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Lithiated (*E*)-*N*-Isopropyl-5-tosyl-4-pentenamide: Synthetic Applications as New δ-Acyldienyl Anion Equivalent

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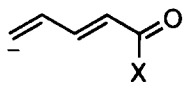
Abstract: The vinyl sulfone (*E*)-*N*-isopropyl-5-tosyl-4-pentenamide (**14**), prepared from 4-pentenoic acid by stereoselective iodosulfonylation-dehydroiodination and further amidation, reacts with two equiv of n-butyllithium at -78°C to give presumably a dilithiated lactam **25**. After reaction with aldehydes and propylene oxide or alkyl halides (2*E*,4*E*)-6-hydroxy and 7-hydroxy-2,4-hexadienamides **15** and **21** or alkylated dienamides **18** and **20** are stereoselectively obtained, respectively. In the case of carboxylic acid chlorides or cyclohexyl isocyanate, dilithiated lactam **25** undergoes acylation to afford the corresponding lactam derivatives **22**. The 6-hydroxy-2,4-dienamide **15f** has been transformed into the 6-oxo-2,4-dienamide **41** by oxidation or into the (2*E*,4*E*,6*E*)-trienamide **42** by bromination reactions.

INTRODUCTION

δ-Acyldienyl anion equivalents of the type **1** are umpoled d[5] carbanionic reagents acting as valuable synthons to transfer the (2*E*,4*E*)-dienoic unit present in many natural products.[1,2] However, to the best of our knowledge there is only one example of a δ-acyldienyl anion equivalent of the type **1**, the dianions derived from (allylthio)acetates **2** after a multi-step procedure.[3]



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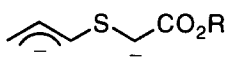

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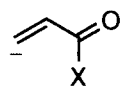

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The previously demonstrated synthetic usefulness of γ-oxosulfones **4**,[4] derived from α,β-unsaturated carboxylic acids **6**, as β-acylvinyl anions equivalents **3** prompted us to study the use of vinylogous ε-oxosulfones **8** or **11** as precursors of δ-acyldienyl anion equivalents **7** or **10**, respectively. These ε-oxosulfones could be prepared from the corresponding unsaturated systems **9** and **12** by sulfinic acid addition or by iodosulfonylation-dehydroiodination procedures, respectively. However, previous attempts to add *p*-toluenesulfinic acid to pentadienamides failed.[5] Moreover, allyl sulfones of the type **8** have a great tendency to suffer δ-dehydrosulfinylation under basic conditions instead of deprotonation.[6] For these reasons, vinyl sulfones of the type **11** should be better candidates to be lithiated at the vinylic position[7] and, after reaction with electrophiles, could suffer isomerization of the double carbon-carbon bond and δ-elimination of the sulfinic acid under basic conditions providing the corresponding 5-substituted diene systems.[8] Therefore, these type of umpoled d[5] carbanionic reagents **10** can be promising intermediates to transfer the α,β,γ,δ-unsaturated functionality.

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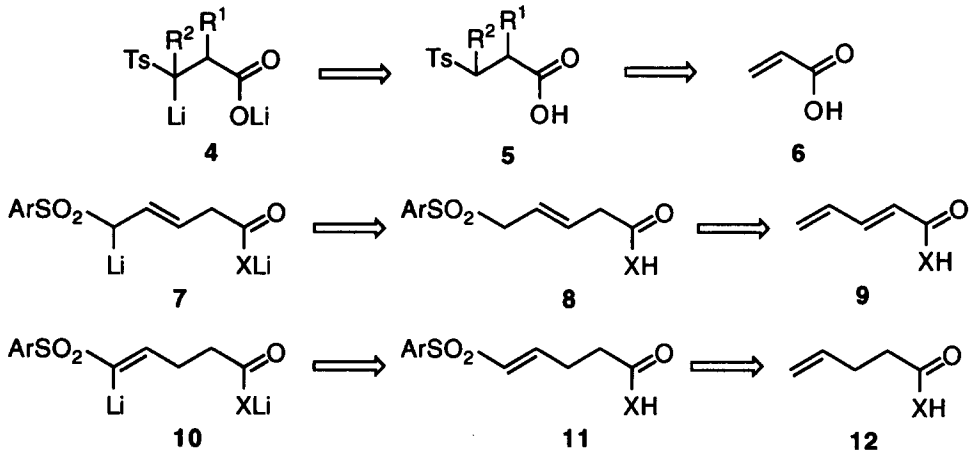


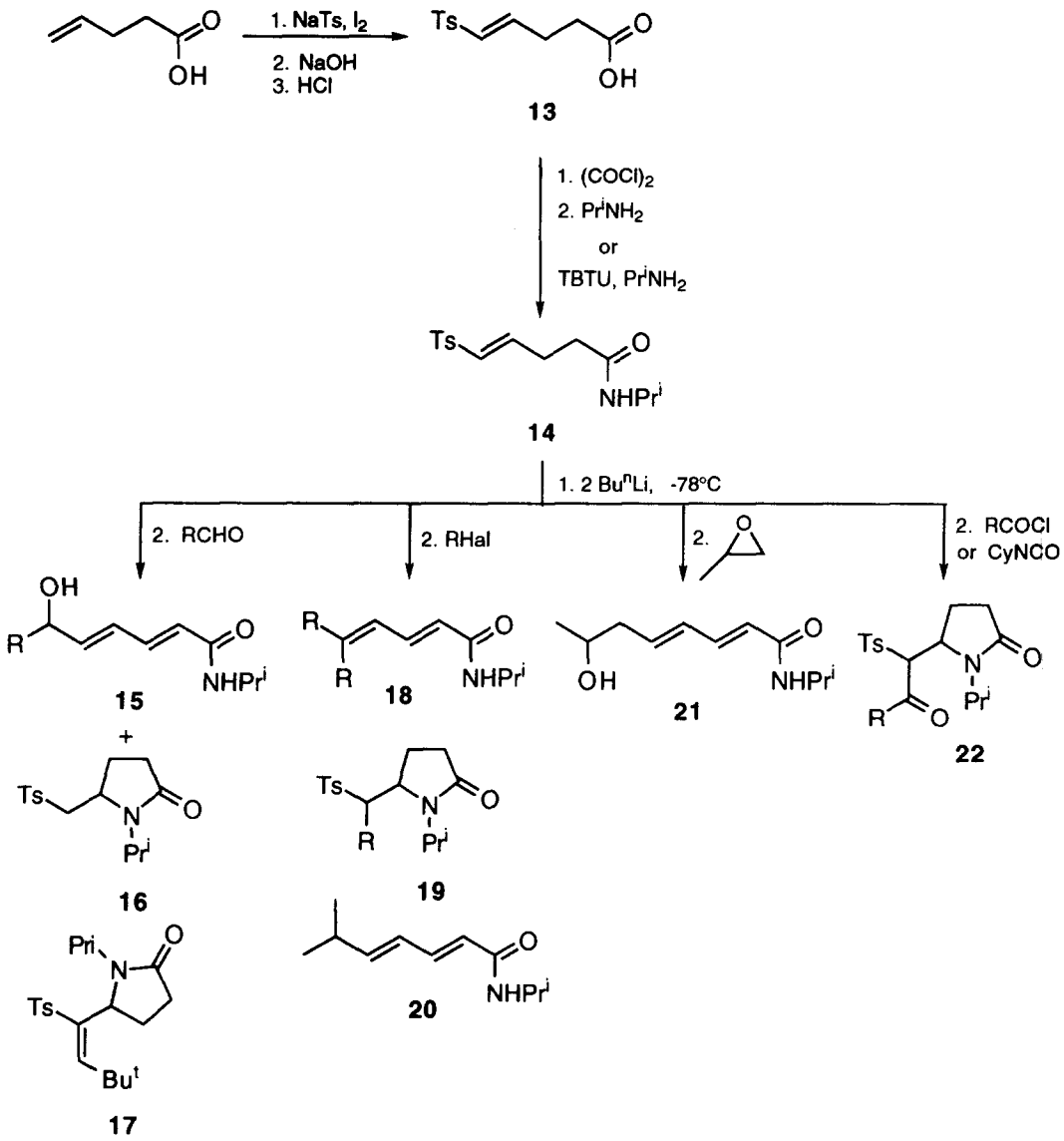
RESULTS AND DISCUSSION

The amide **14** was selected as starting sulfone of the type **11** (XH = NHPr^i) instead of the acid because the presence of the carboxamido group should allow the double bond isomerization and the final base-induced dehydrosulfinylation in a more efficient way. The preparation of this amide is shown in Scheme 1: the vinyl sulfone **13**, derived from 4-pentenoic acid, was stereoselectively prepared in 71% yield by iodosulfonylation with sodium *p*-toluenesulfinate and iodine in methanol followed by *in situ* dehydroiodination with 0.5M sodium hydroxide and acidification with HCl.[9] This acid was transformed into (*E*)-*N*-isopropyl-5-tosyl-4-pentenamide (**14**) either by treatment with oxalyl chloride and further *in situ* reaction with isopropylamine or by direct amidation in the presence of *N,N,N',N'*-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU) in 70% or 80% yield, respectively (Scheme 1).

The lithiation reaction of amide **14** with 2 equiv of n-butyllithium at -78°C in THF followed by addition of different aldehydes gave steroselectively the expected (2*E*,4*E*)-6-hydroxydienamides **15** together with variable amounts of lactam **16** (up to 30%). They can be easily separated by flash chromatography except in the case of compound **15b** derived from propanal, which was transformed into its tetrahydropyranyl derivative by reaction with 3,4-dihydro-2*H*-pyran.[10] Further chromatographic separation from lactam **16** and deprotection (MeOH, TsOH) provided pure hydroxydienamide **15b**. In the case of pivalaldehyde, a 17% of lactam **17** with *E*-configuration (deduced by NOE difference experiments) together with compound **15d** was also obtained (Scheme 1 and Table 1).

When alkyl halides such as methyl and *n*-butyl iodides were used as electrophiles mainly δ-dialkylated dienamides **18** were obtained. In the case of benzyl bromide a *ca.* 1:1 mixture of dienamide **18c** and lactam **19c** was formed. However, in the case of isopropyl iodide the δ-monoalkylated dienamide **20** was exclusively obtained. Epoxides were reluctant to react as electrophiles and only in the case of propylene oxide the 7-hydroxydienamide **21** was obtained in low yield (23%). When carboxylic acid chlorides or cyclohexyl isocyanate were used as electrophiles, acylated lactams **22** were isolated, as *erythro/threo* mixture of diastereomers (Scheme 1 and Table 1).

In order to explain the formation of the different products **15-22** we studied the lithiation-hydrolysis or deuterolysis processes. The reaction of amide **14** with one equiv of *n*-butyllithium at -78°C followed by water



Scheme 1.

addition at -78°C afforded lactam **16** as the only obtained product in 90% yield, whereas after deuterolysis with MeOD monodeuterated lactam **24** (90% of deuterium incorporation[11]) was obtained in 68% yield. These results revealed that the deprotonated amide gave rise to monolithiated lactam **23** by an intramolecular conjugate addition to the vinyl sulfone (Scheme 2). However, in the dilithiation reaction a 3:1 mixture of dideuterated lactam **26** (91% of deuterium incorporation[12]) and *Z*-dideuterated amide **29** (90% of deuterium incorporation[12]) was obtained in 79% overall yield. Compound **26** was probably formed from dilithiated lactam **25** (one of the lithium atoms could be at the oxygen of the sulfone group[13]), whereas the formation of compound **29** could be explained by ring opening of intermediate **25** through a β-elimination reaction[14] followed

Table 1. Reaction of Dilithiated (*E*)-*N*-Isopropyl-5-tosyl-4-pentenamide **14** with Electrophiles. Synthesis of Compounds **15-22.**

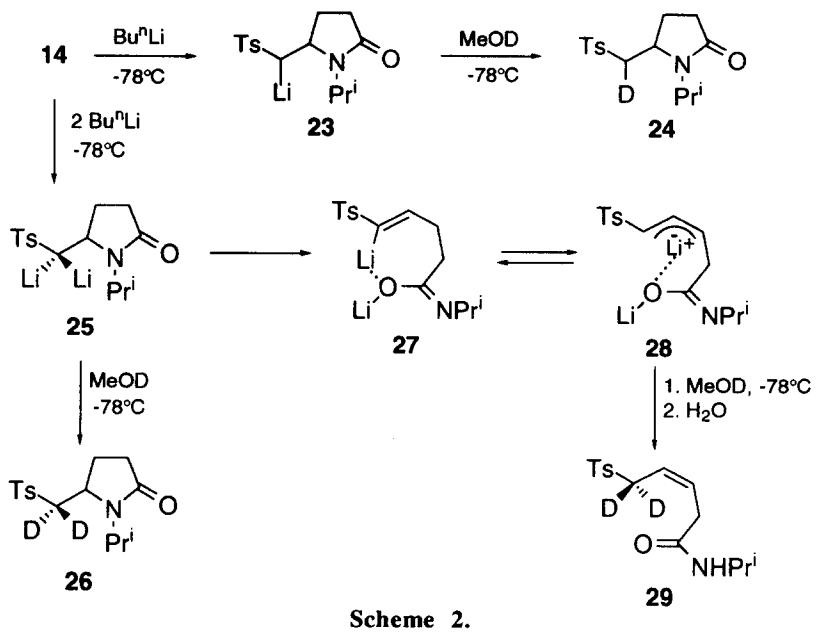
		product			
entry	electrophile	no.	R	yield (%)[a]	mp (°C)[b] or R_f[c]
1	CH_2O	**15a**	H	42	0.29
2	EtCHO	**15b**	Et	47[d]	0.36
3	Pr^iCHO	**15c**	Pr^i	52	139-140
4	Bu^tCHO	**15d**	Bu^t	58[e]	0.56
5	PhCHO	**15e**	Ph	21	137-138
6	$PhCH_2CHO$	**15f**	$PhCH_2$	48	121-122
7	MeI	**18a**	Me	40	0.70
8	Bu^nI	**18b**	Bu^n	42	0.78
9	$PhCH_2Br$	**18c**	$PhCH_2$	40[f]	0.82
10	Pr^iI	**20**	Pr^i	30	0.60
11	propylene oxide	**21**	$MeCH(OH)CH_2$	23	0.33
12	$PhCH_2OCOCl$	**22a**	OCH_2Ph	47[g]	0.71[g]
13	PhCOCl	**22b**	Ph	62[h]	0.65[h]
14	CyN=C=O	**22c**	NHCy	58[i]	0.70, 0.56

[a] Isolated yield based on amide **14**, after column chromatography on silica gel. [b] Hexane/EtOAc. [c] EtOAc. [d] After treatment of the reaction crude with dihydropyran (see text), column chromatography and deprotection. [e] A 17% of compound **17** (Scheme 1) was also obtained. [f] A 25% of compound **19c** (R = $PhCH_2$) was also obtained. [g] A 9/1: *threo/erythro* diastereomers mixture. [h] A 3.5/1: *threo/erythro* diastereomers mixture. [i] A 3/1: *threo/erythro* diastereomers mixture.

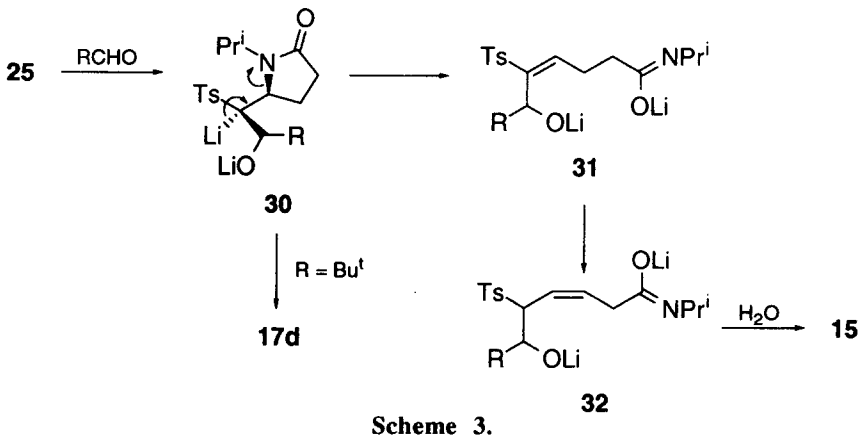
by isomerization to the allyl sulfone anion **27**. This intermediate was deuterated and again deprotonated by the lithium-amide or by the *in situ* generated lithium methoxide giving finally dideuterated product **29** (Scheme 2).

The formation of 6-hydroxydienamides **15** can be explained by reaction of the dilithiated lactam **25** with the aldehyde to give addition products **30**. These β-amido organolithium intermediates undergo ß-elimination leading to the formation of **31** which isomerise to **32**, and after final δ-dehydrosulfinylation (probably during the hydrolysis step) furnished compounds **15** (Scheme 3). The formation of compound **17d** in the reaction of dianion **14** with pivalaldehyde demonstrates the participation of intermediate **30** and can be explained by β-

elimination of the β-oxido[14] instead of the β-amido organolithium compound.



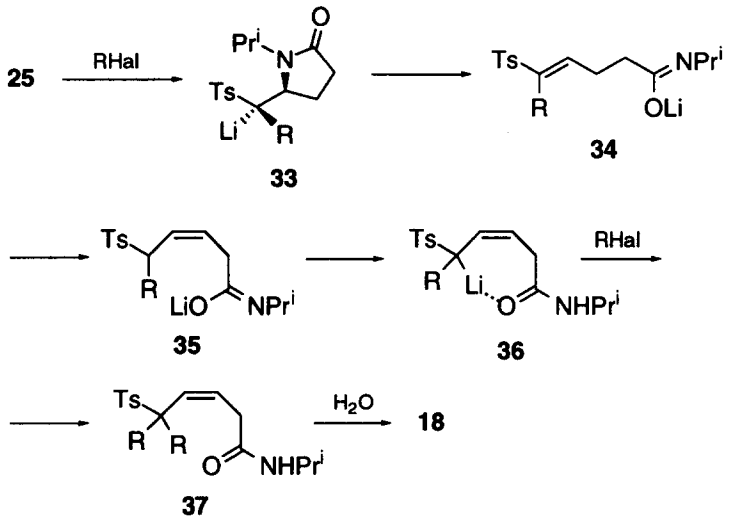
Scheme 2.



Scheme 3.

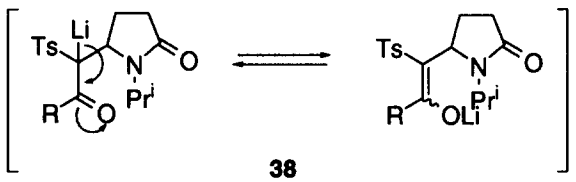
The best alkylation reaction conditions of dilithiated amide **25** were one equiv. of alkyl halide in the presence of *N,N'*-dimethylpropylenurea (DMPU). The formation of δ-dialkylated dienamides **18** could be explained by a sequential alkylation process which starts by monoalkylation of dianion **25** followed by ring opening giving intermediate **34** through a β-elimination process. After vinyl to allyl sulfone isomerization, the resulting intermediate **35** could be deprotonated intramolecularly or by dianion **25** affording **36**, which suffers final alkylation to **37** and further formation of compounds **18** after hydrolytic work-up (Scheme 4). In the case of the more sterically hindered isopropyl iodide, intermediate **36** did not suffer the second alkylation process and the corresponding monoalkylated dienamide **20** (Scheme 1) was obtained. The alkylation by

means of propylene oxide would provide intermediates of the type **34** and **35** and the obtained compound **21** after final hydrolysis (Scheme 1).

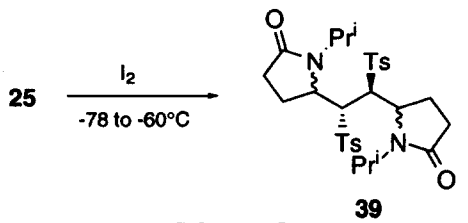


Scheme 4.

In the reaction of dianion **25** with acyl chlorides or cyclohexyl isocyanate lactams **22** were obtained, presumably because after the acylation step intermediates **38** did not suffer β-elimination due to their stability as enolates. Compounds **22** were isolated as mixture of *erythro/threo* diastereomers the latter being the major one (determined by ^{1}H NMR and assigned according to coupling constant values between vicinal protons[15]).

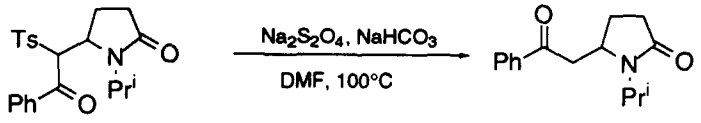


Dilithiated lactam **25** suffered stereoselective dimerization[16] giving bis-lactam **39** in 75% yield by treatment with 1 equiv of iodine for 1 h between -78 and -60°C (Scheme 5). From the corresponding NMR spectra can be deduced that a 5/1 mixture of very symmetrical diastereomers was obtained, presumably the two *meso* compounds *threo/erythro*.[17]



Scheme 5.

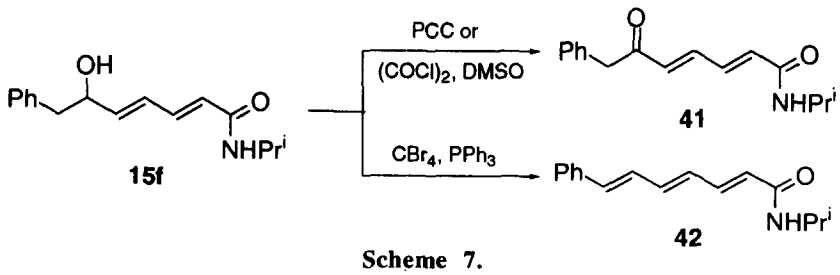
Reductive desulfonylation of the acylated lactam **22b** has been achieved by using sodium dithionite in DMF[18] at 100°C to afford compound **40** in 40% yield (Scheme 6).



22b **40**

Scheme 6.

Representative 6-hydroxydienamide[19] **15f** has been transformed into 6-oxodienamide **41** either by oxidation with PCC[20] or Swern[21] oxidation reactions in 40% yield (Scheme 7). Attempts to carry out dehydration of **15f** to the corresponding trienamide by mesylation and acylation reactions of the hydroxy group failed. However, during the bromination reaction with carbon tetrabromide-triphenylphosphine under acetonitrile reflux,[22] the (2*E*,4*E*,6*E*)-heptatrienamide **42** was stereoselectively obtained in 50% yield (Scheme 7).



15f **41** **42**

Scheme 7.

As conclusion, the dilithiation of (*E*)-*N*-isopropyl-5-tosyl-4-pentenamide, readily accessible from 4-pentenoic acid, afforded mainly a dilithiated lactam which acts as a δ-acyldienyl monoanion and dianion equivalent in its reaction with aldehydes or propylene oxide and alkyl halides, respectively. This methodology is an adequate and direct strategy to prepare 6-hydroxy and 7-hydroxy substituted as well as δ-alkylated (2*E*,4*E*)-dienamides in a stereoselective manner.

EXPERIMENTAL SECTION

General. See reference 7.

Synthesis of (*E*)-5-Tosyl-4-pentenoic Acid (13). A suspension of 4-pentenoic acid (1.05 mL, 10 mmol), sodium *p*-toluenesulfinate (5.16 g, 20 mmol) and iodine (3.05 g, 12 mmol) in methanol (50 mL) was stirred for 2 d at room temperature. Then, the solvent was evaporated (15 Torr) and the resulting residue was dissolved in EtOAc (50 mL) and washed with aqueous 0.2M $Na_2S_2O_3$. The organic phase was decanted and extracted with aqueous 0.5M NaOH. This aqueous solution was acidified with concentrated HCl, extracted with EtOAc (3x30 mL) and the organic layers dried with Na_2SO_4. The solvent was evaporated (15 Torr) and the resulting residue was recrytallized from hexane/EtOAc affording 1.78 g of acid **13** (71% yield): mp 93-94°C; R_f 0.55 (ether); ν (Nujol) 2840 (OH), 1690 (C=O), 1280 and 1140 cm^{-1} (SO_2); δ_H 2.42 (s, 3H, CH_3Ar), 2.57 [m, 4H, $(CH_2)_2$], 6.39 (d, *J*=14.9, 1H, SCH); 6.96 (dt, *J*=14.9, 6.1, 1H, SCH=C*H*), 7.33

and 7.74 (2d, *J*=8.1, ArH), 9.84 (br s, 1H, OH); δ_C 21.4 (*C*H_3Ar), 26.0 (CH*C*H_2), 31.55 (*C*H_2CO), 131.6, 143.7 (CH=CH), 127.4, 129.8, 137.0, 144.3 (ArC), and 177.1 (CO); *m/z* 254 (M^+, 19%), 155 (16), 99 (33), 92 (29), 91 (100), 90 (24), 85 (16), 83 (56), 82 (14), 65 (29), 55 (21), 43 (16) (Found: C, 56.39;H, 5.59; S, 13.03. Calcd. for $C_{12}H_{14}O_4S$: C, 56.68; H, 5.55; S, 12.61).

Synthesis of (*E*)-*N*-Isopropyl-5-tosyl-4-pentenamide (14). *1st Method.* To a solution of (*E*)-5-tosyl-4-pentenoic acid (**13**) (254 mg, 1 mmol) in CH_2Cl_2 (5 mL), containing a little amount of dry DMF (4 droops), was added slowly $(COCl)_2$ (219 μL, 2.5 mmol) and the reaction mixture was stirred under argon for 5 h. Then, solvent was evaporated in vacuo (15 Torr) without heating giving the corresponding acid chloride. This compound was dissolved in dry ether (5 mL), and Pr^iNH_2 (221 μL, 2.2 mmol) was added at 0°C with stirring, allowing to react at room temperature for 1 h. Then, EtOAc was added and the resulting organic layer was washed with 2M HCl (3x30 mL) and saturated $NaHCO_3$ (3x30 mL), dried (Na_2SO_4) and concentrated (15 Torr) to give the corresponding crude amide. This crude amide was recrystallized from hexane/EtOAc affording 207 mg of pure amide **14** as a white solid (70% yield). *2nd Method.* A solution of acid **13** (1.27 g, 5 mmol) in CH_3CN (40 mL) was treated with Et_3N (1.45 mL, 10 mmol), Pr^iNH_2 (530 μL, 5.2 mmol) and TBTU (1.69 g, 5.2 mmol), stirring the reaction mixture at room temperature for 1 h. Then, brine was added (30 mL) and this mixture was extracted with EtOAc (3x20 mL). The organic layers were washed with 2M HCl (25 mL), water (20 mL), 5% $NaHCO_3$ (25 mL) and finally with water (20 mL) and were dried over Na_2SO_4. The solvent was removed in vacuo (15 Torr) giving a solid which was recrystallized from hexane/EtOAc to yield 236 mg of amide **14** (80%): mp 113-114°C (hexane/EtOAc); ν 3440 (NH), 1700 (C=O) 1350, and 1135 cm^{-1} (SO_2); δ_H 1.08 [d, *J*=6.7, 6H, (CH_3)$_2$CH], 2.29 (t, *J*=7.2, 2H, CH_2CO), 2.43 (s, 3H, CH_3Ar), 2.57 (dt, *J*=7.2, 6.9, 2H, CHCH_2), 4.00 (m, 1H, CHN), 5.91 (s, 1H, NH), 6.37 (d, *J*=15.1, 1H, CHS), 6.93 (dt, *J*=15.1, 6.9, 1H, C*H*CH$_2$), 7.33, and 7.73 (2d, *J*=8.1, 4H, ArH); δ_C 21.4 (*C*H_3Ar), 22.4 [(*C*H_3)$_2$CH], 27.1 (*C*H_2CO), 34.0 (CH*C*H_2), 41.3 (CHN), 131.2, 144.7 (CH=CH), 127.4, 129.8, 137.2, 144.3 (ArC), and 169.8 (CO); *m/z* 280 (M^+-CH_3, 1%), 141 (13), 140 (100), 139 (15), 98 (38), 92 (14), 91 (34), 65 (17), 58 (10), 55 (11), 53 (10), 44 (32), 43 (18), 42 (11), and 41 (13) (Found: C, 60.72; H, 6.96; N, 4.26; S, 10.16. Calcd. for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74; S, 10.85).

Lithiation of (*E*)-*N*-Isopropyl-5-tosyl-4-pentenamide (14) and Reaction with Electrophiles. General Procedure. To a solution of (*E*)-*N*-isopropyl-5-tosyl-4-pentenamide (**14**) (59 mg, 0.2 mmol) in dry THF (3 mL) cooled at -78°C and under argon, was added a 1.6M solution of *n*-butyllithium in hexanes (300 μL, 0.48 mmol). After 30 min stirring, the corresponding electrophile was added (0.22 mmol) and the reaction mixture was warmed up to room temperature for 1 d. Then, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (3x20 mL). The organic layer was dried (Na_2SO_4), evaporated and the residue was purified by flash chromatography giving the corresponding compounds **15-22**. Yields and physical data are included in Table 1, spectral and analytical data follow:

***(2E,4E)*-N-*Isopropyl-6-hydroxy-2,4-hexadienamide* (15a):** ν 3293 (OH, NH), 1660 (C=O), 1633, and 1613 cm^{-1} (C=CH); δ_H 1.18 (d, *J*=6.4, 6H, 2xCH_3), 1.85 (br s, 1H, OH), 4.14 (m, 1H, CHN), 5.59 (br d, *J*=7.6, 1H, NH), 5.82 (d, *J*=15.0, 1H, CHCO), 6.16 (dt, *J*=15.5, 4.9, 1H, HOCH$_2$C*H*), 6.39 (m, 1H, C*H*CH=CHCO), 7.20 (dd, *J*=15.0, 11.0, 1H, C*H*=CHCO); δ_C 22.7 (2x*C*H_3), 41.5 (CHN), 62.6 (CHOH), 124.2, 127.8, 139.7,

139.9 (2xCH=CH), and 165.2 (CO); *m/z* 169 (M^+, 1%), 151 (33), 140 (26), 138 (12), 126 (15), 98 (20), 83 (31), 82 (11), 51 (10), 44 (100), and 41 (65) (Found: M^+ 169.1097. Calcd. for $C_9H_{15}NO_2$: 169.1103).

***(2E,4E)*-N-*Isopropyl-6-hydroxy-2,4-octadienamide* (15b):** ν 3292 (OH, NH), 1658 (C=O), 1630, and 1612 cm^{-1} (C=CH); δ_H 0.93 (t, *J*=7.3, 3H, CH_3CH_2), 1.18 [d, *J*=6.7, 6H, $(CH_3)_2CH$], 1.59 (m, 2H, CH_2), 1.72 (br s, 1H, OH), 4.17 (m, 2H, CHN, CHOH), 5.40 (br s, 1H, NH), 5.81 (d, *J*=15.0, 1H, CHCO), 6.05 (dd, *J*=15.3, 5.8, 1H, HOCHCH), 6.32 (dd, *J*=15.3, 11.0, 1H, CHCH=CHCO), 7.20 (dd, *J*=15.0, 11.0, 1H, CH=CHCO); δ_C 9.5 (CH_3CH_2), 22.8 [$(CH_3)_2CH$], 30.0 (CH_2), 41.45 (CHN), 73.3 (CHOH), 124.2, 127.6, 140.0, 143.2 (2xCH=CH), and 165.1 (CO); *m/z* 197 (M^+, 1%), 141 (10), 140 (100), 111 (10), 109 (17), 98 (32), 93 (12), 86 (13), 83 (24), 82 (16), 81 (65), 80 (11), 79 (14), 77 (15), 69 (10), 67 (11), 65 (11), 58 (16), 57 (84), 55 (39), 54 (14), 53 (43), 52 (14), 51 (10), 44 (78), 43 (83), 42 (47), and 41 (65) (Found: M^+ 197.1423. Calcd. for $C_{11}H_{19}NO_2$: 197.1416).

***(2E,4E)*-N-*Isopropyl-6-hydroxy-7-methyl-2,4-octadienamide* (15c):** ν 3306 (OH, NH), 1656 (C=O), 1626, and 1605 cm^{-1} (C=CH); δ_H 0.91, 0.93 [2d, *J*=6.6, 6H, $(CH_3)_2CHN$], 1.19 [d, *J*=6.7, 6H, $(CH_3)_2CHCHOH$], 1.58 (s, 1H, OH), 1.77 [m, 1H, $(CH_3)_2CHCHOH$], 4.00 (t, *J*=6.0, 1H, CHOH), 4.17 (m, 1H, CHN), 5.30 (s, 1H, NH), 5.80 (d, *J*=15.1, 1H, CHCO), 6.06 (dd, *J*=15.3, 6.0, 1H, HOCHCH), 6.33 (dd, *J*=15.3, 11.3, 1H, CHCH=CHCO), and 7,21 (dd, *J*=15.3, 11.3, 1H, CH=CHCO); δ_C 17.7, 18.15 [$(CH_3)_2CHCHOH$], 22.8 [$(CH_3)_2CHN$], 34.0 (CHCHOH), 41.5 (CHN), 77.2 (CHOH), 124.2, 128.4, 140.0, 141.9 (2xCH=CH), and 165.1 (CO); *m/z* 211 (M^+, 1%), 140 (53), 109 (22), 101 (11), 98 (15), 86 (20), 83 (30), 82 (11), 81 (26), 71 (11), 60 (12), 58 (12), 55 (18), 53 (21), 44 (23), 43 (100), and 41 (36) (Found: M^+ 211.1583. Calcd. for $C_{12}H_{21}NO_2$: 211.1572).

***(2E,4E)*-N-*Isopropyl-6-hydroxy-7,7-dimethyl-2,4-octadienamide* (15d):** ν 3292 (OH, NH), 1656 (C=O), 1628, and 1613 cm^{-1} (C=CH); δ_H 0.92 [s, 9H, $(CH_3)_3C$], 1.18 [d, *J*=6.4, 6H, $(CH_3)_2CH$], 1.82 (br s, 1H, OH), 3.87 (d, *J*=6.3, 1H, CHOH), 4.17 (m, 1H, CHN), 5.41 (d, *J*=7.0, 1H, NH), 5.81 (d, *J*=15.0, 1H, CHCO), 6.12 (dd, *J*=15.3, 6.3, 1H, HOCHCH), 6.33 (dd, *J*=15.3, 10.9, 1H, CHCH=CHCO), and 7.21 (dd, *J*=15.0, 10.9, 1H, CH=CHCO); δ_C 22.8 [$(CH_3)_2CH$], 25.6 [$(CH_3)_3C$], 35.42 (C), 41.45 (CHN), 79.95 (CHOH), 124.1, 129.1, 140.0, 140.8 (2xCH=CH), and 165.1 (CO); *m/z* 225 (M^+, 1%), 169 (37), 140 (27), 109 (11), 101 (53), 86 (47), 84 (35), 83 (22), 82 (17), 81 (21), 66 (41), 58 (18), 57 (71), 55 (20), 53 (21), 44 (34), 43 (100), 42 11), and 41 (68) (Found: M^+ 225.1730. Calcd. for $C_{13}H_{23}NO_2$: 225.1729).

***(2E,4E)*-N-*Isopropyl-6-phenyl-6-hydroxy-2,4-hexadienamide* (15e):** ν 3300 (OH, NH), 1651 (C=O), 1622, and 1598 cm^{-1} (C=CH); δ_H 1.17 [d, *J*=6.4, 6H, $(CH_3)_2CH$], 1.75 (s, 1H, OH), 4.14 (m, 1H, CHN), 5.30 (d, *J*=5.8, 1H, CHOH), 5.41 (d, *J*=6.4, 1H, NH), 5.83 (d, *J*=15.0, 1H, CHCO), 6.20 (dd, *J*=15.1, 5.8, 1H, HOCHCH), 6.42 (dd, *J*=15.1, 11.0, 1H, CHCH=CHCO), 7.20 (dd, *J*=15.0, 11.0, 1H, CH=CHCO), and 7.34 (m, 5H, ArH); δ_C 22.8 [$(CH_3)_2CHN$], 41.5 (CHN), 74.3 (CHOH), 124.8, 126.4, 127.7, 128.0, 128.5, 128.7, 130.15 (2xCH=CH, ArC), and 164.9 (CO); *m/z* 207 (M^+-38, 5%), 44 (58), and 40 (100) (Found: C, 73.28; H, 7.45; N, 5.53. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71).

***(2E,4E)*-N-*Isopropyl-7-phenyl-6-hydroxy-2,4-heptadienamide* (15f):** ν 3434, 3324 (OH, NH), 3085, 3062, 3030, 1622, 1593 (C=CH), and 1650 cm^{-1} (CO); δ_H 1.18 (d, *J*=6.4, 6H, 2xCH_3), 1.82 (br s, 1H, OH), 2.81 (dd, *J*=13.6, 7.8, 1H, HCHCHOH), 2.91 (dd, *J*=13.6, 5.3, 1H, HCHCHOH), 4.16 (m, 1H, CHN), 4.47 (m, 1H, CHOH), 5.33 (br d, *J*=7.0, 1H, NH), 5.78 (d, *J*=15.0, 1H, CHCO), 6.10 (dd, *J*=15.2, 5.5, 1H, HOCHCH), 6.33 (dd, *J*=15.2, 11.1, 1H, CHCH=CHCO), and 7.20 (m, 6H, ArH, CH=CHCO); δ_C 22.8 (2xCH_3), 41.5

(CHN), 43.8 (CH_2), 72.6 (CHOH), 124.4, 126.8, 127.7, 128.6, 129.5, 137.1, 139.85, 142.1 (ArC, 2xCH=CH), and 165.0 (CO); *m/z* 259 (M^+, 6%), 191 (12), 168 (67), 156 (13), 155 (18), 140 (12), 126 (14), 109 (47), 92 (37), 91 (100), 86 (35), 83 (54), 82 (13), 81 (32), 77 (11), 65 (31), 60 (23), 58 (21), 55 (17), 53 (29), 51 (11), 44 (26), 43 (88), and 41 (25) (Found: C, 73.76; H, 8.08; N, 5.19. Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40).

N-*Isopropyl-γ-(tosylmethyl)-γ-butyrolactam* (16): R_f 0.39 (EtOAc); mp 107-108°C (hexane/EtOAc); ν 1684 (C=O), 1302, and 1147 cm^{-1} (SO_2); δ_H 1.14, 1.16 [2d, *J*=6.4, 6H, (CH_3)$_2$CH], 2.13-2.48 (m with s at 2.48, 7H, (CH_2)$_2$, CH_3Ar), 3.19 (dd, *J*=13.8, 10.2, 1H, SHCH), 3.33 (dd, *J*=13.8, 1.8, 1H, SHCH), 4.11 [m, 2H, (CH_3)$_2$CH, CH_2CHCH_2], 7.41, and 7.82 (2d, *J*=8.2, 4H, ArH); δ_C 19.7, 21.6 [(CH_3)$_2$CH], 21.4 (CH_3Ar), 25.4, 29.55 [(CH_2)$_2$], 44.5 [(CH_3)$_2$CH], 51.7 (CH_2CHCH_2), 59.3 (CH_2S), 127.85, 130.2, 136.4, 145.4 (ArC), and 174.5 (CO); *m/z* 295 (M^+, 1%), 280 (21), 140 (22), 139 (100), 126 (50), 124 (27), 111 (25), 110 (10), 98 (48), 92 (11), 91 (59), 89 (10), 84 (96), 83 (11), 70 (14), 69 (10), 65 (31), 56 (12), 55 (49), 43 (19), 42 (21), and 41 (29) (Found: C, 60.96; H, 7.26; N, 4.36; S, 10.57. Calcd. for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74; S, 10.85).

N-*Isopropyl-γ-[(E)-(3,3-dimethyl-1-tosyl)-1-butenyl]-γ-butyrolactam* (17): R_f 0.58 (EtOAc); ν 1681 (C=O), 1301, and 1144 cm^{-1} (SO_2); δ_H 1.05 [d, *J*=6.7, 6H, (CH_3)$_2$CHN], 1.27 [s, 9H, (CH_3)$_3$C], 2.08-2.32 (m, 3H, CH_2HCH), 2.42 (s, 3H, CH_3Ar), 2.83 (m, 1H, CH_2HCH), 3.37 [m, 1H, (CH_3)$_2$CHN], 5.10 (dd, *J*=10.4, 3.4, 1H, CCHN), 7.02 (s, 1H, CH=C), 7.32, and 7.69 (2d, *J*=8.2, 4H, ArH); δ_C 18.5, 19.8 [(CH_3)$_2$CH], 21.55 (CH_3Ar), 31.0 [(CH_3)$_3$C], 34.15 [(CH_3)$_3$C], 46.7 [(CH_3)$_2$CH], 54.2 (CSCHN), 128.1, 129.8, 138.8, 144.3 (ArC), 142.8, 153.8 (CH=C), and 177.3 (CO); *m/z* 363 (M^+, 2%), 348 (12), 209 (12), 208 (85), 152 (38), 151 (18), 150 (96), 149 (11), 139 (21), 126 (26), 123 (10), 122 (11), 121 (12), 119 (11), 109 (16), 108 (19), 107 (20), 98 (10), 97 (14), 95 (15), 94 (11), 93 (16), 92 (12), 91 (53), 85 (11), 84 (70), 83 (18), 82 (15), 81 (50), 79 (18), 77 (14), 71 (21), 70 (15), 69 (100), 68 (18), 67 (28), 65 (24), 58 (45), 57 (46), 56 (16), 55 (59), 53 (15), 44 (22), 43 (58), 41 (16), and 40 (80) (Found: C, 65.88; H, 8.07; N, 3.52; S, 9.16. Calcd. for $C_{20}H_{29}NO_3S$: C, 66.08; H, 8.04; N, 3.85; S, 8.82).

***(2E)*-N-*Isopropyl-5-methyl-2,4-hexadienamide* (18a):** ν 3295 (NH), 1682 (CO), and 1669 cm^{-1} (C=CH); δ_H 1.18 [d, *J*=6.7, 6H, (CH_3)$_2$CH], 1.85, 1.88 [2s, 6H, (CH_3)$_2$C], 4.17 (m, 1H, CHN), 5.32 (s, 1H, NH), 5.68 (d, *J*=14.7, 1H, CHCO), 5.93 (d, *J*=11.6, 1H, C=CH), 7.49 (dd, *J*=14.7, 11.6, 1H, CH=CHCO); δ_C 18.8, 26.45 [(CH_3)$_2$C], 22.8 [(CH_3)$_2$CH], 41.4 (CHN), 121.4, 123.5, 137.25, 144.4 (C=CHCH=CH), and 165.8 (CO); *m/z* 167 (M^+, 41%), 152 (30), 110 (39), 109 (72), 96 (14), 95 (24), 82 (20), 81 (93), 80 (14), 79 (30), 67 (21), 58 (50), 55 (16), 53 (30), 44 (45), 43 (100), and 42 (16) (Found: M^+ 167.1351. Calcd. for $C_{10}H_{17}NO$: 167.1310).

***(2E)*-N-*Isopropyl-5-butyl-2,4-nonadienamide* (18b):** ν 3305 (NH), 1651 (CO), and 1643 cm^{-1} (C=CH); δ_H 0.90 (t, *J*=7.3, 6H, 2xCH_3CH_2), 1.18 [d, *J*=6.1, 6H, (CH_3)$_2$CH], 1.35 [m, 8H, 2xCH_3(CH_2)$_2$], 2.09, 2.25 [2m, 4H, (CH_2)$_2$C], 4.17 (m, 1H, CHN), 5.33 (br d, *J*=6.7, 1H, NH), 5.69 (d, *J*=14.7, 1H, CHCO), 5.91 (d, *J*=11.6, 1H, C=CH), and 7.52 (dd, *J*=14.7, 11.6, 1H, CH=CHCO); δ_C 13.9, 13.9 (2xCH_3CH_2), 22.8 [(CH_3)$_2$CH], 22.5, 22.8, 30.2, 30.9, 31.2, 37.3 [2x(CH_2)$_3$], 41.3 (CHN), 121.7, 122.8, 137.1, 153.0 (C=CHCH=CH), and 165.8 (CO); *m/z* 251 (M^+, 10%), 194 (60), 152 (14), 125 (19), 121 (15), 109 (13), 101 (18), 98 (18), 95 (16), 86 (14), 83 (26), 81 (21), 79 (13), 69 (12), 67 (23), 58 (30), 57 (24), 55 (47), 53 (12), 44 (40), 43 (100), and 42 (13) (Found: M^+ 251.2238. Calcd. for $C_{16}H_{29}NO$: 251.2249).

***(2E)*-N-*Isopropyl-5-benzyl-6-phenyl-2,4-hexadienamide* (18c):** ν 3303, 3238 (NH), 3060, 3027, 1617, 1601, 978 (C=CH), and 1647 cm^{-1} (C=O); δ_H 1.18 (d, *J*=6.4, 6H, 2xCH_3), 3.32, 3.57 (2s, 4H, 2xCH_2), 4.18 (m, 1H, CHN), 5.26 (d, *J*=8.2, 1H, NH), 5.83 (d, *J*=14.8, 1H, CHCO), 6.09 (d, *J*=11.6, 1H, C=CH), 7.11, 7.26 (2m, 10H, ArH), 7.68 (dd, *J*=14.8, 11.6, 1H, C*H*=CHCO); δ_C 22.85 (2xCH_3), 36.4, 41.4 (2xCH_2), 43.1 (CHN), 124.2, 125.9, 126.3, 126.4, 128.4, 128.5, 128.8, 129.2, 136.35, 138.7, 138.8, 148.7 (C=CHCH=CH, ArC), and 165.35 (CO); *m/z* 319 (M^+, 0.3%), 228 (17), 143 (15), 91 (69), 65 (11), 44 (100), and 43 (52) (Found: C, 82.82; H, 8.10; N, 4.32. Calcd. for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38).

***N*-*Isopropyl-γ-(2-phenyl-1-tosylethyl)-γ-butyrolactam* (19c):**[23] R_f 0.62 (AcOEt); ν 1684 (C=O), 1301, and 1143 cm^{-1} (SO_2); δ_H 1.15, 1.17 [2d, *J*=6.7, 6H, (CH_3)$_2$CH], 2.13-2.69 [m with s at 2.48, 7H, (CH_2)$_2$, CH_3Ar], 2.82 (dd, *J*=14.3, 10.9, 1H, *H*CHCHS), 3.10 (dd, *J*=14.3, 3.0, 1H, HC*H*CHS), 3.48 (dt, *J*=10.9, 3.0, 1H, CHS), 3.96 [m, 2H, (CH_3)$_2$C*H*, SCHC*H*N], 6.92, 7.09, 7.23 (3m, 5H, ArH), 7.39, and 7.80 (2d, *J*=8.1, 4H, ArH); δ_C 19.0, 21.2, 21.6 [(*C*H_3)$_2$CH, *C*H_3Ar], 20.2 (*C*H_2CHS), 30.7, 33.5 [(CH_2)$_2$], 44.8 [(CH_3)$_2$*C*H], 56.0 (CHSC*H*N), 67.0 (CHS), 127.3, 128.3, 128.5, 128.9, 130.0, 136.35, 136.5, 145.0 (ArC), and 175.85 (CO); *m/z* 385 (M^+, 0.3%), 229 (27), 186 (12), 128 (11), 127 (10), 126 (99), 115 (11), 92 (23), 91 (87), 84 (100), 77 (14), 65 (35), 56 (13), 55 (11), 43 (18), and 41 (27) (Found: C, 68.17; H, 7.44; N, 3.55; S, 8.78. Calcd. for $C_{22}H_{27}NO_3S$: C, 68.54; H, 7.06; N, 3.63; S, 8.32).

***(2E,4E)*-N-*Isopropyl-6-methyl-2,4-heptadienamide* (20):** ν 3272 (NH), 1656 (CO), 1628, and 1613 cm^{-1} (C=CH); δ_H 1.03 [d, *J*=6.7, 6H, (CH_3)$_2$CHCH], 1.18 [d, *J*=6.4, 6H, (CH_3)$_2$CHN], 2.40 [m, 1H, (CH_3)$_2$C*H*CH], 4.16 (m, 1H, CHN), 5.27 (br s, 1H, NH), 5.72 (d, *J*=15.0, 1H, CHCO), 6.05 [m, 2H, (CH_3)$_2$CHC*H*=C*H*], and 7.17 (dd, *J*=15.0, 9.2, 1H, C*H*=CHCO); δ_C 21.9 [(*C*H_3)$_2$CHCH], 22.9 [(*C*H_3)$_2$CHN], 31.4 [(CH_3)$_2$*C*HCH], 41.3 (CHN), 122.2, 125.3, 141.3, 149.5 (2xCH=CH), and 165.4 (CO); *m/z* 181 (M^+, 8%), 138 (14), 123 (13), 96 (18), 95 (28), 81 (17), 67 (13), 58 (21), 55 (14), 44 (100), and 43 (48) (Found: M^+ 181.1501. Calcd. for $C_{11}H_{19}NO$: 181.1467).

***(2E,4E)*-N-*Isopropyl-7-hydroxy-2,4-octadienamide* (21):** ν 3282 (OH, NH), 1657 (C=O), 1629, and 1610 cm^{-1} (C=CH); δ_H 1.18 [d, *J*=6.4, 6H, (CH_3)$_2$CHN], 1.22 (d, *J*=6.1, 3H, CH_3CHOH), 1.58 (s, 1H, OH), 2.32 (m, 2H, CH_2), 3.90 (m, 1H, CHN), 4.17 (m, 1H, C*H*OH), 5.27 (s, 1H, NH), 5.75 (d, *J*=15.0, 1H, CHCO), 6.06 (m, 1H, CH_2C*H*=CH), 6.22 (dd, *J*=15.0, 10.5, 1H, C*H*CH=CHCO), 7.19 (dd, *J*=15.0, 10.5, 1H, C*H*=CHCO); δ_C 22.8 [(*C*H_3)$_2$CHN], 23.0 (*C*H_3CHOH), 41.4 (CHN), 42.7 (CH_2), 67.15 (CHOH), 123.1, 131.2, 137.8, 140.4 (2xCH=CH), and 165.15 (CO); *m/z* 197 (M^+, 0.5%), 149 (22), 140 (21), 139 (81), 126 (42), 124 (39), 111 (27), 98 (41), 91 (32), 84 (100), 83 (12), 70 (19), 69 (11), 65 (17), 58 (15), 57 (18), 56 (19), 55 (68), 44 (54), 43 (58), and 42 (25) (Found: M^+ 197.1418. Calcd. for $C_{11}H_{19}NO_2$: 197.1416).

erythro/threo-*Benzyl 2-(1-Isopropyl-5-oxotetrahydro-1H-2-pyrrolyl)-2-tosylacetate* (22a): ν 3062, 3038, 1596 (C=CH), 1740 (OC=O), 1693 (NC=O), 1304, and 1147 cm^{-1} (SO_2);[24] δ_H 1.18, 1.22 (2d, *J*=7.0, 6H, 2xCH_3), 1.25-2.31 (m, 3H, CH_2*H*CHCO), 2.43 (s, 3H, CH_3Ar$_{erythro}$), 2.44 (s, 3H, CH_3Ar$_{threo}$), 2.57 (m, 1H, HC*H*CO$_{threo}$), 2.84 (m, 1H, HC*H*CO$_{erythro}$), 3.62 [m, 1H, (CH_3)$_2$C$H_{erythro}$], 3.98 [m, 1H, (CH_3)$_2$CH_{threo}], 4.18 (d, *J*=6.4, 1H, CHS$_{erythro}$), 4.26 (d, *J*=2.8, 1H, CHS$_{threo}$), 4.33 (m, 1H, CHSC*H*N$_{erythro}$), 4.51 (m, 1H, CHSC*H*N$_{threo}$), 4.92 (m, 2H, $CH_2O_{erythro}$), 5.01, 5.08 (2d, *J*=12.0, 2H, CH_2O_{threo}), 7.19, 7.31 (2m, 7H, ArH), and 7.73 (d, *J*=7.7, 2H, ArH); δ_C 19.3, 21.2, 21.7 (*C*H$_3$Ar$_{threo}$, 2xCH$_{3threo}$), 19.7, 20.15, 21.0 (*C*H$_3$Ar$_{erythro}$, 2xCH$_{3erythro}$), 20.54 (*C*H$_2$CHN$_{threo}$), 24.1 (*C*H$_2$CHN$_{erythro}$), 29.6 (*C*H$_2$CO$_{erythro}$), 30.1 (*C*H$_2$CO$_{threo}$), 45.15 [(CH_3)$_2$*C*HN$_{threo}$], 47.7 [(CH_3)$_2$*C*HN$_{erythro}$], 55.7 (CHS*C*HN$_{threo}$), 58.65 (CHS*C*HN$_{erythro}$), 60.3 ($CH_2O_{erythro}$),

68.3 (CH_2O_{threo}), 70.6 (CHS_{threo}), 72.0 ($CHS_{erythro}$), 128.6, 128.8, 128.8, 129.0, 129.1, 129.75, 129.9, 133.7, 133.9, 134.8, 135.3, 145.65, 145.85 (ArC), 164.0, 164.9 (2xNC=O), 175.2, and 176.2 (2xOC=O); *m/z* 338 (M^+-CH_2Ph, 0.2%), 139 (17), 126 (44), 92 (11), 91 (100), 84 (40), 65 (17), 43 (12), and 41 (19).[24,25]

erythro/threo-N-*Isopropyl-γ-(2-phenyl-2-oxo-1-tosylethyl)-γ-butyrolactam* (22b): ν 3069, 1596 (C=CH), 1681 (C=O, NC=O), 1304, and 1150 cm^{-1} (SO_2);[24] δ_H 1.16 (d, *J*=6.7, 6H, 2xCH_3), 2.05, 2.32 (2m, 3H, CH_2CHN, *H*CHCO), 2.43 (s, 3H, CH_3Ar), 2.61 (m, 1H, HC*H*CO_{threo}), 3.03 (m, 1H, HC*H*$CO_{erythro}$), 3.44 [m, 1H, $(CH_3)_2CHN_{erythro}$], 3.94 [m, 1H, $(CH_3)_2CHN_{threo}$], 4.31 (m, 1H, CHSC*H*$N_{erythro}$), 4.56 (m, 1H, CHSC*H*N_{threo}), 5.27 (d, *J*=7.6, 1H, $CHS_{erythro}$), 5.36 (d, *J*=2.4, 1H, CHS_{threo}), 7.36, 7.56, and 7.70 (3m, 9H, ArH); δ_C 19.55, 21.0 (2xCH_{3threo}), 19.6, 20.1 (2x$CH_{3erythro}$), 21.3 (CH_2CHN_{threo}), 21.6 ($CH_3Ar_{erythro}$), 21.7 (CH_3Ar_{threo}), 25.6 ($CH_2CHN_{erythro}$), 30.5 (CH_2CO_{threo}), 30.85 ($CH_2CO_{erythro}$), 45.6 [$(CH_3)_2CHN_{threo}$], 48.8 [$(CH_3)_2CHN_{erythro}$], 57.4 ($CHSCHN_{threo}$), 59.6 ($CHSCHN_{erythro}$), 70.1 (CHS_{threo}), 71.0 ($CHS_{erythro}$), 128.5, 128.6, 128.8, 128.9, 129.6, 129.9, 134.1, 134.2, 134.7, 134.9, 136.7, 137.6, 145.7, 146.0 (ArC), 175.8, 176.5 (2xNC=O), 192.0, and 192.1 (2xSCHC=O); *m/z* 244 (M^+-Ts, 30%), 243 (10), 242 (10), 187 (10), 126 (93), 110 (40), 105 (78), 91 (46), 84 (100), 77 (66), 65 (27), 58 (22), 56 (13), 55 (17), 51 (19), 44 (13), 43 (26), 42 (15), and 41 (35).[24,25]

erythro/threo-N-*Cyclohexyl-2-(1-isopropyl-5-oxotetrahydro-1H-2-pyrrolyl)-2-tosylacetamide* (22c): ν 3293 (NH), 1662 (2xC=O), 1303, and 1146 cm^{-1} (SO_2);[24] δ_H 1.13-1.31 (m with d at 1.29, *J*=7.0, 12H, 2xCH_3, Cy), 1.73 (m, 4H, Cy), 2.18 [m, 7H, $(CH_2)_2CO_{threo}$, $CH_2HCHCO_{erythro}$], 2.45 (s, 3H, CH_3Ar$_{erythro}$), 2.47 (s, 3H, CH_3Ar$_{threo}$), 2.62 (m, 1H, HC*H*$CO_{erythro}$), 3.74, 3.94-4.03 [2m, with d at 4.03, *J*=2.7, 3H, $(CH_3)_2CHN$, $(CH_2)_2CHN$, CHS], 4.38 (m, 1H, CHSC*H*$N_{erythro}$), 4.47 (m, 1H, CHSC*H*N_{threo}), 6.51 (br d, *J*=7.9, 1H, NH_{threo}), 6.92 (br d, *J*=6.9, 1H, $NH_{erythro}$), 7.39, 7.75 (2d, *J*=8.2, 4H, $ArH_{erythro}$), 7.39, and 7.79 (2d, *J*=8.1, 4H, ArH_{threo}); δ_C 19.4, 21.7 (2xCH_{3threo}), 19.9, 19.95 (2x$CH_{3erythro}$), 21.3 (CH_3Ar_{threo}), 21.6 ($CH_3Ar_{erythro}$), 21.4, 24.6, 24.6 25.3, 30.5, 32.4 [$(CH_2)_2CO_{threo}$, $(CH_2)_{5threo}$], 24.7, 29.2, 29.6, 30.9, 32.2, 32.25, 32.6 [$(CH_2)_2CO_{erythro}$, $(CH_2)_{5erythro}$], 45.35, 49.0 [$(CH_3)_2CHN_{threo}$, CH_2CHNCH_{2threo}], 41.4, 48.6 [$(CH_3)_2CHN_{erythro}$, $CH_2CHNCH_{2erythro}$], 56.0 ($CHSCHN_{threo}$), 58.95 ($CHSCHN_{erythro}$), 71.25 (CHS_{threo}), 73.3 ($CHS_{erythro}$), 129.1, 129.9, 134.5, 146.0 (ArC_{threo}), 128.8, 129.8, 135.2, 145.7 ($ArC_{erythro}$), 161.0 ($CONH_{threo}$), 162.1 ($CONH_{erythro}$), 175.5 (CON_{threo}), and 176.8 ($CON_{erythro}$); *m/z* 420 (M^+, 0.6%), 265 (35), 209 (13), 166 (14), 139 (15), 126 (89), 125 (14), 124 (17), 110 (28), 98 (28), 96 (12), 91 (42), 84 (100), 83 (12), 82 (13), 81 (13), 68 (11), 67 (13), 65 (17), 58 (15), 56 (32), 55 (59), 54 (12), 53 (15), 44 (42), 43 (48), 42 (23), and 41 (72).[24]

Lithiation of (*E*)-*N*-Isopropyl-5-tosyl-4-pentenamide (14) and Deuterolysis. Synthesis of Compounds 24, 26, and 29. To a solution of (*E*)-*N*-isopropyl-5-tosyl-4-pentenamide (**14**) (59 mg, 0.2 mmol) in dry THF (3 mL) cooled at -78°C under argon, was added a 1.6M solution of *n*-butyllithium in hexanes (150 μL, 0.24 mmol) for the monoanion and (300μL, 0.48 mmol) for the dianion. After 30 min stirring, CH_3OD was added (100 μL) and the reaction mixture was kept at this temperature for 15 min. Then, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (3x20 mL). The organic layer was dried (Na_2SO_4), evaporated and the residue was purified by flash chromatography giving the corresponding compounds **24**, **26**, and **29**.

N-*Isopropyl-γ-[tosyldeuteriomethyl]-γ-butyrolactam* (24):[24] mp 107-108°C (hexane/EtOAc); ν 1684 (C=O), 1302, and 1147 cm^{-1} (SO_2); δ_H 1.13, 1.16 [2d, *J*=6.6, 6H, $(CH_3)_2CH$], 2.13-2.48 (m with s at 2.48, 7H, $(CH_2)_2$, CH_3Ar), 3.18 (d, *J*=10.7, 1H, SCHD), 4.02-4.17 [m, 2H, $(CH_3)_2CH$, CHSC*H*N], 7.41, and 7.82 (2d,

J=8.5, 4H, ArH); δ_C 19.7, 21.6 [(CH_3)$_2$CH], 21.35 (CH_3Ar), 25.4, 29.5 [(CH_2)$_2$], 44.4 [(CH_3)$_2$CH], 51.6 (CHS*C*HN), 59.0 (t, *J*=20.8, CHD), 127.8, 130.2, 136.4, 145.4 (ArC), and 174.5 (CO); *m/z* 296 (M^+, 0.6%), 281 (18), 141 (64), 140 (64), 139 (13), 126 (45), 125 (30), 124 (18), 112 (20), 111 (12), 99 (35), 98 (17), 91 (38), 85 (23), 84 (100), 82 (10), 70 (13), 65 (22), 58 (14), 57 (12), 56 (46), 55 (46), 54 (11), 44 (14), 43 (32), 42 (27), and 41 (53) (Found: C, 60.26; H+D, 7.46; N, 4.70; S, 10.49. Calcd. for $C_{15}H_{20}DNO_3S$: C, 60.78; H+D, 7.48; N, 4.73; S, 10.82).

N-*Isopropyl-γ-[tosyldideuteriomethyl]-γ-butyrolactam* (26): (impurified by **29**) R_f 0.39 (AcOEt); ν 1684 (C=O), 1302, and 1147 cm^{-1} (SO_2); δ_H 1.16 [d, *J*=6.4, 6H, (CH_3)$_2$CH], 2.13-2.48 (m with s at 2.48, 7H, (CH_2)$_2$, CH_3Ar), 4.09 [m, 2H, (CH_3)$_2$ C*H*, CH_2CHCH_2], 7.41, and 7.82 (2d, *J*=8.2, 4H, ArH); δ_C 19.7, 21.6 [(CH_3)$_2$CH], 21.4 (CH_3Ar), 25.4, 29.55 [(CH_2)$_2$], 44.45 [(CH_3)$_2$CH], 51.5 (CD_2CH), 59.0 (quint., *J*=21.6, CD_2), 127.8, 130.2, 136.4, 145.4 (ArC), and 174.5 (CO); *m/z* 297 (M^+, 1%), 282 (17), 156 (18), 142 (34), 141 (90), 140 (26), 139 (15), 127 (18), 126 (76), 125 (29), 113 (18), 112 (17), 100 (35), 99 (20), 98 (12), 92 (39), 91 (45), 86 (44), 85 (34), 84 (100), 83 (17), 65 (24), 58 (25), 57 (59), 56 (40), 55 (56), 44 (34), 43 (79), 42 (25), 41 (53), and 40 (11).

***(Z)*-N-*Isopropyl-5,5,-dideuterio-5-tosyl-3-pentenamide* (29):** (impurified by **26**) R_f 0.39 (AcOEt); ν 1684 (C=O), 1302, and 1147 cm^{-1} (SO_2); δ_H 1.15 [d, *J*=6.4, 6H, (CH_3)$_2$CH], 2.46 (s, 3H, CH_3Ar), 2.96 (dd, *J*=7.8, 1.5, 2H, CH_2CO), 4.02 (m, 1H, CHN), 5.45 (m, 1H, CD_2CH), 6.04 (dt, *J*=10.7, 7.8, 1H, $CHCH_2$), 6.36 (br s, 1H, NH), 7.37, and 7.76 (2d, *J*=8.1, 4H, ArH); δ_C 21.6 (CH_3Ar), 22.5 [(CH_3)$_2$CH], 36.4 (CH_2CO), 41.6 (CHN), 54.8 (q, *J*=22.6, CD_2), 117.6, 127.6, 128.2, 129.9, 133.4, 145.1 (CH=CH, ArC), and 168.5 (CO); *m/z* 297 (M^+, 1%), 282 (17), 156 (18), 142 (34), 141 (90), 140 (26), 139 (15), 127 (18), 126 (76), 125 (29), 113 (18), 112 (17), 100 (35), 99 (20), 98 (12), 92 (39), 91 (45), 86 (44), 85 (34), 84 (100), 83 (17), 65 (24), 58 (25), 57 (59), 56 (40), 55 (56), 44 (34), 43 (79), 42 (25), 41 (53), and 40 (11).

Synthesis of 1-Isopropyl-5-[(1*R,2*S**)-2-(1-isopropyl-5-oxotetrahydro-1*H*-2-pyrrolyl)-1,2-ditosylethyl]-2-pyrrolidinone (39).** To a solution of (*E*)-*N*-isopropyl-5-tosyl-4-pentenamide (**14**) (59 mg, 0.2 mmol) in dry THF (3 mL) cooled at -78°C under argon, was added a 1.6M solution of *n*-butyllithium in hexanes (300μL, 0.48 mmol). After 30 min stirring, iodine was added (0.2 mmol) and the reaction mixture was warmed up to -60°C for 1 h. Then, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (3x20 mL). The organic layer was dried (Na_2SO_4), evaporated and the residue was purified by flash chromatography and recrystallization giving the corresponding compound **39** (75% yield): mp 174-175°C (hexane/EtOAc);[24] R_f 0.60 (AcOEt);[24] ν 1678 (C=O), 1305, and 1149 cm^{-1} (SO_2);[24] δ_H 1.17, 1.23 [2d, *J*=7.0, 12H, 2x(CH_3)$_2$CH], 2.19, 2.70 [2m, 8H, 2x(CH_2)$_2$], 2.50 (s, 6H, CH_3Ar), 3.96 [m, 4H, 2x(CH_3)$_2$C*H*, 2xCHC*H*CH_2], 5.17 (d, *J*=1.8, 2H, 2xCHS), 7.43, and 7.86 (2d, *J*=8.4, 8H, ArH); δ_C 19.1 [2x(CH_3)$_2$CH], 21.7 (2xCH_3Ar), 23.15 (2xCHCH_2), 30.1 (2xCH_2CO), 45.0 [2x(CH_3)$_2$CH], 52.0 (2xCHCHS), 57.0 (2xCHS), 129.5, 130.1, 133.0, 146.25 (ArC), and 174.85 (2xCO); *m/z* 406 (M^+-2x91, 0.9%), 126 (100), 96 (15), 91 (30), 84 (55), 65 (15), 43 (13), and 41 (16) (Found: C, 60.72; H, 6.96; N, 4.26; S, 10.16. Calcd. for $C_{30}H_{40}N_2O_6S_2$: C, 61.20; H, 6.85; N, 4.76; S, 10.89).[24]

Synthesis of *N*-Isopropyl-γ-(2-phenyl-2-oxoethyl)-γ-butyrolactam (40). To a solution of compound **22b** (80 mg, 0.2 mmol) in DMF (4 mL) and water (2 mL) was added $Na_2S_2O_4$ (102 mg, 0.5 mmol) y $NaHCO_3$ (42 mg, 0.5 mmol) stirring the mixture for 1 d at 100°C. Then, water was added and this mixture was

extracted with EtOAc (3x20 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo (15 Torr) to give a residue which was chromatographied (silica gel, hexane/EtOAc) affording 19 mg of pure compound **40** (40% yield): R_f 0.40 (AcOEt); ν 1670 cm^{-1} (2xC=O); δ_H 1.29, 1.30 (2d, *J*=6.9, 6H, 2xCH_3), 1.71 (m, 1H, *H*CHCH$_2$CO), 2.30 (m, 1H, HC*H*CH$_2$CO), 2.49 (m, 2H, CH$_2$CON), 3.20 (dd, *J*=17.2, 9.5, 1H, CO*H*CHCHN), 3.32 (dd, *J*=17.2, 3.5, 1H, COHC*H*CHN), 4.16 [m, 1H, $(CH_3)_2CHN$], 4.35 (m, 1H, CH$_2$C*H*N), 7.50, 7.61, and 7.94 (3m, 5H, ArH); δ_C 19.9, 21.6 (2xCH_3), 25.9 (*C*H$_2$CH$_2$CO), 30.15 (CH$_2$*C*H$_2$CO), 43.6 (COC*H*$_2$CHN), 44.5 [$(CH_3)_2$*C*HN], 53.4 (CH$_2$*C*HN), 127.95, 128.8, 133.6, 136.65 (ArC), 174.9 (CON), and 197.6 (ArCO); *m/z* 245 (*M*$^+$, 4%), 217 (10), 202 (19), 126 (39), 125 (11), 110 (47), 105 (100), **84 (98)**, 77 (39), 55 (19), 51 (15), 43 (14), 42 (11), and 41 (37) (Found: *M*$^+$ 245.1413. Calcd. for $C_{15}H_{19}NO_2$: 245.1416).

Synthesis of (2*E*,4*E*)-*N*-Isopropyl-7-phenyl-6-oxo-2,4-heptadienamide (41). *1st Method.* To a solution of compound **15f** (52 mg, 0.2 mmol) in CH_2Cl_2 (4 mL) was added PCC (88 mg, 0.4 mmol) and the mixture was allowed to react at room temperature for 1 h. Then, this crude mixture was filtered by a short pad of florisil, and the solvent was removed to give a residue which was purified by flash chromatography yielding 21 mg of 1,6-dicarbonyl compound **41** (40% yield). *2nd Method.* To a solution of $(COCl)_2$ (19 μL, 0.22 mmol) in CH_2Cl_2 (2 mL) was added at -50°C dry DMSO (32 μL, 0.44 mmol) stirring the mixture for 2 min. Then, the solution of compound **15f** (52 mg, 0.2 mmol) in CH_2Cl_2 (3 mL) was added at the same temperature and after 5 min Et_3N (141 μL, 1 mmol) was added. The reaction was warmed up to room temperature for 1 d and then hydrolyzed with water and extracted with CH_2Cl_2 (3x15 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo (15 Torr), and the resulting crude was purified to give 20 mg of compound **41** (40% yield): R_f 0.74 (EtOAc); ν 3306 (NH), 3062, 3033, 1635, 1616 (C=CH), 1693 (CO), and 1651 cm^{-1} (NC=O); δ_H 1.19 (d, *J*=6.4, 6H, 2xCH_3), 3.85 (s, 2H, CH_2), 4.15 (m, 1H, CHN), 5.46 (br s, 1H, NH), 6.14 (d, *J*=13.4, 1H, CHCON), 6.48 (d, *J*=14.3, 1H, C*H*COCH$_2$), and 7.27 (m, 7H, ArH, 2xC*H*=CHCO); δ_C 22.7 (2xCH_3), 41.8 (CHN), 127.2, 128.85, 129.5, 132.2, 133.2, 133.8, 137.6, 139.5 (2xCH=CH, ArC), 163.7 (NCO), and 197.0 (CO); *m/z* 257 (*M*$^+$, 2%), 81 (13), 44 (100), and 43 (35).

Synthesis of (2*E*,4*E*,6*E*)-*N*-Isopropyl-7-phenyl-2,4,6-heptatrienamide (42). To a solution of compound **15f** (52 mg, 0.2 mmol) in CH_3CN (2 mL) was added CBr_4 (74 mg, 0.22 mmol) and Ph_3P (58 mg, 0.22 mmol), stirring the mixture for 1 d at 90°C. Then, EtOAc was added to the cooled reaction mixture and this organic layer was washed with water (3x15 mL) and dried (Na_2SO_4). The elimination of solvent gave a residue which was purified by flash chromatography affording 24 mg of trienamide **42** (50%): mp 178-179°C (hexane/EtOAc); ν 3283 (NH), 3056, 3017, 1629, 1603 (C=CH), and 1650 cm^{-1} (CO); δ_H 1.20 [d, *J*=6.1, 6H, $(CH_3)_2$CH], 4.19 (m, 1H, CHN), 5.32 (d, *J*=7.9, 1H, NH), 5.84 (d, *J*=14.6, 1H, CHCO), 6.40 (dd, *J*=15.0, 11.3, 1H, C*H*CH=CHCO), 6.64-6.72 (m with d at 6.70, *J*=15.5, 2H, ArC*H*, C*H*=CHCH=CHCO), 6.86 (dd, *J*=15.5, 10.7, 1H, ArCH=C*H*), and 7.34 (m, 6H, ArH, C*H*=CHCO); δ_C 22.85 [$(CH_3)_2$CH], 41.5 (CHN), 123.8, 126.7, 128.2, 128.2, 128.7, 130.4, 135.7, 136.8, 139.4, 140.5 (3xCH=CH, ArC), and 165.15 (CO); *m/z* 241 (*M*$^+$, 35%), 198 (23), 183 (23), 182 (19), 181 (27), 156 (50), 155 (90), 154 (32), 153 (37), 152 (19), 141 (14), 129 (14), 128 (29), 127 (13), 115 (27), 91 (32), 86 (13), 78 (15), 77 (50), 76 (19), 58 (26), 55 (10), 51 (25), 46 (10), 44 (37), 43 (100), and 42 (11) (Found: C, 79.21; H, 7.76 ; N, 5.75. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80).

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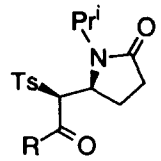
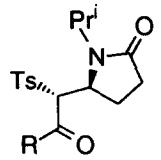


erythro



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24. Mixture of diastereomers.
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