114. Synthesis of Ethyl (2*RS*,3*SR*)-1-Tosyl-3-vinylazetidine-2-carboxylate and Ethyl (2*RS*,*E*)-3-Ethylidene-1-tosylazetidine-2-carboxylate (= *rac*-Ethyl *N*-Tosylpolyoximate)[1])

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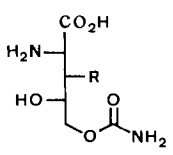
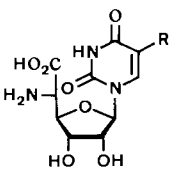
The synthesis of 3-ethylideneazetidine-2-carboxylic acid (= polyoximic acid; **3**) is approached in two different ways leading to potential precursors of **3**. The first way involved a ring closure to a vinyl-substituted azetidine. Thus, *Ireland-Claisen* rearrangement of the Boc-glycinates **6** and **10** of (*Z*)- and (*E*)-2-butene-1,4-diol afforded, after exchange of the *N*-protecting groups, the isomeric 2-(tosylamino)-3-vinylbutanolides **13** and **14** with high stereoselectivity. Only the *cis*-isomer **14** could be further transformed to 3-(bromomethyl)-2-(tosylamino)-4-pentenoate **17**, and in a smoth cyclization with K_2CO_3, to *trans*-3-vinylazetidine-2-carboxylate **18** *(Scheme 2)*. In the second approach, the 3-ethylidene isomer **19** of **18** was obtained more directly by a [2 + 2] cycloaddition, together with the two isomers **23** and **24**, from methylallene **20** and (tosylimino)acetate **21** *(Scheme 3)*. The main product of this reaction was, however, 2-(tosylamino)-4-hexinoate **22**, the product of an ene reaction.

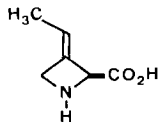
Introduction. – The polyoxins are an interesting group of structurally related nucleoside peptide antibiotics produced by the soil microorganism *Streptomyces Cacaoi* var. *Asoensis* [2]. While most of the polyoxins are dipeptides of one of the polyhydroxylated amino acids **1a** or **1b** and the nucleoside **2a**, **2b**, or **2c**, four structures are tripeptides extended at the C-terminus by polyoximic acid (= (2*S*)-3-ethylideneazetidine-2-carboxylic acid; **3**) [3]. The fungicidal [4] and insecticidal [5] properties of polyoxins could be related to competitive inhibition of the enzyme chitin synthetase [4–6]. The unique structural features and the interesting biological activity of these antibiotics led to syntheses of polyoxamic acid (**1a**) [7], the nucleoside **2a** [7a], and of structural analogues



1a R = OH
b R = H



2a R = CH_3
b R = CH_2OH
c R = CO_2H



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[1]) This work is part of the Ph. D. thesis of *H. B.* [1].
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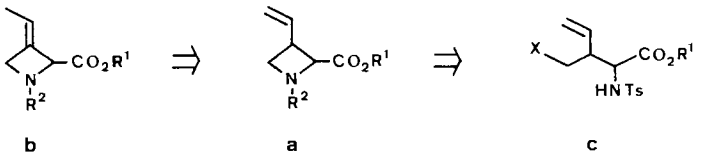
[8]. Up to now, however, no synthesis of the third amino acid, **3**, has been reported, although its biosynthesis from isoleucine has been elucidated [9].

Since polyoximic acid (**3**) combines structural features of two interesting antimetabolites, azetidine-2-carboxylate [10] and β,γ-unsaturated amino acids [11], we decided to synthesize this challenging molecule.

Scheme 1



b **a** **c**

R^1, R^2 = suitable protecting groups

A retrosynthetic plan for a first approach is depicted in *Scheme 1*. The stability of polyoximic acid (**3**) towards boiling 3N HCl during the hydrolysis of polyoxin A [3b] suggested that the isomerization of a 3-vinylazetidine-2-carboxylate **a** to the corresponding 3-ethylidene derivative **b** should in principle be possible. Due to the combination of strain and entropic factors, the ring closure to azetidines is a comparatively unfavorable process [12]. Thus, with the selected strategy, additional problems of the ring formation due to the strain exerted by the exocyclic double bond are avoided. Since cyclization of 4-halogeno-substituted 2-(tosylamino)butyrates is one of the most efficient methods to prepare azetidine-2-carboxylates [13], we chose sulfonamide **c** with a leaving group X as precursor for **a**[3]).

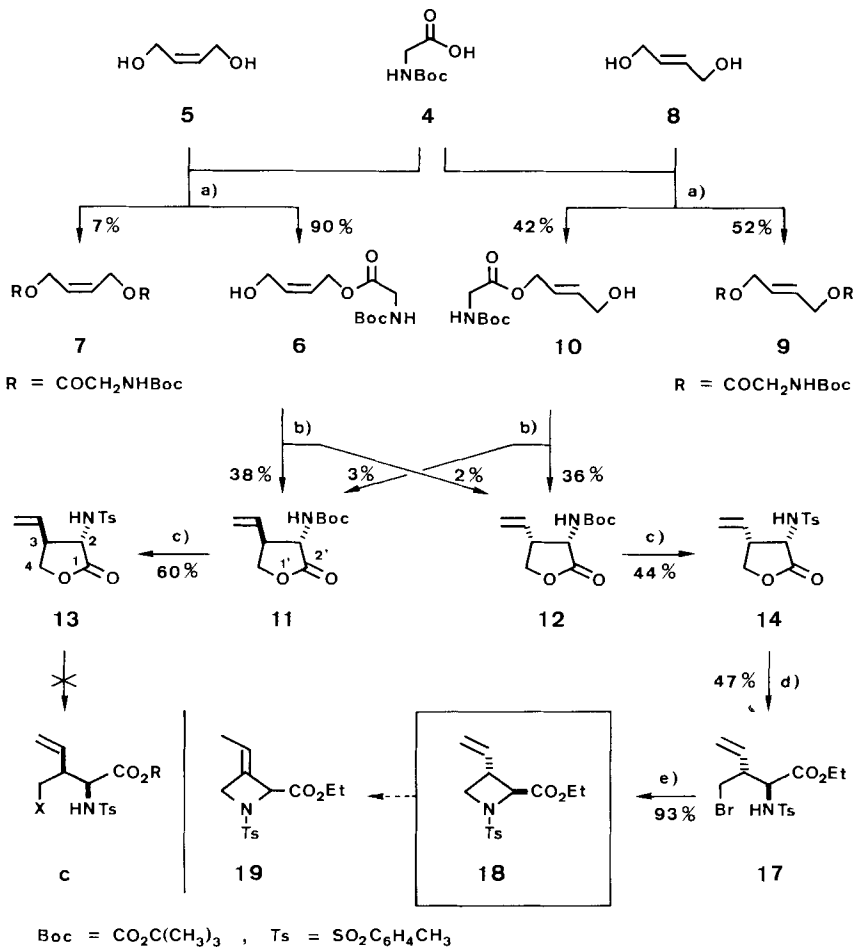
A second, more direct way to **b** was realized by a [2 + 2] cycloaddition.

Results. – Compound **c**, a γ,δ-unsaturated α-amino-acid derivative, should be accessible by the *Ireland-Claisen* rearrangement of an appropriate allyl glycinate [15][4]). Our results along these lines are shown in *Scheme 2*. Glycine protected as *tert*-butyl carbamate **4** was esterified with an excess of (*Z*)-2-butene-1,4-diol (**5**) using dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-(dimethylamino)pyridine to give 90% of monoester **6** together with some bis-glycinate **7** (7%). When (*E*)-2-butene-1,4-diol (**8**), obtained in 80% yield by $LiAlH_4$ reduction of 2-butyne-1,4-diol, was reacted analogously, the amount of diester **9** (52%) formed together with mono-glycinate **10** (42%) was larger. However, additional monoester **10** could be obtained by acid-catalyzed transesterification of **9** with 1 equiv. of diol **8**. The OH functions of **6** and **10** were then protected by silylation with hexamethyldisilazane. Subsequent *Ireland-Claisen* rearrangement according to [15] gave the epimeric 3-vinylhomoserine-lactone derivatives **11** and **12** in moderate

[3]) In another approach to **a**, ethyl 2-bromo-3-(bromomethyl)-4-pentenoate (1:1 epimeric mixture) was reacted with (diphenylmethyl)amine, following the azetidine-2-carboxylate synthesis of *Rodebaugh* and *Cromwell* [14]. However, the desired epimeric 3-vinylazetidine-2-carboxylates were formed in 5% yield only, the major pathway of the reaction (43% of products) being monosubstitution followed by HBr elimination (for details, *cf.* [1]).

[4]) Another approach to compound **c**, the ene reaction of (tosylimino)acetates [16], failed with several 2-butenyl derivatives (*cf.* [1]). Successful, as reported later by *Weinreb et al.* [17], was an intramolecular version of this reaction.

Scheme 2



a) DCC/(Me_2N)Py (cat.); *b)* 1. hexamethyldisilazane/reflux, 2. lithium cyclohexyl(isopropyl)amide/THF/−78°, 3. chlorotrimethylsilane/−78° to reflux, 4. CH_3OH/0°, 5. citric acid; *c)* 1. TsOH·H_2O/CH_3CN, 2. TsCl/pyridine; *d)* 6.7N HBr/EtOH; *e)* K_2CO_3/acetone.

yield (*ca.* 40%)[5]). This rearrangement proceeded with high stereoselectivity, the (*Z*)-allyl ester **6** giving predominantly the *trans*-substituted lactone **11** and the (*E*) allyl ester **10** leading to the *cis*-epimer **12**[6]). The transformation of the carbamates to the *N*-sulfonyl-protected lactones turned out to be more difficult than anticipated, as the usual methods for the cleavage of *tert*-butyl carbamates like treatment with CF_3CO_2H failed. Successful, albeit with moderate yield, was finally the treatment of **11** and **12** with TsOH·H_2O in

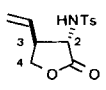
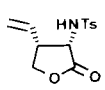
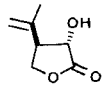
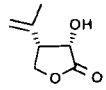
[5]) The low yield of this rearrangement compared with simpler systems [15] could be due to the bulk of the trimethylsilyloxy group. No rearrangement was observed, when **6** was protected as *tert*-butyl dimethylsilyl ether (*cf.* [1]).

[6]) For the determination of configuration see below.

CH_3CN [18]. Subsequent sulfonation gave the *p*-toluenesulfonamides **13** and **14**, respectively[7]).

The relative configuration of the racemic lactones **11–14** was determined by ^{1}H-NMR analysis. Comparison of the coupling constants of **13** and **14** with the corresponding values reported for the closely related 2-hydroxy-3-(isopropenyl)butanolides **15** and **16** [19] *(cf. Table)* allows an unambiguous configurational assignment. It is interesting to note that the differences between the stereoisomers are more pronounced for the 2 H–C(4)/H–C(3) than for the H–C(2)/H–C(3) couplings. Our result is, furthermore, in line with the stereochemical course of similar *Ireland-Claisen* rearrangements of allyl glycinates [15]. It is also evident from comparison of ^{1}H-NMR data measured in acetone (*cf.* [1], p. 45) that the *cis*-isomer **14** corresponds to the product obtained by the intramolecular ene reaction of (*E*)-2-butenyl (tosylimino)acetate described by *Weinreb et al.* [17]. These authors, however, assigned the *trans* geometry to this compound [17]. Since their conclusions are based on NOE measurements of, as we believe, erroneously assigned signals, our assignment should be correct. The stereochemistry of the intramolecular ene reaction of (*E*)-2-butenyl (tosylimino)acetate is, therefore, analogous to the one of 3-hexenyl (tosylimino)acetates [17] and (*Z*)-2-butenyl thioxoacetate, or prenyl thioxoacetate [20].

Table. *^{1}H-NMR Coupling Constants of Disubstituted γ-Lactones*

				
	13	**14**	**15** [19]	**16** [19]
J(2,3) [Hz]	11.5[a])	7.5[a])	10.2	7.8
J(3,4) [Hz]	10.5, 8.0	5.0, 1.2	10.4, 9.0	5.5, 3.0

[a]) Determined by NH decoupling.

The next step involving the transformation of the lactones **13** and **14** to intermediates of type **c** *(Scheme 1)* revealed remarkable differences in reactivity between the diastereoisomers **13** and **14**. While the *cis*-isomer **14** could be transformed to the desired bromide **17** by heating in ethanolic HBr [13b], the *trans*-epimer resisted such treatment[8]). Under forcing conditions, decomposition and isomerization to **14** was observed. Reaction of **13** with BBr_3 in CH_3CN and methanolysis according to [22], finally, gave a low yield of isomeric bromides, with the methyl ester corresponding to **17** as major component (*cf.* [1]). This rate difference for the substitution by Br at C(4) must be a steric and/or stereoelectronic effect. According to the ^{1}H-NMR data of **13** and **14** *(cf. Table)*, the dihedral angle of the C(3)–C(4) bond and, therefore, also of the C(4)–O bond appears to be different for the two isomeric butanolides.

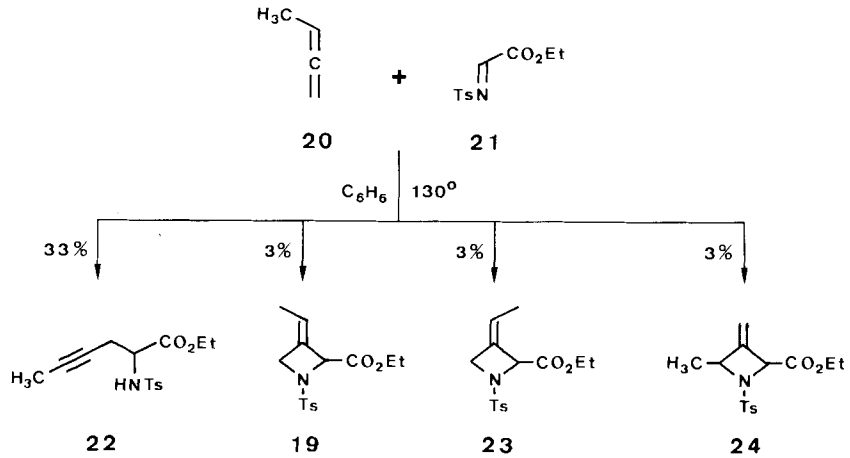
Treatment of the bromide **17** with K_2CO_3 in boiling acetone afforded the *trans*-disubstituted azetidine **18** in high yield. The 3-unsubstituted methyl or ethyl 1-tosylazetidine-2-carboxylate could be prepared by this method in excellent yield as well (*cf.* [1]). These conditions are preferable to the procedure of *Miyoshi et al.* [13b], NaH in wet DMF.

Except for the last step, the synthesis of 3-vinylazetidine-2-carboxylate **18** turned out to be more difficult than anticipated. With an overall yield of *ca.* 4% based on Boc-

[7]) A more direct access to the lactones **13** and **14** would be the rearrangement of allyl *N*-tosylglycinates. Reaction of the *N*-tosyl analog of **6** gave, however, only 7% of **13**, even when the highly unstable Li enolate was quenched *in situ* with chlorotrimethylsilane (*cf.* [1]).

[8]) Alternatively, reaction of **14** with trichloro(methyl)silane/NaI according to *Olah et al.* [21] and esterification with CH_2N_2 gave 30% of the iodo methyl ester corresponding to **17** (*cf.* [1]).

Scheme 3



glycine (**4**), the effort for the preparation of sufficient quantities of **18** for studying the isomerization to **19** was considered to be too high.

Among several other approaches (*cf.* [1] and the subsequent paper), the construction of 3-alkylideneazetidines by [2 + 2] cycloaddition seemed an intriguing access to polyoximic acid. Like other cumulenes, allenes undergo [2 + 2] cycloadditions with relative ease (*cf.* [23]). According to this strategy, the skeleton of **3** should then be obtained by reaction of methylallene (**20**) and an electron-deficient derivative of iminoacetate. To the best of our knowledge, no such reactions have so far been reported. Related are, however, the photoaddition of allene to enones [24], the cycloaddition to fumarate [25], and reactions with chlorosulfonyl isocyanate affording 3-alkylidene-2-azetidinones [26]. The result of the thermal reaction between methylallene (**20**)[9]) and (tosylimino)acetate **21** [30][10]) is shown in *Scheme 3*. Not quite unexpectedly, the major low molecular weight component of this reaction mixture was 2-(tosylamino)-4-hexynoate **22**, the product of an ene reaction[11]). HPLC separation of a less polar fraction, however, afforded the desired cycloadducts **19**, **23**, and **24** in small quantities. It is evident from the ^{1}H-NMR data that **19** corresponds to the frame of polyoximic acid (**3**) and that **23** is its double-bond isomer. Characteristic for **19**, **23**, and also for **3** [3b] is the splitting of the ^{1}H-NMR signal of $CH_3CH{=}C(3)$ to a pseudo-*q* by the three H-atoms of the azetidine ring. The double-bond geometry of **19** and **23** could be assigned unambiguously by difference-NOE measurements (*cf.* [1]).

With this low-yield but short procedure, a derivative of polyoximic acid (**3**) could be prepared for the first time by chemical synthesis. Improvement of this process, the

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[9]) Methylallene (**20**) [27] was prepared by reduction of 1,2-dibromo-2-butene [27], actually a mixture with 2,3-dibromo-1-butene, with Zn in pentyl acetate according to [28]. In contrary to such reductions in EtOH [28] [29], this procedure yields allenes which are essentially free of solvents and isomeric alkynes.

[10]) In one experiment which unfortunately could not be reproduced, the (tosylimino)acetate **21** was obtained in a very pure nicely crystalline form, the starting ethyl glyoxylate was prepared according to *Hook* [31].

[11]) The structure elucidation of **22** mainly relies on the ^{13}C-NMR signals at 72.3 and 79.8 ppm, assigned to the acetylenic C-atoms C(4) and C(5).

deprotection of **19**, and other approaches to **3**, some of them already outlined in [1] and the subsequent paper, are under investigation.

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Experimental Part

General. The usual workup procedure consists in dissolving the reaction mixture in an org. solvent and H_2O, extracting the aq. phase 3 times with this solvent, washing the org. phases separately with sat. NaCl soln. to neutrality, drying ($MgSO_4 \cdot 2\ H_2O$) and evaporating. Column chromatography: silica gel *60* (0.063–0.200; *Merck* or *Macherey-Nagel & Co.*) using multi-bore columns as described in [32]. Small-scale column chromatography and flash chromatography (FC) [33]: silica gel *60* (0.040–0.063; *Merck*) in normal columns. The collected fractions are listed in the order of elution. TLC: precoated plates, silica gel *60 F254 (Merck)*; visualization by UV light (254 nm), by I_2 vapors, by Ce $(SO_4)_2$ (1%) and $H_3[P(MoO_{10})_4]$ (2%) in 10% H_2SO_4 and heating, or by 0.1N $KMnO_4$ with or without heating. HPLC: *DuPont Instruments* HPLC system using *DuPont* prep. columns (25 cm/21.2 mm outer diameter, 7 µm silica gel). M.p.: non-corrected; in open capillaries, *Büchi* apparatus. IR spectra (in cm^{-1}): *Perkin-Elmer-297* spectrometer. ^{1}H-NMR spectra: *Bruker-WP-80, Varian-EM-390*, or *Bruker-WM-300* spectrometer; chemical shifts in ppm (δ values), coupling constant J in Hz. ^{13}C-NMR spectra: *Varian-XL-100* (25.2 MHz) or *Bruker-WM-300* instrument (75.4 MHz); chemical shifts, measured by broad-band ^{1}H-decoupling, in ppm (δ values); multiplicity of the signals determined either by off-resonance ^{1}H-decoupling or by gated spin-echo techniques. MS: *Hitachi-Perkin-Elmer-RMU-6M* spectrometer; rel. peak intensities in % of the base peak; no mention means indirect introduction of the samples and ionization at 70 eV/200°; d.i. = direct injection.

(Z)-4-Hydroxy-2-butenyl N-(tert-*Butoxycarbonyl)glycinate* (**6**). To a soln. of N-(tert-*butoxycarbonyl)-glycine* (**4**; 3.855 g, 22 mmol), *(Z)-2-butene-1,4-diol* (**5**; 3.21 g, 36 mmol), and 4-(dimethylamino)pyridine (269 mg, 2.2 mmol) in 45 ml of CH_2Cl_2, DCC (4.767 g, 23.1 mmol) was added under ice-cooling. After stirring for 20 h at r.t., the mixture was filtered and the filtrate quenched with ice-water and extracted with CH_2Cl_2. Washing with 10% HCl and sat. NaCl soln., drying, and chromatography of the residue (silica gel, CH_2Cl_2/CH_3OH 97:7) gave 0.619 g (7%) of **7** and 4.918 g (90%) of **6**.

Data of **6**: IR (CCl_4): 3615*w*, 3440*m*, 3030*w*, 3000*w*, 2978*m*, 2930*m*, 1748*s*, 1720*s*, 1500*s*, 1450*m*, 1410*m*, 1390*m*, 1380*m*, 1368*s*, 1275*m*, 1250*m*, 1195*s*, 1165*s*, 1058*m*, 1030*m*, 960*m*, 910*m*, 862*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.45 (*s*, $(CH_3)_3C$); 2.27 (*t*, J = 5.5, OH–C(4′)); 3.90 (*d*, J = 6, 2 H–C(2)); 4.26 (*t*, $J \approx 5$, 2 H–C(4′)); 4.75 (*d*, J = 6, 2 H–C(1′)); 5.09 (*m*, $w_{1/2} \approx 15$, NH); 5.6–5.7, 5.85–5.95 (2*m*, H–C(2′), H–C(3′)). MS: 189 (0.4, $M^{+\cdot} - 56$), 171 (0.7), 130 (2), 120 (15), 102 (7), 84 (7), 82 (11), 74 (9), 71 (7), 70 (18), *57* (100), 44 (15), 41 (45).

(Z)-2-Butene-1,4-diyl Bis[N-(tert-*butoxycarbonyl)glycinate]* (**7**). IR (KBr): 3470*m*, 3430*m*, 2980*m*, 2930*m*, 2850*m*, 1770–1670*s*, 1625*m*, 1570*m*, 1520*s*, 1448*w*, 1390*w*, 1365*m*, 1348*w*, 1315*m*, 1302*m*, 1270*m*, 1245*s*, 1160*s*, 1085*w*, 1050*w*, 1030*w*, 970*m*, 945*m*, 890*w*, 868*w*, 828*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.45 (*s*, 2 $(CH_3)_3C$); 3.91 (*d*, $J \approx 6$, 2 $C(O)CH_2N$); 4.7–4.8 (*m*, 2 main peaks, 2 H–C(1′), 2 H–C(4′)); 5.07 (*m*, $w_{1/2} \approx 15$, 2 NH); 5.7–5.85 (*m*, H–C(2′), H–C(3′)).

(E)-2-Butene-1,4-diol (**8**). To a stirred soln. of 2-butyne-1,4-diol (10.75 g, 125 mmol) in THF (190 ml), $LiAlH_4$ (10 g, 262 mmol) was added at 0° in portions. After heating for 13 h under reflux, the mixture was cooled, *Celite* added, and the mixture carefully hydrolyzed by addition of sat. $(NH_4)_2SO_4$ soln. Removal of inorg. salts by filtration, washing of the filter cake with wet Et_2O and CH_2Cl_2, evaporation, and bulb-to-bulb distillation of the residue at 170°/0.5 Torr yielded 9.482 g (86%) of **8**.

(E)-4-Hydroxy-2-butenyl N-(tert-*Butoxycarbonyl)glycinate* (**10**). To a soln. of **4** (1.74 g, 10 mmol), **8** (880 mg, 10 mmol), and 4-(dimethylamino)pyridine (244 mg, 2 mmol) in 50 ml of CH_2Cl_2, 2.166 g (10.5 mmol) of DCC was added. After stirring for 4½ days at r.t., the mixture was worked up as described above for **6**. Chromatography (silica gel, CH_2Cl_2/AcOEt 4:1) gave 1.049 g (52%) of **9** and 1.031 g (42%) of **10**.

Data of **10**: IR (CCl_4): 3600*w*, 3445*w*, 2980*w*, 2935*w*, 1742*m*, 1710*s*, 1500*m*, 1448*w*, 1390*m*, 1368*m*, 1358*m*, 1162*s*, 1090*w*, 1058*w*, 970*m*, 860*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.45 (*s*, $(CH_3)_3C$); 1.92 (*m*, $w_{1/2} \approx 10$, OH–C(4′)); 3.91 (*d*, $J \approx 6$, 2 H–C(2)); 4.16 (*d*, $J \approx 5$, 2 H–C(4′)); 4.65 (*dd*, J = 6, 1, 2 H–C(1′)); 5.1 (*m*, $w_{1/2} \approx 15$, NH); 5.8 (*dtt*, J = 15.5, 6, 1), 5.93 (*dt*, J = 15.5, 5) (H–C(2′), H–C(3′)).

(E)-2-Butene-1,4-diyl Bis[N-(tert-Butoxycarbonyl)glycinate] (**9**). IR ($CHCl_3$): 3445*w*, 2980*m*, 2938*m*, 2860*w*, 1745*m*, 1710*s*, 1500*m*, 1448*m*, 1390*m*, 1368*m*, 1160*s*, 1058*m*, 970*m*, 860*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.45 (*s*, 2 $(CH_3)_3C$); 3.92 (*d*, $J \approx 6$, 2 C(O)CH_2N); 4.65 (*m*, 4 main peaks, 2 H–C(1'), 2 H–C(4')); 5.02 (*m*, $w_{1/2} \approx 15$, 2 NH); 5.85–5.87 (*m*, 7 main peaks, H–C(2'), H–C(3')).

Equilibration of Diester **9** *and Diol* **8**. A soln. of **9** (1.026 g, 2.55 mmol), **8** (2.25 g, 25.5 mmol), 4-(dimethylamino)pyridine (62 mg, 0.5 mmol), and pyridinium *p*-toluenesulfonate (50 mg) in CH_2Cl_2 (20 ml) and DMSO (2 ml) was heated under reflux for 19 h. Aq. workup, washing with 5% $NaHCO_3$ soln., H_2O, and sat. NaCl soln., and chromatography (silica gel, CH_2Cl_2/AcOEt 4:1) gave 272 mg (27%) of **9** and 506 mg (40%) of **10**.

Claisen *Rearrangement of* **6**. A mixture of **6** (490 mg, 2 mmol) and hexamethyldisilazane (1 ml) was heated under reflux for 4 h. The excess of reagent was evaporated, the residue dried under high vacuum, dissolved in THF (3 ml), and added at –78° within 40 min to a THF (3 ml) soln. of lithium cyclohexyl(isopropyl)amide (4.46 mmol; prepared by deprotonation of cyclohexyl(isopropyl)amine with BuLi in hexane at 0°, evaporation of hexane, and addition of THF). After stirring for 10 min at –78°, chlorotrimethylsilane (0.35 ml, 2.765 mmol) was added. The mixture was kept for 30 min at –78°, for 30 min at 0°, and for 30 min at r.t. before being heated under reflux for 1 h. CH_3OH (2 ml) was added, the reaction quenched with 5% citric acid, the mixture extracted with CH_2Cl_2, and the extract washed with sat. NaCl soln. Chromatography (silica gel, CH_2Cl_2/AcOEt 4:1) afforded **12** (11 mg, 2%) and **11** (175 mg, 38%).

tert-*Butyl* N-*[(3'RS,4'RS)-2',3',4',5'-Tetrahydro-2'-oxo-4'-vinylfuran-3'-yl]carbamate* (**11**). M.p. 117°. IR ($CHCl_3$): 3440*w*, 3080*w*, 3030*w*, 2980*m*, 2930*m*, 2850*w*, 1782*s*, 1715*s*, 1640*w*, 1500*m*, 1455*m*, 1392*m*, 1368*m*, 1310*m*, 1280*w*, 1158*s*, 1058*m*, 1010*m*, 985*m*, 930*m*, 855*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.45 (*s*, $(CH_3)_3C$); 3.05–3.25 (*m*, 5 main peaks, H–C(4')); 3.99 (*dd*, J = 10.5, 9), 4.42 (*dd*, J = 9, 8) (2 H–C(5')); 4.1–4.3 (*m*, H–C(3')); 4.85–5.05 (*m*, NH); 5.24 (*dt*, J = 10, 1), 5.26 (*dt*, J = 17, 1) (2 H–C(2'')); 5.82 (*ddd*, J = 17, 10, 8, H–C(1'')). MS (d.i.): 212 (0.4, $M^+ - 15$), 171 (12), 154 (3), 127 (7), 82 (11), 59 (17), *57* (100), 54 (18), 41 (21). Anal. calc. for $C_{11}H_{17}NO_4$ (227.25): C 58.13, H 7.54, N 6.16; found: C 58.05, H 7.54, N 6.10.

tert-*Butyl* N-*[(3'RS,4'SR)-2',3',4',5'-Tetrahydro-2'-oxo-4'-vinylfuran-3'-yl]carbamate* (**12**). M.p. 86°. IR ($CHCl_3$): 3440*w*, 3080*w*, 3030*w*, 2980*m*, 2930*m*, 2910*w*, 1782*s*, 1710*s*, 1640*w*, 1500*s*, 1450*w*, 1390*m*, 1368*s*, 1328*w*, 1315*m*, 1272*m*, 1160*s*, 1060*w*, 1032*m*, 1018*m*, 972*m*, 935*m*, 905*w*, 858*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.45 (*s*, $(CH_3)_3C$); 3.40–3.55 (*m*, 4 main signals, H–C(4')); 4.3 (*d*, J = 9.5, further split, $w_{1/2} \approx 3$), 4.44 (*dd*, J = 9.5, 5) (2 H–C(5')); 4.59 (*t*, $J \approx 7$, H–C(3')); 4.80–5.05 (*m*, $w_{1/2} \approx 15$, NH); 5.26 (*dt*, J = 17, 1), 5.30 (*d*, J = 10.5, further split, $w_{1/2} \approx 3$) (2 H–C(2'')); 5.69 (*ddd*, J = 17, 10.5, 9, H–C(1'')). MS (d.i.): 171 (11, $M^+ - 56$), 154 (3), 127 (8), 126 (2), 83 (3), 82 (11), 59 (16), *57* (100), 54 (19), 41 (24). Anal. calc. for $C_{11}H_{17}NO_4$ (227.45): C 58.13, H 7.54, N 6.16; found: C 58.12, H 7.56, N 6.08.

Claisen *Rearrangement of* **10**. A mixture of **10** (600 mg, 2.45 mmol) and hexamethyldisilazane (1 ml) was heated under reflux for 4 h. Excess of reagent was evaporated, the residue dried under high vacuum, dissolved in THF (5 ml), and added within 2 min to a soln. of lithium cyclohexyl(isopropyl)amide (5.14 mmol) in THF (15 ml) at –78°. After stirring for 10 min at –78°, chlorotrimethylsilane (0.65 ml, 5.135 mmol) was added. The mixture was then treated and worked up as above. Chromatography (silica gel, CH_2Cl_2/AcOEt 19:1) gave 200 mg (36%) of **12** and 19 mg (3%) of **11**.

(2RS,3RS)-2-(Tosylamino)-3-vinyl-4-butanolide (**13**). A mixture of **11** (84 mg, 0.37 mmol), $TsOH \cdot H_2O$ (176 mg, 0.926 mmol), and CH_3CN (10 ml) was stirred for 14 h at r.t. After, evaporation, TsCl (78 mg, 0.409 mmol) followed by pyridine (1 ml) was added. After stirring for 5 h at r.t., the reaction was quenched with 10% HCl soln. Extraction with $CHCl_3$, followed by chromatography (silica gel, hexane/AcOEt 9:1) afforded 62 mg (60%) of **13**. M.p. 127°. IR ($CHCl_3$): 3380–3320*w*, 3020*w*, 2905*w*, 1785*s*, 1640*w*, 1595*m*, 1490*w*, 1478*w*, 1425*w*, 1375*m*, 1345*m*, 1305*m*, 1290*m*, 1265*w*, 1160*s*, 1148*m*, 1090*m*, 1010*m*, 985*m*, 965*w*, 930*m*, 888*w*, 865*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.42 (*s*, $CH_3C_6H_4SO_2$); 3.0–3.2 (*m*, H–C(3)); 3.96 (*dd*, J = 11, 9), 4.38 (*dd*, J = 9, 8, 2 H–C(4)); 4.0 (*dd*, J = 11, 7, H–C(2)); 5.11 (*dt*, J = 17, 1), 5.19 (*dt*, J = 10.5, 1) (2 H–C(2')); 5.25 (*d*, J = 7, further broadened, $w_{1/2} \approx 3$, NH); 5.65–5.82 (*m*, H–C(1')); 7.26–7.36, 7.74–7.86 (2*m*, $CH_3C_6H_4SO_2$). ^{1}H-NMR (300 MHz, (D_6)acetone): 2.39 (*s*, $CH_3C_6H_4SO_2$); 3.05–3.22 (*m*, H–C(3)); 4.05 (*dd*, J = 10.5, 9), 4.34 (*dd*, J = 9, 8) (2 H–C(4)); 4.3–4.45 (*m*, irradiation at 6.98→4.35, (*d*, $J \approx 11.5$), H–C(2)); 5.00 (*d*, J = 10.5, further split, $w_{1/2} \approx 3$), 5.12 (*dt*, J = 17, 1) (2 H–C(2')); 5.71 (*ddd*, J = 17, 10.5, 7.5, H–C(1')); 6.98 (*m*, $w_{1/2} \approx 13$, NH); 7.25–7.4, 7.75–7.85 (2*m*, $CH_3C_6H_4SO_2$). MS (d.i.): 281 (10, M^+), 236 (10), 155 (28), 139 (4), 126 (72), 98 (6), *91* (100), 89 (7), 82 (12), 80 (13), 65 (29), 55 (11), 54 (63), 41 (10), 39 (16).

(2RS,3RS)-2-(Tosylamino)-3-vinyl-4-butanolide (**14**). To a soln. of **12** (308 mg, 1.35 mmol) in CH_3CN (10 ml), $TsOH \cdot H_2O$ (645 mg, 3.39 mmol) was added, and the mixture stirred for 1.5 h at r.t. TsCl (517 mg, 2.714 mmol) was then added, followed by slow addition of pyridine (1 ml) in CH_3CN (5 ml). The mixture was stirred for 16 h at r.t. and worked up as above (chromatography with hexane/AcOEt 4.1): 123 mg (44%) of **14**. M.p. 133°. IR

($CHCl_3$): 3360*w*, 3020*w*, 2910*w*, 1785*s*, 1595*w*, 1490*w*, 1475*w*, 1400*w*, 1370*m*, 1340*m*, 1305*w*, 1290*w*, 1160*s*, 1130*m*, 1090*m*, 1025*m*, 1018*w*, 1008*w*, 970*m*, 955*w*, 935*w*, 875*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.43 (*s*, $CH_3C_6H_4SO_2$); 3.25–3.40 (*m*, H–C(3)); 4.23 (*dd*, J = 7.5, 6, H–C(2)); 4.30 (*d*, J = 9.5, further split, $w_{½} \approx 2$), 4.37 (*dd*, J = 9.5, 4.5) (2 H–C(4)); 4.93 (*d*, J = 6, further broadened, $w_{½} \approx 6$, NH); 5.19 (*dt*, J = 17, 1), 5.32 (*d*, J = 10.5, further split, $w_{½} \approx 2$) (2 H–C(2′)); 5.73 (*ddd*, J = 17, 10.5, 8, H–C(1′)); 7.29–7.33, 7.77–7.81 (2*m*, $CH_3C_6H_4SO_2$). ^{1}H-NMR (300 MHz, (D_6)acetone): 2.42 (*s*, $CH_3C_6H_4SO_2$); 3.2–3.35 (*m*, H–C(3)); 4.20 (*dd*, J = 9.5, 1), 4.50 (*dd*, J = 9.5, 5) (2 H–C(4)); 4.59–4.67 (*m*, irradiation at 6.86→4.62 (*d*, $J \approx 7.5$), H–C(2)); 4.98 (*dt*, J = 17, 1), 5.14 (*d*, J = 10.5, further split, $w_{½} \approx 3$) (2 H–C(2′)); 5.74 (*ddd*, J = 17, 10.5, 8.5, H–C(1′)); 6.86 (*d*, J = 8, further broadened, $w_{½} \approx 7$, NH); 7.3–7.45, 7.75–7.85 (2*m*, $CH_3C_6H_4SO_2$). MS (d.i.): 281 (6, M^+), 236 (10), 155 (29), 139 (4), 126 (72), 98 (5), *91* (100), 89 (6), 82 (13), 80 (11), 65 (26), 55 (14), 54 (73), 41 (11), 39 (14).

Preparation of HBr in EtOH. To tetralin (266 g, 2.012 mol) preheated to 50–60°, Br_2 (757 g, 4.734 mmol) was added within 4 h. The gaseous HBr evolved was bubbled through tetralin and absorbed into 800 ml of EtOH: 6.7N HBr/EtOH, according to titration with 0.1N NaOH.

Ethyl (2SR,3RS)-3-(Bromomethyl)-2-(tosylamino)-4-pentenoate (**17**). A soln. of **14** (69 mg, 0.42 mmol) in 10 ml of 6.7N HBr/EtOH (see above) was heated under reflux for 2 h. Aq. workup, extraction with $CHCl_3$, and chromatography (silica gel, CH_2Cl_2/AcOEt 19:1) afforded 45 mg (47%; 72% based on converted **14**) of **17** and 24 mg (35%) of **14**. *Data of* **17**. IR (CCl_4): 3338*w*, 3270*w*, 3080*w*, 2980*w*, 2920*w*, 1735*s*, 1598*w*, 1490*w*, 1425*m*, 1368*m*, 1352*m*, 1302*m*, 1288*w*, 1248*w*, 1220*w*, 1195*m*, 1182*m*, 1168*s*, 1090*m*, 1020*m*, 990*w*, 928*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.10 (*t*, J = 7, CH_3CH_2O); 2.42 (*s*, $CH_3C_6H_4SO_2$); 2.70 (*dq*, J = 8.5, 6.5, H–C(3)); 3.41 (*dd*, J = 10, 6.5), 3.55 (*dd*, J = 10, 6.5) ($BrCH_2$–C(3)); 3.88 (*dq*, J = 10.5, 7), 3.93 (*dq*, J = 10.5, 7) (CH_3CH_2O); 4.08 (*dd*, J = 9.5, 6.5, H–C(2)); 5.16 (*ddd*, J = 17, 1.5, 0.5), 5.21 (*dd*, J = 10, 1.5) (2 H–C(5)); 5.19 (*d*, J = 9.5, further broadened, $w_{½} \approx 4$, NH); 5.56 (*ddd*, J = 17, 10, 8.5, H–C(4)); 7.22–7.34, 7.7–7.8 (2*m*, $CH_3C_6H_4SO_2$). MS (d.i.): 392 (0.1, M^+), 390 (0.3, M^+), 318 (13), 316 (13), 310 (2), *256* (100), 236 (4), 155 (91), 97 (12), 91 (62), 85 (13), 83 (20), 71 (19), 69 (18), 65 (11), 57 (33), 55 (24), 43 (27), 41 (25).

Ethyl (2SR,3RS)-1-Tosyl-3-vinylazetidine-2-carboxylate (**18**). To a soln. of **17** (26 mg, 0.066 mmol) in acetone (1 ml), powdered K_2CO_3 (28 mg) was added and the mixture heated under reflux for 1 h. Filtration, evaporation, and chromatography of the residue (silica gel, CH_2Cl_2/AcOEt 19:1) gave 19 mg (93%) of **18**. IR ($CHCl_3$): 3030*w*, 2980*m*, 2930*w*, 1740*s*, 1640*w*, 1598*w*, 1490*w*, 1465*w*, 1445*w*, 1430*w*, 1395*w*, 1370*m*, 1350*m*, 1330*m*, 1305*m*, 1290*w*, 1182*w*, 1158*s*, 1090*s*, 1030*m*, 990*m*, 930*m*, 880*w*, 855*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.23 (*t*, J = 7, CH_3CH_2O); 2.44 (*s*, $CH_3C_6H_4SO_2$); 3.2–3.3 (*m*, 5 main peaks, H–C(3)); 3.71 (*t*, J = 7.5); 3.86 (*t*, J = 7.5, further split by small couplings) (2 H–C(4)); 4.15, 4.19 (2 *dq*, J = 10.5, 7, CH_3CH_2O); 4.38 (*d*, J = 7.5, H–C(2)); 5.09 (*dt*, J = 17, 1), 5.10 (*dt*, J = 10.5, 1) (2 H–C(2′)); 5.71 (*ddd*, J = 17, 10.5, 7, H–C(1′)); 7.3–7.4, 7.76–7.84 (2*m*, $CH_3C_6H_4SO_2$). MS (d.i.): 236 (69, $M^+ - 73$), 209 (3), 155 (68), 154 (23), 139 (6), 127 (3), 126 (8), 98 (12), *91* (100), 81 (23), 80 (21), 65 (18), 54 (16), 53 (12), 41 (5), 39 (10).

Reaction of Ethyl (Tosylimino)acetate (**21**) *with 1,2-Butadiene* (**20**). A soln. of 1.834 g (7.19 mmol) of **21** and *ca.* 970 mg (18 mmol) of **20** in 6 ml of dry benzene was heated in a closed ampule to 130° for 24 h. The cooled mixture was diluted with Et_2O and washed with 5% $NaHCO_3$ and sat. NaCl soln. Chromatography of the residue on silica gel (260 g, cyclohexane/CH_2Cl_2/AcOEt 9:9:2) gave a mixture of non-polar compounds (300 mg) and 735 mg (33%) of **22**. HPLC of the non-polar fraction (hexane/Et_2O 4:1, 60 bar, 32 ml/min, detection at 228 nm) yielded 73 mg (3%) of **24** (t_R 12.4 min), 65 mg (3%) of **19** (t_R 15 min), and 81 mg (4%) of **23** (t_R 16.8 min).

Ethyl 2-(Tosylamino)-4-hexynoate (**22**). IR (CCl_4): 3350*w*, 2980*m*, 2920*m*, 1740*s*, 1596*m*, 1490*w*, 1425*m*, 1368*m*, 1350*s*, 1302*m*, 1208*m*, 1182*m*, 1168*s*, 1112*m*, 1090*m*, 1025*m*, 906*m*, 850*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.15 (*t*, J = 7, CH_3CH_2O); 1.72 (*t*, J = 2.5, irradiation at 2.66→*s*, 3 H–C(6)); 2.41 (*s*, $CH_3C_6H_4SO_2$); 2.56 (*ddq*, J = 17, 5.5, 2.5), 2.64 (*ddq*, J = 17, 4.5, 2.5) (2 H–C(3)); 3.96–4.12 (*m*, CH_3CH_2O, H–C(2)); 5.38 (*d*, J = 9, further broadened, $w_{½} \approx 4$, NH); 7.25–7.29, 7.71–7.75 (2*m*, $CH_3C_6H_4SO_2$). ^{13}C-NMR (25 MHz, $CDCl_3$): 3.4 (C(6)); 13.9 (CH_3CH_2O); 21.5 ($CH_3C_6H_4SO_2$); 24.3 (C(3)); 54.5 (C(2)); 61.8 (CH_3CH_2O); 72.3 (C(5)); 79.8 (C(4)); 127.2 (C(3′), C(5′)); 129.6 (C(2′), C(6′)); 137.1 (C(4′)); 143.7 (C(1′)); 169.9 (C(1)). MS (d.i.): 309 (1, M^+), 256 (40), 236 (30), 155 (89), 139 (5), *91* (100), 65 (16), 53 (6), 39 (5).

Ethyl (E)-3-Ethylidene-1-tosylazetidine-2-carboxylate (**19**). IR (CCl_4): 3060*w*, 3020*w*, 2980*m*, 2960*m*, 2938*m*, 2918*m*, 2860*w*, 1755*s*, 1730*s*, 1595*m*, 1490*w*, 1440*m*, 1375*w*, 1362*m*, 1330*s*, 1302*m*, 1270*m*, 1258*m*, 1190*m*, 1182*m*, 1158*s*, 1092*s*, 1028*m*, 988*w*, 900*w*, 860*w*, 673*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.25 (*t*, J = 7, CH_3CH_2O); 1.5 (*d*, J = 7, further split by small couplings, '*q*', $J \approx 1.8$, CH_3CH=C(3)); 2.44 (*s*, $CH_3C_6H_4SO_2$); 4.15, 4.22 (2 *dq*, J = 10.5, 7, CH_3CH_2O); 4.32, 4.46 (2*d*, J = 12, $w_{½} \approx 7$, 2 H–C(4)); 5.13 (*quint.*, $J \approx 2$, H–C(2)); 5.52–5.63 (*m*, 13 main peaks, CH_3CH=C(3)); 7.28–7.4, 7.75–7.87 (2*m*, $CH_3C_6H_4SO_2$). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.0, 13.9 (2 CH_3); 24.4 ($CH_3C_6H_4SO_2$); 56.2 (C(4)); 61.4 (CH_3CH_2O); 68.4 (C(2)); 120.0 (CH_3CH=C(3)); 124.1 (C(3)); 128.0

(C(3'), C(5')); 129.5 (C(2'), C(6')); 133.6 (C(4')); 144.0 (C(1')); 167.6 (CO_2Et). MS (d.i.): 236 (87, M^+), 184 (4), 155 (68), 139 (12), *91* (100), 80 (11), 65 (20), 53 (8), 43 (10), 41 (10), 39 (10).

Ethyl (Z)-3-Ethylidene-1-tosylazetidine-2-carboxylate (**23**). IR (CCl_4): 3060*w*, 3025*w*, 2980*m*, 2935*w*, 2920*w*, 2865*w*, 1750*s*, 1732*s*, 1595*m*, 1490*w*, 1440*m*, 1362*s*, 1330*s*, 1302*w*, 1268*m*, 1182*m*, 1165*s*, 1160*s*, 1090*m*, 1030*m*, 1015*w*, 905*w*, 675*m*, 663*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.26 (*t*, $J = 7$, CH_3CH_2O); 1.59 (*d*, $J = 7$, further split, '*q*', $J \approx 2$, CH_3CH=C(3)); 2.44 (*s*, $CH_3C_6H_4SO_2$); 4.19, 4.24 (2*dq*, $J = 10.5$, 7, CH_3CH_2O); 4.31–4.46 (*m*, 2 H–C(4)); 5.13–5.21 (*m*, H–C(2)); 5.35–5.48 (*m*, CH_3CH=C(3)); 7.3–7.4, 7.75–7.85 (2*m*, $CH_3C_6H_4SO_2$). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.1, 14.0 (2 CH_3); 21.6 ($CH_3C_6H_4SO_2$); 57.6 (C(4)); 61.7 (CH_3CH_2O); 68.9 (C(2)); 121.8 (CH_3CH=C(3)); 127.2 (C(3)); 128.1 (C(3'), C(5')); 129.7 (C(2'), C(6')); 133.6 (C(4')); 144.2 (C(1')); 167.8 (CO_2Et). MS (d.i.): 309 (1, M^+), 256 (8), 236 (80), 155 (80), 139 (4), *91* (100), 80 (10), 65 (17), 53 (7), 39 (7).

Ethyl 4-Methyl-3-methylidene-1-tosylazetidine-2-carboxylate (**24**). IR (CCl_4): 3040*w*, 2980*m*, 2922*m*, 2862*w*, 1755*s*, 1735*s*, 1598*w*, 1442*m*, 1345*s*, 1302*m*, 1288*m*, 1192*m*, 1180*m*, 1160*s*, 1095*m*, 1040*m*, 1025*m*, 928*w*, 898*m*, 667*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.22 (*t*, $J = 7$, CH_3CH_2O); 1.50 (*d*, $J = 6.5$, CH_3–C(4)); 2.41 (*s*, $CH_3C_6H_4SO_2$); 4.15 (*q*, $J = 7$, CH_3CH_2O); 4.95–5.10 (*m*, 2 H), 5.12–5.18 (*m*, 1 H), 5.2–5.27 (*m*, 1 H) (H–C(2), H–C(4), CH_2=C(3)); 7.2–7.36, 7.75–7.9 (2*m*, $CH_3C_6H_4SO_2$). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.7 (CH_3–C(4)); 18.0 (CH_3CH_2O); 21.5 ($CH_3C_6H_4SO_2$); 61.7 (CH_3CH_2O); 69.2, 69.3 (C(2), C(4)); 107.5 (CH_2=C(3)); 127.5 (C(3'), C(5')); 129.4 (C(2'), C(6')); 137.9 (C(4')); 141.1 (C(3?)); 143.4 (C(1')); 168.0 (CO_2Et). MS: 236 (50, $M^+ - 73$), 155 (58), 139 (11), *91* (100), 80 (17), 65 (23).

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