Chem. Pharm. Bull. 28(3) 984—988 (1980)

Synthesis of 8,10-Diaza-estrane[1,2]

Hiroki Takahata, Hideo Okajima,[3a] Masanori Nagata,[3b] and Takao Yamazaki[3a]

Faculty of Pharmaceutical Sciences[3a] and Faculty of Medicine,[3b] Toyama Medical and Pharmaceutical University[3]

(Received September 14, 1979)

Reductive condensation of the amine (**5**) with the acid (**2**), followed by reduction of the carbonyl group and pyridine ring gave the *cis*-seco-8,10-diazasteroid (**12**). Reductive cyclization of **12** with lithium aluminum hydride afforded two configurational isomers (**14a, b**) of 8,10-diaza-estran. The stereochemistry of both isomers is discussed.

Keywords——diazasteroid; 8,10-diaza-estrane; reductive cyclization; stereochemistry; configurational isomer

Much attention has been devoted to the synthesis of heterocyclic steroids[4] in view of their biological interest.[5] Following our previous paper,[1] an interest in the synthesis of diazasteroids prompted us to investigate the preparation of 8,10-diaza-estrane, which could have some physiological activity. The synthesis of the 8,10-diazasteroid was performed by reductive annelation of an intramolecular sec-amine-lactam system with lithium aluminum hydride.[6] We de- scribe here the results of our studies.

Meltzer *et al.* have reported the condensation of *m*-methoxyphenethylamine (**1**) with 2-methyl-2-(β-carboxyethyl)cyclopentene-1,3-dione (**2**) followed by reduction with Pd-C to afford a single keto-lactam (**4**) with a *cis*-C/D ring junction.[7] We adopted the above-mentioned procedure for fixing the *cis*-C/D ring junction using 2-aminoethyl-2-pyridine (**5**) instead of **1** to avoid complexity of the stereochemistry. First, condensation of the amine (**5**) with the acid (**2**) in refluxing benzene, with azeotropic removal of water, gave the unsaturated lactam (**6**) in 46% yield. The nuclear magnetic resonance (NMR) spectrum of **6** showed a triplet (J=2.3 Hz) at δ 5.23, indicating a vinyl proton. Next, catalytic reduction of 6 with 10% Pd-C under a pressure of 50 atm at 50° proceeded to give a single keto-lactam (**7**) having a *cis*-C/D ring junction in 45% yield, which exhibited one spot on thin-layer chromatography (TLC) and had a sharp singlet at δ 0.90 in its NMR spectrum, assigned to a methyl group. On the other hand, reductive condensation of the amine (**5**) with the acid (**2**) (60 atm, 50°) afforded **7** directly in 43% yield. This was identical with the above sample prepared from **6** with respective to infrared (IR) and NMR data and chromatographic properties.

Reduction of the carbonyl group of compound **7** to a methylene group was carried out by two methods. First, thioketalization of the ketone, followed by desulfurization gave com-

1) This paper forms Part XIII of "Synthesis in the Diazasteroid Group." Part XII: H. Takahata, M. Hara, A. Tomiguchi, T. Yamazaki, and R.N. Castle, *J. Heterocycl. Chem.*, submitted for pubilication.
2) Presented at the 98 th Meeting of the Pharmaceutical Society of Japan, Okayama, April, 1978, Abstracts p. 220.
3) Location: *2630, Sugitani, Toyama 930-01, Japan.*
4) *a*) P. Morand and J. Lyall, *Chem. Rev.*, **68**, 85 (1968); *b*) H.O. Husman, *Angew. Chem. Int. Ed. Engl.*, **10**, 450 (1971); *c*) I. Ninomiya, *J. Org. Syn.* (Japan), **30**, 318 (1972).
5) *a*) L.F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corporation, New York, NY, 1959, chapter 22; *b*) I.Y. Tao and R.T. Blickenstaff, *J. Pharm. Sci.*, **67**, 283 (1978).
6) T. Yamazaki, M. Nagata, K. Matoba, H. Takahata, and R.N. Castle, *J. Heterocycl. Chem.*, **14**, 469 (1977).
7) R.E. Brown. D.M. Lusgarten, R.J. Stanaback, and R.I. Meltzer, *J. Org. Chem.*, **31**, 1489 (1966).

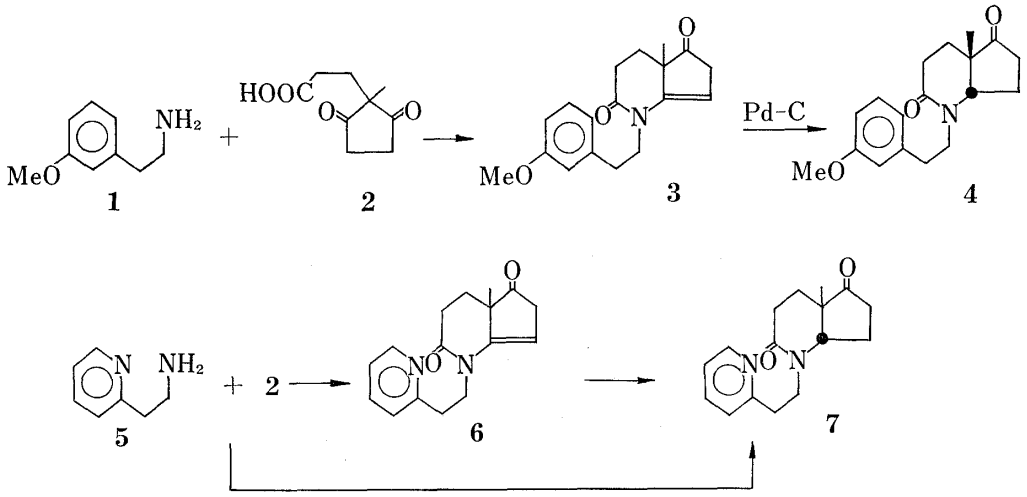
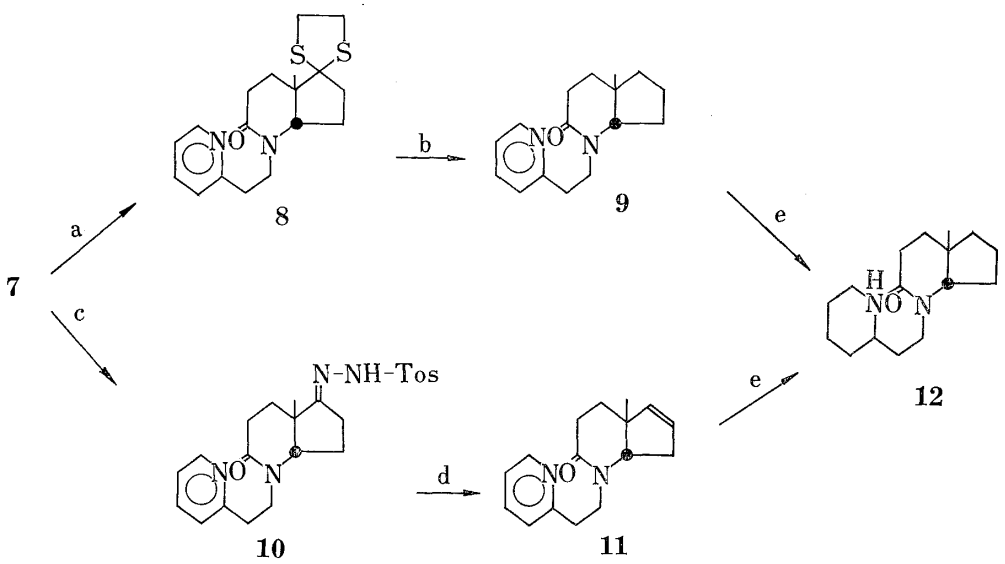


Chart 1

pound **9** in 64% yield from **7**. Secondly, we employed modified Wolff-Kishner reduction;[8] toylhsydrazonation of the ketone followed by treatment with $NaBH_4$ furnished compound **11** in 53% yield; its NMR spectrum showed signals at δ 5.3—5.4, indicating vinyl protons. Subsequently, reduction of **9** and **11** with PtO_2 in AcOH afforded the same stereoisomeric mixture of **12** in 78 and 68% yields, respectively.



a) $HSCH_2CH_2SH$, BF_3–Et_2O b) Ra–Ni c) *p*-TosNHNH$_2$ d) $NaBH_4$ e) PtO_2/H_2

Chart 2

Reductive cyclization of **12** with lithium aluminum hydride afforded the corresponding 8,10-diazasteroid; the seco-compound **12** was treated with lithium aluminum hydride under argon in absolute ether under reflux for 18 hr. Separation of the reaction mixture was effected by column chromatography to give the 8,10-diazasteroids **14a** and **14b**, and the non-cyclized product (**15**) in 16%, 21%, and 32% yields, respectively; these compounds gave satisfactory elemental analyses as their dipicrates, as well as appropriate mass spectral data. The reductive cyclization, forming an N-C-N bond, would presumably occur by attack of the intramolecular

8) R.H. Shapiro, "Organic Reactions," Vol. 23, ed. by W.G. Dauben, John Wiley and Sons, Inc., New York, 1976, p. 405.

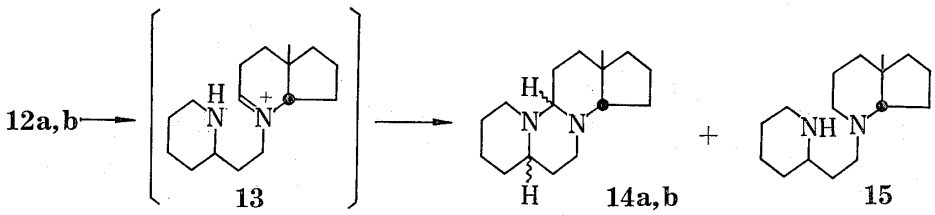


Chart 3

secondary amine towards the immonium intermediate (**13**), whereas overreduction of **13** by hydride gave the non-cyclized compound (**15**).

An examination of Dreiding models of **13** suggested that an attack by piperidine nitrogen from an equatorial direction would occur on the top face of the immonium derivative, leading to a *syn* arrangement of methine hydrogens at C_5 and C_9, because the equatorial nucleophile can come very close to the electrophilic carbon atom of **13** without any strain or other interactions. On the other hand, an attack of sec-amine from the axial direction, leading to an *anti* configuration (C_5–H/C_9–H), would lead to evident strain.[9] Based on the above mechanistic considerations, products **14a,b** would probably be obtained by ring closure from the equatorial direction of piperidine nitrogens of mixtures **12a,b**[10] of the seco-compounds, resulting in *syn* configurations at C_5–H and C_9–H.

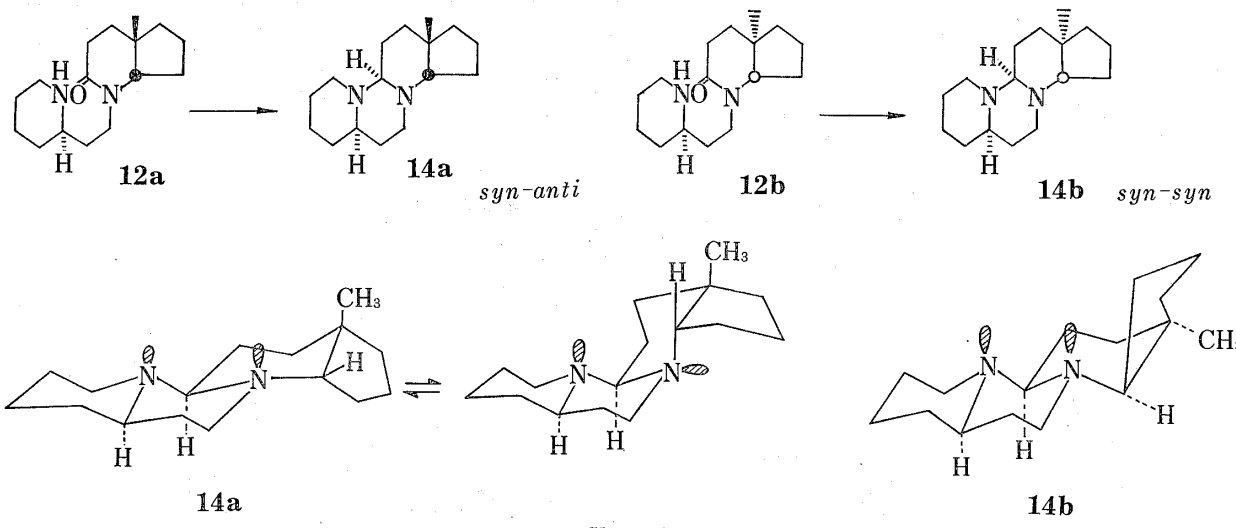


Chart 4

The structure of **14a,b** were also supported by their IR and NMR spectra. IR spectra of **14a,b** showed intense bands in the 2810—2550 cm^{-1} region, commonly known as Bohlmann bands,[11] which are characteristic of conformation having two or more protons in a 1,2-*trans*-diaxial arrangement with respect to a nitrogen lone pair. The NMR spectrum of **14a** shows a signal due to the C_9–H at δ 3.5—3.8, whereas that of **14b** shows no signals below δ 3.3. This observation supports the view that **14b** has protons 1,2-*trans*-diaxial to both nitrogen lone pairs,[12] and the conformation which satisfy this criterion is the *trans-syn-trans-syn-cis*[13] (*syn-*

9) Similar considerations have led to an elegant structure proof and synthesis of *dl*-elaeocarpidine: W.G. Gribble, *J. Org. Chem.*, **35**, 1944 (1970).
10) W.A. Ayer and K. Piers, *Can. J. Chem.*, **45**, 451 (1967). They cannot be separated by chromatography.
11) F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957).
12) *a*) T.A. Crabb, R.F. Newton, and D. Jackson, *Chem. Rev.*, **71**, 109 (1971); *b*) M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Am. Chem. Soc.*, **86**, 3364 (1964).
13) Here *trans* or *cis* refers to ring junction and syn or anti to the relative orientations at (C_5-H and C_9-H) (C_9-H and C_{14}-H).

syn configuration). This value in the NMR spectrum of **14a** is about midway between the chemical shifts observed for the pure *trans*-quinolizidine and the pure *cis*-quinolizidine.[14] This is interpreted as due to a conformational equilibrium,[14] as shown in Chart **4**, but the configuration is *syn-anti*.

Experimental

All melting points are uncorrected. IR spectra were taken on a Hitachi 215 grating infrared sectrophotometer. NMR spectra were measured in $CDCl_3$ solution with a JEOL C-60H spectrometer using tetramethylsilane as an internal standard. Coupling constants (J) are given in Hz, and the following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplets. Mass spectra (MS) were taken on a JEOL TMS-OISG (75 ev, direct inlet system) spectrometer. For elemental analyses and mass spectra of 7, 8, 9, 12, 14a, b, and 15 the picrates were used, whereas IR and NMR spectra were obtained with the free bases.

8,10-Diaza-9,10-seco-1,3,5,14-estratetraene-9,17-dione (6)——A solution of **5** (2 g, 0.0164 mol) in benzene (10 ml) was added to a solution of 2 (3g, 0.0164 mol) in benzene (200 ml) under reflux. After completion of addition, the reaction mixture was refluxed for 18 hr in a Dean-Stark apparatus for water separation. Removal of the solvent gave an oil, which was purified by column chromatography on alumina using ethyl acetate: ether (1:5) as an eluant to afford **6** (2.14 g, 46%), bp 175—178° (0.07 mmHg). IR ν_{max}^{Neat} cm^{-1}: 1750 (C=O), 1670 (C=C), 1630 (lactam C=O). NMR δ: 0.87 (3H, s, CH_3), 5.23 (1H, t, J=2.3, CH=C). MS *m/e*: 270 (M^+), 149, 106. *Anal.* Calcd for $C_{16}H_{18}N_2O_2$: C, 71.11; H, 6.67; N, 10.39. Found: C, 71.32; H, 6.89; N, 10.24.

***cis*-8,10-Diaza-9,10-seco-1,3,5-estratriene-9,17-doine (7)**——a) Compound **6** (2 g, 0.074 mol) was hydrogenated over 10% palladium on carbon in ethanol (80 ml) at 50° under a pressure of 60 atm in an autoclave for 24 hr. The mixture was then filtered to remove the catalyst and the solvent was evaporated off to leave an oil, which was purified by column chromatography on alumina to give **6** (451 mg, 22%) using benzene: ethyl acetate (1: 5) as an eluant, followed by **7** (1.95 g, 45%) using ethyl acetate, mp 122—123° as the picrate. IR ν_{max}^{Neat} cm^{-1}: 1740 (C=O), 1640 (lactam C=O). NMR δ: 0.90 (3H, s, CH_3). MS *m/e*: 272 (M^+). *Anal.* Calcd for $C_{22}H_{23}N_5O_9$: C, 52.69; H, 4.62; N, 13.97. Found: C, 52.77; H, 4.59; N, 13.73.

b) A mixture of **2** (2 g, 0.011 mol) and **5** (1.32 g, 0.011 mol) in ethanol (80 ml) was hydrogenated overnight over 10% palladium on carbon (1g) under a presence of 60 atm at 50°. The catalyst and solvent were removed. The residual oil was purified by column chromatography on alumina using ethyl acetate as an eluent to afford **7** (1.36 g. 43%), which was identical with the above sample (IR and NMR data and chromatographic properties).

***cis*-8,10-Diaza-9,10-seco-1,3,5-estratriene-9-one 7-Ethylene Thioketal (8)**——A solution of **7** (3 g, 0.011 mol) and ethane dithiol (6 ml) in AcOH (30 ml) was treated with BF_3–Et_2O (6 ml) at 50° and then the reaction mixture was stirred at room temperature overnight. Removal of the solvent *in vacuo* gave an oil, which was neutralized with 10% NaOH solution. The mixture was extracted with $CHCl_3$ and the extract was dried over anhyd. K_2CO_3. Removal of the solvent *in vacuo* afforded **8** (3.1 g, 81.5%), mp 194—196° as the picrate (EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1640 (lactam C=O). NMR δ: 1.07 (3H, s, CH_3), 3.23 (4H, s, S–CH_2CH_2–S). *Anal.* Calcd for $C_{24}H_{27}N_5O_8S_2$: C, 49.92; H, 4.68; N, 12.13. Found: C, 49.95; H, 4.61; N, 11.94.

***cis*-8,10-Diaza-9,10-seco-1,3,5-estratriene-9-one (9)**——A mixture of **8** (3.1 g, 0.009 mol), Raney Ni (W2) (30 g), EtOH (240 ml) and acetone (140 ml) was refluxed for 2 hr. The reaction mixture was filtered off and the filtrate was concentrated *in vacuo* to give **9** (1.8 g, 78%). mp 146—148° as the picrate (EtOH).
IR ν_{max}^{Neat} cm^{-1}: 1640 (lactam C=O). NMR δ: 0.99 (3H, s, CH_3). MS *m/e*: 238 (M^+). *Anal.* Calcd for $C_{22}H_{25}N_5O_7$: C, 54.20; H, 5.17; N, 14.37. Found: C, 54.32; H, 5.05; N. 14.15.

***cis*-8,10-Diaza-9,10-seco-1,3,5,16-estratetraene-9-one (11)**——A solution of *p*-toluenesulfonyl hydrazide (1.12 g, 0.006 mol) in MeOH (40 ml) was added to a solution of **7** (800 mg, 0.003 mol) in MeOH (20 ml). The mixture was refluxed for 5 hr and then concentrated *in vacuo* to afford an oil **10** (1.1 g). The IR spectrum of **10** showed no ketone absorptions. A solution of **10** (1.1 g) in dioxane (30 ml) was treated $NaBH_4$ (1 g) and then the reaction mixture was refluxed for 24 hr. After cooling, water was added dropwise to the mixture. The mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over anhyd. $MgSO_4$, and concentrated *in vacuo* to leave an oil, which was purified by column chromatography on alumina using ethyl acetate as an eluant to give **11** (401 mg, 53%) as an oil. IR ν_{max}^{Neat} cm^{-1}: 1640 (lactam C=O).
NMR δ: 1.00 (3H, s, CH_3), 5.5 (2H, m, CK=CH). MS *m/e*: 256 (M^+). *Anal.* Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 74.42; H, 7.92; N, 10.66.

***cis*-8,10-Diaza-9,10-seco-estran-9-one (12)**——a) Compound **9** (1.5 g, 0.0043 mol) was hydrogenated over PtO_2 (350 mg) in AcOH (50 ml) at room temperature under a pressure of 4 atm overnight. The reaction

14) For the basis of this argument, see: R.E. Brown, A.I. Meyers, L.M. Trefons, R.L.R. Towns, and J.N. Brown, *J. Heterocycl. Chem.*, **8**, 279 (1971).

mixture was filtered off and the filtrate was concentrated *in vacuo* to give an oil. which was made basic with 10% Na_2CO_3 solution. The mixture was extraceted with ether. The extract was dried over anhyd. K_2CO_3 and was concentrated *in vacuo* to leave an oil, which was purified by column chromatography on alumina using $CHCl_3$ as an eluant to give **12** (1.2 g, 78%) as oil, mp 136—138° as the dipicrate. IR ν_{max}^{Neat} cm^{-1}: 3250 (NH), 1640 (lactam C=O). NMR δ: 1.10 (3H, s, CH_3), 3.46 (1H, s, NH). MS *m/e*: 264 (M^+). *Anal.* Calcd for $C_{22}H_{31}N_5O_8$: C, 53.54; H, 6.07; N. 14.19. Found: C, 53.82; H, 6.07; N, 14.24.

b) As described in (a) above, compound **11** (400 mg, 0.0016 mol) was hydrogenated over PtO_2 (100 mg) in AcOH (30 ml) to give **12** (260 mg, 63%), which was identical with the above sample with respect to IR and NMR data and TLC behavior.

8,10-Diaza-estranes (14a, b) and *cis*-8,10-Diaza-9,10-seco-estrane (15)——A solution of **12** (2.7 g, 0.01 mol) in ether (200 ml) was treated under reflux with a suspension of $LiAlH_4$ (250 mg, 0.0064 mol) in ether (50 ml) over 30 min. The reaction mixture was refluxed with stirring under argon for 18 hr. After cooling, water was added to the reaction mixture with ice cooling. Thre yellow precipitate was removed by filtration, then washed with ether. The filtrate and ether washing were combined, dried over anhyd. K_2CO_3 and concentrated *in vacuo* to leave an oil, which was separated by column chromatography on alumina to afford a mixture **14a, b** using benzene: ether (1: 1) as an eluant, followed by **15** (793 mg, 32%) using $CHCl_3$. The mixture, **14a, b**, was separated by column chromatography on silica gel to give **14a** (396 mg, 16%) and subsequently **14b** (520 mg, 21%) using $CHCl_3$: EtOH (10: 1) as an eluant. **14a**, mp 192—193° as the dipicrate. IR ν_{max}^{Neat} cm^{-1}: 2810, 2795, 2730, 2700, 2765, 2675, 2625, 2610, 2550. (Bohlmann band). NMR δ: 1.13 (3H, s, CH_3), 3.5—3.8 (1H, m, C_9-H). MS *m/e* 248 (M^+), 148, 96. *Anal.* Calcd for $C_{28}H_{34}N_8O_4$: C, 47.61; H, 4.81; N, 15.86. Found: C, 47.58; H, 4.82; N, 15.59. **14b**, mp 177—179° as the dipicrate. IR ν_{max}^{Neat} cm^{-1}: 2805, 2795, 2750, 2730, 2685, 2680, 2650, 2600, 2550, (Bohlmann band). NMR δ: 0.90 (3H, s, CH_3). MS *m/e*: 248 (M^+), 148, 96. *Anal.* Calcd for $C_{28}H_{34}N_8O_{14}$: C, 47.61; H, 4.81; N, 15.86. Found: C, 47.48; H, 5.01; N, 16.12. **15**, mp 190° as the dipicrate. IR ν_{max}^{Neat} cm^{-1}: 3260 (NH). NMR δ: 1.10 (3H, s, CH_3), 2.40 (1H, s, NH). MS *m/e*: 250 (M^+), 111. *Anal.* Calcd for $C_{28}H_{36}N_8O_{14}$: C, 47.45; H, 5.12; N, 15.18. Found: C, 47.41; H, 5.12; N, 15.13.

Acknowledgement We are grateful to Messrs. M. Morikoshi and H. Hori for microanalyses as well as NMR and mass spectral measurements.