fluoride and stirred for 12 h at 25 °C under a N_2 atmosphere. After usual workup, the hydroxy aldehydes 1-4 (R = H; X = CHO) (0.16 g) were separated into two fractions. Less polar fraction I (0.096 g, 56%) was the 1:1 mixture (^{1}H NMR) of *E*-(1*R*)-4(e)-4 and *Z*-(1*R*)-4(e)-2. Polar fraction II gave 0.06 g (35%) of a 4:6 mixture (^{1}H NMR) of *E*-(1*R*)-4(a)-3 and *Z*-(1*R*)-4(a)-1, respectively.

(b) A solution of (*Z*)-(1*R*)-4(a)-[(dimethyl-*tert*-butylsilyl)-oxy]-2-adamantylideneacetaldehyde (0.50 g, $[\alpha]^{25}_{Hg}$ -58.98 ± 0.18°, 84% ee) in THF was treated with tetra-*n*-butylammonium fluoride as above. The reaction mixture after workup and separation yielded two fractions. The less polar fraction I (0.08 g, 26%) was found to be a 1:1 mixture (^{1}H NMR) of *E*-(1*R*)-4(e)-4 and *Z*-(1*R*)-4(e)-2, and the more polar fraction II (0.17 g, 55%), a 4:6 mixture (^{1}H NMR) of *E*-(1*R*)-4(a)-3 and *Z*-(1*R*)-4(a)-1 (R = H; X = CHO), respectively.

Reaction with NaH. (a) A mixture of methyl (*Z*)-(1*R*)-4-(a)-hydroxy-2-adamantylideneacetate (33 mg, $[\alpha]^{25}_{Hg}$ -46.89 ± 0.07°, 92% ee) and NaH (50 mg) in 2 mL of dry THF was stirred for 1 h. The reaction mixture was decomposed on ice and extracted with ether (2 × 15 mL). The combined ether solution was washed with water, dried (Na_2SO_4), and concentrated. The crude product upon ^{1}H NMR and HPLC analyses showed mainly the starting material 1 (R = H; X = $COOCH_3$).

(b) (*E*)-(1*R*)-4(a)-Hydroxy-2-adamantylideneacetaldehyde (36 mg, $[\alpha]^{25}_{Hg}$ +10.57 ± 0.41°, 92% ee) in dry THF was treated with NaH as above. The reaction mixture after workup and analytical HPLC analysis gave a ratio of 17:18:40:25 for the hydroxy-aldehydes **2**, **4**, **1**, and **3** (R = H; X = CHO), respectively.

(c) A solution of 12 mg *E*-(1*R*)-4(a)-hydroxy-2-adamantylideneacetone ($[\alpha]^{24}_{Hg}$ +38.52 ± 0.82°, 92% ee) in dry THF was treated with NaH as earlier. After workup, a ratio of 27:32:7.7:33 was estimated, respectively, for the hydroxy methyl ketones **2**, **1**, **4**, and **3** (R = H; X = $COCH_3$) by HPLC analysis of the crude mixture.

(d) Via the earlier procedure, NaH was added to a stirred solution of (*E*)-(1*R*)-4(e)-hydroxy-2-adamantylidenepropene (16 mg, $[\alpha]^{27}_{Hg}$ +47.12 ± 0.27°, 92% ee) in dry THF. After 1 h the reaction mixture was worked up to give pure starting material 4 (R = H; X = CH=CH_2) (^{1}H NMR, HPLC).

Alternative Practical Syntheses of Spiro(poly)cyclic Imino Thio- and Selenoethers

Christophe Bochu, Axel Couture,* and Pierre Grandclaudon

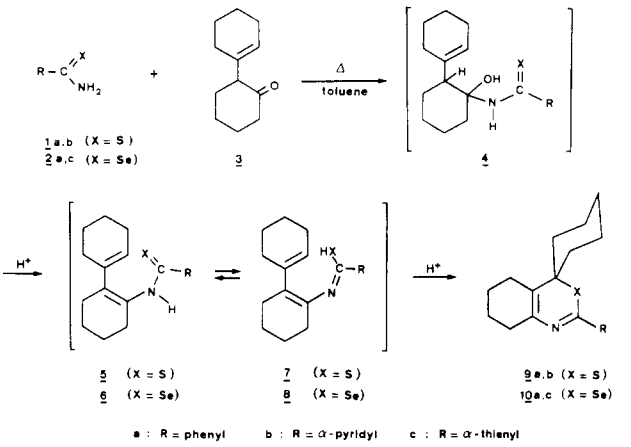
Laboratoire de Chimie Organique Physique (UA CNRS No. 351), Université des Sciences et Techniques de Lille Flandres-Artois, 59655 Villeneuve d'Ascq Cédex, France

Received January 20, 1988

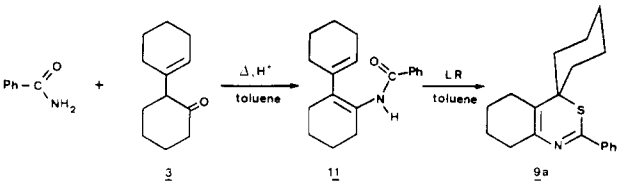
We recently reported[1] that aromatic and aliphatic dienamides, a class of little studied compounds, can serve as photochemical precursors of diversified imino ethers possessing a spiro heterocyclic framework. The present paper deals with the synthetic potential of these polyenic compounds and their use in the elaboration of a variety of spirothiazines and selenazines.

Thus the cyclohexanespiro-2-(5-aza-4-phenyl-3-thiabicyclo[4.4.0]deca-1(6),4-dienes) **9a,b** are easily accessible by direct condensation of the appropriate thiocarboxamide **1a,b** with 2-(cyclohex-1-enyl)cyclohexanone (**3**), a product of the aldol dimerization of cyclohexanone (Scheme I). Reactions are carried out in a Dean-Stark apparatus by refluxing an equimolar mixture of the aromatic thioamides and the β,γ-unsaturated ketone in toluene in the presence of a catalytic amount of β-naphthalenesulfonic acid. The results are listed in Table I. These reactions can be extended to the synthesis of the spiro seleno derivatives **10a,c** which are obtained from the bicyclic ketone **3** and the aromatic selenocarboxamides **2a,c**.[2] The spiro structure of **9a** and **10a** was confirmed mainly by 100-MHz ^{13}C NMR spectroscopy (Table II). The quaternary character of the carbon nucleus (D) α to the sulfur and selenium atoms was unambiguously established by comparison of DEPT spectra with different pulse angles θ.

Scheme I



Scheme II



Scheme III

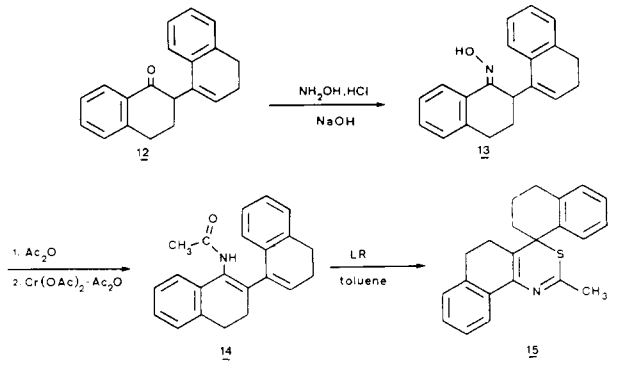


Table I. Yields of Products from Reactions of 1a,b, 2a,c and Benzamide with 3 and from Treatment of 11, 14, and 16 with the Lawesson Reagent

starting material		reaction product
method A[a]	method B[b]	(yield, %)
1a		**9a** (63)
1b		**9b** (55)
2a		**10a** (55)
2c		**10c** (49)
benzamide		**11** (65)
	11	**9a** (89)
	14	**15** (93)
	trans-**16**	*trans*-**17** (90)

[a] Direct condensation under acidic conditions with 2-(cyclohex-1-enyl)cyclohexanone (**3**). [b] Treatment with the Lawesson reagent.

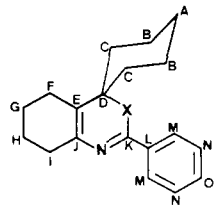
(1) Bochu, C.; Couture, A.; Granclaudon, P.; Lablache-Combier, A. *J. Chem. Soc., Chem. Commun.* **1986**, 839.

(2) Obtained from the nitriles.[3]

(3) Cohen, V. I. *Synthesis* **1978**, 668.

0022-3263/88/1953-4852$01.50/0

Table II. ^{13}C Chemical Shifts for Compounds 9a and 10a



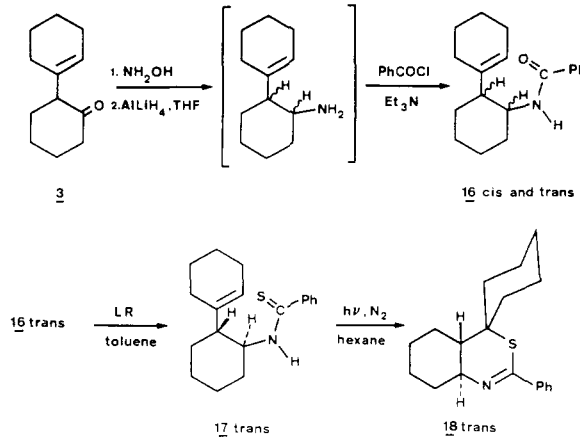
carbon	X = S	X = Se
A	26.20	28.35
B	21.91	23.20
C	33.68	34.58
D	48.79	50.76
E	121.19	121.88
F	24.56	24.87
G	23.05	23.03
H	23.60	23.70
I	31.94	32.34
J	141.78	143.88
K	155.30	158.15
L	139.38	140.74
M	128.00	130.78
N	128.39	128.41
O	130.77	131.02

It is likely that these heterocyclization reactions proceed via the thio- and selenodienamides **5** and **6** as shown in Scheme I. Indeed treatment with the Lawesson sulfurating reagent of the dienamide **11**, which is the exclusive product of the acidic condensation of benzamide with the β,γ-unsaturated ketone **3**, gives rise to the spirocyclohexanethiazine **9a** (Scheme II). Moreover, this reaction can be extended to the synthesis of polycyclic nitrogen compounds such as **15** as illustrated by Scheme III.

Polycyclic ketone **12** is the aldol dimerization product of α-tetralone prepared according to an optimized method recently described by Eisenbraun in which he used titanium tetrachloride and triethylamine as condensating agents.[4] Probably on account of steric effects the dimeric ketone **12** fails to condense with any carboxamide under acidic conditions. Polycyclic dienamide **14** was then prepared by adapting the convenient method described by Barton[5] for the preparation of monoenamides. It consists of the reductive acylation of the oxime acetate of the dimeric ketone **12**, which can be efficiently effected by using chromium(II) diacetate in acetic anhydride (Scheme III). Treatment of the polycyclic dienamide **14** with the Lawesson reagent gives rise to the polycyclic spirothiazine **15** with the excellent yield of 93%.

A marked degree of conjugated character for the parent models seems to be a prerequisite to these spiroannelation reactions. It results in an important participation of the tautomeric forms **7** and **8**. The Markovnikov addition products **9** and **10** would arise from the acid-catalyzed addition[6] of the thiol group on the γ,δ double bond. This hypothesis is corroborated by the chemical behavior of α,β- and γ,δ-monounsaturated enamides. Indeed treatment of these unconjugated compounds[7] with the Lawesson reagent

Scheme IV



leads exclusively to the corresponding thio derivatives as illustrated by Scheme IV.

Bicyclic γ,δ-unsaturated amide **16** was synthesized by benzoylation under Schotten–Baumann conditions of 2-(cyclohex-1-enyl)cyclohexylamine, obtained by reduction of the oxime of the bicyclic ketone **4** with $LiAlH_4$. A mixture of the cis and trans isomers was then obtained in the ratio 40:60. The trans form was treated with the Lawesson reagent, and γ,δ-monoenamide **16** was converted almost quantitatively into its thio analogue **17**. The spiroannelation of thioenamide *trans*-**17** was achieved photochemically by irradiating a carefully degassed hexane solution of **17** (5×10^{-3} M, Rayonet RPR 208, 3000 Å) (Scheme IV). Spirothiazine **18** was obtained in the trans configuration with a fairly good yield (85%). Although not identified, it appears plausible that the photoheterocyclization reaction proceeds via the thioenol form of **17** and that cyclic imino thioether **18** is issued from an intramolecular photochemical addition of the thiol on the γ,δ double bond, a very well documented phenomenon.[9]

The different reactions reported here represent therefore a novel method for preparing a wide variety of spiro(poly)cyclic imino thio- and selenoethers from easily available starting materials. In particular these (photo)heterocyclization reactions allow the creation of a spiro carbon center in one step. Such compounds can indeed by prepared by only a few limited methods, and generally the synthetic challenge is particularly demanding.[10]

Experimental Section

General Techniques. Melting points (uncorrected) were taken on a Reichert Thermopan apparatus. ^1H NMR (60 MHz) spectra were run in $CDCl_3$ on a Bruker WP 60 spectrometer. ^{13}C NMR (100 MHz) spectra were obtained on a Bruker AM 400 WB in C_6D_6. The chemical shifts are reported in δ values relative to tetramethylsilane, which was used as an internal standard. The UV spectrum was measured on a Jobin-Yvon spectrophotometer. IR spectra were recorded on a Perkin-Elmer 157G instrument. Mass spectra were registered on a Riber 10-10 apparatus, and for accurate mass determination, the samples were analyzed on a Varian MAT 311A. For column chromatography, Merck 70–230-mesh silica gel 60 was employed. Elemental analyses were performed at the CNRS microanalysis center.

Starting Materials. Thiobenzamide (**1a**) and thionicotinamide (**1b**) are commercially available. Selenobenzamide (**2a**) and 2-thiopheneselenocarboxamide (**2c**) were synthesized according to an already reported procedure[3] by treating the corresponding nitriles with Al_2Se_3[11] in basic medium.

(4) Holba, A. G.; Premasager, V.; Barot, B. C.; Eisenbraun, E. J. *Tetrahedron Lett.* **1985**, *26*, 571.
(5) Boar, R. B.; McGhie, J. F.; Robinson, M.; Barton, D. H. R.; Horwell, D. C.; Stick, R. V. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1237.
(6) (a) Ipatieff, V. N.; Pines, H.; Friedman, B. S. *J. Am. Chem. Soc.* **1938**, *60*, 2731. (b) Boustany, K. S.; Jacot-Guillarmot, A. *Chimia* **1969**, *23*, 331.
(7) We have already reported[8] that the treatment of α,β-unsaturated enamides with the Lawesson reagent simply results in a carbonyl–thiocarbonyl conversion.
(8) Couture, A.; Dubiez, R.; Lablache-Combier, A. *J. Org. Chem.* **1984**, *49*, 714.
(9) Walling, C. In *Free Radicals in Solution*; Wiley: New York, 1957; Chapter 7, 313.
(10) (a) Krapcho, A. P. *Synthesis* **1976**, 425. (b) Trost, B. M.; Adams, B. R. *J. Am. Chem. Soc.* **1983**, *105*, 4849 and references cited therein.

2-(Cyclohex-1-enyl)cyclohexanone (3) is prepared in the following manner. A solution of cyclohexanone (30 g, 0.3 mol) in toluene (250 mL) is refluxed for 15 h in the presence of a catalytic amount of *p*-toluenesulfonic acid (2.50 mg). The water formed during the reaction is eliminated by azeotropic distillation. The toluene is removed in vacuo in a rotatory evaporator and the 2-(cyclohex-1-enyl)cyclohexanone (3) is distilled [120 °C, 35 mm] (16.3 g, 0.09 mol, 61%).

General Procedure for the Direct Condensation of Thio- and Selenocarboxamides with the Bicyclic Ketone 3. A mixture of the appropriate aryl thio- or selenocarboxamides **1a,b** and **2a,c** (0.05 mol), respectively, and 2-(cyclohex-1-enyl)cyclohexanone (3) in toluene (200 mL) was refluxed in the presence of a catalytic amount of β-naphthalenesulfonic acid (250 mg). A Dean–Stark apparatus was used in order to remove the water formed by azeotropic distillation. Reflux was maintained for 24 h and after cooling, the mixture was washed with an aqueous sodium carbonate solution and dried ($MgSO_4$). The toluene was removed in vacuo in a rotatory evaporator, and the crude product was purified by chromatography on silica gel with ethyl acetate–petroleum ether (1:3) as eluent.

Cyclohexanespiro-2-(5-aza-4-phenyl-3-thiabicyclo[4.4.0]deca-1(6),4-diene) (9a): mp 89–90 °C; ^1H NMR ($CDCl_3$) δ 1.30–1.95 (m, 14 H, CH_2), 2.05–2.60 (m, 4 H, $CH_2C{=}C$), 7.30–7.50 (m, 3 H, aromatic CH), 7.80–8.10 (m, 2 H, aromatic CH); MS, *m/e* (relative intensity) 297 (M^+, 7), 135 ($C_6H_5CSN^+$, 100), 103 ($C_6H_5CN^+$, 77); IR (KBr) ν 1610 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NS$: C, 76.73; H, 7.80; N, 4.71; S, 10.76. Found: C, 76.69; H, 7.87; N, 4.21; S, 10.59.

Cyclohexanespiro-2-(5-aza-4-(α-pyridyl)-3-thiabicyclo[4.4.0]deca-1(6),4-diene) (9b): mp 122–123 °C; ^1H NMR ($CDCl_3$) δ 1.25–1.95 (m, 14 H, CH_2), 2.00–2.50 (m, 4 H, $CH_2C{=}C$), 7.35, 8.25, 8.70, 9.15 (m, 4 H, pyridine CH); MS *m/e* (relative intensity) 298 (M^+, 4), 136 ($C_5H_4NCSN^+$, 82), 104 ($C_5H_4NCN^+$, 100); precise mass determination calcd for $C_{18}H_{22}N_2S$ 298.15036, found 298.1506; IR ($CDCl_3$) ν 1610 cm^{-1}. Anal. Calcd for $C_{18}H_{22}N_2S$: C, 72.45; H, 7.43; N, 9.39; S, 10.72. Found: C, 72.51; H, 7.43; N, 9.40; S, 10.75.

Cyclohexanespiro-2-(5-aza-4-phenyl-3-selenabicyclo[4.4.0]deca-1(6),4-diene) (10a): ^1H NMR ($CDCl_3$) δ 1.30–1.90 (m, 14 H, CH_2), 2.05–2.60 (m, 4 H, $CH_2C{=}C$), 7.05–7.50 (m, 3 H, aromatic CH), 7.75–8.05 (m, 2 H, aromatic CH); MS *m/e* (relative intensity) 345 (M^+, 1), 265 (M^+ – Se, 100), 162 (M^+ – C_6H_5, CSeN, 75); IR ($CDCl_3$) ν 1610 cm^{-1}; precise mass determination calcd for $C_{19}H_{23}NSe$ 345.09957, found 345.0988.

Cyclohexanespiro-2-(5-aza-4-(α-thienyl)-3-selenabicyclo[4.4.0]deca-1(6),4-diene) (10c): ^1H NMR ($CDCl_3$) δ 1.35–2.00 (m, 14 H, CH_2), 2.05–2.50 (m, 4 H, $CH_2C{=}C$), 6.90–7.75 (m, 3 H, thienyl); MS *m/e* (relative intensity) 351 M^+, 3), 271 (M^+ – Se, 100), 162 (M^+ – C_4H_3SCSeN, 77); IR ($CDCl_3$) ν 1610 cm^{-1}; precise mass determination calcd for $C_{17}H_{21}NSeS$ 351.05599, found 351.0564.

The direct condensation of benzamide (6 g, 50 mmol) with 2-(cyclohex-1-enyl)cyclohexanone (3) (8.5 g, 50 mmol) following the general procedure described above afforded exclusively 1-benzamido-2-(cyclohex-1-enyl)cyclohex-1-ene (11) (9.1 g, 30 mmol, yield 65%): mp (hexane–toluene) 81–82 °C; ^1H NMR ($CDCl_3$) δ 1.40–1.70 (m, 8 H, CH_2), 1.70–2.20 (m, 6 H, $CH_2C{=}C$), 2.75 (m, 2 H, $C{=}CCH_2$ α to N), 5.60 (m, 1 H, vinyl H), 6.90–7.60 (m, 6 H, aromatic CH and NH, D_2O exchanged); ^{13}C NMR (C_6D_6) δ 164.6 (C=O); MS *m/e* (relative intensity) 281 (M^+, 13), 105 ($C_6H_5CO^+$, 100), 176 (M^+ – C_6H_5CO, 23); IR ($CDCl_3$) ν 3420, 1670, 1570 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.09; H, 8.09; N, 4.88.

Synthesis of 1-Acetamido-3,3′,4,4′-tetrahydro-1′,2-binaphthalene (14). The aldol dimerization product **12** of α-tetralone was prepared according to a procedure recently reported by Eisenbraun.[4] The oxime of the polycyclic ketone **12** was prepared in the usual manner.[12] 3,3′,4,4′-Tetrahydro-1′,2-binaphthalene-1(2*H*)-one oxime: mp 191–192 °C; ^1H NMR ($CDCl_3$) δ 1.90–2.80 (m, 9 H, CH_2 and CH), 5.60 (m, 1 H, vinyl H), 7.10–7.50 (m, 8 H, aromatic CH and OH, D_2O exchanged), 8.00 (m, 1 H, aromatic CH); MS *m/e* (relative intensity) 289 (M^+, 100), 272 (M^+ – OH, 93); IR (KBr) ν 3150, 1640, 920 cm^{-1}. Anal. Calcd for $C_{20}H_{19}NO$: C, 83.59; H, 5.96; N, 4.88. Found: C, 83.35; H, 6.01; N, 4.99.

To a solution of the oxime **13** (5.8 g, 20 mmol) in dimethylformamide (10 mL) was slowly added 10 mL of reagent grade acetic anhydride (10 mL), and the mixture was stirred under nitrogen until no oxime could be detected by TLC (1 h). Anhydrous chromium(II) acetate[13] (10.2 g, 75 mmol) was then added and the stirring was continued for 20 h. The solvent was removed under reduced pressure, 1 N sodium carbonate solution (100 mL) was added, and the mixture was extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated. The crude product was then chromatographed on silica gel, using ethyl acetate–petroleum ether (1:3) as eluent. The dienamide **14** was recrystallized from toluene–hexane (5.7 g, 18 mmol, 89%): mp 202–204 °C; ^1H NMR ($CDCl_3$) δ 1.80 (s, 3 H, CH_3), 2.20–3.00 (m, 8 H, CH_2), 5.90 (m, 1 H, vinyl H), 6.40 (m, 1 H, NH, D_2O exchanged), 7.00–7.20 (m, 8 H, aromatic CH); MS *m/e* (relative intensity) 315 (M^+, 8), 272 (M^+ – CH_3CO, 100); IR ($CDCl_3$) ν 3440, 1670, 1570 cm^{-1}. Anal. Calcd for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44. Found: C, 83.45; H, 6.78; N, 4.31.

Synthesis of 1-Benzamido-2-(cyclohex-1-enyl)cyclohexane (*cis*- and *trans*-16). The oxime of the bicyclic ketone **3** was prepared according to the classical method and was reduced in the following manner. To a suspension of $LiAlH_4$ (1.9 g, 50 mmol) in anhydrous tetrahydrofuran (20 mL) was slowly added a solution of the crude oxime (4 g, 20 mmol) in tetrahydrofuran (20 mL). The mixture was refluxed for 16 h and then cooled and slowly poured, by small portions and under stirring, on crushed ice. The crude reaction mixture was filtered on a Celite pad, extracted with ether, dried ($MgSO_4$), and concentrated. The crude mixture of amines was acylated under the classical conditions of Schotten–Bauman reactions. To a solution of the cis and trans amines and triethylamine (2 g, 20 mmol) in anhydrous diethyl ether (30 mL) was added dropwise a solution of benzoyl chloride (2.8 g, 20 mmol) in ether (20 mL), and the mixture was refluxed for 1 h. After cooling, 10% sodium bicarbonate solution (100 mL) was added, and the mixture was filtered and extracted twice with ethyl acetate (2 × 100 mL). The combined extracts were dried ($MgSO_4$) and evaporated, and the residual product was chromatographed on silica gel, using ethyl acetate–hexane (3:7) as eluent. The cis isomer was eluted first, and the two isomers were recrystallized in methanol.

***cis*-1-Benzamido-2-(cyclohex-1-enyl)cyclohexane (*cis*-16)**: 1.92 g, yield 34% (40% of the mixture of isomers): mp 114–115 °C; ^1H NMR (400 MHz, C_6D_6) δ 1.23–2.31 (m, 17 H, CH_2 and CH), 4.34 (m, 1 H, J_{NH} = 5.60 Hz, J_1 = 0.93 Hz, J_2 = 3.03 Hz, J_3 = 6.75 Hz, CH next to N), 5.41 (m, 1 H, vinyl H), 5.9 7 (broad d, 1 H, J = 5.60 Hz), 7.35–7.42 (m, 3 H, aromatic CH), 7.58–7.66 (m, 2 H, aromatic CH); MS *m/e* (relative intensity) 283 (M^+, 18), 178 (M^+ – C_6H_5CO, 36), 105 ($C_6H_5CO^+$, 100); IR (KBr) ν 3420, 1650, 1570 cm^{-1}. Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 79.96; H, 8.87; N, 4.84.

***trans*-1-Benzamido-2-(cyclohex-1-enyl)cyclohexane (*trans*-16)**: 2.88 g, yield 51% (60% of the mixture of isomers): mp 127–129 °C; ^1H NMR (400 MHz, C_6D_6) δ 1.06–2.35 (m, 17 H, CH_2 and CH), 3.80 (m, 1 H, J_{NH} = 6.30 Hz, J_{aa} = 10.95 Hz, J_{aa} = 11.18 Hz, J_{ae} = 3.96 Hz, CH next to N), 5.47 (m, 1 H, vinyl H), 5.92 (broad d, 1 H, J = 6.30 Hz, NH), 7.32–7.40 (m, 3 H, aromatic CH), 7.58–7.64 (m, 2 H, aromatic CH); MS *m/e* (relative intensity) 283 (M^+, 23), 178 (M^+ – C_6H_5CO, 37), 105 ($C_6H_5CO^+$, 100); IR (KBr) ν 3420, 1650, 1570 cm^{-1}. Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.29; H, 9.08; N, 4.84.

General Procedure for the Treatment of Mono- and Dienamides with the Lawesson Reagent. A mixture of the dienamides **11**, **14** or of the γ,δ-monosaturated amide *trans*-**16** (5 mmol), $(CH_3OC_6H_4)_2P_2S_4$ (1 g, 2.5 mmol), and dry toluene (10 mL) was heated at 100 °C for 2 h in an atmosphere of argon. TLC indicated that all the amides **11**, **14**, and *trans*-**16** had been consumed. The toluene was removed in vacuo, and the residue was purified by flash chromatography on silica gel with ethyl acetate–petroleum ether (1:3) as eluent.

(11) Waitkins, G. R.; Schutt, R. *Inorg. Synth.* **1946**, *2*, 183.
(12) Lachman, A. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 70.
(13) Hanson, J. R. *Synthesis* **1974**, 1.

1′,2′,3′,4′-Tetrahydronaphthalenespiro-2-(5-aza-7,8-benzo-4-methyl-3-thiabicyclo[4.4.0]deca-1(6),4,7-triene) (15): mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 1.70–2.20 (m, 6 H, CH_2), 2.25 (s, 3 H, CH_3), 2.50–2.90 (m, 4 H, C=CCH_2), 7.00–7.40 (m, 6 H, aromatic CH), 7.45 (m, 1 H, aromatic CH), 7.75 (m, 1 H, aromatic CH); MS *m/e* (relative intensity) 331 (M^+, 77), 270 (M^+ – CH_3CSN, 100); IR ($CDCl_3$) ν 1605 cm^{-1}. Anal. Calcd for $C_{22}H_{21}NS$: C, 79.73; H, 6.39; N, 4.23; S, 9.66. Found: C, 79.47; H, 6.52; N, 4.16; S, 9.84.

***trans*-1-(Thiobenzamido)-2-(cyclohex-1-enyl)cyclohexane (*trans*-17)**: mp 111–113 °C; ^{1}H NMR ($CDCl_3$) δ 1.20–2.50 (m, 17 H, CH_2 and CH), 4.20–4.50 (m, 1 H, CH next to N), 5.50 (m, 1 H, vinyl H), 7.10–7.65 (m, 5 H, aromatic CH); MS *m/e* (relative intensity) 299 (M^+, 100), 121 ($C_6H_5CS^+$, 35); IR ($CDCl_3$) ν 3250, 1600, 1590 cm^{-1}; UV (hexane) λ_{max} 295 nm (ε 18500), 440 (ε 2000). Anal. Calcd for $C_{19}H_{25}NS$: C, 76.22; H, 8.42; N, 4.68; S, 10.69. Found: C, 76.03; H, 8.51; N, 4.65; S, 10.81.

Photolysis of the Thioenamide *trans*-17. A solution of the thioenamide *trans*-17 (300 mg, 5×10^{-3} M) in hexane (350 mL) was placed in a water-cooled quartz reactor equipped with a dry argon inlet and a magnetic stirrer. The solution was purged by bubbling argon through it for 2 h and then irradiated with eight Rul 3000-Å lamps in a Rayonet RPR photochemical reactor for 45 min. The solvent was removed under vacuum and the crude photoreaction product was finally purified by elution chromatography, using ethyl acetate–hexane (1:4) as eluent.

***trans*-Cyclohexanespiro-2-(5-aza-4-phenyl-3-thiabicyclo-[4.4.0]dec-4-ene) (*trans*-18)**: 255 mg, 85%; mp 123–125 °C; ^{1}H NMR ($CDCl_3$) δ 1.20–2.50 (m, 19 H, CH_2 and CH), 3.05 (m, 1 H, CH next to N), 7.20–7.75 (m, 5 H, aromatic CH); MS *m/e* (relative intensity) 299 (M^+, 11), 164 ($M^+ - C_6H_5CSN$, 100), 121 ($C_6H_5CS^+$, 22), 103 ($C_6H_5CN^+$, 34); IR ($CDCl_3$) ν 1615 cm^{-1}. Anal. Calcd for $C_{19}H_{25}NS$: C, 76.22; H, 8.42; N, 4.68; S, 10.69. Found: C, 76.28; H, 8.42; N, 4.68; S, 10.71.

Registry No. **1a**, 2227-79-4; **1b**, 5346-38-3; **2a**, 5977-82-2; **2c**, 54679-69-5; **3**, 1502-22-3; **3** (oxime), 37575-86-3; **9a**, 115464-12-5; **9b**, 115464-10-3; **10a**, 115464-13-6; **10c**, 115464-11-4; **11**, 105983-29-7; **12**, 23804-16-2; **13**, 115464-14-7; **14**, 115464-15-8; **15**, 115464-16-9; *cis*-**16**, 115464-17-0; *trans*-**16**, 115464-18-1; **17**, 115464-19-2; **18**, 115464-20-5; benzamide, 55-21-0; *cis*-1-(2-aminocyclohexyl)cyclohexene, 115464-21-6; *trans*-1-(2-aminocyclohexyl)cyclohexene, 115464-22-7; cyclohexanone, 108-94-1.

Total Synthesis of *rac*-9,11-Dehydrodigitoxigenin 3-Tetrahydropyranyl Ether

Andrzej Robert Daniewski,* Marek Michał Kabat, Marek Masnyk, Jerzy Wicha, and Wanda Wojciechowska

Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, ul. Kasprzaka 44, Poland

Helmut Duddeck

Lehrstuhl für Strukturchemie, Ruhr-Universität Bochum, Postfach 10 21 48, D-4630 Bochum 1, FRG

Received March 10, 1988

There are many publications[1] dealing with partial synthesis of cardenolides. Most of these papers concern linking of the lactone ring to the steroidal skeleton and the introduction of a hydroxyl group in the 14β-position.

We present the total synthesis of the title compound in which the lactone ring was added to an earlier synthesized derivative **4** of androstane, containing a hydroxyl group in the 14β-position. Starting from racemic Mieschner–Wieland ketone **1**, which can also be obtained by asymmetric synthesis in pure enantiomeric form,[2] we obtained seco-compound **2** in five steps[3] (Scheme I). Base-catalyzed cyclization of **2** was very erratic. Control of temperature as well as pH of the reaction mixture was essential. At temperatures lower than −15 °C, the rate of cyclization was slow, whereas above −10 °C the reaction components decomposed. Under optimal conditions, the yield of **3** was 40%, and about 20% of starting compound **2** was recovered. Selective hydrogenation[3] of **3** over palladium on $SrSO_3$ furnished **4**, which served as a substrate for synthesis of the title compound. Retainment of the 14β-hydroxyl in compound **4** was an important requirement of the synthetic program. However, for continuation of the synthesis it was necessary to develop a new approach to construction of 17β-orientated lactones. Hydrogenation of ethylenic bonds in position 16–17 or 17–20 of steroids with a cis C/D ring junction is known to proceed from the less hindered β side of the molecule and furnishes products with 17α-substituents. We intended to introduce a 17β-substituent by an S_N2 type free-radical reaction of a 17α-iodo derivative. For this purpose, **4** was hydrogenated to **5**, which was converted to **6** by K-Selectride at −40 °C in a THF–toluene mixture. Compound **7** was obtained by treatment of the crude hydrazone of **6** with iodine according to a known procedure[4] (Scheme II). Hydrogenation of **7** with diimide afforded iodide **8** suitable for the substitution reaction. Direct exchange of the iodine atom for the cyano group was unsuccessful,[5] but using a procedure for protection of the 14β-hydroxyl group in the form of THP and trimethylsilyl ethers,[6] we could achieve substitution of iodine by cyanide (NaCN–DMSO, 110 °C), though only in moderate yield (40%), and complications developed during attempts to hydrolyze the protecting groups. Hence, attention was directed to free-radical reactions which do not require protection of the hydroxyl group and presumably afford a product resulting from substitution from the less hindered side. After unsuccessful attempts to attach 2-buten-1,4-olide, 3-bromo-2-buten-1,4-olide, and 3-(tributyltin)-2-buten-1,4-olide groups by a free-radical reaction[7] initiated by tributyltin hydride and AIBN, we found that reaction of iodide **8** with *tert*-butyl isocyanide in the presence of tributyltin chloride, sodium cyanoborohydride, and AIBN in boiling *tert*-butyl alcohol[8] afforded nitrile **9** in 82% yield. The β orientation of the cyano group was proved as follows. Nitrile **10** was transformed into lactone **11** (IR 1775 cm^{-1}) in 25% yield by reaction with DIBAH followed by PCC oxidation of the intermediate aldehyde.

Having on hand the nitrile **10**, we intended to prepare the corresponding derivative 21-hydroxy-20-oxopregnane and then to form the butenolide ring according to a known

(1) Wicha, J.; Kabat, M. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1601. Stork, G.; Stryker, J. M. *Tetrahedron Lett.* **1983**, *24*, 4887. Welzel, P.; Stein, H.; Milkowa, T. *Liebigs Ann. Chem.* **1982**, 2119. Marini-Bettolo, R.; Flecker, P.; Tsai, T. Y. R.; Wiesner, K. *Can. J. Chem.* **1981**, *59*, 1403.

(2) W. Ger. Pat. 2102623, Jan 21, 1970. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. Gitzwiller, J.; Buchschacher, P.; Furts, A. *Synthesis* **1977**, 167. Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496.

(3) Daniewski, A. R.; White, P.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 1397. Daniewski, A. R.; Valenta, Z.; White, P. *Bull. Pol. Acad. Sci., Chem.* **1984**, *32*, 29.

(4) Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962**, 470.

(5) A similar reaction has been published by Kabat et al.: Kabat, M. M.; Kurek, A.; Masnyk, M.; Repke, K. R. H.; Schönfeld, W.; Wieland, J.; Wicha, J. *J. Chem. Res., Synop.* **1987**, 218.

(6) The hydroxyl groups in **8** at the 3- and 14-positions were protected (in 40%) as THP ethers by using the Grieco method (*J. Org. Chem.* **1977**, *42*, 3772). The TMS ether grouping in the 3- and 14-positions in **8** was obtained in 85% yield by the reaction of **8** with TMSCN in DMF with addition of a catalytic amount of the $ZnCl_2$·Py complex.

(7) Baldwin, J. E.; Kelly, D. R.; Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1984**, 133.

(8) Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384.

0022-3263/88/1953-4855$01.50/0