Synthesis of 1-Substituted 1,2,3,4-Tetrahydroisoquinolines from Enamino Ketones

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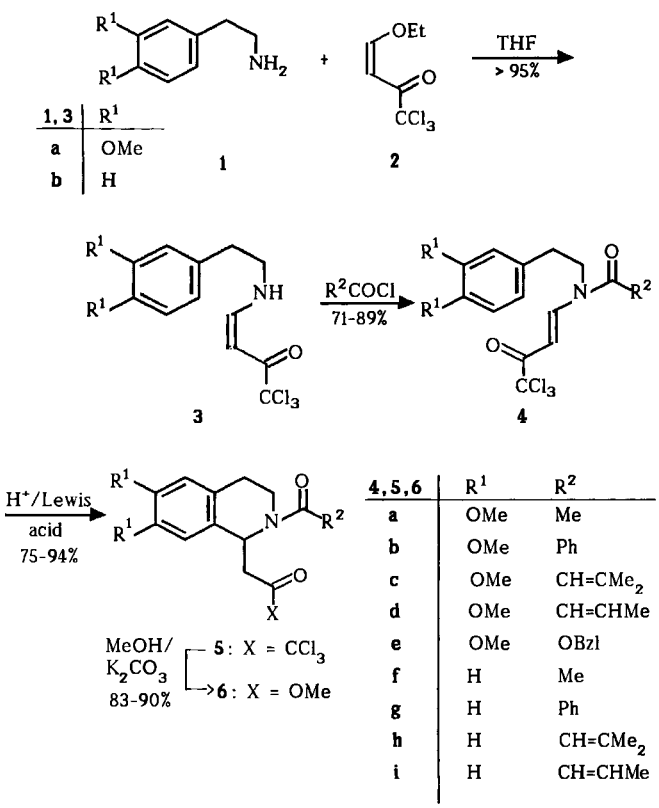
The reaction of the *N*-acylated enamino ketones **4a–d** with trifluoroacetic acid, TMS triflate, or Lewis acids leads to the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **5a–d** in 84 to 94% yield. The enamino ketones **4f–i** can only be cyclized with trifluoromethanesulfonic acid to the 1,2,3,4-tetrahydroisoquinolines **5f–i** in 75–84% yield. For the synthesis of **5e** from the enamino ketone **4e** carrying the benzyloxycarbonyl group TMS triflate is the best mediator (93%). The trichloromethylcarbonyl group in **5** can easily be transformed into a methoxycarbonyl group by treatment with K_2CO_3 in methanol to give **6** in 83–90% yield.

The 1-substituted 1,2,3,4-tetrahydroisoquinoline moiety is found in many alkaloids as the main structural element[1]. Its synthesis is usually accomplished by a Bischler-Napieralski reaction[2] using amides of 2-phenylethylamines. The Pictet-Spengler reaction[3] which is an excellent method for the synthesis of 1,2,3,4-tetrahydro-β-carbolines is much less effective due to the lower reactivity of the intermediately formed imine.

In this paper, however, we demonstrate that *N*-acylated enamino ketones[4] of 2-(3,4-dimethoxyphenyl)ethylamines, which are activated by a trichloromethyl group at the carbonyl moiety, can easily be cyclized under mild conditions by using trifluoroacetic acid, trimethylsilyl trifluoromethanesulfonate (TMS triflate), or Lewis acids[5] such as $SnCl_4$ or $TiCl_4$ to give 1-substituted 1,2,3,4-tetrahydroisoquinolines. In contrast, *N*-acylenamino ketones of the unsubstituted 2-phenylethylamine do not cyclize under these conditions; in order to achieve the cyclization of these compounds trifluoromethanesulfonic acid must be used.



The condensation of homoveratrylamine (**1a**) and 2-phenylethylamine (**1b**) with 1,1,1-trichloro-4-ethoxy-3-buten-2-one (**2**), which can be obtained from trichloroacetic acid chloride and ethyl vinyl ether according to Effenberger[6], at room temperature for 24 h in tetrahydrofuran gives the enamino ketones **3a** and **3b** in nearly quantitative yield. All attempts, however, to cyclize these compounds by using Brönsted acids like trifluoroacetic acid or trifluoromethanesulfonic acid, Lewis acids such as $SnCl_4$ or $TiCl_4$, as well as TMS triflate have failed. These results have not been unexpected, since enamino ketones of type **3** can be conceived as vinylogous amides, which have a low reactivity. Therefore, we have transformed **3** into the vinylogous imides **4** by acylation at the nitrogen atom in 71–89% yield by using acid chlorides in dichloromethane in the presence of pyridine as well as benzyloxycarbonyl chloride in tetrahydrofuran in the presence of sodium hydride.

The cyclization of these compounds can easily be accomplished in excellent yields with Brönsted or Lewis acids at room temperature in dichloromethane as solvent. For the transformation of the enamino ketones **4a–4d** derived from homoveratrylamine (**1a**) trifluoracetic acid is sufficient as mediator. However, for the less reactive compounds **4f–i** derived from 2-phenylethylamine (**1b**) trifluoromethanesulfonic acid must be employed. The more reactive enamino ketones **4a–4d** can also be cyclized by the use of Lewis acids such as $SnCl_4$ or $TiCl_4$ as well as TMSOTf. Thus, the enamino ketone **4e** is transformed into the 1,2,3,4-tetrahy-

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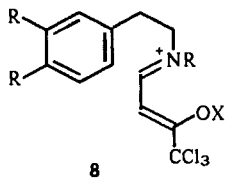
droisoquinoline **5e** with TMSOTf in dichloromethane at 0°C in excellent yield (93%). In this special case Brönsted and Lewis acids are less appropriate because of the sensitivity of the benzyloxycarbonyl group.

Table 1. Synthesis of 1,2,3,4-tetrahydroisoquinolines **5** and **6**

Substrate	Product	Mediator (°C)/[t]	Yield (%)
4a	**5a**	TFA (20)/[24h]	89
4a	**5a**	$SnCl_4$ (20)/[24h]	87
4a	**5a**	$TiCl_4$ (20)/[24h]	85
4a	**5a**	TMSOTf (20)/[12h]	94
4b	**5b**	TFA (20)/[24h]	86
4c	**5c**	TFA (20)/[24h]	84
4d	**5d**	TFA (20)/[24h]	81
4e	**5e**	TMSOTf (0)/[1h]	93
4f	**5f**	TFMSA (20)/[4h]	81
4g	**5g**	TFMSA (20)/[4h]	78
4h	**5h**	TFMSA (20)/[4h]	77
4i	**5i**	TFMSA (20)/[4h]	75
5a	**6a**	K_2CO_3,MeOH (20)/[24h]	89
5e	**6e**	K_2CO_3,MeOH (20)/[24h]	90
5f	**6f**	K_2CO_3,MeOH (20)/[24h]	83

We assume that in the reaction of **4** an iminium ion **8** is formed as an intermediate. However, an electrophilic aromatic substitution of the α,β-unsaturated carbonyl group would also explain the results.



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The trichloromethylcarbonyl moiety in **5** can easily be transformed into an ester moiety by using potassium carbonate in the presence of an alcohol. Thus, stirring of **5a**, **5e**, or **5f** in methanol with potassium carbonate for 24 h at room temperature gives the 1,2,3,4-tetrahydroisoquinolines **6a**, **6e**, or **6f**, respectively, in excellent yield (83–90%). The compounds are used for the biomimetic synthesis of ipecacuanha alkaloids[7].

The structure of the new compounds has been determined mainly by ^{1}H- and ^{13}C-NMR spectroscopy. The double bond in **3** has a (*Z*) configuration, because the signals of 3-H and 4-H appear at δ = 5.60–5.63 and δ = 6.92–6.97, respectively with a coupling constant of *J* = 8.0 Hz. The double bond in **4** is (*E*)-configurated, since a large coupling constant of *J* = 13.0–14.0 Hz is found for the signals of the two vicinal hydrogens atoms at δ = 6.15–6.23 (3-H) and 8.13–8.47 (4-H).

The ^{1}H- and ^{13}C-NMR spectra of the 1,2,3,4-tetrahydroisoquinolines **5** and **6** show a double set of signals because the compounds exist at room temperature in two rotameric forms. Thus, the signals of 1-H of **5** and **6** appear at δ = 5.42–5.76 and 5.99–6.18, respectively.

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Experimental

^{1}H NMR and ^{13}C NMR: Varian XL-200, VXR-200, and FT-80 A; multiplicities were determined with the APT pulse sequence. – IR: Bruker IFS 25. – UV: Varian Cary 219. – Melting points: Kofler hot stage or Mettler FP 61. – Elemental analyses were carried out in the analytical laboratory of the university. – All solvents were distilled prior to use. Reagents and materials were obtained from commercial suppliers and were used without further purification. All reactions were carried out under N_2 and monitored by TLC (Macherey-Nagel, Polygram SIL G/UV_{254}). Products were isolated by column chromatography on silica gel (ICN Silica 63–200, 60 A, ICN Biomedicals). All chiral compounds are obtained as racemic mixtures.

Synthesis of Enamino Ketones **3a–b**. – *1,1,1-Trichloro-4-[2-(3,4-dimethoxyphenyl)ethylamino]-3-buten-2-one* (**3a**): To a stirred solution of **1a** (8.37 g, 46.2 mmol) in anhydrous tetrahydrofuran (100 ml) was added **2** (10.0 g, 46.2 mmol) at room temp., and the mixture was stirred for 24 h. After evaporation of the solvent in vacuo, the residue was purified by column chromatography (ethyl acetate) and recrystallized to give **3a** (15.8 g, 97%). – R_f = 0.37. – M.p. 104°C (ethanol). – UV (CH_3CN): λ_{max} (lg ε) = 202 nm (4.599), 231 (3.946), 288 (3.179), 328 (4.209). – IR (KBr): $\tilde{\nu}$ = 3324 cm^{-1} (NH); 2938, 2836 (CH); 1644 (C=O); 1586 (C=C). – ^{1}H NMR ($CDCl_3$): δ = 2.84 (t, *J* = 7.0 Hz, 2H, 2′-H), 3.54 (q, *J* = 7.0 Hz, 2H, 1′-H), 3.86 (s, 6H, OCH_3), 5.60 (d, *J* = 8.0 Hz, 1H, 3-H), 6.67 (d, *J* = 3.0 Hz, 1H, 2″-H), 6.72 (dd, *J* = 8.0, 3.0 Hz, 1H, 6″-H), 6.84 (d, *J* = 8.0 Hz, 1H, 5″-H), 6.92 (dd, *J* = 12.0, 8.0 Hz, 1H, 4-H), 9.81 (br., 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 36.88 (C-2″); 51.46 (C-1′); 55.83, 55.87 (OCH_3); 84.47 (C-3); 96.76 (C-1); 111.5, 112.2 (C-2″, C-5″); 120.7 (C-6″); 129.9 (C-1″); 147.9, 149.0 (C-3″, C-4″); 157.7 (C-4); 182.0 (C-2).

$C_{14}H_{16}Cl_3NO_3$ (352.6) Calcd. C 47.69 H 4.57
Found C 47.82 H 4.83

1,1,1-Trichloro-4-(2-phenylethylamino)-3-buten-2-one (**3b**): To a stirred solution of **1b** (5.00 g, 41.3 mmol) in anhydrous tetrahydrofuran (70 ml) was added **2** (8.94 g, 41.3 mmol) at room temp., and the mixture was stirred for 24 h. After evaporation of the solvent in vacuo, the residue was purified by column chromatography (ethyl acetate) and recrystallized to give **3b** (11.8 g, 98%). – R_f = 0.63. – M.p. 48°C (ethyl acetate). – UV (CH_3CN): λ_{max} (lg ε) = 327 nm (4.262). – IR (KBr): $\tilde{\nu}$ = 3292 cm^{-1} (NH), 1644 (C=O), 1586 (C=C). – ^{1}H NMR ($CDCl_3$): δ = 2.92 (t, *J* = 7.0 Hz, 2H, 2′-H), 3.58 (q, *J* = 7.0 Hz, 2H, 1′-H), 5.63 (d, *J* = 8.0 Hz, 1H, 3-H), 6.97 (dd, *J* = 12.0, 8.0 Hz, 1H, 4-H), 7.14–7.44 (m, 5H, Ph-H), 9.80 (br., 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 37.25 (C-2′); 51.10 (C-1′); 84.52 (C-3); 96.75 (C-1); 126.9, 128.7 (CH-Ph); 137.3 (C-*i*); 157.5 (C-4); 181.9 (C-2).

$C_{12}H_{12}Cl_3NO$ (292.6) Calcd. C 49.26 H 4.13
Found C 49.35 H 4.16

Acylation of Enamino Ketones **3a–b**. – *General Procedure I:* To a stirred solution of enamino ketone **3** (1 equiv.) and pyridine (1.2 equiv.) in anhydrous dichloromethane (50 ml) was added dropwise at 0°C the acyl chloride (1.2 equiv.) dissolved in anhydrous dichloromethane (20 ml), and stirring was continued at room temp. for 12 h. Afterwards the mixture was washed with 1 N HCl (1 × 30 ml),

saturated aqueous $NaHCO_3$ solution (1 × 30 ml), and brine (1 × 30 ml). After drying (Na_2SO_4), the solvent was removed in vacuo and the crude product purified by cristallization.

4-[N-Acetyl-2-(3,4-dimethoxyphenyl)ethylamino]-1,1,1-trichloro-3-buten-2-one (**4a**): Acylation of **3a** (3.00 g, 8.50 mmol) with acetyl chloride (0.80 g, 10.2 mmol) and pyridine (0.81 g, 10.2 mmol) according to general procedure I yielded **4a** (2.95 g, 88%). – M.p. 107°C (ethyl acetate/hexane). – UV (CH_3CN): λ_{max} (lg ε) = 202 nm (4.657), 231 (4.016), 311 (4.263). – IR (KBr): $\tilde{\nu}$ = 2936 cm^{-1}, 2918, 2840 (CH); 1696, 1654 (C=O); 1582 (C=C). – ^1H NMR ($CDCl_3$): δ = 2.38 (s, 3H, $COCH_3$), 2.84 (t, *J* = 7.0 Hz, 2H, 2′-H), 3.86, 3.89 (2 s, 6H, OCH_3), 3.94 (t, *J* = 7.0 Hz, 2H, 1′-H), 6.18 (d, *J* = 14.0 Hz, 1H, 3-H), 6.69–6.86 (m, 3H, 2″-H, 5″-H, 6″-H), 8.29 (d, *J* = 14.0 Hz, 1H, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 21.89 ($COCH_3$); 32.53 (C-2′); 45.48 (C-1′); 55.85 (OCH_3); 96.70 (C-1); 96.99 (C-3); 111.4, 111.7 (C-2″, C-5″); 120.7 (C-6″); 130.0 (C-1″); 146.4 (C-4); 148.0, 149.1 (C-3″, C-4″); 170.2 (NCO); 180.5 (C-2).

$C_{16}H_{18}Cl_3NO_4$ (394.7) Calcd. C 48.65 H 4.60
Found C 48.45 H 4.60

4-[N-Benzoyl-2-(3,4-dimethoxyphenyl)ethylamino]-1,1,1-trichloro-3-buten-2-one (**4b**): Acylation of **3a** (3.00 g, 8.50 mmol) with benzoyl chloride (1.43 g, 10.2 mmol) and pyridine (0.81 g, 10.2 mmol) according to general procedure I yielded **4b** (2.95 g, 76%). – M.p. 93°C (ethanol/hexane). – UV (CH_3CN): λ_{max} (lg ε) = 200 nm (4.644), 227 (4.179), 312 (4.311). – IR (KBr): $\tilde{\nu}$ = 1704 cm^{-1}, 1686 (C=O); 1588 (C=C). – ^1H NMR ($CDCl_3$): δ = 2.98 (t, *J* = 7.0 Hz, 2H, 2′-H), 3.86, 3.87 (2 s, 6H, OCH_3), 4.11 (t, *J* = 7.0 Hz, 2H, 1′-H), 6.20 (d, *J* = 14.0 Hz, 1H, 3-H), 6.74–6.85 (m, 3H, 2″-H, 5″-H, 6″-H), 7.38–7.59 (m, 5H, Ph-H), 8.18 (d, *J* = 14.0 Hz, 1H, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 32.55 (C-2′); 46.19 (C-1′); 55.83, 55.88 (OCH_3); 96.71 (C-1); 96.83 (C-3); 111.4, 111.8 (C-2″, C-5″); 120.8 (C-6″); 128.5, 128.9 (CH-Ph); 130.0 (C-1″); 132.0 (CH-Ph); 132.7 (C-*i*); 148.5 (C-4); 148.1, 149.2 (C-3″, C-4″); 171.5 (NCO); 180.3 (C-2).

$C_{21}H_{20}Cl_3NO_4$ (456.8) Calcd. C 55.22 H 4.41
Found C 55.33 H 4.45

1,1,1-Trichloro-4-[2-(3,4-dimethoxyphenyl)-N-(3,3-dimethylacryloyl)-ethylamino]-3-buten-2-one (**4c**): Acylation of **3a** (3.00 g, 8.50 mmol) with 3,3-dimethylacryloyl chloride (1.21 g, 10.2 mmol) and pyridine (0.81 g, 10.2 mmol) according to general procedure I yielded **4c** (2.81 g, 76%). – M.p. 101°C (ethanol/hexane). – UV (CH_3CN): λ_{max} (lg ε) = 202 nm (4.693), 232 (4.164), 322 (4.318). – IR (KBr): $\tilde{\nu}$ = 1692 cm^{-1}, 1680, 1666 (C=O); 1568 (C=C). – ^1H NMR ($CDCl_3$): δ = 1.97, 2.00 (2 d, *J* = 2.0 Hz, 6H, CH_3); 2.85 (t, *J* = 7.0 Hz, 2H, 2′-H); 3.85, 3.88 (2 s, 6H, OCH_3); 3.94 (t, *J* = 7.0 Hz, 2H, 1′-H); 5.98 (m_c, 1H, NCOCH); 6.15 (d, *J* = 14.0 Hz, 1H, 3-H); 6.65–6.86 (m, 3H, 2″-H, 5″-H, 6″-H); 8.39 (d, *J* = 14.0 Hz, 1H, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 20.92, 27.18 (CH_3); 32.70 (C-2′); 45.48 (C-1′); 55.85 (OCH_3); 96.18 (C-4); 96.89 (C-1); 111.4, 111.8 (C-2″, C-5″); 115.0 (CH); 120.8 (C-6″); 130.2 (C-1″); 147.2 (C-4); 148.0, 149.2 (C-3″, C-4″); 156.3 (C_q); 167.2 (NCO); 180.7 (C-2).

$C_{19}H_{22}Cl_3NO_4$ (434.7) Calcd. C 52.49 H 5.10
Found C 52.35 H 5.11

1,1,1-Trichloro-4-[2-(3,4-dimethoxyphenyl)-N-(3-methylacryloyl)-ethylamino]-3-buten-2-one (**4d**): Acylation of **3a** (3.00 g, 8.50 mmol) with 3-methylacryloyl chloride (1.08 g, 10.2 mmol) and pyridine (0.81 g, 10.2 mmol) according to general procedure I yielded **4d** (2.83 g, 79%). – M.p. 87°C (ethanol/hexane). – UV (CH_3CN): λ_{max} (lg ε) = 202 nm (4.694), 232 (4.195), 320 (4.334). – IR (KBr): $\tilde{\nu}$ = 1698 cm^{-1}, 1684, 1636 (C=O); 1586 (C=C). – ^1H NMR ($CDCl_3$): δ = 1.99 (dd, *J* = 6.0, 2.0 Hz, 3H, CH_3); 2.86 (t, *J* = 7.0 Hz, 2H, 2′-H); 3.88, 3.93 (2 s, 6H, OCH_3); 3.97 (t, *J* = 7.0 Hz, 2H, 1′-H); 6.21 (d, *J* = 14.0 Hz, 1H, 3-H); 6.45 (dq, *J* = 14.0, 2.0 Hz, 1H, NCOCH); 6.74–6.91 (m, 3H, 2″-H, 5″-H, 6″-H); 7.21 (dq, *J* = 14.0, 6.0 Hz, 1H, $CHCH_3$); 8.47 (d, *J* = 14.0 Hz, 1H, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 18.74 (CH_3); 32.76 (C-2′); 46.04 (C-1′); 55.85 (OCH_3); 96.83 (C-1, C-3); 111.4, 111.8 (C-2″, C-5″); 119.8 (NCOCH); 120.7 (C-6″); 130.1 (C-1″); 146.4 (C-4); 147.8 (C=CHCH$_3$); 148.0, 149.2 (C-3″); 166.2 (NCO); 180.6 (C-2).

$C_{18}H_{20}Cl_3NO_4$ (420.7) Calcd. C 51.39 H 4.79
Found C 51.50 H 4.86

1,1,1-Trichloro-4-[N-(benzyloxycarbonyl)-2-(3,4-dimethoxyphenyl)ethylamino]-3-buten-2-one (**4e**): To a stirred suspension of NaH (288 mg, 6.24 mmol; twice washed with hexane) in anhydrous tetrahydrofuran (30 ml) was added **3a** (2.00 g, 5.67 mmol) in tetrahydrofuran (10 ml) at 0°C over a period of 5 min. After stirring for 5 min, a solution of benzyloxycarbonyl chloride (1.00 g, 5.67 mmol) in tetrahydrofuran (10 ml) was added dropwise to the mixture, and stirring was continued for 15 min at 0°C and for 1 h at room temp. After hydrolysis with water, the mixture was extracted with diethyl ether (70 ml), and the organic layer was washed with water (1 × 40 ml) and brine (1 × 30 ml), dried with Na_2SO_4, and the solvent was evaporated in vacuo. The residue was purified by crystallization (diethyl ether) to yield **4e** (2.26 g, 82%). – M.p. 83°C (diethyl ether). – UV (CH_3CN): λ_{max} (lg ε) = 202 nm (4.746), 230 (3.985), 303 (4.298). – IR (KBr): $\tilde{\nu}$ = 1714 cm^{-1} (C=O); 1604, 1590 (C=C). – ^1H NMR ($CDCl_3$): δ = 2.84 (t, *J* = 7.5 Hz, 2H, 2′-H); 3.81, 3.84 (2 s, 6H, CH_3); 3.88 (t, *J* = 7.5 Hz, 2H, 1′-H); 5.25 (s, 2H, OCH_2); 6.11 (d, *J* = 14.0 Hz, 1H, 3-H); 6.64–6.80 (m, 3H, Ph-H); 7.38 (s, 5H, Ph-H); 8.52 (d, *J* = 14.0 Hz, 1H, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 32.84 (C-2′); 47.04 (C-1′); 55.75, 55.83 (CH_3); 69.50 (OCH_2); 96.63 (C-3); 96.85 (C-1); 111.4, 111.7 (C-2″, C-5″); 120.7 (C-6″); 128.4, 128.7, 128.8 (CH-Ph); 129.9 (C-1″); 134.6 (C-*i*); 146.8 (C-4); 147.9, 149.1 (C-3″, C-4″); 152.8 (C=O); 180.2 (C-2).

$C_{22}H_{22}Cl_3NO_5$ (486.8) Calcd. C 54.28 H 4.56
Found C 54.37 H 4.54

4-(N-Acetyl-2-phenylethylamino)-1,1,1-trichloro-3-buten-2-one (**4f**): Acylation of **3b** (3.00 g, 10.3 mmol) with acetyl chloride (0.97 g, 12.4 mmol) and pyridine (0.98 g, 12.4 mmol) according to general procedure I yielded **4f** (2.93 g, 85%). – M.p. 88°C (ethanol/hexane). – IR (KBr): $\tilde{\nu}$ = 1700 cm^{-1} (C=O); 1626 (C=O); 1584 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 192 nm (4.624), 310 (4.335). – ^1H NMR ($CDCl_3$): δ = 2.36 (s, 3H, $COCH_3$), 2.88 (t, *J* = 7.0 Hz, 2H, 2′-H), 3.84 (t, *J* = 7.0 Hz, 2H, 1′-H), 6.22 (d, *J* = 13.0 Hz, 1H, 3-H), 7.16–7.41 (m, 5H, Ph-H), 8.30 (d, *J* = 13.0 Hz, 1H, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 21.75 (CH_3); 32.83 (C-2′); 45.17 (C-1′); 96.72 (C-1); 96.87 (C-3); 126.9, 128.6, 128.8 (CH-Ph); 137.5 (C-*i*); 146.5 (C-4); 170.1 (NCO); 180.4 (C-2).

$C_{14}H_{14}Cl_3NO_2$ (333.6) Calcd. C 50.25 H 4.22
Found C 50.42 H 4.23

4-(N-Benzoyl-2-phenylethylamino)-1,1,1-trichloro-3-buten-2-one (**4g**): Acylation of **3b** (3.00 g, 10.3 mmol) with benzoyl chloride (1.75 g, 12.4 mmol) and pyridine (0.98 g, 12.4 mmol) according to general procedure I yielded **4g** (3.02 g, 74%). – M.p. 87°C (ethanol/hexane). – IR (KBr): $\tilde{\nu}$ = 1694 cm^{-1} (C=O), 1642 (C=O), 1578 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 310 nm (4.291). – ^1H NMR ($CDCl_3$): δ = 3.02 (t, *J* = 7.0 Hz, 2H, 2′-H), 4.12 (t, *J* = 7.0 Hz, 2H, 1′-H), 6.17 (d, *J* = 13.0 Hz, 1H, 3-H), 7.05–7.75 (m, 10H, Ph-H), 8.13 (d, *J* = 13.0 Hz, 1H, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 32.80 (C-2′); 45.76 (C-1′); 96.70 (C-1, C-3); 126.9, 128.4, 128.8, 130.5, 131.8 (CH-Ph); 132.6, 137.4 (C-*i*); 148.4 (C-4); 171.3 (NCO); 180.2 (C-2).

$C_{19}H_{16}Cl_3NO_2$ (396.9) Calcd. C 57.50 H 4.06
Found C 50.64 H 4.14

1,1,1-Trichloro-4-[N-(3,3-dimethylacryloyl)-2-phenylethylamino]-3-buten-2-one (**4h**): Acylation of **3b** (3.00 g, 10.3 mmol) with 3,3-dimethylacryloyl chloride (1.46 g, 12.3 mmol) and pyridine (0.97 g, 12.3 mmol) according to general procedure I yielded **4h** (2.93 g, 76%). – M.p. 86°C (ethanol/hexane). – IR (KBr): $\tilde{\nu}$ = 1698 cm^{-1}, 1674 (C=O); 1634 (C=O); 1574 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 318 nm (4.352). – ^1H NMR ($CDCl_3$): δ = 1.96, 1.99 (2 d, *J* = 1.5 Hz, 6H, CH_3); 2.91 (t, *J* = 7.0 Hz, 2H, 2′-H); 3.95 (t, *J* = 7.0 Hz, 2H, 1′-H); 5.99 (m_c, 1H, NCOCH); 6.16 (d, *J* = 13.0 Hz, 1H, 3-H); 7.16–7.44 (m, 5H, Ph-H); 8.43 (d, *J* = 13.0 Hz, 1H, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 20.87, 27.80 (CH_3); 32.01 (C-2′); 45.21 (C-1′); 96.10 (C-3); 96.89 (C-1); 115.0 (NCO*C*H); 126.9, 128.7 (CH-Ph); 137.6 (C-*i*); 147.4 (C-4); 156.2 (CH=C_q); 167.0 (NCO); 180.6 (C-2).

$C_{17}H_{18}Cl_3NO_2$ (374.7) Calcd. C 54.49 H 4.84
Found C 54.41 H 4.73

1,1,1-Trichloro-4-[N-(3-methylacryloyl)-2-phenylethylamino]-3-buten-2-one (**4i**): Acylation of **3b** (3.00 g, 10.3 mmol) with 3-methylacryloyl chloride (1.29 g, 12.3 mmol) and pyridine (0.97 g, 12.3 mmol) according to general procedure I yielded **4i** (2.64 g, 71%). – M.p. 84°C (ethanol/hexane). – IR (KBr): $\tilde{\nu}$ = 1700 cm^{-1}, 1678 (C=O); 1636 (C=O); 1578 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 319 nm (4.306). – ^1H NMR ($CDCl_3$): δ = 1.99 (dd, *J* = 7.0, 1.5 Hz, 3H, CH_3), 2.92 (t, *J* = 7.0 Hz, 2H, 2′-H), 3.98 (t, *J* = 7.0 Hz, 2H, 1′-H), 6.23 (d, *J* = 13.0 Hz, 1H, 3-H), 6.44 (dq, *J* = 14.0, 1.5 Hz, 1H, NCOCH), 7.12 (dq, *J* = 14.0, 7.0 Hz, 1H, C=C*H*CH_3), 7.18–7.37 (m, 5H, Ph-H), 8.34 (d, *J* = 13.0 Hz, 1H, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 18.66 (CH_3); 33.10 (C-2′); 45.77 (C-1′); 96.77 (C-3, C-1); 119.9 (NCO*C*H); 126.9, 128.7, 128.8 (CH-Ph); 137.6 (C-*i*); 146.3 (C=*C*HCH_3); 147.7 (C-4); 166.1 (NCO); 180.6 (C-2).

$C_{16}H_{16}Cl_3NO_2$ (360.7) Calcd. C 53.28 H 4.47
Found C 53.06 H 4.31

Cyclization of N-Acylated Enamino Ketones **4a–d** *with Trifluoroacetic Acid. – General Procedure II:* To a stirred solution of the enamino ketones **4a–d** (3.00 g) in anhydrous dichloromethane (50 ml) trifluoroacetic acid (3 ml, 40.5 mmol) was added dropwise over a period of 5 min. The mixture was stirred at room temp. for 24 h, washed with water (25 ml) and brine (40 ml), and dried (Na_2SO_4). The solvent was removed in vacuo and the residue purified by column chromatography (ethyl acetate) or crystallization.

(1RS)-2-Acetyl-6,7-dimethoxy-1-(3,3,3-trichloro-2-oxopropyl)-1,2,3,4-tetrahydroisoquinoline (**5a**). – a) Reaction of **4a** (7.60 mmol) according to general procedure II; yield after crystallization (ethyl acetate/hexane) 2.67 g (89%) of **5a**.

b) Reaction of **4a** (1.00 g, 2.53 mmol) with TMS triflate (0.55 ml, 3.04 mmol) at room temp. for 12 h in anhydrous dichloromethane (30 ml) and further workup according to general procedure II; yield after crystallization 0.94 g (94%) of **5a**.

c) Reaction of **4a** (1.00 g, 2.53 mmol) in anhydrous dichloromethane (30 ml) at room temp. for 24 h with (i) $SnCl_4$ (0.79 g, 3.04 mmol) or (ii) $TiCl_4$ (0.57 g, 3.04 mmol) followed by quenching with a saturated $NaHCO_3$ solution, extraction with chloroform (2 × 30 ml) and further workup according to general procedure II; yield (i) 0.87 g (87%) or (ii) 0.85 g (95%) of **5a**. – R_f = 0.63. – M.p. 134°C (ethyl acetate/hexane). – UV (CH_3CN): λ_{max} (lg ε) = 205 nm (4.625), 287 (3.581). – IR (KBr): $\tilde{\nu}$ = 2954 cm^{-1}, 2932, 2836 (CH); 1740, 1640 (C=O); 1612 (C=C). – ^1H NMR ($CDCl_3$): δ = 2.18 (s, 1.8H, CH_3); 2.27 (s, 1.2H, CH_3); 2.81–3.19 (m, 2.4H, CH_2); 3.23–3.42 (m, 1.6H, CH_2); 3.65–3.82 (m, 1.6H, CH_2); 3.85 (2 s, 6H, OCH_3); 4.62–4.75 (m, 0.4H, CH_2); 5.48 (dd, *J* = 8.5, 4.5 Hz, 0.4H, 1-H); 6.03 (t, *J* = 6.5 Hz, 0.6H, 1-H); 6.57, 6.63 (2 s, 1H, 5-H); 6.62, 6.68 (2 s, 1H, 8-H). – ^{13}C NMR ($CDCl_3$): δ = 21.55, 21.97 (CH_3); 27.16, 28.44 (C-4); 35.68, 41.89 (C-3); 40.75, 41.82 (C-1′); 50.02, 53.58 (C-1); 55.89, 56.02 (OCH_3); 96.08, 96.37 (C-3′); 108.9, 110.1 (C-5); 111.1, 111.8 (C-8); 125.8, 126.6 (C-4a); 126.7, 127.3 (C-8a); 147.8, 147.9 (C-6); 148.3, 148.6 (C-7); 169.9, 170.0 (NCO); 186.8, 187.7 (C-2′).

$C_{16}H_{18}Cl_3NO_4$ (394.7) Calcd. C 48.65 H 4.60
Found C 48.44 H 4.67

(1RS)-2-Benzoyl-6,7-dimethoxy-1-(3,3,3-trichloro-2-oxopropyl)-1,2,3,4-tetrahydroisoquinoline (**5b**): Reaction of **4b** (6.57 mmol) according to general procedure II; yield after crystallization 2.58 g (86%) of **5b**. – R_f = 0.81. – M.p. 144°C (ethanol). – UV (CH_3CN): λ_{max} (lg ε) = 203 nm (4.766), 286 (3.629). – IR (KBr): $\tilde{\nu}$ = 2998 cm^{-1}, 2936, 2912 (CH); 1756, 1634 (C=O); 1578 (C=C). – ^1H NMR ($CDCl_3$): δ = 2.61–3.02 (m, 2H, CH_2), 3.37–3.92 (m, 4H, CH_2), 3.87 (s, 6H, OCH_3), 6.18 (t, *J* = 6.0 Hz, 1H, 1-H), 6.61 (s, 1H, 5-H), 6.73 (s, 1H, 8-H), 7.43 (s, 5H, Ph-H). – ^{13}C NMR ([D_6]DMSO): δ = 28.07 (C-4); 40.16 (C-3); 41.11 (C-1′); 49.07 (C-1); 55.50, 55.62 (OCH_3); 96.11 (C-3′); 110.3 (C-5); 112.1 (C-8); 125.7 (C-4a); 126.5, 128.4, 129.5 (CH-Ph); 126.9 (C-8a); 136.0 (C-*i*); 147.6 (C-6); 148.1 (C-7); 170.0 (NCO); 187.1 (C-2′).

$C_{21}H_{20}Cl_3NO_4$ (456.8) Calcd. C 55.22 H 4.41
Found C 55.35 H 4.50

(1RS)-2-(3,3-Dimethylacryloyl)-6,7-dimethoxy-1-(3,3,3-trichloro-2-oxopropyl)-1,2,3,4-tetrahydroisoquinoline (**5c**): Reaction of **4c** (6.90 mmol) according to general procedure II; yield after column chromatography 2.52 g (84%) of **5c** as a yellow oil. – R_f = 0.78. – UV (CH_3CN): λ_{max} (lg ε) = 204 nm (4.634), 284 (3.707). – IR (film): $\tilde{\nu}$ = 2938 cm^{-1}, 2914, 2838, (CH); 1752, 1624 (C=O). – ^1H NMR ($CDCl_3$): δ = 1.83, 1.87 (2 d, *J* = 1.0 Hz, 3H, CH_3); 1.90, 1.93 (2 d, *J* = 1.0 Hz, 3H, CH_3); 2.61–3.74 (m, 5.5H, CH_2); 3.87 (s, 6H, OCH_3); 4.60–4.76 (m, 0.5H, CH_2); 5.61 (dd, *J* = 8.5, 4.5 Hz, 0.5H, 1-H); 5.84, 6.02 (2 s, 1H, C=CH); 6.05 (t, *J* = 6.5 Hz, 0.5H, 1-H); 6.57, 6.62 (2 s, 1H, 5-H); 6.62, 6.70 (2 s, 1H, 8-H). – ^{13}C NMR ($CDCl_3$): δ = 20.29, 26.36 (CH_3); 27.45, 28.68 (C-4); 35.59, 41.34 (C-3); 40.92, 41.99 (C-1′); 49.80, 53.46 (C-1); 55.90, 56.04 (OCH_3); 96.44 (C-3′); 109.1, 110.0 (C-5); 111.2, 111.7 (C-8); 117.6, 117.7 (CH); 126.0, 126.7 (C-4a); 127.1, 127.5 (C-8a); 147.8, 147.9 (C-6); 148.0 (C_q); 148.3, 148.5 (C-7); 167.7, 167.8 (NCO); 186.8, 187.3 (C-2′).

$C_{19}H_{22}Cl_3NO_4$ (434.7) Calcd. C 52.49 H 5.10
Found C 52.60 H 5.07

(1RS)-6,7-Dimethoxy-2-(3-methylacryloyl)-1-(3,3,3-trichloro-2-oxopropyl)-1,2,3,4-tetrahydroisoquinoline (**5d**): Reaction of **4d** (7.13 mmol) according to general procedure II; yield after column chromatography 2.43 g (81%) of **5d** as a yellow oil. – R_f = 0.75. – UV (CH_3CN): λ_{max} (lg ε) = 204 nm (4.678), 283 (3.690). – IR (film): $\tilde{\nu}$ = 2938 cm^{-1}, 2916, 2838 (CH); 1754, 1660 (C=O); 1614 (C=C). – ^1H NMR ($CDCl_3$): δ = 1.86–1.98 (m, 3H, CH_3); 2.61–3.84 (m, 5.5H, CH_2); 3.85 (s, 6H, OCH_3); 4.54–4.71 (m, 0.5H, CH_2); 5.63 (dd, *J* = 8.0, 4.5 Hz, 0.5H, 1-H); 6.05 (t, *J* = 6.0 Hz, 0.5H, 1-H); 6.58, 6.62 (2 s, 1H, 5-H); 6.62, 6.70 (2 s, 1H, 8-H); 6.31, 6.54 (2 dq, *J* = 14.0, 1.0 Hz, 1H, NCOCH); 6.79–7.01 (m, 1H, C=C*H*CH_3). – ^{13}C NMR ($CDCl_3$): δ = 18.36 (CH_3); 27.21, 28.57 (C-4); 36.50, 41.34 (C-3); 40.85, 42.15 (C-1′); 50.49, 52.80 (C-1); 55.90, 56.03 (OCH_3); 96.10, 96.36 (C-3′); 109.1, 110.1 (C-5); 111.1, 111.7 (C-8); 121.5 (NCO*C*H); 125.9, 126.7 (C-4a); 126.8, 127.4 (C-8a); 142.8, 143.2 (CH); 147.8, 147.9 (C-6); 148.3, 148.5 (C-7); 166.5, 166.6 (NCO); 186.8, 187.6 (C-2′).

$C_{18}H_{20}Cl_3NO_4$ (420.7) Calcd. C 51.39 H 4.79
Found C 51.22 H 4.86

(1RS)-2-Benzyloxycarbonyl-6,7-dimethoxy-1-(3,3,3-trichloro-2-oxopropyl)-1,2,3,4-tetrahydroisoquinoline (**5e**): To a stirred solution of **4e** (1.00 g, 2.05 mmol) in anhydrous dichloromethane (30 ml)

was added slowly at 0°C TMS triflate (0.45 ml, 2.46 mmol), and stirring was continued for 1 h. Further workup according to general procedure II; yield after column chromatography [ethyl acetate/petroleum ether (1:1)] 0.93 g (93%) of **5e** as a yellow oil. – R_f = 0.42. – UV (CH_3CN): λ_{max} (lg ε) = 203 nm (4.761), 285 (3.639). – IR (film): $\tilde{\nu}$ = 1752 cm^{-1}, 1702 (C=O); 1612 (C=C). – ^1H NMR ($C_2D_2Cl_4$, 120°C): δ = 2.70–3.04 (m, 2H, 4-H); 3.34–3.60 (m, 3H, 1′-H, 3-H_{ax}); 3.86, 3.89 (2 s, 6H, CH_3); 4.12 (ddd, J = 13.5, 5.5, 5.0 Hz, 1H, 3-H_{eq}); 5.24 (s, 2H, OCH_2); 5.76 (t, J = 6.0 Hz, 1H, 1-H); 6.68 (s, 1H, 8-H); 6.72 (s, 1H, 5-H); 7.40 (s, 5H, Ph-H). – ^{13}C NMR ($CDCl_3$): δ = 27.65, 28.02 (C-4); 38.45, 39.36 (C-3); 41.15, 41.79 (C-1′); 51.85, 52.03 (C-1); 55.86, 56.01 (CH_3); 67.33, 67.56 (OCH_2); 96.39 (C-3′); 109.4, 109.8 (C-8); 111.3, 111.5 (C-5); 126.2, 126.4 (C-8a); 127.1, 127.3 (C-4a); 128.1, 128.2, 128.5 (CH-Ph); 136.2, 136.5 (C-*i*); 147.7 (C-7); 148.3 (C-6); 154.9, 155.3 (C=O); 186.6 (C-2′).

$C_{22}H_{22}Cl_3NO_5$ (486.8) Calcd. C 54.28 H 4.56
Found C 54.46 H 4.69

Cyclization of N-Acylated Enamino Ketones **4f–i** *with Trifluoromethanesulfonic Acid. – General Procedure III:* To a solution of the *N*-acylated enamino ketones **4f–i** (1.00 g) in anhydrous dichloromethane (30 ml) was added dropwise trifluoromethanesulfonic acid (1.00 ml, 8.85 mmol) at room temp. over a period of 5 min. The mixture was stirred for 4 h, washed with water (20 ml) and brine (30 ml), and dried (Na_2SO_4). The solvent was removed in vacuo and the residue purified by column chromatography.

(1RS)-2-Acetyl-1-(3,3,3-trichloro-2-oxopropyl)-1,2,3,4-tetrahydroisoquinoline (**5f**): Reaction of **4f** (2.99 mmol) according to general procedure III; yield after column chromatography [ethyl acetate/hexane (1:1)] 0.81 g (81%) of **5f** as a yellow oil. – R_f = 0.40. – UV (CH_3CN): λ_{max} (lg ε) = 317 nm (2.916). – IR (film): $\tilde{\nu}$ = 2932 cm^{-1}, 2842 (CH); 1750, 1644 (C=O); 1584 (C=C). – ^1H NMR ($CDCl_3$): δ = 2.18 (s, 1.8H, CH_3), 2.28 (s, 1.2H, CH_3), 2.68–3.44 (m, 4H, CH_2), 3.69–3.82 (m, 1.6H, CH_2), 4.62–4.75 (m, 0.4H, CH_2), 5.56 (dd, J = 4.5, 8.5 Hz, 0.4H, 1-H), 6.03 (t, J = 6.5 Hz, 0.6H, 1-H), 7.11–7.29 (m, 4H, 5-H, 6-H, 7-H, 8-H). – ^{13}C NMR ($CDCl_3$): δ = 21.43, 22.02 (CH_3); 27.55, 28.89 (C-4); 35.63, 41.79 (C-3); 40.61, 41.79 (C-1′); 50.47, 53.86 (C-1); 96.04, 96.33 (C-3′); 126.4, 126.6, 126.9, 127.2, 127.5, 127.8, 128.5, 129.5, (C-5, C-6, C-7, C-8); 133.8, 134.6, 135.0, 135.4 (C-4a, C-8a); 169.9, 170.0 (NCO); 186.5, 187.4 (C-2′).

$C_{14}H_{14}Cl_3NO_2$ (334.6) Calcd. C 50.25 H 4.22
Found C 50.02 H 4.34

(1RS)-2-Benzoyl-1-(3,3,3-trichloro-2-oxopropyl)-1,2,3,4-tetrahydroquinoline (**5g**): Reaction of **4g** (2.52 mmol) according to general procedure III; yield after column chromatography [ethyl acetate/hexane (1:3)] 0.78 g (78%) of **5g** as a yellow oil. – R_f = 0.42. – UV (CH_3CN): λ_{max} (lg ε) = 321 nm (3.036). – IR (film): $\tilde{\nu}$ = 1750 cm^{-1}, 1716, 1634 (C=O); 1602 (C=C). – ^1H NMR ($CDCl_3$): δ = 2.64–3.96 (m, 6H, CH_2), 6.18–6.34 (m, 1H, 1-H), 7.08–7.54 (m, 9H, 5-H, 6-H, 7-H, 8-H, Ph-H). – ^{13}C NMR ([D_6]DMSO): δ = 29.22 (C-4); 40.39 (C-3); 41.99 (C-1′); 50.52 (C-1); 96.35 (C-3′); 126.7, 126.9, 127.0, 127.4, 128.3, 128.5, 129.0, 129.8, 130.0 (C-5, C-6, C-7, C-8, CH-Ph); 133.4, 135.1, 135.7 (C-4a, C-8a, C-*i*); 171.2 (NCO); 186.5 (C-2′).

$C_{19}H_{16}Cl_3NO_2$ (396.9) Calcd. C 57.50 H 4.06
Found C 57.69 H 4.08

(1RS)-2-(3,3-Dimethylacryloyl)-1-(3,3,3-trichloro-2-oxopropyl)-1,2,3,4-tetrahydroisoquinoline (**5h**): Reaction of **4h** (2.67 mmol) according to general procedure III; yield after column chromatography [ethyl acetate/hexane (1:3)] 0.77 g (77%) of **5h** as a yellow oil. – R_f = 0.40. – UV (CH_3CN): λ_{max} (lg ε) = 325 nm (3.573). – IR (film): $\tilde{\nu}$ = 2972 cm^{-1}, 2934, 2916 (CH); 1750, 1706, 1642, (C=O); 1626 (C=C). – ^1H NMR ($CDCl_3$): δ = 1.82, 1.87 (2 d, J = 1.0 Hz, 3H, CH_3); 1.89, 1.93 (2 d, J = 1.0 Hz, 3H, CH_3); 2.71–3.97 (m, 5.5H, CH_2); 4.60–4.74 (m, 0.5H, CH_2); 5.69 (dd, J = 8.5, 4.5 Hz, 0.5H, 1-H); 5.84, 6.02 (2 s, 1H, C=CH); 6.12 (t, J = 6.5 Hz, 0.5H, 1-H), 7.08–7.33 (m, 4H, 5-H, 6-H, 7-H, 8-H). – ^{13}C NMR ($CDCl_3$): δ = 20.25, 26.37 (CH_3); 27.85, 29.14, (C-4); 35.53, 41.28 (C-3); 40.77, 41.86 (C-1′); 50.27, 53.74 (C-1); 96.38 (C-3′); 117.6, 117.7 (CH); 126.4, 126.6, 126.9, 127.1, 127.4, 127.6, 128.7, 129.5, (C-5, C-6, C-7, C-8); 133.9, 134.6, 135.4, 135.5 (C-4a, C-8a); 148.0, 148.1 (C_q); 148.3, 148.5 (C-7); 167.7, 167.8 (NCO); 186.5, 186.9 (C-2′).

$C_{17}H_{18}Cl_3NO_2$ (374.7) Calcd. C 54.49 H 4.84
Found C 54.29 H 4.85

(1RS)-2-(3-Methylacryloyl)-1-(3,3,3-trichloro-2-oxopropyl)-1,2,3,4-tetrahydroisoquinoline (**5i**): Reaction of **4i** (2.77 mmol) according to general procedure III; yield after column chromatography [ethyl acetate/hexane (1:3)] 0.75 g (75%) of **5i** as a yellow oil. – R_f = 0.34. – UV (CH_3CN): λ_{max} (lg ε) = 322 nm (3.617). – IR (film): $\tilde{\nu}$ = 2958 cm^{-1}, 2932, 2874, (CH); 1750, 1726, 1660 (C=O); 1620 (C=C). – ^1H NMR ($CDCl_3$): δ = 1.91 (d, J = 7 Hz, 3H, CH_3); 2.61–3.94 (m, 5.5H, CH_2); 4.53–4.70 (m, 0.5H, CH_2); 5.71 (dd, J = 8.0, 4.5 Hz, 0.5H, 1-H); 6.12 (t, J = 6.0 Hz, 0.5H, 1-H); 6.31, 6.57 (2 d, J = 14.0 Hz, 1H, NCOCH); 6.81–7.03 (m, 1H, C=C*H*CH_3); 7.09–7.34 (m, 4H, 5-H, 6-H, 7-H, 8-H). – ^{13}C NMR ($CDCl_3$): δ = 18.33 (CH_3); 27.62, 29.05 (C-4); 36.37, 41.28 (C-3); 38.68, 42.11 (C-1′); 50.89, 53.01 (C-1); 96.35 (C-3′); 121.7 (NCO-*C*H); 126.5, 126.6, 126.9, 127.3, 127.5, 127.7, 128.8, 129.5 (C-5, C-6, C-7, C-8); 133.9, 134.8, 135.2, 135.5 (C-4a, C-8a); 142.6, 142.8 (CH); 166.3, 166.4 (NCO); 186.5, 187.3 (C-2′).

$C_{16}H_{16}Cl_3NO_2$ (360.7) Calcd. C 53.28 H 4.47
Found C 53.57 H 4.60

Transformation of **5** *into* **6**. – *(1RS)-2-Acetyl-6,7-dimethoxy-1-(methoxycarbonylmethyl)-1,2,3,4-tetrahydroisoquinoline* (**6a**): A mixture of **5a** (10.0 g, 25.3 mmol) and potassium carbonate (0.70 g, 5.07 mmol) in anhydrous methanol (100 ml) was stirred at room temp. for 24 h. After evaporation of the solvent in vacuo, the residue was purified by column filtration [methanol/chloroform (1:4)] and recrystallization to yield **6a** (6.93 g, 89%). – R_f = 0.31 (ethyl acetate). – M.p. 112°C (ethanol). – UV (CH_3CN): λ_{max} (lg ε) = 207 nm (4.589), 284 (3.656). – IR (KBr): $\tilde{\nu}$ = 2968 cm^{-1}, 2948, 2926 (CH); 1724, 1640 (C=O); 1610 (C=C). – ^1H NMR ($CDCl_3$): δ = 2.16 (s, 1.5H, $COCH_3$); 2.24 (s, 1.5H, $COCH_3$); 2.56–3.12 (m, 4.5H, CH_2); 3.52–3.82 (m, 1H, CH_2); 3.68 (s, 1.5H, OCH_3); 3.73 (s, 1.5H, OCH_3); 3.84, 3.85 (2 s, 6H, OCH_3); 4.62–4.76 (m, 0.5H, CH_2); 5.48 (dd, J = 8.5, 5.5 Hz, 0.5H, 1-H); 5.93 (t, J = 7.0 Hz, 0.5H, 1-H); 6.61, 6.70, (2 s, 2H, 5-H, 8-H). – ^{13}C NMR ($CDCl_3$): δ = 21.47, 21.81 (CH_3); 27.32, 28.51 (C-4); 35.21, 40.91 (C-3); 41.12, 41.96 (C-1′); 49.48, 53.88 (C-1); 51.84, 52.02 (CO_2CH_3); 55.88, 55.96, 56.00 (OCH_3); 109.1, 109.9 (C-5); 111.2, 111.7 (C-8); 125.6, 126.5 (C-4a); 127.4, 128.0 (C-8a); 147.6, 147.8 (C-6); 148.0, 148.4 (C-7); 169.3, 169.7 (NCO); 171.1, 171.2 (C-2′).

$C_{16}H_{21}NO_5$ (307.3) Calcd. C 62.54 H 6.89
Found C 62.34 H 6.73

(1RS)-2-(Benzyloxycarbonyl)-6,7-dimethoxy-1-(methoxycarbonylmethyl)-1,2,3,4-tetrahydroisoquinoline (**6e**): A mixture of **5e** (2.00 g, 4.11 mmol) and potassium carbonate (114 mg, 0.82 mmol) in anhydrous methanol (40 ml) was stirred at room temp. for 24 h. After evaporation of the solvent in vacuo, the residue was purified by column filtration [methanol/chloroform (1:4)] and recrystallization to yield **6e** (1.80 g, 90%). – R_f = 0.43 [ethyl acetate/petroleum ether (1:1)]. – M.p. 83°C (diethylether/petroleum ether). – UV (CH_3CN): λ_{max} (lg ε) = 203 nm (4.756), 282 (3.812). – IR (KBr): $\tilde{\nu}$ = 2950 cm^{-1}, 2938, 2858 (CH); 1732, 1702 (C=O); 1612

(C=C). – ^{1}H NMR ($C_2D_2Cl_4$, 120°C): δ = 2.66–3.00 (m, 4H, 1′-H, 4-H); 3.37–3.52 (m, 1H, 3-H_{ax}); 3.67 (s, 3H, OCH_3); 3.87, 3.89 (2 s, 6H, CH_3); 4.08–4.24 (m, 1H, 3-H_{eq}); 5.24 (s, 2H, OCH_2); 5.60 (t, *J* = 7.0 Hz, 1H, 1-H); 6.68 (s, 1H, 8-H); 6.76 (s, 1H, 5-H); 7.36–7.47 (m, 5H, Ph-H). – ^{13}C NMR ($C_2D_2Cl_4$, 120°C): δ = 27.67 (C-4); 38.58 (C-3); 41.97 (C-1′); 51.76 (OCH_3); 51.80 (C-1); 56.28, 56.46 (CH_3); 66.98 (OCH_2); 111.9 (C-8); 113.4 (C-5); 126.5 (C-8a); 127.4, 127.6, 128.2 (CH-Ph); 128.7 (C-4a); 136.8 (C-*i*); 148.4 (C-7); 148.9 (C-6); 154.9 (C=O); 170.6 (C=O).

$C_{22}H_{25}NO_6$ (399.4) Calcd. C 66.15 H 6.31
Found C 66.29 H 6.51

(1RS)-2-Acetyl-1-(methoxycarbonylmethyl)-1,2,3,4-tetrahydroisoquinoline (**6f**): A mixture of **5f** (5.00 g, 14.9 mmol) and potassium carbonate (0.41 g, 2.98 mmol) in anhydrous methanol (50 ml) was stirred at room temp. for 24 h. After evaporation of the solvent in vacuo, the residue was purified by column filtration [methanol/chloroform (1:4)] to yield **6f** (3.06 g, 83%) as a yellow oil. – R_f = 0.46 (ethyl acetate). – UV (CH_3CN): λ_{max} (lg ε) = 272 nm (3.026). – IR (film): $\tilde{\nu}$ = 2950 cm^{-1} (CH); 1736, 1642, (C=O); 1582 (C=O). – ^{1}H NMR ($CDCl_3$): δ = 2.17 (s, 1.5H, $COCH_3$), 2.24 (s, 1.5H, $COCH_3$), 2.66–3.21 (m, 4.5H, CH_2), 3.57–3.86 (m, 1H, CH_2), 3.68 (s, 1.5H, OCH_3), 3.73 (s, 1.5H, OCH_3), 4.62–4.76 (m, 0.5H, CH_2), 5.42 (dd, *J* = 8.5, 5.5 Hz, 0.5H, 1-H), 5.99 (t, *J* = 7.0 Hz, 0.5H, 1-H), 7.10–7.36 (m, 4H, 5-H, 6-H, 7-H, 8-H). – ^{13}C NMR ($CDCl_3$): δ = 21.42, 21.85 (CH_3); 27.69, 28.90 (C-4); 35.25, 41.01 (C-3); 41.12, 41.97 (C-1′); 49.86, 54.15 (C-1); 51.82, 52.01 (OCH_3); 126.3, 126.4, 126.7, 127.1, 127.2, 127.5, 128.6, 129.5 (C-5, C-6, C-7, C-8); 133.6, 134.4, 135.6, 136.0 (C-4a, C-8a); 169.5, 169.8 (NCO); 170.9, 171.0 (C-2′).

$C_{14}H_{17}NO_3$ (247.3) Calcd. C 68.00 H 6.93
Found C 68.10 H 6.99

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