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Stereoselectivity in nucleophilic additions to the carbonyl group of methyl 1,4,5-tris(trimethylsilyl)-3-dehydroquinate

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Summary — Methyl 1,4,5-tris(trimethylsilyl)-3-dehydroquinate was synthesized in a three-step procedure and condensed with various nucleophiles (CH_2COOEt, CH_2SO_2Ph, $CH_2C{\equiv}CH$, H). The diastereoselectivity of the reaction, leading to the creation of a new quaternary (or tertiary) asymmetric carbon atom was examined. The preferential axial attack on the C=O group of the cyclohexanone system is discussed. The deprotected products were evaluated as DHQase inhibitors.

methyl 3-dehydroquinate / nucleophilic addition / diastereoselectivity

Résumé — Stéréosélectivité dans les additions nucléophiles sur le groupe carbonyle de 1,4,5-tris(triméthylsilyl)-3-déhydroquinate de méthyle. 1,4,5-Tris(triméthylsilyl)-3-déhydroquinate de méthyle a été synthétisé en trois étapes et condensé avec des nucléophiles différents (CH_2COOEt, CH_2SO_2Ph, $CH_2C{\equiv}CH$, H). La diastéréosélectivité de la réaction conduisant à la création d'un atome de carbone asymétrique quaternaire (ou tertiaire) a été examinée. L'attaque préférentielle axiale sur le groupement cétonique C=O du cycle est discutée. Les produits déprotégés ont été testés comme inhibiteurs de la DHQase.

3-dehydroquinate de méthyle / addition nucléophile / diastéréosélectivité

Introduction

Asymmetric inductions occurring in additions to chiral aldehydes and ketones has been a topic of great interest during the last decades [1]. Since the early 1950's when Cram [2] proposed a rule to rationalize the stereochemistry of nucleophilic additions to acyclic chiral carbonyl compounds and Dauben [3] for the same reactions with cyclohexanone derivatives, many other contributions and explanations [4] have been proposed for these phenomena. We can notice especially the work of Anh and Eisenstein [4c], that have rendered the interpretation of the addolisation results based on ab initio calculations very popular. In the case of the stereochemistry of nucleophilic additions to cyclohexanones and related systems the most detailed experimental study has been carrried out by Cieplak [5] while computational studies were made by Houk [6a] and Bertz [6b].

In the course of our studies on chiral polyhydroxylated compounds [7, 8] we were interested in substrate analogues of 3-dehydroquinate dehydratase, an enzyme involved in the shikimate pathway [9]. It catalyzes the third step of this process, ie, the conversion of 3-dehydroquinic acid (3-DHQ) to 3-dehydroshikimic acid (3-DHS). The mechanism that has already been established (scheme 1) [10] involves a Schiff base formation (with a lysine moiety of the enzyme) before enantioselective deprotonation and hydroxy elimination. Compounds possessing an active methylene group were synthesized as potential inhibitors, analogues of the carbinolamine intermediate (I).

The purpose of the current study was to examine the diastereofacial selectivity of nucleophilic additions to methyl 1,4,5-tris(trimethylsilyl)-3-dehydroquinate and to evaluate the inhibitory activity of the adducts.

Results

Synthesis of methyl 1,4,5-tris(trimethylsilyl)-dehydroquinate

The synthesis of the title compound was achieved by a three-step procedure and a total yield of 22%, (scheme 2) [11]. Quinic acid was oxidized in the presence of nitric acid to 3- and 5-dehydroquinic acids which were separated by an anion exchange column. The presence of 3-dehydroquinic acid was detected by the appearance of an intense red colour when aliquots were added to a solution of triphenyltetrazolium chloride in 1 M NaOH. Methyl 3-dehydroquinate was obtained from **1** using Amberlite resin in methanol, along with methyl 3-dehydroshikimate (yield 20%) and methyl protocatechuate (yield 25%). Silylation of **2** in the presence of

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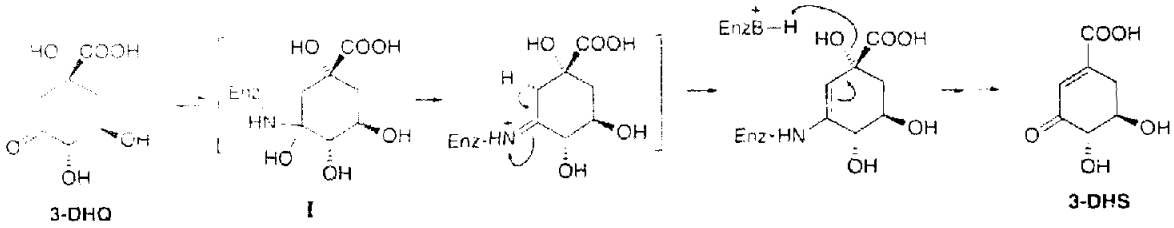
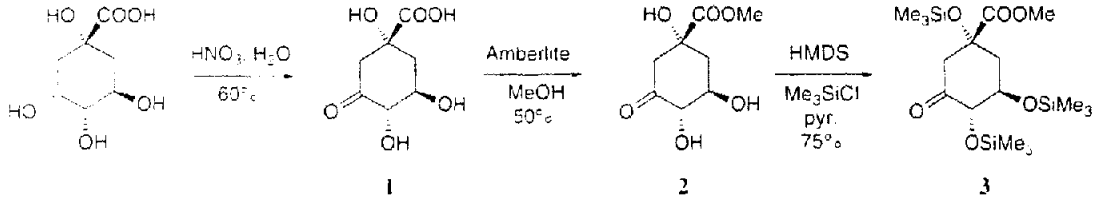


Scheme 1



Scheme 2

hexamethyldisilazane and Me_3SiCl in pyridine afforded **3** in 75% yield.

Nucleophilic additions

1,4,5-tris(trimethylsilyl)-3-dehydroquinate was allowed to react with three different nucleophiles of the type ACH_2M (scheme 3). The condensation products were separated by HPLC chromatography using petroleum ether/ethyl acetate as eluent. Diastereoisomers **4a**, **5a**, **5b**, **6a** were separated and characterized while **4b** was characterized from a **4b/4a** (80:20) mixture. The synthesis of these adducts was a rather complicated problem since the starting ketone is polyfunctional and can allow β-eliminations in the C1 or C5 positions.

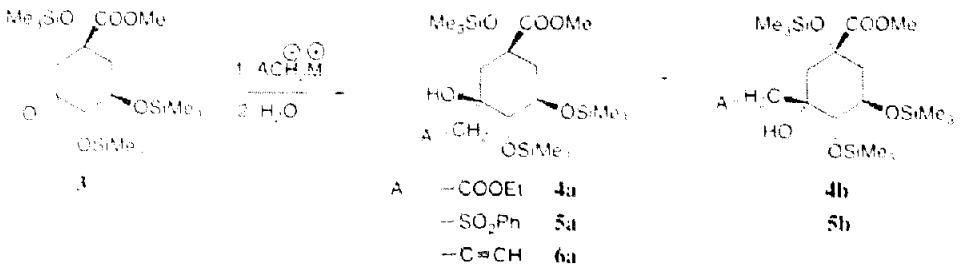
When cyclohexanone **3** was added at −78 °C to a THF solution of ethyl lithioacetate (1 equiv) the condensation products were obtained in poor yields (table I). Addition of two equiv of enolate is necessary to improve the yield of the reaction. Under these experimental conditions only one diastereoisomer was obtained for even shorter reaction times. The increase of the reaction temperature (−78 °C → −40 °C) leads in moderate yields to a mixture (80:20) of two inseparable diastereoisomers along with starting material and degradation products, essentially silylated methyl 3-dehydroshikimate. Using metal exchange (Li^+ to Mg^{2+}) on the Reformatsky reaction conditions with ethyl bromoacetate in formaldehyde dimethylacetal as solvent we obtained the desired condensation products in extremely poor yields (< 10%).

Table I. Reaction of ethyl lithioacetate with protected methyl 3-dehydroquinate **3**.

T (°C)	*Reaction time (h)*	*Enolate equiv*	*Yield (%) 4a + 4b*	Ratio *4a:4b*
−78	0.3	1	15	> 99:1
−78	2	2	34	> 99:1
−78	1	2	57	> 99:1
−40	3	1	26	80:20

Ketone **3** was also allowed to react with the magnesium derivative of methyl phenyl sulfone in dry ether benzene solutions to produce exclusively one diastereoisomer in poor to fairly good yields (table II). Reactions carried out with the lithium derivative lead to the same unique diastereoisomer at low temperature (−78 °C) and to a separable mixture (4:1) of both compounds when the reaction temperature is increased.

Finally, when cyclohexanone **3** was reacted with propargyl magnesium bromide in anhydrous ether at −40 °C only one diastereoisomer was obtained (**6a**) in 63% yield. The reactivity of the dehydroquinate keto

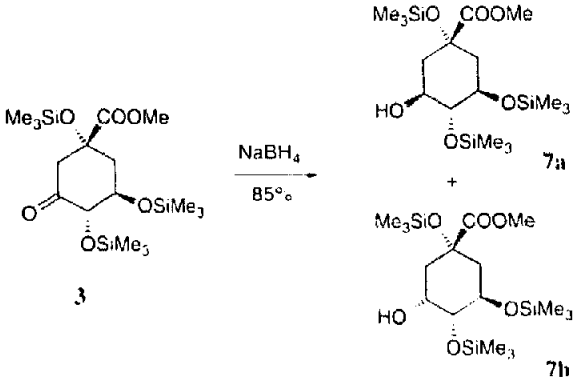


Scheme 3

Table II. Reaction of the methyl phenyl sulfone carbanion with protected methyl 3-dehydroquinate **3**.

Metal	*T (°C)*	*Reaction time (h)*	*Yield (%) 5a–5b*	*Ratio 5a:5b*
Mg	+20	2.5	14	> 99:1
Mg	+20	12	65	> 99:1
Li	−78	2.5	39	> 99:1
Li	−60	2.5	33	83:17
Li	−35	2.5	27	82:18

function towards $NaBH_4$ reduction was also studied (scheme 4). When the reduction is carried out at low temperature (−78 °C) only one diastereoisomer, **7a**, was obtained. When we operate at −20 °C or 0 °C we obtained a 60:40 and 46:54 mixture of the two diastereoisomers **7a** and **7b** respectively. Compound **7b** after $SiMe_3$ deprotection was found to be identical to D-(−)-methyl quinate.



Scheme 4

Inhibition tests

Compounds **4a**, **5a** and **6a** were desilylated by using Amberlite IR120 resin in methanol, yielding quantitatively compounds **8a**, **9a** and **10a**. No inhibition was observed against DHQase for compounds **9a** and **10a** in their acidic form obtained after treatment with pig liver esterase.

Stereochemical assignments: Discussion

The stereochemistry of the new C3 chiral centre was determined on the basis of (a) an experimental approach through analysis of vicinal proton–proton coupling constants to determine preferential conformations in solution as well as on ^{13}C NMR data and (b) on an NOE experiment to identify proton pairs that are close to one another.

The 300 MHz ^1H NMR spectra of compounds **4a**, **4b**, **5a**, **5b** and **6a** were analysed by using irradiation techniques and 2D ^1H-COSY experiments. ^{13}C NMR analysis and carbon determination was also completed by heteronuclear ^1H–^{13}C COSY experiments. Results and data collected are summarized in tables III–VI.

Table III. ^1H NMR spectroscopical assignments for compounds **4a**, **4b**.

Attributions	*δ (ppm)*			*J(Hz)*	
	4a	*4b*		*4a*	*4b*
OEt	4.09	4.19	$J_{CH_2-CH_3}$	7.1	7.1
H_5	4.02	4.12	$J_{H_5H_4}$	8.7	1.3
			$J_{H-H_{6ax}}$	4.3	4.0
			$J_{H-H_{6eq}}$	11.3	11.8
OCH_3	3.70	3.71			
H_4	3.64	3.52	$J_{H_4H_5}$	8.7	1.3
CH_2-CO	ν_A 2.61	ν_A 2.54	J_{AB}	15.6	16.0
	ν_B 2.48	ν_B 2.38			
H_{2a}	2.22	1.79	$J_{H_{2a}H_{2e}}$	14.1	13.3
H_{6e}	2.09	2.26	$J_{H_{6e}H_{6a}}$	13.3	11.8
			$J_{H_{6e}H_{2e}}$	3.3	3.0
			$J_{H_{6e}H_5}$	4.3	1.0
H_{2e}	2.06	2.21	$J_{H_{2e}H_{2a}}$	14.1	13.3
			$J_{H_{2e}H_{6e}}$	3.3	3.0
H_{6a}	1.88	1.78	$J_{H_{6a}H_{6e}}$	13.3	11.8
			$J_{H_{6a}H_5}$	11.3	11.8
CH_3(Et)	1.22	1.26	$J_{CH_3CH_2}$	7.1	7.1
$SiMe_3$	0.11; 0.09	0.12;0.11;0.09			

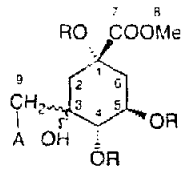
Table IV. ^1H NMR spectroscopical assignments for compounds **5a**, **5b**.

Attributions	*δ (ppm)*			*J(Hz)*	
	5a	*5b*		*5a*	*5b*
H arom	7.95–7.56	7.95–7.50			
H_5	3.98	4.08	$J_{H_5H_4}$	8.7	1.6
			$J_{H_5H_{6ax}}$	4.8	4.5
			$J_{H_5H_{6eq}}$	11.5	12.0
OCH_3	3.75	3.73			
H_4	3.56	3.81	$J_{H_4H_5}$	8.7	1.6
CH_2–SO_2	ν_A 3.54	ν_A 3.35	J_{AB}	14.4	14.0
	ν_B 3.21	ν_B 3.19			
H_{2e}	2.60	2.49	$J_{H_{2e}H_{2a}}$	14.7	13.5
			$J_{H_{2e}H_{6eq}}$	3.1	1.4
H_{2a}	2.29	1.82	$J_{H_{2a}H_{2e}}$	14.7	13.5
H_{6eq}	2.14	2.18	$J_{H_{6eq}H_{6ax}}$	13.6	12.0
			$J_{H_{6eq}H_{2e}}$	3.1	1.4
			$J_{H_{6eq}H_5}$	4.8	4.5
H_{6ax}	1.89	1.80	$J_{H_{6ax}H_{6eq}}$	13.6	12.0
			$J_{H_{6ax}H_5}$	11.5	12.0
$SiMe_3$	0.31;0.25;0.20	0.29;0.27;0.17			

Table V. ^1H NMR spectroscopical assignments for compound **6a**.

Attribution	*δ (ppm)*	*J (Hz)*	
H_5	4.02	$J_{H_5H_4}$	8.9
		$J_{H_5H_{6eq}}$	4.5
		$J_{H_5H_{6ax}}$	11.2
OCH_3	3.71		
H_4	3.65	$J_{H_4H_5}$	8.9
CH_2–CH	ν_A 2.59	J_{AB}	16.7
	ν_B 2.22	$J_{H_6H_{11}}$	2.8
H_{2a}	2.20	$J_{H_{2a}H_{2e}}$	14.0
H_{6eq}	2.14	$J_{H_{6eq}H_{6ax}}$	13.5
		$J_{H_{6eq}H_5}$	3.3
		$J_{H_{6eq}H_4}$	1.5
H_{11}	2.03	$J_{H_{11}H_4}$	2.8
H_{2e}	1.93	$J_{H_{2e}H_{2a}}$	14.0
		$J_{H_{2e}H_{6eq}}$	3.3
H_{6ax}	1.88	$J_{H_{6ax}H_{6eq}}$	13.5
		$J_{H_{6ax}H_5}$	11.2
$SiMe_3$	0.2; 0.18; 0.15		

Table VI. ^{13}C NMR spectroscopical assignments for compounds 4a, 4b, 5a, 5b

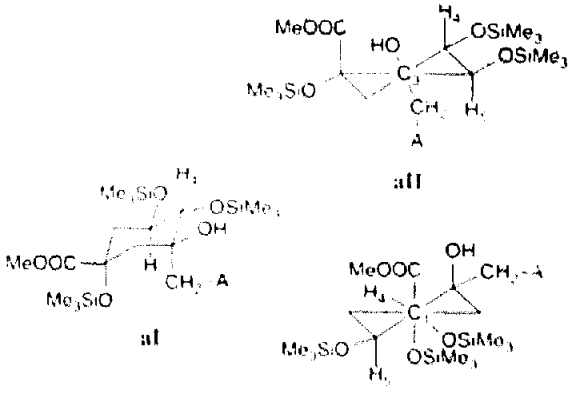


C	—C(=O)OCH$_2$CH$_3$		—SO$_2$—C$_6$H$_5$		C=CH$_2$
	4a	**4b**	**5a**	**5b**	**6a**
C1	74.57	73.63	75.16	77.28	75.71
C2	41.92	37.95	41.22	37.92	42.11
C3	78.73	75.76	78.50	[illegible]3	78.18
C4	78.90	75.40	80.12	[illegible]	78.96
C5	68.63	67.27	68.75	67.03	69.01
C6	42.09	41.59	42.89	41.51	42.05
C7	173.62	173.54	173.37	173.57	173.65
C8	52.51	51.95	52.79	52.13	52.57
C9	42.72	41.81	62.89	62.25	29.37
C10	170.82	173.01	133.48	134.92	80.97
C11	60.21	60.76	129.08	129.48	71.55
C12	14.17	14.17	127.66	127.57	
C13			141.46	141.20	
C(Si Me$_3$)	1.61; 0.57; 0.17	1.84; 0.88; 0.79	1.80; 0.96; 0.83	1.60; 0.70; 0.18	1.88; 0.90; 0.84

All three major *diastereoisomers* **4a**, **5a**, **6a** have close values of vicinal $^3J_{H-H}$ and $^1J_{H-H}$ coupling constants for the substituted cyclohexane ring (tables III–V), indicating that they possess very similar preferential conformations in solution. The same behaviour is also observed for the two minor diastereoisomers **4b**, **5b**. Analogous trends are also observed for the ^{13}C NMR spectra (table VI).

In the case of major diastereoisomers **4a**, **5a**, **6a**, large values of vicinal coupling constants for H_3 H_4 and H_5 H_{6a} ($J_{H_3-H_4}$ = 8.7–8.9 Hz and $J_{H_5-H_{6a}}$ = 11.2–11 Hz) were observed. While the determination of a conformation based on the values of the coupling constants can be limited by the extent of internal motion and/or extensive averaging of various conformer populations, the values obtained indicate that the major conformers should have H_3, H_5, H_{6a} protons axial (or pseudoaxial). This kind of proton disposition in six-membered rings with large dihedral angles (≈180°) is related through Karplus-type equations to coupling constants between 8–12 Hz while the disposition between axial-equatorial and equatorial-equatorial protons leads to values in the range of 2–4 Hz. Among the possible starting geometries, three can be reasonably retained: a chair conformation where the C1 carboxylate group is equatorial and two twist chair conformations namely C3–C6 and C1–C4 (scheme 5).

The minor products **4b**, **5b** present only one large value of coupling constant ($J_{H_5-H_{6a}}$ = 11.8 Hz), while all other values are small. Among the number of twist forms which can be present in solution, the predominant ones should have H_5, H_{6a} protons axial (or pseudoaxial) and a dihedral angle $H_4C_4C_5H_5$ in a 80–100° range. Minor adducts **4b**, **5b** could also be attributed to compounds where a C4 epimerisation has occurred.



Scheme 5

Nevertheless some experimental facts are against this hypothesis. First, under optimum experimental conditions and for the condensations examined, we obtained the two adducts along with the unreacted starting compound **3** and silylated methyl 3-dehydroshikimate. No C4 epimerisation on these ketone compounds has ever been observed. Second, as we have already reported [7], the reaction of compound **3** with Et$_3$N (CH$_2$Cl$_2$, room temperature, 18 h) gave quantitatively silylated methyl 3-dehydroshikimate. Again no epimerisation on C4 was observed. Finally, the order of addition of reagents which was examined in the case of methyl phenyl sulfone does not alter the yield of the reaction and the final ratio of the adducts. Epimerisation on the metallated

adducts (after addition of the nucleophile) is rather improbable, taking into account the nature of the silyloxy group which is not easily metallated or solvated [12].

Configuration of the C3 quaternary centre

The nuclear Overhauser effect (NOE) is an experimental tool for stereochemical assignment [13]. NOE experiments were performed on the three major addition adducts **4a**, **5a**, **6a**. They showed a slight effect, for compounds **5a**, **6a**, between the hydrogen atom of the C3 hydroxy group formed during the condensation reaction and the methyl group of the C1 carboxylate. This indicates that in a conformational equilibrium the two aforementioned groups are *cis* on the cyclohexane ring. According to this finding the twist conformation C1 C4 (scheme 5, **aIII**) must be the preferential one among the three possible ones cited before. No such effect was observed for compound **4a**, probably due to either predominant chair conformation or to hydrogen bond formation between the hydroxy group and the ethyl carboxylate as shown by IR spectroscopy ($\nu_{C=O}$ = 1736 cm^{-1}).

A number of indications on ^{13}C NMR data are also relevant for the C3 carbon configuration. It is known that compounds assigned with axial hydroxy groups on cyclohexane rings exhibit the carbon signals in ^{13}C NMR spectra at higher fields compared to the equatorial hydroxy ones [14]. The large δ ^{13}C difference of chemical shifts between the carbinol carbon atom C3 of the diastereoisomers **a**/**b** ($\Delta\delta$ = 2.97 and 2.87 ppm) indicates an equatorial (or pseudo-equatorial) position of the hydroxy groups for **4a**, **5a** (consequently **6a**) compounds. The differences also observed for the C1 carbon atom ($\Delta\delta$ = 3.5, 1.69 ppm) in conjunction with the H C4 ^{1}H NMR coupling constants of the different diastereoisomers are also relevant for the equatorial (or pseudo-equatorial) versus axial (or pseudo-axial) position of the C1 $OSiMe_3$ group on the major diastereoisomers. Differences on the C5 carbon atom are too small to be significant.

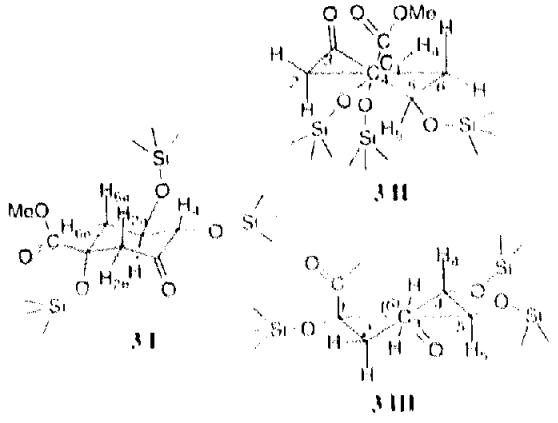
Taking into account the above observations of the diastereoisomers **a** and **b** we can assume that the major compounds **4a**, **5a**, **6a** arise from the same axial diastereofacial nucleophilic attack conferring a C3 (*R*), C3 (*S*) and C3 (*S*) configuration respectively.

We postulate that the selectivity of the reaction at 78 °C can be retained as the kinetic result which presents no (or very limited) degradation products; we observed that the temperature of the reaction did not play an important role in determining the stereochemical outcome even if the chemical yield can be affected. Notice also that difference in size or structure of the nucleophile, which can vary from a delocalized O-metallated species to a charge-localized hydride did not affect the diastereofacial preference which always appears to result from an axial attack on the carbonyl.

These results can be rationalized in terms of stereoelectronic control using the frontier orbital model [15]. From ^{1}H NMR conformational analysis of compound **3**, the large values of vicinal coupling constants H_1, H_{6a} and the existence of the $^4J_{H_1,\ H_{6e}}$ coupling constant (table VII) are in agreement with three main geometries (scheme 6) where the chair conformation is the more stable [16].

Table VII. ^{1}H NMR analysis of cyclohexanone **3**.

Attribution	*δ (ppm)*	*J (Hz)*	
H_1	3.98	H_1, H_{6e}	5.0
H_5	3.88	H_1, H_5	8.5
		H_5, H_{6a}	9.5
OCH_3	3.71		
H_{2a}	2.76	H_{2a}, H_{2e}	14.0
H_{2e}	2.55	H_{2a}, H_{2e}	14.0
		H_{2e}, H_{6e}	2.5
H_{6a}	2.47	H_{6a}, H_5	9.5
		H_{6a}, H_{6e}	14.0
H_{6e}	2.32	H_{6e}, H_5	5.0
		H_{6e}, H_{2e}	2.5
		H_{6a}, H_{6e}	14.0
$SiMe_3$	0.07; 0.04		



Scheme 6

According to studies by Reetz [6b] on the substituted cyclohexanone ring systems the axial attack is preferred because of better overlap between the HOMO of the nucleophile and the (π^* C=O) LUMO of the cyclohexanone reagent. He clearly demonstrated, by using ab initio quantum chemical methods, the non-equivalent distribution of the LUMO on the two faces of the carbonyl group, the larger one being on the axial side rather than on the equatorial. Axial preference is enhanced according to FMO theory when electron-withdrawing or electronegative groups are present at the C3e (equatorial) position of the cyclohexanone ring. The presence of the equatorial C1 carboxylate and C5 ($OSiMe_3$) groups in the more stable chair conformation of cyclohexanone **3** results in an increase of axial attack on the carbonyl. Thus at low temperature, when lithium carbanionic species are used, no minor diastereoisomer is observed.

Our results can also been explained by the theoretical approach developed by Anh et al [17] concerning the nucleophilic addition to cyclohexanones. Anh proposed the "flattening rule"; the selectivity on the nucleophilic addition was found to be correlated to the capac-

ity of the cyclohexanone ring to adopt a flattened position which allows an increasing axial attack on the carbonyle. In our case, in order to reduce the steric interactions due to the presence of the axial C1 $OSiMe_3$ group, a flattened configuration of the cyclohexanone can be adopted. A preferential attack on the Re face of the carbonyl is then expected to lead to the major adducts **4a–6a**.

An alternative rationale to explain the observed diastereoselectivity of the nucleophilic additions on the cyclohexanone **3** is based on the Cieplak's model [5, 18]. According to this model and considering only the more stable chair conformation, the transition state arising from axial attack of the carbonyl is stabilized by the interaction of the incipient bond with the σ^* antibonding orbitals of the axial C2 and C4 carbon hydrogen bonds. In fact, because of the greater electron-donating power of σ_{C-H} bonds [18] versus σ_{C-C} bonds, the axial approach is facilitated. The preference for the axial attack may also be enhanced by the presence of electronegative or electron-withdrawing groups β to the carbonyl group independently, be they axial or equatorial.

Increasing the temperature of the reaction when using lithioacetate, an α-lithiosulfone derivative, allows the formation of the minor diastereoisomer; this can be due to retroaldolisation and equilibration between the diastereoisomers. Minor changes with temperature in the cyclohexanone conformational equilibrium can also reduce the contribution of axial attack in favour of the equatorial one. A more significant change with temperature in the diastereoisomeric ratio is observed in the reduction with $NaBH_4$. The increase of the extent of the minor isomer during the reduction compared to other nucleophiles might result from the differences of steric hindrance between the incoming nucleophiles (CH_2A^- and H^-).

Conclusion

We have described addition reactions of metallated nucleophiles with fully protected methyl 3-dehydroquinate. Despite the rather sensitive structure of the starting compound, experimental conditions have been proposed which allow the specific synthesis of tetrahedral C3 adducts in 55–65% yields. These compounds do not constitute good mimics for the carbinolamine intermediate postulated to be formed at the active site of the DHQase. The absence of the carbonyl group on C3, or the steric constraints between the active site aminoacids present in the vicinity of the C3 carbon atom and the functional groups of the addition adducts, can be responsible for their ineffectiveness. The structural assignment of the adducts was obtained from NMR analysis, the major diastereoisomer is formed from the Re face attack on the carbonyl group. The specificity can be understood in terms of stereoelectron control in agreement with previous results.

Experimental section

^{1}H NMR spectra were recorded on a Bruker AC 200 and AC 400 apparatus. ^{13}C NMR spectra were recorded at 50.32 MHz. Chemical shifts are given in ppm (δ) relative to tetramethylsilane. IR spectra were determined with a Perkin-Elmer 783 or 883 spectrometer. Optical rotation was measured on a Perkin-Elmer 141 polarimeter, while mass spectra were performed on a Nermag R10-10 apparatus. Melting points were taken with a Kofler hot stage. HPLC was performed on a Jobin-Yvon apparatus using a 6–35 µ Amicon silica. All solvents were distilled before use.

Enzymatic tests

3-Dehydroquinase has been purified from an overproducing strain of *Escherichia Coli* in the laboratory of Prof Coggins [19]. Compounds were tested according to the following enzymatic sequence:

$$3-\mathrm{DHQ} \xrightarrow{3\text{-DHQase}} 3-\mathrm{DHS} \xrightarrow[\mathrm{NADPH}]{\mathrm{SHOrase}} \text{shikimic acid} + \mathrm{NADP}$$

The assay contains 630 (or 640) µL K_2CO_3 buffer solution (pH = 8.5), 200 µL 3-dehydroshikimate (10 mM solution in H_2O), 50 µL 3-dehydroquinate (10 mM solution in H_2O), 100 µL NADPH (1 mM solution in H_2O), 10 µL (or 5 µL) dehydroquinase (1unit/mL solution) and 10 µL (or 5 µL) shikimate dehydrogenase (1 unit/mL solution). Variation of the enzymatic activity was measured at 25 °C and at 340 nm by following the decrease in NADPH absorption. To measure the inhibitory activity of our compounds, a 1 mL incubation of enzyme (1 unit dehydroquinase) was set up, in an Eppendorf tube, containing a known concentration of inhibitor. Eventual loss of enzyme activity with time was then monitored by withdrawing a small aliquot (10 µL or 5 µL) at a known time point in the assay cuvette in replacement of 3-dehydroquinase.

- ***(1S, 3S, 4S, 5S) and (1S, 3R, 4S, 5S)-3-Hydroxy-3-[(methoxycarbonyl)methyl]-1,4,5-tris[(trimethylsilyl)-oxy]cyclohexane-1-carboxylic acid methyl ester* 4a**

To a solution of 1,4,5-tris(trimethylsilyl)-3-dehydroquinate (0.42 g, 1 mmol) in anhydrous THF (5 mL) at −78 °C and under Ar, it was added dropwise 1 mL of a preformed solution of lithium enolate of ethyl acetate (5 mmol in 10 mL THF). The reaction mixture was stirred at −78 °C for 1 h then it was quenched with an aqueous NH_4Cl solution, and extracted with ether. The organic phase was dried over $MgSO_4$, the solvent evaporated and the crude product was purified on silica gel column chromatography (eluent petroleum ether/ethyl acetate, 9:1) yielding diastereoisomer **4a** (185 mg, 57%). When using 1 equiv of lithium enolate (2 mL of the 5 mmol/10 mL THF solution) and performing the reaction at −40 °C we obtained pure diastereoisomer **4a** (102 mg) and an inseparable mixture of **4a** + **4b** (24 mg **4a**/**4b**, 20/80). Total yield 26%.

R_f (eluent: petroleum ether/ethyl acetate, 9:1): **4a** 0.31, **4b** 0.33. **4a** $[\alpha]_D^{25}$ = −42.75 (*c* = 1.3, $CHCl_3$).

IR ($CHCl_3$): **4a** 3480, 1740, 1730.

MS (*m/z*): 510 (0.4%), 491 (0.4), 362 (99), 147 (11), 129 (14), 73 (100).

Anal. calc. for $C_{23}H_{46}O_8Si_3$: C, 49.77; H, 8.72. Found: C, 49.81; H, 8.75.

- ***(1S, 3R, 4S, 5S) and (1S, 3S, 4S, 5S)-3-Hydroxy-3-[(phenylsulfonyl)methyl]-1,4,5-tris[(trimethylsilyl)-oxy]cyclohexane-1-carboxylic acid methyl ester* 5a, 5b**

Method a

A solution of methyl phenyl sulfone (421 mg, 2.7 mmol) in anhydrous benzene (10 mL) was added under stirring

at room temperature, to a preformed solution of EtMgBr (1 mmol) in diethyl ether (5 mL). The reaction mixture is stirred at room temperature (15 min) then heated rapidly under reflux (1 min). A solution of methyl 1,4,5-tris(trimethylsilyl)dehydroquinate (840 g, 2 mmol) in anhydrous diethyl ether (15 mL) was then added dropwise under stirring at room temperature. After 12 h the reaction mixture was quenched with an aqueous NH_4Cl solution and extracted with diethyl ether. The organic phase was dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by silica gel column chromatography yielding diastereoisomer **5a** (733 mg, 65%).

Method b

Methyl phenyl sulfone (312 mg, 2 mmol) in anhydrous THF (4 mL) was added dropwise under stirring and argon at −35 °C to an LDA solution (2 mmol) in THF (5 mL). After stirring for 30 min at −35 °C a solution of methyl 1,4,5-tris(trimethylsilyl)-3-dehydroquinate (840 mg, 2 mmol) in THF (5 mL) was added dropwise at the same temperature. After 3 h the reaction was quenched with aqueous NH_4Cl and the mixture extracted with diethyl ether. The organic phase was dried over $MgSO_4$, the solvent evaporated and the crude product was purified on silica gel (eluent:petroleum ether/ethyl acetate, 8:12) yielding diastereoisomers **5a** (248 mg, 22%) and **5b** (56 mg, 5%).

R_f (eluent: petroleum ether/ethyl acetate, 8:12) **5a** 0.23; **5b** 0.18. **5a** $[\alpha]_{25}^{D}$ = −12.03 (*c* = 1.4, $CHCl_3$); **5b** $[\alpha]_{25}^{D}$ = −8.21 (*c* = 1, $CHCl_3$). Mp (**5a**) 109–110 °C.

IR (**5a**, **5b**, $CHCl_3$): 3 488; 1 746; 1 310; 1 150.

MS (*m/z*): 576 (0.2%); 499 (1); 131 (2); 117 (10); 129 (11); 73 (100).

Anal calc for $C_{24}H_{44}O_6Si_3$: C, 49.97; H, 7.69. Found: C, 49.85; H, 7.73 (**5a**). C, 49.75; H, 7.65 (**5b**).

- *(1S, 3S, 4S, 5S)-3-Hydroxy-3-propargyl-1,4,5-tris(trimethylsilyl)oxycyclohexane-1-carboxylic acid methyl ester* **6a**

Propargyl bromide (1.21 g, 10.2 mmol) was added in diethyl ether containing magnesium turnings (250 mg, 10.2 mmol) and a crystal of $HgCl_2$. The mixture was heated under reflux till consumption of magnesium. From this solution 2 mmol (2 mL) was taken and then added via a syringe at −40 °C under argon to a stirred solution of methyl 1,4,5-tris(trimethylsilyl)-3-dehydroquinate (420 mg, 1 mmol) in diethyl ether (5 mL). The mixture was allowed to reach room temperature and was stirred for a total of 6 h. An aqueous NH_4Cl solution was then added and the mixture extracted with diethyl ether. The organic phase was dried over $MgSO_4$, the solvent evaporated and the crude product was purified on silica gel (eluent: petroleum ether/ethyl acetate, 9:1) yielding compound **6a** (401 mg, 60%).

R_f (eluent: petroleum ether/ethyl acetate, 9:1) 0.47; $[\alpha]_{25}^{D}$ = −21.4 (*c* = 1.2, $CHCl_3$).

IR ($CHCl_3$): 3 480; 3 300; 1 730; 905.

MS (*m/z*): 404 (2%); 145 (89); 345 (100); 254 (70); 265 (34).

Anal calc for $C_{20}H_{40}O_4Si_3$: C, 52.13; H, 8.75. Found: C, 52.05; H, 8.79.

- *(1S, 3S, 4S, 5S) and (1S, 3R, 4S, 5S)-3-Hydroxy-1,4,5-tris(trimethylsilyl)oxycyclohexane-1-carboxylic acid methyl ester* **7a**, **7b**

To a solution of methyl 1,4,5-tris(trimethylsilyl) dehydroquinate (299 mg, 0.71 mmol) in dry methanol at 0 °C under stirring was added sodium borohydride (265 mg, 7.12 mmol). The mixture was stirred for 30 min before quenching it at the same temperature with aqueous NH_4Cl (10 mL). It was then extracted with $CHCl_3$, the organic phase dried over $MgSO_4$ and the solvent evaporated. After purification by silica gel column chromatography (eluent: petroleum ether/ethyl acetate, 9:1) we obtained diastereoisomers **7a** (117 mg) and **7b** (137 mg) in a total yield of 85%.

R_f (eluent: petroleum ether/ethyl acetate, 9:1) **7a** 0.37; **7b** 0.24. **7a** $[\alpha]_{25}^{D}$ = −8.20 (*c* = 1.4, $CHCl_3$); **7b** $[\alpha]_{25}^{D}$ = −14.49 (*c* = 1.5; $CHCl_3$).

7a

IR ($CHCl_3$): 3 470; 1 740; 895.

^1H NMR ($CDCl_3$): 4.19 (dddd, $J_{H_{3a}-H_4}$ = 2.8, $J_{H_{3a}-H_{2a}}$ = 11, $J_{H_{3a}-H_{2e}}$ = 4.70 Hz, 1H, H_{3a}); 3.98 (ddd, $J_{H_{5e}-H_{6e}}$ = 2.9, $J_{H_{5e}-H_{6a}}$ = 1.9, $J_{H_{5e}-H_4}$ = 4 Hz, 1H, H_{5e}); 3.45 (dd, $J_{H_{4}-H_{5e}}$ = 4, $J_{H_4-H_{3a}}$ = 2.8 Hz, 1H, H_4); 2.22 (dd, $J_{H_{2e}-H_{2a}}$ = 4.70, $J_{H_{2e}-H_{3a}}$ = 13.5 Hz, 1H, H_{2e}); 2.21 (dd, $J_{H_{6e}-H_{5e}}$ = 1.9, $J_{H_{6e}-H_{6a}}$ = 13 Hz, H_{6e}); 1.89 (dd, $J_{H_{6a}-H_{5e}}$ = 2.9, $J_{H_{6a}-H_{6e}}$ = 13 Hz, 1H, H_{6a}); 1.71 (dd, $J_{H_{2a}-H_{2e}}$ = 11, $J_{H_{2a}-H_{3a}}$ = 13.5 Hz, 1H, H_{2a}); 0.14, 0.07, 0.03 (3s, 3 × $(CH_3)_3$).

^{13}C NMR ($CDCl_3$): 173.49 (s); 75.67 (s); 72.08 (d, C_4); 69.19 (d, C_5); 67.41 (d, C_3); 51.69 (q, CH_3); 38.88 (t, C_2); 38.26 (t, C_6); 1.96, 0.47, 0.09 (3q, $(CH_3)_3$).

Anal calc for $C_{17}H_{38}O_6Si_3$: C, 48.30; H, 9.06. Found: C, 48.52; H, 9.11.

7b

IR ($CHCl_3$): 3 470; 1 471; 900.

^1H NMR ($CDCl_3$): 3.96 (dddd, $J_{H_3-H_4}$ = 3.1, $J_{H_3-H_2}$ = 7.5, $J_{H_3-H_{2'}}$ = 3.5 Hz, 1H, H_3); 3.89 (dddd, $J_{H_5-H_4}$ = 6.5, $J_{H_5-H_6}$ = 1.95, $J_{H_5-H_{6'}}$ = 7.5 Hz, 1H, H_5); 3.45 (dd, $J_{H_4-H_5}$ = 6.5, $J_{H_4-H_3}$ = 3.1 Hz, 1H, H_4); 2.12 (dd, $J_{H_{2'}-H_3}$ = 3.5, $J_{H_{2'}-H_{2}}$ = 13.2 Hz, 1H, $H_{2'}$); 1.97 (dd, $J_{H_2-H_3}$ = 7.5, $J_{H_2-H_{2'}}$ = 13.5 Hz, 1H, H_2); 1.92 (dd, $J_{H_{6'}-H_5}$ = 1.95, $J_{H_{6'}-H_{6}}$ = 13.5 Hz, 1H, $H_{6'}$); 1.86 (dd, $J_{H_6-H_5}$ = 7.5, $J_{H_6-H_{6'}}$ = 13.2 Hz, 1H, H_6); 0.11, 0.09, 0.05 (3 s, 3 × $(CH_3)_3$).

^{13}C NMR ($CDCl_3$): 173.59 (s); 77.31 (s, C1); 74.89 (d, C_4); 68.91 (d, C_3); 68.81 (d, C_5); 52.07 (q, CH_3); 68.81 (d, C_3); 39.45 (d, C_2 and C_6); 1.90, 0.41, 0.09 (q, 3 × $(CH_3)_3$).

Anal calc for $C_{17}H_{38}O_6Si_3$: C, 48.30; H, 9.06. Found: C, 48.52; H, 9.06.

Desilylation: general procedure

To a solution of silylated compound **4a**, **5a** or **6a** (0.17 mmol) in dry methanol (1 mL) was added Amberlite IR120 resin (400 mg) and a drop of water. The mixture was stirred for 1 h at room temperature. After filtration and evaporation of the solvents we obtained quantitatively the deprotected compounds.

- *3-(Ethoxycarbonyl)methyl-1,3,4,5-tetrahydroxycyclohexane-1-carboxylic acid methyl ester* **8a**

R_f (ether/methanol/THF: 90:5:5): 0.23; $[\alpha]_{25}^{D}$ = −10.8 (*c* = 1.2, MeOH).

IR (liq): 3 480; 1 740; 1 735.

^1H NMR ($CDCl_3$): 4.13 (q, *J* = 7.1 Hz, 2H, CH_2); 3.95 (dddd, $J_{H_5-H_{6e}}$ = 1.5, $J_{H_5-H_{6a}}$ = 11.5, $J_{H_5-H_4}$ = 9.1 Hz, 1H, H_5); 3.75 (s, 3H, OCH_3); 3.37 (d, $J_{H_4-H_5}$ = 9.1 Hz, 1H, H_4); 2.68 (d, *J* = 15 Hz, 1H, H_X, CH_2CO_2); 2.6 (d, *J* = 15 Hz, H_X, CH_2CO); 2.19 (d, $J_{H_{6a}-H_{5a}}$ = 11.5 Hz, 1H, H_{6a}); 2.16 (dddd, $J_{H_{6e}-H_{6a}}$ = 2.7, $J_{H_{6e}-H_5}$ = 9.5, $J_{H_{6e}-H_{6a}}$ = 13.5 Hz, 1H, H_{6e}); 2.12 (dd, $J_{H_{2e}-H_{2a}}$ = 2.7, $J_{H_{2e}-H_{6a}}$ = 11.5 Hz, 1H, H_{2e}); 1.81 (dd, $J_{H_{2a}-H_{2e}}$ = 11.5, $J_{H_{2a}-H_{6a}}$ = 13.5 Hz, 1H, H_{6a}); 1.25 (t, *J* = 7.1 Hz, 3H, CH_3).

^{13}C NMR (CD_3OD): 175.00 (s), 172.55 (s), 78.71 (d, C_4), 76.18, 75.41 (s, C_1 and C_3), 68.41 (d, C_5), 60.63

[illegible] (CH_2CO), 52.62 (q, OCH_3), 43.30 (t, CH_2O), 42.41 (t, C_6), 41.40 (t, C_2), 14.46 (q, CH_3).

Anal calc for $C_{12}H_{20}O_6$: C, 49.31; H, 6.90. Found: C, 49.05; H, 6.95.

- *6-(Phenylsulfonyl)methyl-1,3,4,5-tetrahydroxycyclohexane-1-carboxylic acid methyl ester* **9a**

R_f (ether-methanol-THF, 90:5:5): 0.23; $[\alpha]_D^{20}$ = [illegible] 10.02 (c = 1.2, MeOH).

IR (liq): 3 490, 1 740, 1 260, 1 150.

^1H NMR ($CDCl_3$): 7.97–7.61 (m, 5H), 3.95 (ddd, $J_{H_3-H_4}$ = 9.5, $J_{H_3-H_{2ax}}$ = 11.6, $J_{H_3-H_{2eq}}$ = 4.7 Hz, 1H, H_3), 3.71 (s, 3H, OCH_3), 3.73 (d, J = 14.7 Hz, H_A, CH_2SO_2), 3.50 (d, J = 14.7 Hz, 1H, H_B, CH_2SO_2), 3.13 (d, $J_{H_4-H_3}$ = 9.5 Hz, 1H, H_4), 2.63 (dd, $J_{H_{2eq}-H_{3}}$ = 3.1, $J_{H_{2eq}-H_{2ax}}$ = 14.8, 1H, H_{2eq}), 2.33 (d, $J_{H_{2ax}-H_{2eq}}$ = 14.8 Hz, 1H, H_{2ax}), 2.15 (ddd, $J_{H_{6eq}-H_{5}}$ = 3.1, $J_{H_{6eq}-H_5}$ = 4.7, $J_{H_{6eq}-H_{6ax}}$ = 13.2 Hz, 1H, H_{6eq}), 1.81 (dd, $J_{H_{6ax}-H_5}$ = 11.6, $J_{H_{6ax}-H_{6eq}}$ = 13.2 Hz, 1H, H_{6ax}).

^{13}C NMR (D_2O): 178.06 (s), 141.93, 137.30, 132.28, 130.19 (arom), 79.74 (d, C_4), 77.76, 77.69 (s, C_1 and C_3), 69.1 (d, C_5), 63.96 (t, SO_2CH_2), 55.91 (q, OCH_3), 42.59 (t, C_6), 42.00 (t, C_2).

Anal calc for $C_{15}H_{20}O_8$: C, 49.99; H, 5.59. Found: C, 50.09; H, 5.61.

- *6-Propargyl-1,3,4,5-tetrahydroxycyclohexane-1-carboxylic acid methyl ester* **10a**

R_f (ether-methanol-THF, 90:5:5): 0.32; $[\alpha]_D^{20}$ = [illegible] 7.4 (c = 1.3, MeOH).

IR (liq): 3 500 (br OH), 2 300 (C≡C), 1 740.

^1H NMR ($CDCl_3$): 3.93 (ddd, $J_{H_5-H_4}$ = 9.2, $J_{H_5-H_{6eq}}$ = 4.5, $J_{H_5-H_{6ax}}$ = 11.2 Hz, 1H, H_5), 3.75 (s, 3H, OCH_3), 3.46 (d, J = 9.2 Hz, 1H, H_4), 2.63 (dd, J_{H_A-CH} = 2.93, $J_{H_A-H_B}$ = 16.2 Hz, 1H, H_A, CH_2 C≡), 2.38 (d, J = 2.93, H_C, 1H, ≡C), 2.34 (dd, J_{H_B-CH} = 2.93, $J_{H_A-H_B}$ = 16.2 Hz, 1H, H_B, CH_2 C≡C), 2.24 (d, J = 11.6 Hz, 1H, H_{2ax}), 2.17 (ddd, $J_{H_{6eq}-H}$ = 3.25, J_{H-H} = 4.5, $J_{H_{6eq}-H_{6ax}}$ = 13.5 Hz, 1H, H_{6eq}), 1.95 (dd, J_{H-H} = 3.25, $J_{H_{2eq}-H_{2ax}}$ = 15 Hz, 1H, H_{2eq}), 1.79 (dd, $J_{H_{6ax}-H}$ = 11.5, $J_{H_{6ax}-H_{6eq}}$ = 13.5 Hz, 1H, H_{6ax}).

^{13}C NMR (CD_3OD): 177.85 (s), 81.27 (s, C [illegible]), 77.67 (d, C_4), 76.70, 76.51 (s, C_1 and C_3), 72.42 (d, ≡CH), 68.90 (d, C_5), 53.10 (q, CH_3), 42.61 (t, C_6), 41.21 (t, C_2), 29.6 (t, CH_2).

Anal calc for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.26; H, 6.52.

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