ASYMMETRIC SYNTHESIS OF HETEROORGANIC ANALOGS OF NATURAL COMPOUNDS.

4. DIASTEREO- AND ENANTIOSELECTIVE SYNTHESIS OF (2S, 3S)-4,4,4-TRIFLUOROTHREONINE AND (2S, 3S)-β-PERFLUOROALKYLSERINES

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Perfluorinated aliphatic aldehydes react with the Ni(II) complex of the glycine Schiff base with (S)-2-[N(N'-benzylprolyl)amino]benzophenone in the presence of MeONa to give (2S, 2S)-perfluoroalkylserines, while alkanals react to form (2R, 3S)-diastereomers.

Fluorine-substituted threonines are promising as potential threonine antimetabolites [1] as well as structural blocks for obtaining various types of biologically active substances. Most methods for the synthesis of 4,4,4-trifluorothreonine are based on consecutive conversions of 4,4,4-trifluoroacetoacetic ester or its derivatives – insertion of an amino group into a molecule already containing the required four carbon atoms [2-5]. An alternative approach – involving the condensation of N,N-dibenzylglycine ethyl ester with ethyl trifluoroacetate, reduction of the C=O group, and hydrogenation of the N-benzyl groups [4] – has also been proposed. These methods can be used to obtain racemic trifluorothreonine or trifluoroallothreonine. We have proposed a new approach for synthesizing 4,4,4-trifluorothreonine: condensation of fluoral with glycine and the Ni(II) complex of its Schiff base with (S)-2-[N(N'-benzylprolyl)amino]benzophenone.

Earlier we showed that the Ni(II) complex of glycine (I) in MeONa solution readily reacts with aliphatic or aromatic carbonyl compounds, giving high chemical (about 70%) and stereochemical (about 90%) yields of α-amino-β-hydroxycarboxylic acids with a R-threo configuration [6, 7]. In the reaction of complex (I) with acetaldehyde, R-threonine is formed with an 84% enantiomeric excess at a threo-/allo-isomer ratio of 20/1 [6]. Similar results led us to expect that reaction of a chiral Ni(II) complex of glycine (I) with perfluorinated aldehydes would be a convenient method for synthesizing optically active β-perfluoroalkylserines and trifluorothreonine.

We found that fluoral (IIa), perfluoropentanal (IIb), and ω-hydrododecafluoropentanal (IIc) react with chiral Ni(II) complex of glycine (I) in 2.25 N MeONa in MeOH when heated for a short time (about 10 min) at 50°C. The reaction course was monitored by means of TLC. The reaction does not proceed without heating. This, apparently, is due to the fact that when aldehydes (IIa-c) are added to MeOH, hemiacetals with a low reactivity are formed, which are capable of reacting with complex (I) only upon heating. The possibility of using hemiacetals or perfluorinated aldehyde (IIa-c) hydrates in condensation with complex (I) is attractive in that aldehydes (IIa-c) are obtained and preserved in the form of these derivatives. This eliminates the necessity of preparing free aldehydes (IIa-c), which greatly simplifies the proposed method. Thus our experiments showed that aldehyde (IIa-c) hydrates or aldehyde (IIb, c) ethyl acetals, like free aldehydes (IIa-c), readily react with complex (I) under the same conditions without any change in the yield or the reaction product ratio. A twofold excess of perfluorinated aldehydes (IIa-c) or their hydrates is sufficient for the complete conversion of (I), whereas in the condensation of (I) with acetaldehyde, a tenfold excess of aldehyde is required.

Analysis of products of the reaction of aldehyde (IIa-c) hydrates with complex (I), obtained under the same conditions (see Experimental section), showed that a mixture of diastereomeric complexes (III) and (V), in a ratio of 93.6:6.4 to 95.9:4.1, is formed in

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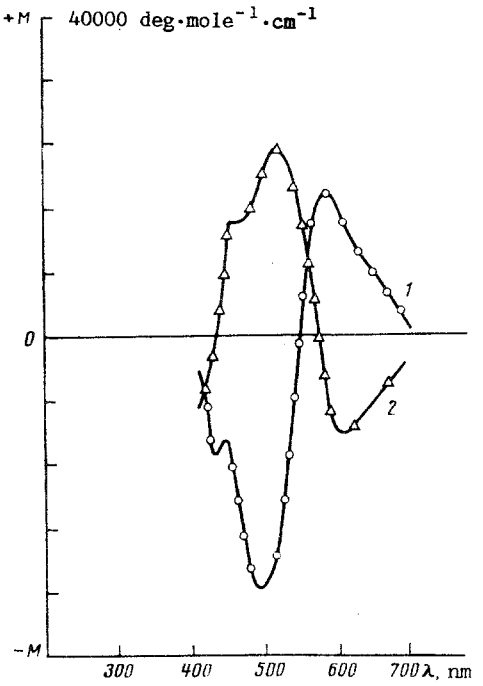


Fig. 1. ORD curves (chloroform, 25°C) of Schiff base Ni(II)-complexes formed from (S)-2-[N(N'-benzylprolyl)amino]benzophenone and amino acids: 1) (2S, 3S)-4,4,4-trifluorothreonine (III); 2) (2R, 3R)-4,4,4-trifluorothreonine (V).

TABLE 1. Properties of Complexes (III) and (V)

Complex	R	Chemical yield, %	Isomer ratio, %	Decomp. temp., °C	$[\alpha]_D$, deg (T, °C) (c in CHCl$_3$)	Empirical formula	Found/Calculated, %		
							C	H	F
(III)	CF_3	71.5	95,5	202–205	+3252.2(25.6) (0.02)	$C_{29}H_{26}F_3N_3NiO_3$	58.21 58,42	4,54 4.40	9.63 9,56
(V)	CF_3	3.3	4.5	215–220	–1292.6(26) (0,02)	$C_{29}H_{26}F_3N_3NiO_3$	58.18 58.42	4,61 4,40	9.28 9.56
(III)	C_4F_9	78.1	95,9	110–116	+2330,4(25.6) (0,01)	$C_{32}H_{26}F_9N_3NiO_3$	51.24 51.50	3,77 3,51	22.68 22,91
(V)	C_4F_9	3.3	4.1	210–212	–1584.5(26) (0.05)	$C_{32}H_{26}F_9N_3NiO_3$	51.19 51,50	3,65 3,51	22.78 22,91
(III)	$H(CF_2)_6$	80.5	93,6	218–220	+2138,5(25,6) (0,03)	$C_{34}H_{27}F_{12}N_3NiO_3$	49.01 49,30	3,17 3,29	27,79 27,52
(V)	$H(CF_2)_6$	5.5	6,4	185–190	–1946,2(26) (0,03)	$C_{34}H_{27}F_{12}N_3NiO_3$	49.08 49.30	3.24 3.29	27,90 27,52

all cases. Complexes (III) and (V) were isolated in a pure state by chromatography of the reaction mixture on SiO_2. Their composition and structure were confirmed by elemental analysis and NMR spectra (Tables 1 and 2).

As noted earlier [6], R-threonine is formed as the major product in the reaction of acetaldehyde with complex (I) at high pH values. However, in the ORD spectra of complexes (III) (Fig. 1), including the complex obtained from trifluoroacetaldehyde, the positive Cotton effects at 580-590 nm are followed by negative effects at 480-490 nm, which corresponds to an α-(S) configuration of amino acids in complexes (III) [6]. The minor reaction products, complexes (V), contain the expected α-(R)-β-perfluoroalkylserines, which is reflected in the ORD spectra of complex (V) as negative Cotton effects at 580-590 nm followed by positive effects. The absolute configuration of the α- and β-carbon atoms of β-perfluoroalkylserines in complex (III) was determined by x-ray diffraction of the complex, with R = $H(CF_2)_6$, which showed that the complex contains (2S, 3S)-3-(6-hydrododecafluoroheptyl)serine (Fig. 2, Table 3).

TABLE 2. PMR Spectra of Complexes (III) and (V)

Compound	R_F	$CDCl_3$, δ, ppm, J, Hz						
		ArH	OH (J_{HH})	α-H (J_{HH})	β-H (J_{HH}) (J_{HF})	CH_2—Bzl * (J_{HH})	C—H(Pro)	other groups
(III) **	CF_3	8.25–6,58 m	5.55 d (10)	4,27 d (5,5)	3,58 m	4,30 3,53 (13)	3.45–1.65 m	–
(V)	CF_3	8.45–6.74 m	5.91 m	4,41 m	3,64 m	4,91 3,95 (13)	4.01–1.74 m	–
III ***	C_4F_9	8.18–6,50 m	5.65 d (10)	4,25 d (5,4)	3,82 d.d.d (10) (26) (5.4)	4,27 3.45 (12)	3.35–1.94 m	–
(V)	C_4F_9	8.50–6,81 m	5.95 m	4,40 d (4)	3.65 d.d (4) (9)	4.94 4.05 (13)	4.31–1.78 m	–
(III)	$H(CF_2)_6$	8.21–6,59 m	5.61 m (10)	4,31 d (5)	3,80 d.d.d (10) (25) (5)	4,30 3,51 (13)	3.40–2.00 m	6.05 tr.t (J_{HF}=50), (J_{HF}=6)

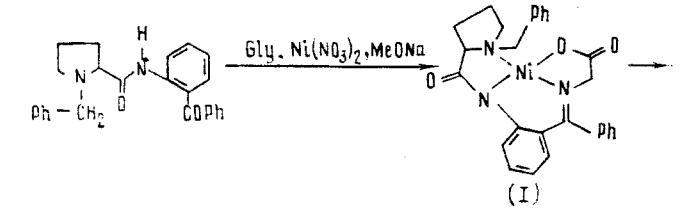
*AB system.

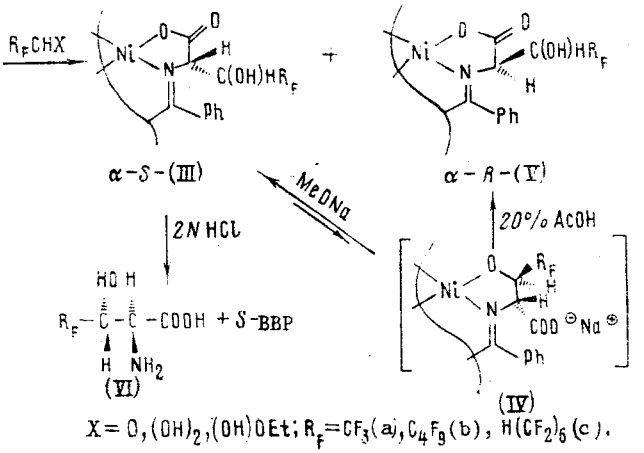
**^{19}F NMR spectrum ($CDCl_3$, δ, ppm): −5.22 d (CF_3, J_{HF} = 7.5 Hz).

***^{19}F NMR spectrum ($CDCl_3$, δ, ppm): 3.0 m (3F, CF_3), 35.5, 47.5 (AB, 2F, CF_2, J_{FF} = 27 Hz), 44.0, 46.5 (AB, 2F, CF_2, J_{FF} = 300 Hz), 46.8, 50.0 (AB, 2F, CF_2, J_{FF} = 287 Hz).

As usual for complexes of this type [8, 9], the Ni atom has a slightly distorted planar-tetragonal coordination. The asymmetric atoms have the following absolute configurations: C^{11}–S, N^3–R, C^2–S, and C^{22}–S. Phenyl ring $C^{31}...C^{36}$ is inclined by 76° toward the plane of the $N^1=C^3$ double bond. The benzyl group is in the exo orientation relative to the metal atom [torsional angle $NiN^3C^{15}C^{16}$ = 159(4)°], which is not characteristic for complexes of this type. Although molecular mechanical calculations show that the exo and endo orientations are energetically equivalent, an endo orientation was found in six out of eight similar crystalline structures investigated earlier; in one structure the endo and exo orientations coexisted, and one had an exo orientation, constrained by an additional apical coordination of the metal atom (Cu) with an H_2O ligand [8, 9]. The proline heterocycle has a conformation similar to that of the C_δ-envelope (Fig. 2).

Thus reactions of perfluorinated aliphatic aldehydes with chiral Ni(II) complexes of glycine (I), unlike those of nonfluorinated analogs [6], are stereochemically reversible with respect to the α-carbon atom, affording (S)-threo-β-perfluoroalkylserines.





α-(R)-Amino acids from complex (I) and the carbonyl compound are formed via an intermediate type (IV) complex in which an ionized hydroxyl group replaces the carbonyl group in the Ni coordination plane [6]. Recently we showed that in the reaction of complex (I) with substituted benzaldehydes the electronic nature of the substituent in the aldehyde ring has a pronounced effect on the ratio of R-threo- and S-threo-β-phenylserines that are formed. The amount of the S-threo isomer increases with an increase in the electron-acceptor properties of the benzaldehyde substituent. Thus when complex (I) is condensed with 4-nitrobenzaldehyde, the ratio of R-threo to S-threo-β-phenylserine is about 83/17, whereas in unsubstituted benzaldehyde it is 94/4 [7]. Presumably, electron-acceptor substituents in benzaldehyde, which decrease the charge density on the carbonyl oxygen atom, destabilize type (IV) structures, which are responsible for the formation of amino acids with an α-(R) configuration. In contrast to β-phenylserines, in which the electron-acceptor effect of the substituent is partially leveled by the π-system of the benzene ring and a monovalent C–C bond, in β-perfluoroalkylserines the hydroxyl group and the R_F[CF_3, C_4F_9, $H(CF_2)_6$] substituent are in a gem position with respect to each other, which increases the effect of the perfluoroalkyl radicals on the acidity of the hydroxyl group.

Thus, according to the literature, the acidity of the hydroxyl group in 4,4,4-trifluorothreonine (12.7 [10]) is much stronger than in unsubstituted threonine. The same increase in acidity (about 3 pK units) is observed in the transition from EtOH (pK_a 15.5)

TABLE 3. Coordinates of Nonhydrogen Atoms of Complex (III), $R = H(CF_2)_6$

Atom	X	Y	Z	Atom	X	Y	Z
Ni	3216(3)	3464(2)	4792(1)	C^{20}	2794(25)	985(13)	2388(14)
O^1	2320(14)	4427(8)	4638(6)	C^{21}	2670(24)	1449(18)	2981(13)
O^2	1751(18)	5504(9)	5222(9)	C^{22}	3695(19)	5097(12)	6190(10)
O^3	5553(17)	1773(9)	4256(7)	C^{23}	4760(23)	5213(14)	5728(12)
O^4	3223(21)	5871(8)	6340(9)	C^{24}	5835(20)	5735(15)	5970(12)
N^1	3203(17)	3669(10)	5772(8)	C^{25}	6877(26)	5871(15)	5682(13)
N^2	4055(15)	2541(10)	4879(9)	C^{26}	7826(55)	6520(34)	5917(27)
N^3	3241(18)	3230(9)	3772(8)	C^{27}	8864(34)	6473(21)	5769(18)
C^1	2247(19)	4841(12)	5202(12)	C^{28}	10229(42)	6772(26)	5898(22)
C^2	2754(20)	4547(13)	5887(10)	C^{31}	3099(20)	3469(11)	7029(10)
C^3	3362(19)	3178(11)	6277(8)	C^{32}	4054(21)	3608(12)	7459(9)
C^4	3677(21)	2333(14)	6170(10)	C^{33}	3824(28)	3806(12)	8171(13)
C^5	3736(23)	1320(12)	6753(10)	C^{34}	2605(25)	3878(14)	8432(10)
C^6	4064(28)	1023(13)	6693(11)	C^{35}	1781(26)	3719(12)	7978(11)
C^7	4366(30)	761(14)	6034(15)	C^{36}	1964(19)	3506(11)	7273(9)
C^8	4419(18)	1199(11)	5464(11)	F^1	5267(14)	4514(8)	5520(7)
C^9	4084(18)	2007(13)	5514(9)	F^2	4476(16)	5607(9)	5062(8)
C^{10}	4794(21)	2309(11)	4302(9)	F^3	6139(18)	5419(10)	6591(9)
C^{11}	4437(20)	2816(12)	3670(11)	F^4	5466(24)	6427(14)	6133(13)
C^{12}	5405(27)	3580(20)	3629(14)	F^5	6944(17)	5637(10)	4995(8)
C^{13}	4552(28)	4288(14)	3391(14)	F^6	7458(20)	5062(12)	5590(10)
C^{14}	3285(25)	3958(11)	3302(10)	F^7	7876(18)	6593(11)	6586(9)
C^{15}	2189(23)	2705(12)	3635(10)	F^8	7566(17)	7129(10)	5403(9)
C^{16}	2295(20)	2216(10)	2951(10)	F^9	9131(17)	6219(10)	4978(9)
C^{17}	1862(23)	2481(12)	2333(11)	F^{10}	9008(19)	5599(11)	6272(10)
C^{18}	1905(28)	2078(17)	1721(13)	F^{11}	10148(22)	6991(14)	6626(12)
C^{19}	2406(31)	1263(16)	1741(12)	F^{12}	9730(23)	7519(14)	5759(12)

to CF_3CH_2OH (pK_a 12.4) [11]. Thus, a pK_a value of 12.7 for the β-hydroxyl group is critical for the formation of complex (IV) for obtaining α-(S)-amino acids.

The x-ray diffraction data suggest that the hydroxyl group participates in an intramolecular hydrogen bond: O^4—H...O^2 (O...O 2.72 Å). Moreover, the small distances between Ni...F^1 (3.18 Å) and Ni...F^2 (3.83 Å) indicate that there may be an interaction between the metal atom (Ni) and F^1, F^2, which, together with intramolecular hydrogen bond O^4—H...O^2, may be the reason for the stabilization of the S-configuration at C^{22}.

On the basis of our data and the results obtained in [6, 7], we conclude that the mechanism for the reaction of the Ni(II) complex of the Schiff base of glycine (I) with aromatic and aliphatic aldehydes (in the presence of NaOMe), proposed in [6], is not general. The ratio of R-threo-/S-threoamino acids, ranging from 95:5 (ArOMe substituent) to 5:95 (R_F substituent), depends on the basicity of the β-hydroxyl group, which, in turn, depends on the electronic nature of the substituent in the β-position of the amino acids that are formed.

Treatment of (S)-threo diastereomers (III) (R_F = CF_3, C_4F_9) with 2 N HCl afforded amino acids (VI) and the chiral inducing agent S-BBP, which was isolated from the reaction mixture without loss of optical activity.

EXPERIMENTAL

NMR spectra were recorded on a Bruker WP-200 (200 MHz) instrument using the internal standards HMDS (^1H) and CF_3COOH (^{19}F). ORD spectra were taken on a Jasco apparatus. Specific optical rotations were measured on a Perkin—Elmer-241 polarimeter.

General Method for the Alkylation of Complex (I) with Perfluorinated Aldehydes or Their Derivatives (Hydrates, Polyacetals). A 6-mmole portion of perfluorinated aldehyde or the corresponding hydrate or polyacetal was added to 3 mmoles of complex (I) in 3 ml of 2.25 N MeONa in MeOH. The mixture was heated for 10 min at 50-60°C and decanted into 80 ml of 20% AcOH in H_2O. The resultant precipitate was filtered, dried in a vacuum, and chromatographed on SiO_2 ($L_{5/10}$) in $CHCl_3$:Me_2CO (7:1). Yields, constants, elemental analysis data, and specific optical rotations of complexes (III) and (V) are shown in Table 1, and their NMR spectral data are shown in Table 2.

Isolation of S-BBP and Amino Acids (VI) from Complexes (III). A 3-mmole portion of complex (III) in 5 ml MeOH was added to 10 ml of boiling 2 N HCl. After the color

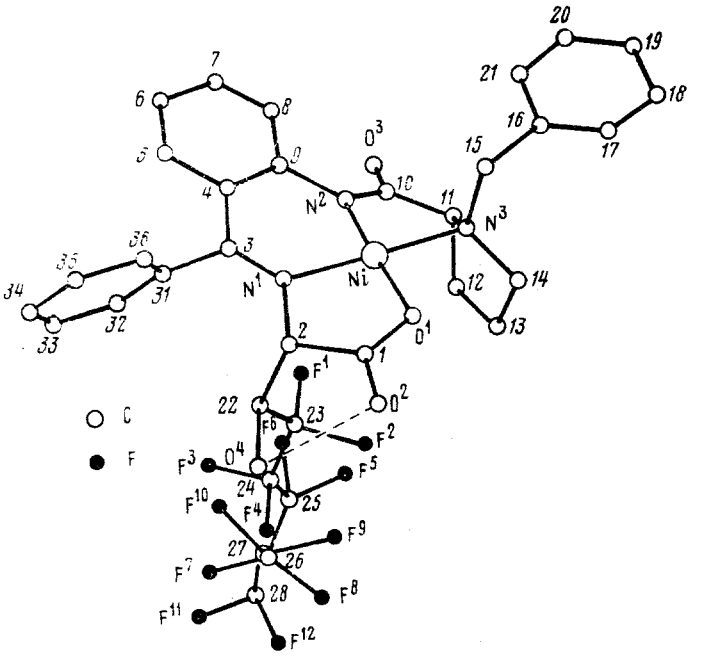


Fig. 2. Structure of molecule (III), R = $H(CF_2)_6$ (H atoms are not shown); bond lengths, Å: Ni–O^1 1.89(1), Ni–N^1 1.88(2), Ni–N^2 1.79(2), Ni–N^3 1.97(1).

disappeared (2-5 min), the reaction mixture was evaporated to a volume of 5 ml, and the resultant S-BBP hydrochloride precipitate was filtered off. The yield of the reagent ranged from 80 to 90% in different experiments. Amino acids were isolated from aqueous solution on Dowex-50 (H^+ form) resin.

(2S, 3S)-4,4,4-Trifluorothreonine (VI) (R_F = CF_3). Yield 87%; decomp. temp., 220-222°C; (from H_2O); $[\alpha]_D^{26}$ −10.7° (c 1.5 H_2O), +1.77° (c 2.0 6 N HCl). Found, %: C 27.84; H 3.58; F 32.81. $C_4H_6F_3NO_3$. Calculated, %: C 27.76; H 3.49; F 32.93.

(2S, 3S)-3-Nonafluorobutylserine (VI) (R_F = C_4F_9). Yield, 83%; decomp. temp., 145-148°C (from H_2O); $[\alpha]_D^{25}$ −7.9° (c 1.3 H_2O), +5.21° (c 2.0 6 N HCl). Found, %: C 26.22; H 1.84; F 52.94. $C_7H_6F_9NO_3$. Calculated, %: C 26.02; H 1.87; F 52.92.

X-Ray Diffraction Studies of (III) (R_F = $H(CF_2)_6$). The experiment was carried out on a Hilger–Watts automatic, four-disk diffractometer at 20°C (MoK_α illumination, graphite monochromator, $\theta/2\theta$-scanning, $2\theta \leq 54°$, 2224 independent reflections with $I \geq 2\sigma$). Calculations were carried out on an Eclipse S/200 computer using an INEXTL program [12]. Rhombic crystals (from acetonitrile) a = 11.115(1), b = 16.475(1), c = 18.901(2) Å, V = 3461.2(5) $Å^3$, lattice group $P2_12_12_1$, Z = 4. The structure was interpreted using the heavy atom method; the absolute configuration was established according to the known (S)-configuration of the proline center. All nonhydrogen atoms were refined by the least squares method in anisotropic approximation with regard to contributions of hydrogen atoms fixed in calculated positions. The strong randomization of the perfluoroalkyl chain (usual for similar compounds in a crystal) renders impossible the reliable localization of the last three CF_2 groups and ensures the fairly high value of R = 0.14. Atomic coordinates are shown in Table 3.

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SIMPLE SYNTHESIS OF ACETOGENIN TRANSOID INSECT PHEROMONES STARTING FROM ACETYLCYCLOPROPANE

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A highly effective synthesis of a series of alkyl and 1-alkenyl cyclopropyl ketones, which are key components in the complete synthesis of a large number of transoid lepidoptera pheromones, has been developed, based on the alkylation of N-cyclohexyl-1-cyclopropylethylideneimine or its condensation with aldehydes.

We have recently proposed that the preparation of alkyl and vinyl cyclopropyl ketones, which are widely used in organic synthesis, can be achieved using acetylcyclopropane (ACP) in the form of its trimethylsilyloxyvinyl derivative, which reacts readily with carbonyl compounds in the presence of a catalytic amount of $ZnCl_2$ [1]. As part of our continuing studies, in the present paper we report the alkylation and aldol condensation reactions of ACP cyclohexylimine (I); these reactions open up a new and direct pathway for the preparation of alkyl and 1-alkenyl cyclopropyl ketones, which are of interest as intermediate products in the total synthesis of a series of acetogenic transoid insect pheromones.

Imine (I) can be deprotonated under mild conditions by treatment with butyllithium [2], and then reacts readily with alkyl halides to generate intermediate ketimines (II) (Scheme 1). Standard procedures for hydrolytic removal or cleavage of these derivatives, such as catalysis by protic or Lewis acids [3], proved ineffective and unsuitable in this case, due to the prolonged reaction times required (≥24 h) and the moderate yields (≤50%) of products (IV). In contrast, it was found that the products (IV) could be generated rapidly (≤15 min) and in high yields by storing the unpurified imines (II) in a "dry state" over a 3-4-fold excess (by weight) of SiO_2 (cf. [4]).

In an analogous manner, reaction of the imine starting material (I) with lithium diisopropylamide, followed by treatment of the resulting Li-derivative with aldehydes, gives intermediate ketimines (III); subsequent hydrolytic cleavage of these intermediates (without additional purification) on SiO_2 in the "dry state" readily generates β-ketols V (Scheme 1). Dehydration of the latter in refluxing benzene in the presence of a catalytic amount of p-toluenesulfonic acid leads to the desired conjugated ketone products (VI) in high overall yields.

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