)_3C]^+$), 357 (5.9, $(M - Si(CH_3)_2H]^+$), 283 (3.7), 243 (26.1), 225 (10.3), 211 (14.5), 193 (11.6), 183 (16.3), 166 (7.0), 155 (5.6), 127 (29.0), 117 (22.0), 89 (13.4), 75 (48.2, $[Si(CH_3)_2H]^+$), 73 (100.0, $[OC(CH_3)_3]^+$), 59 (13.6, $[COOCH_3]^+$), 57 (8.2, $[(CH_3)_3C]^+$). Anal. calc. for $C_{20}H_{40}O_6Si_2$ (432.72): C 55.51, H 9.32; found: C 55.72, H 9.60.

Data of **23**: M.p. 86.5–93.5°. $[\alpha]_D^{22} = -25.0$ (c = 0.66, MeOH). IR (film): 3560 (OH), 3020 (CH, epoxy), 2950, 2930, 2890, 2850, 1735 (C=O, ester), 1265, 1245, 1140. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.10 (*s*, MeSi); 0.11 (*s*, MeSi); 0.15 (*s*, $(CH_3)_2Si$); 0.91 (*s*, *t*-BuSi); 0.93 (*s*, *t*-BuSi); 2.00 (*ABX*, J = 15.4, 5.7, 0.7, H–C(6), OH); 3.02 (*ABX*, J = 15.9, 6.2, H–C(6)); 3.38 (*d*, J = 0.7, H–C(2)); 3.75 (*dd*, J = 3.1, 7.3, H–C(4)); 3.79 (*s*, $COOCH_3$); 3.95 (*m*, H–C(5)); 4.23 (*dd*, J = 1.3, 3.1, H–C(3)). ^{13}C-NMR (101 MHz): −4.8 (MeSi); −4.6 (MeSi); −4.5 (MeSi); −4.2 (MeSi); 18.1 ($(CH_3)_3CSi$); 18.2 ($(CH_3)_3CSi$); 25.8 ($(CH_3)_3CSi$); 25.9 ($(CH_3)_3CSi$); 28.1 (C(6)); 52.8 ($COOCH_3$); 57.5 (C(1)); 62.2 (C(2)); 66.4 (C(3)); 68.2 (C(5)); 71.6 (C(4)); 169.8 ($COOCH_3$). CI-MS: 489 (3.7, $[M + (CH_3)_3C]^+$), 450 (8.8, $[M + NH_4]^+$), 433 (100.0, $[M + H]^+$). EI-MS (70 eV): 375 (3.2, $[M - (CH_3)_3C]^+$), 243 (16.8), 211 (6.6), 183 (7.0), 169 (6.4), 147 (46.8), 133 (9.6), 109 (10.4), 89 (8.1), 75 (38.5, $[Si(CH_3)_2H]^+$), 73 (100.0, $[OC(CH_3)_3]^+$), 59 (13.2, $[COOCH_3]^+$), 57 (15.2, $[(CH_3)_3C]^+$).

Methyl (1R,2S,3S,4R,5R)-5-[(tert-Butyl)dimethylsilyloxy]-1,2-epoxy-3,4-dihydroxycyclohexane-1-carboxylate (**13**). To a soln. of **22** (73 mg, 0.17 mmol) in THF (5 ml), Bu_4NF (53 mg, 0.17 mmol) was added. After 2 min stirring, the reaction was quenched with H_2O (5 ml), the mixture extracted with AcOEt (50 ml), the org. phase washed with H_2O (2 × 25 ml) and brine (2 × 25 ml), the aq. phase washed with AcOEt (2 × 25 ml), the combined org. phase dried and evaporated, and the light yellow oil, submitted to CC (30% AcOEt/hexane): 44 mg (82%) of an oil, that was spectroscopically identified as **13**.

(1S,3R,4R,5R,8S)-3,4-Bis[(tert-butyl)dimethylsilyloxy]-8-hydroxy-1-(phenylthio)-6-oxabicyclo[3.2.1]-octan-7-one (**25**). To a soln. of **22** (48 mg, 0.11 mmol) in DMSO (2.5 ml) was added thiophenol (26 µl, 0.25 mmol) followed by sodium thiophenolate (28 mg, 0.21 mmol). The soln. was stirred for 4 h at r.t. under Ar and subsequently extracted with CH_2Cl_2 (4 × 50 ml) and washed with H_2O (2 × 50 ml) and brine (50 ml). Evaporation of the org. phases gave a yellow solid that was purified by CC (10% AcOEt/hexane): 49.2 mg (82%) of crude product. Recrystallization from hexane delivered 27 mg (45%) of **25** as colorless needles. M.p. 145–147°. IR (KBr): 3490 (OH), 2950, 2890, 2860, 1770 (γ-lactone), 1470, 1255, 1170, 1120, 1065, 840. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.00 (MeSi), 0.01 (MeSi), 0.06 (MeSi), 0.09 (MeSi), 0.80 (*t*-BuSi); 0.90 (*t*-BuSi); 1.21 (*ABX*, J = 13.3, 10.9, H_{ax}–C(6)); 2.25 (*ABX*, J = 13.3, 7.2, H_{eq}–C(6)); 3.23 (*s*, OH); 3.53 (*dd*, J = 7.3, 1.1, H–C(4)); 3.74 (*s*, H–C(2)); 3.81 (*ddd*, J = 7.2, 7.2, 10.5, H–C(5)); 4.60 (*d*, J = 1.1, H–C(3)). ^{13}C-NMR (101 MHz): −4.71 (MeSi); −4.67 (MeSi); −4.21 (MeSi); −4.19 (MeSi); 17.89 ($(CH_3)_3CSi$); 17.93 ($(CH_3)_3CSi$); 25.75 ($(CH_3)_3SiC$); 25.80 ($(CH_3)_3CSi$); 38.4 (C(6)); 60.8 (C(1)); 72.2 (C(5)); 75.1 (C(3))[3]; 75.3 (C(4))[3]; 85.5 (C(2)); 126.9 (C_p); 129.6, 130.3 ($C_{m,o}$); 136.8 (C_{ipso}); 173.3 (C=O). CI-MS: 528 (100.0, $[M + NH_4]^+$), 511 (48.3, $[M + H]^+$). EI-MS (70 eV): 453 (12.5, $[M - (CH_3)_3C]^+$), 293 (75.5), 147 (51.0), 109 (7.5, $[C_6H_5S]^+$), 73 (100.0, $[OC(CH_3)]^+$).

(1R,2S,3S,4S,5R)-3,5-Bis[(tert-butyl)dimethylsilyloxy]-1,2-epoxy-4-hydroxycyclohexane-1-carboxylic Acid (**26**). To a stirred soln. of **22** (40 mg, 0.09 mmol) in THF (3 ml) was added dropwise KOH (6.2 mg, 0.11 mmol) in H_2O (1 ml). The resulting yellow soln. was stirred for 1 h and then loaded onto *Dowex 50 WX8* (H^+ form, 20–50 mesh; column 1 cm × 8 cm) and eluted with H_2O (25 ml). The eluate was evaporated, and traces of H_2O were removed azeotropically with abs. EtOH: **26** (quant.), light-beige solid. M.p. 163–168.5°. $[\alpha]_D^{22}$ = +48.0 (c = 0.1, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.05 (*s*, MeSi); 0.08 (*s*, MeSi); 0.13 (*s*, MeSi); 0.15 (*s*, MeSi); 0.85 (*s*, *t*-BuSi); 0.93 (*s*, *t*-BuSi); 2.27 (*ABX*, J = 16.0, 3.6, H–C(6)); 2.54 (*ABX*, J = 15.9, 2.4, H–C(6)); 3.49 (br. *s*, H–C(2)); 3.67 (*dd*, J = 4.7, 4.7, H–C(4)); 4.11 (*ddd*, J = 4.8, 2.8, 2.8, H–C(5)); 4.35 (*dd*, J = 2.5, 4.6, H–C(3)). ^{13}C-NMR (101 MHz): −5.1 (MeSi); −5.0 (MeSi); −4.8 (MeSi); −4.7 (MeSi); 17.9 ($(CH_3)_3CSi$); 18.2 ($(CH_3)_3CSi$); 25.6 ($(CH_3)_3CSi$); 25.8 ($(CH_3)_3CSi$); 27.3 (C(6)); 57.8 (C(1)); 60.7 (C(2)); 65.9 (C(3)); 68.8 (C(5)); 71.2 (C(4)); 172.8 (COOH). EI-MS (70 eV): 361 (0.7, $[M - (CH_3)_3C]^+$), 343 (2.8, $[M - Si(CH_3)_2H]^+$), 229 (10.8), 211 (12.8), 183 (9.6), 167 (17.9), 155 (6.1), 129 (11.4), 117 (23.5), 75 (74.3, $[Si(CH_3)_2H]^+$), 73 (100.0, $[OC(CH_3)_3]^+$), 57 (13.9, $[(CH_3)_3C]^+$). FAB-MS (nitrobenzyl alcohol): 463 (1.2, $[M + 2Na]^+$), 441 (12.4, $[M + Na]^+$), 419 (3.5, $[M + H]^+$).

Methyl (1R,3R,4S,5R)-3,5-Bis[(tert-butyl)dimethylsilyloxy]-1,4-dihydroxycyclohexane-1-carboxylate (**27**). According to [25], a soln. of methyl quinate (*Fluka*; 214 mg, 1.04 mmol) in DMF (5 ml), Et_3N (365 µl, 2.62 mmol), *t*-$BuMe_2SiCl$ (330 mg, 2.19 mmol), and 4-(dimethylamino)pyridine (64 mg, 0.52 mmol) were stirred for 5 h at 0°. The reaction was quenched with H_2O (5 ml), the mixture diluted with AcOEt (150 ml), the org. phase washed with H_2O (3 × 50 ml) and with sat. NH_4Cl soln. (3 × 50 ml), the aq. phase washed with AcOEt (2 × 150 ml), the combined org. phase dried and evaporated, and the yellow oil submitted to CC (20% AcOEt/hexane): 326 mg (72%) of pure **27**. Colorless solid. M.p. 78.5–82°. $[\alpha]_D^{22}$ = +6.02 (c = 1.18, MeOH). IR (KBr): 3510 (OH), 3430 (OH), 2960, 2930, 2900, 2860, 1750 (C=O, ester), 1250, 1130, 1100. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.07 (*s*, MeSi); 0.09 (*s*, MeSi); 0.12 (*s*, MeSi); 0.13 (*s*, MeSi); 0.88 (*s*, *t*-BuSi); 0.89 (*s*, *t*-BuSi); 1.82 (*ABX*, J = 13.1, 10.3, H_{ax}–C(6)); 1.99 (*ABX*, J = 14.4, 4.4, 2.4, H_{eq}–C(2)); 2.03 (*ABX*, J = 14.4, 2.9, H_{ax}–C(2)); 2.16 (*ABX*, J = 13.1, 4.5, 2.4, H_{eq}–C(6)); 2.29 (*d*, J = 2.9, OH–C(4)); 3.40 (*ddd*, J = 2.7, 8.4, 2.7, H–C(4)); 3.74 (*s*, $COOCH_3$); 4.09 (*ddd*, J = 8.6, 10.2, 4.5, H–C(5)); 4.34 (*ddd*, J = 2.7, 2.7, 4.4, H–C(3)); 4.49 (br. *s*, OH). ^{13}C-NMR (101 MHz): −5.1 (MeSi); −4.8 (MeSi); −4.7 (MeSi); −4.4 (MeSi); 18.0 ($2(CH_3)_3CSi$); 25.8 ($2(CH_3)_3CSi$); 37.8 (C(2))[3]; 42.6 (C(6))[3]; 52.6 ($COOCH_3$); 68.5 (C(5)); 71.5 (C(3)); 76.0 (C(4)); 76.1 (C(1)); 173.9 ($COOCH_3$). CI-MS: 435 (100.0, $[M + H]^+$). EI-MS (70 eV): 377 (19.4, $[M - (CH_3)_3C]^+$), 359 (5.7), 267 (5.7), 245 (6.3), 227 (88.6), 209 (3.5), 185 (18.0), 167 (11.5), 143 (13.4), 129 (6.0), 115 (5.9, $[OSi(CH_3)_2C(CH_3)_3]^+$), 101 (7.6), 89 (14.1), 75 (85.5, $[Si(CH_3)_2H]^+$), 73 (100.0, $[OC(CH_3)_3]^+$), 59 (16.7, $[COOCH_3]^+$), 57 (14.7, $[(CH_3)_3C]^+$).

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