Pergamon

Tetrahedron, Vol. 52, No. 26, pp. 8725-8732, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00428-0

A Key Step towards EPC Synthesis of (+)-Heptelidic Acid

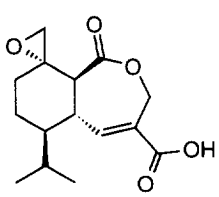
Gerhard Riehs[a], Ernst Urban*,[a] and Horst Völlenkle[b]

[a] Institut für Pharmazeutische Chemie, Universität Wien,
Althanstraße 14, A-1090 Wien, Austria

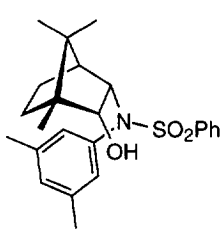
[b] Institut für Mineralogie, Kristallographie und Strukturchemie, Technische Universität Wien,
Getreidemarkt 9, A-1060 Wien, Austria

Abstract: Absolute configuration of enoates **3n** and **4n**, which have been prepared as chiral building blocks for the EPC synthesis of the antibiotic (+)-heptelidic acid, was determined by X-ray structure analysis. Conjugate addition of an acetal protected vinylcuprate to the 5'R configurated enoate **3n** gave adduct **9n** as a single diastereomer in 79% yield. Further, cleavage of the auxiliary and of the acetal protecting group from **9n** were studied. Finally, we obtained the silyl protected β-ketoester **13** in enantiomerically pure form, which is a known intermediate for the synthesis of heptelidic acid.

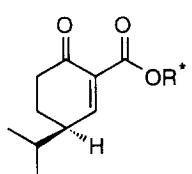
(+)-Heptelidic acid (**1**) is a well investigated epoxylactone of fungal origin,[1,2] which has attracted our attention because of its specific antibacterial activity[3] and its interesting mechanism of action.[4] A total synthesis of (±)-heptelidic acid has been published by Danishefsky[5] in 1988, which is based on a conjugate addition of a silyl protected side chain fragment to an appropriate substituted enoate.



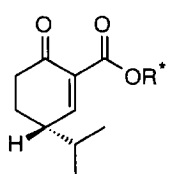
(+)-heptelidic acid (**1**)



2n R*OH



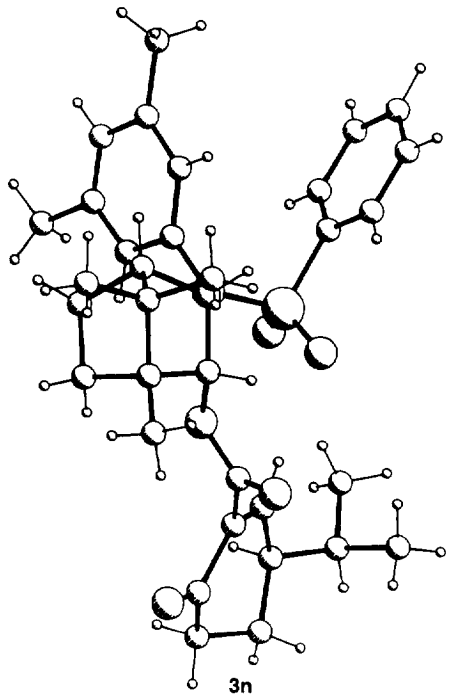
3n

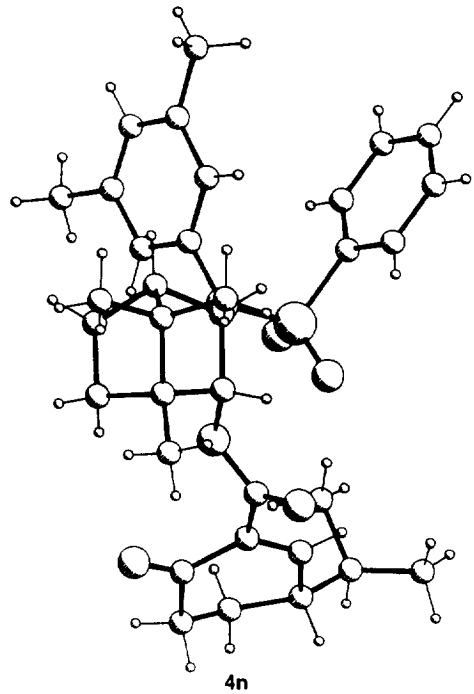


4n

Scheme 1

Aiming at an EPC synthesis of **1** we set our hopes to an auxiliary approach using enoates derived from the concave alcohol **2n**[6] as chiral starting compounds. In a preceding paper[7] we reported on asymmetric shielded 2-oxo-5-isopropyl-cyclohexenecarboxylates **3n** and **4n** which were prepared by a five step synthesis. In accordance with our expectations the additional chiral centers of the auxiliary stabilized the labile asymmetric carbon (C-5') of the vinylogous β-ketoesters **3n** and **4n**, so that we were able to obtain the well crystallizable enoates **3n** and **4n** in diastereomerically pure form (>99%, HPLC) after separation by chromatography.



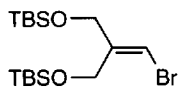


Scheme 2

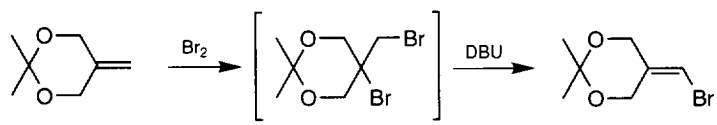
Table 1. Crystal Data Collection and Refinement Parameters of Auxiliary Shielded Enoates **3n** and **4n**.

Identification code	**3n**	**4n**	Identification code	**3n**	**4n**
Empirical formula	$C_{34}H_{43}NO_5S$	$C_{34}H_{43}NO_5S$	F(000)	620	1240
Formula weight	577.75	577.75	Crystal size (mm)	0.03 x 0.16 x 0.40	0.30 x 0.40 x 0.60
Temperature	293(2)	293(2)	Theta range	3 to 22°	3 to 24°
Wavelength	0.71069 Å	0.71069 Å	Scan mode	ω	ω
Crystal system	monoclinic	orthorhombic	Index range	$-12 \le h \le 11$	$0 \le h \le 24$
Space group	$P2_1$	$P2_1\,2_1\,2_1$		$0 \le k \le 12$	$0 \le k \le 14$
Unit cell dimensions	a = 12.060(10) Å	a = 21.765(6) Å		$0 \le l \le 12$	$0 \le l \le 13$
	b = 11.890(10) Å	b = 12.417(4) Å	Reflections collected	2217	2868
	c = 12.130(10) Å	c = 11.947(4) Å	Independent reflections	2103 [R(int)=0.0416]	2868
	α = 90°	α = 90°	Refinement method	Full-matrix,	Full-matrix,
	β = 110.98(6)°	β = 90°		least-squares on F^2	least-squares on F^2
	γ = 90°	γ = 90°	Data/restrains/parameters	2103 / 1 / 379	2868 / 0 / 373
Volume	1624(2) $Å^3$	3229(2) $Å^3$	Goodness-of-fit on F^2	0.971	0.945
Z	2	4	Weighting scheme	a = 0.0500, b = 0.00	a = 0.1000, b = 0.00
Density (calculated)	1.181 Mg m^{-3}	1.189 Mg m^{-3}		$w = 1/(\sigma^2(F_0^2) + (aP)^2 + bP)$ with	
Absorption coefficient	0.139 mm^{-1}	1.140 mm^{-1}		$P = (Max(F_0^2, F_0) + F_c^2)/3$	
			Final R indices [$I>2\sigma(I)$]	R_1 = 0.0720	R_1 = 0.0593
				wR_2 = 0.1151	wR_2 = 0.1402
			R indices (all data)	R_1 = 0.1415	R_1 = 0.1041
				wR_2 = 0.1547	wR_2 = 0.1814
			Largest diff. peak / hole	0.213 / −0.189 e.$Å^{-3}$	0.179 / −0.179 e.$Å^{-3}$

X-ray structure determinations[8,9] of **3n** and **4n** (Scheme 2) outlined that conformations of the auxiliary parts of the molecules were almost identical, while conformations of the enoate substructures were quite different. Hence, we detected that the enoate was not planar but twisted along the bond between carboxyl carbon and α-carbon {(R*O)-(C=O)-(C-1')-(C-2'), $\Phi = -112.9°$ for **3n** and $\Phi = -61.8°$ for **4n**}. Atoms of the cyclohexenone ring were arranged in a half-chair conformation with a 5'R configurated asymmetric carbon in **3n** and a 5'S configurated chiral center in **4n**. The refinement of enoate **4n** exhibited two rotameric conformations for the isopropyl group in a ratio of 1:1 {(iPr H)-(iPr C)-(C-5')-(5'-H), $\Phi = +62.7°$ for rotamer 1 (shown in Scheme 2) and $\Phi = -54.8°$ for rotamer 2 of **4n**}.



5



6 **7** **8**

Scheme 3

Next we studied the conjugate addition of organocopper reagents to enoate **3n**, which proved to be 5'R configurated like the target molecule **1**. First we prepared in analogy to Danishefsky[5] the Lipshutz cuprate[12] from the silylprotected side chain fragment **5** by halogen-metal exchange reaction (1.9 eq tBuLi in ether at -78 °C) and subsequent treatment with 2-thienylcyanocuprate, but the conjugate addition to enoate **3n** failed. This was in contrast to our previous report on addition of simpler vinylcuprates to enoate **3n** and **4n**, which proceeded in good yields (83-84%).[7] Hence, we assumed that cuprates derived from the silyl protected vinylbromide **5** were too bulky for addition to the auxiliary substituted enoate **3n**. Thus, we set our hopes to the less bulky acetonide **8**, which we prepared from the olefin **6** by addition of bromine and elimination of HBr (Scheme 3). Olefin **6** was prepared from commercially available 5-norbornene-2-carbaldehyde by known methods.[10,11] In accordance with our expectations both the Gilman cuprate (R_2CuLi) and the Lipshutz cuprate[12] ($R(2\text{-Th})Cu(CN)Li_2$) derived from **8** gave the desired addition product **9n** (Scheme 4) in good yields (75-79%) as a single diastereomer according to the NMR spectroscopy.

Further, cleavage of the auxiliary and of the acetal protecting group from **9n** were studied. Removal of the auxiliary from the highly crowded β-ketoester **9n** was accomplished by transesterification with methanol at 130 °C as previously described for simpler β-ketoesters.[13] In the presence of Et_3N the auxiliary was selectively cleaved and the acetal protecting group was conserved to give **10** (75%), while in the absence of Et_3N both the auxiliary and the acetal protecting group were removed yielding **12** (71%). A selective removal of the acetal protecting group from **9n** succeeded with dilute acid resulting in **11n** (90%). Reprotection of diol **12** with tButyldimethylsilylchlorid/Et_3N gave the silylprotected derivative **13** (87%) in enantiomerically pure form, which was described as a racemate by Danishefsky.[5]

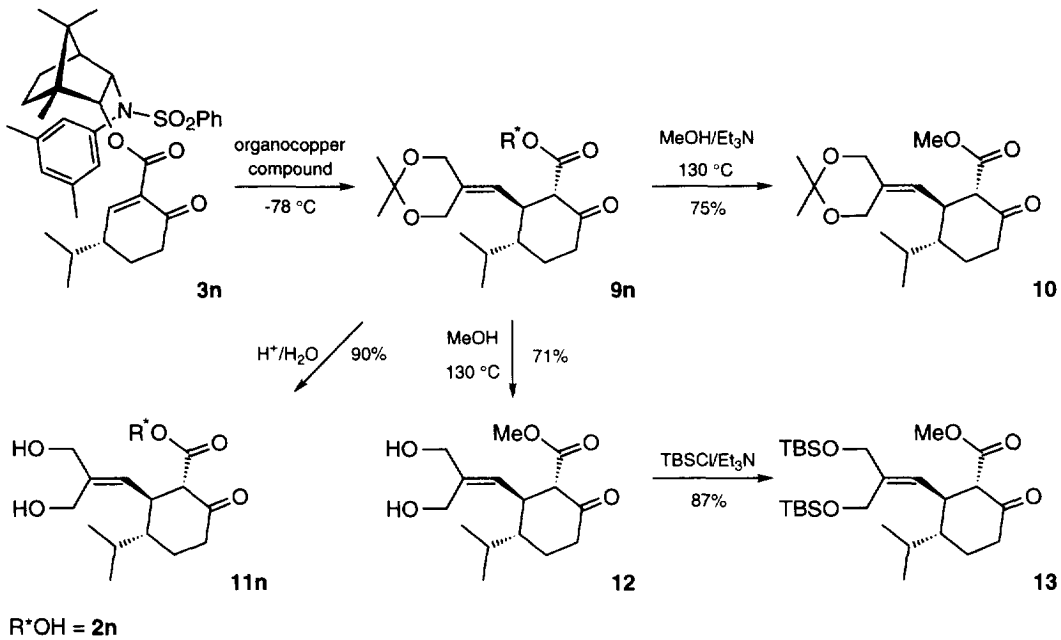
Table 2. ^{13}C NMR Shifts ($CDCl_3$, δ in ppm) of 6-Substituted 2-Oxo-5-isopropyl-cyclohexanecarboxylates.[a]

	9n[b]		**10**[b]		**11n**[c]	**12**[b]		**13**[b]	
	ketone	enol	ketone	enol	ketone	ketone	enol	ketone	enol
C-1	51.65	51.47	–	–	51.68	–	–	–	–
C-2	77.21	75.67	–	–	77.55	–	–	–	–
C-3	59.48	59.22	–	–	59.57	–	–	–	–
C-4	49.00	49.60	–	–	48.90	–	–	–	–
C-5	19.39	19.64	–	–	19.35	–	–	–	–
C-6	26.58	26.81	–	–	26.57	–	–	–	–
C-7	45.77	45.32	–	–	45.83	–	–	–	–
Ar-CH_3	20.98	21.18	–	–	21.20	–	–	–	–
Ar-CH_3	20.98	21.18	–	–	20.89	–	–	–	–
CH_3	19.68	19.51	–	–	19.66	–	–	–	–
CH_3	19.35	19.32	–	–	19.29	–	–	–	–
CH_3	14.02	14.20	–	–	13.97	–	–	–	–
NAr C-1	137.20	137.20	–	–	137.37	–	–	–	–
NAr C-2	130.30	130.16	–	–	130.46	–	–	–	–
NAr C-3	138.14	138.14	–	–	138.20	–	–	–	–
NAr C-4	129.24	129.24	–	–	129.57	–	–	–	–
NAr C-5	137.74	137.74	–	–	136.96	–	–	–	–
NAr C-6	127.47	127.15	–	–	127.36	–	–	–	–
SO_2Ar C-1	138.78	138.78	–	–	138.31	–	–	–	–
SO_2Ar C-2, C-6	128.13	128.62	–	–	128.29	–	–	–	–
SO_2Ar C-3, C-5	127.83	127.97	–	–	127.85	–	–	–	–
SO_2Ar C-4	132.30	132.54	–	–	132.71	–	–	–	–
OCH_3	–	–	51.97	51.36	–	52.20	51.38	51.64	51.06
–COO–	169.11	172.59	169.53	172.95	170.16	170.94	172.57	169.43	172.80
C-1'	62.18	100.25	62.59	99.00	63.14	62.75	98.99	62.86	99.59
C-2'	206.29	172.74	204.74	172.97	205.85	204.76	173.12	204.94	173.01
C-3'	41.57	26.02	40.78	26.67	41.59	40.90	26.62	40.89	26.72
C-4'	24.33	19.86	23.94	19.32	24.34	24.08	19.19	24.04	19.34
C-5'	45.86	46.83	45.67	45.24	45.59	45.47	45.47	45.98	45.71
C-6'	41.92	33.17	42.56	33.25	42.50	42.99	33.74	42.78	33.52
iPr CH	27.53	26.90	27.72	26.89	27.54	27.66	26.84	27.49	26.83
iPr CH_3	20.57	20.90	21.51	21.65	21.69	21.50	21.64	21.55	21.64
iPr CH_3	15.56	20.00	15.46	18.86	15.30	15.17	18.94	15.33	18.97
=CH–	124.47	129.99	122.97	127.38	127.21	128.59	134.21	124.87	130.13
=C<	139.19	136.02	135.86	131.31	141.08	140.65	136.27	140.66	136.95
CH_2O	65.50	64.04	64.17	64.43	64.70	66.08	67.01	63.81	64.37
CH_2O	60.92	59.87	59.84	59.97	59.69	59.44	59.80	58.62	58.81

[a] Further data are presented in the experimental part.

[b] **9n** (ketone:enol = 67:33), **10** (ketone:enol = 70:30), **12** (ketone:enol = 80:20), **13** (ketone:enol = 47:53).

[c] **11n** exclusively ketoform detectable.



Scheme 4

^{1}H and ^{13}C NMR spectra of **9n**, **10**, **12** and **13** (Table 2) provided both resonances of the keto and the enol form, while spectra of the diol **11n** showed exclusively signals of the keto form. Close examination of the keto signals revealed coupling constants between 1'-H and 6'-H (11.5 - 11.8 Hz) and between 5'-H and 6'-H (10.1 - 10.9 Hz), which indicated that the ester moiety, the vinyl group and the isopropyl residue were attached equatorial at the cyclohexanone ring, like previously observed for simpler vinyl adducts.[7] Because of the fact, that the configuration of the precursor **3n** at C-5' was known from the X-ray structure analysis to be 5'R and the *trans* disposition of the substituents at C-5' and C-6' was deducted from the ^{1}H NMR spectra of the derivatives **9n**, **10**, **11n**, **12** and **13**, we regarded as save, that the absolute configuration at the chiral centers was 5'R and 6'S, which was an essential requirement for further use of **13** in an EPC synthesis of (+)-heptelidic acid.

In conclusion, the stereocontrolled addition of the acetal protected vinylcuprate derived from **8** to the asymmetric shielded enoate **3n** turned out to be a key step towards an EPC synthesis (+)-heptelidic acid. Removal of the auxiliary and the acetal protecting group followed by reprotection gave the enantiomerically pure silyl ether **13** which is a known intermediate for the synthesis of heptelidic acid. We now want to enlarge the scale of preparation for **13** and hope to report soon on a completion of this natural product synthesis.

EXPERIMENTAL SECTION

Melting points were determined with a Kofler melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured with a Varian unity plus 300 spectrometer by B. Richter using TMS as an internal standard. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Microanalyses were determined by J. Theiner (Institute of Physical Chemistry, University of Vienna).

X-ray diffraction intensities were measured on a four cycle diffractometer (PW 1100) using graphite-monochromated Mo Kα radiation. Crystal data collection and refinement parameters are listed in table 1. The atomic co-ordinates and other data for **3n** and **4n** are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

5-Bromomethylene-2,2-dimethyl-1,3-dioxane (8)

A solution of **6**[10,11] (12.2 g, 95.0 mmol) in CH_2Cl_2 (100 ml) was treated with a solution of Br_2 (15.2 g, 95.0 mmol) in CH_2Cl_2 (20 ml) at -78 °C for 10 min. Then the mixture was allowed to warm up to 20 °C and the solvent was removed at reduced pressure. The residue was dissolved in benzene (200 ml), Diazabicyclo-undecen (57.9 g, 380 mmol) was added and the mixture was refluxed for 7 h. Then the precipitate was removed by filtration, the filtrate was cooled to 0 °C and carefully neutralized with 1.00 M HCl (285 ml). The organic layer was separated and the aqueous layer was extracted with ether (2x200 ml). The combined organic layers were washed with a solution of $NaHCO_3$ (5%, 200 ml), dried (Na_2SO_4) and passed through a short column filled with silica gel (50 g). The filtrate was evaporated at reduced pressure to give **8** (16.1 g, 82%), colourless oil, bp 80 °C/3 mbar. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.41 (s, 6H, CH_3), 4.21 (s, 2H, CH_2O), 4.39 (s, 2H, CH_2O), 5.99 (s, 1H, =CHBr). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 23.97 (CH_3), 61.94 (C-4), 62.87 (C-6), 99.19 (=CHBr), 99.66 (C-2), 139.11 (C-5). Anal. Calcd for $C_7H_{11}O_2Br$: C, 40.60; H, 5.35. Found C, 40.65; H, 5.31.

(1R,2R,3S,4S)-{3-[N-Benzenesulfonyl-N-(3,5-dimethylphenyl)-amino]-2-bornyl}-(1S,5R,6S)-6-(2,2-dimethyl-1,3-dioxan-5-ylidene)-methyl-2-oxo-5-isopropyl-cyclohexane-carboxylate (9n)

Method A: A solution of **8** (414 mg, 2.00 mmol) in ether (10 ml) was cooled to -78 °C, a solution of tBuLi in pentane (2.18 ml, 1.74 M, 3.60 mmol) was added and the mixture was stirred at -78 °C for 2 h. Then the mixture was transferred with a double-tipped needle to a precooled (-78 °C) suspension of CuI (191 mg, 1.00 mmol) in THF (20 ml) and the mixture was stirred at -78 °C for 1 h. A solution of **3n**[7] (462 mg, 0.80 mmol) in THF (10 ml) was added and stirring was continued at -78 °C for 2 h. Then the reaction mixture was transferred to a flask filled with a mixture of NH_3 (25 ml, 2 M) and a solution of NH_4Cl (25 ml, 5%). The mixture was stirred at 20 °C for 1 h and extracted with CH_2Cl_2 (3x50 ml). The organic layer was dried (Na_2SO_4) and the solvent distilled off *in vacuo*. Purification of the residue by flash chromatography (40 g, silica gel, hexane/EtOAc = 75:25) gave **9n** (445 mg, 79%), colourless oil.

Method B: A solution of **8** (1.04 g, 5.00 mmol) in ether (50 ml) was cooled to -78 °C, a solution of tBuLi in pentane (5.45 ml, 1.74 M, 9.50 mmol) was added and the mixture was stirred at -78 °C for 2 h. Then the mixture was transferred with a double-tipped needle to a precooled (-78 °C) solution of lithium 2-thienyl-cyano-cuprate (50.0 ml, 0.10 M in THF, 5.00 mmol) and the mixture was stirred at -78 °C for 1 h. A solution of **3n**[7] (2.31 g, 4.00 mmol) in THF (50 ml) was added and stirring was continued at -78 °C for 2 h. Then the reaction mixture was transferred to a flask filled with a mixture of NH_3 (125 ml, 2 M) and a solution of NH_4Cl (125 ml, 5%). The mixture was stirred at 20 °C for 1 h and extracted with CH_2Cl_2 (3x150 ml). The organic layer was dried (Na_2SO_4) and the solvent distilled off *in vacuo*. Purification of the residue by flash chromatography (200 g, silica gel, hexane/EtOAc = 75:25) gave **9n** (2.13 g, 75%), colourless oil.

^1H NMR (300 MHz, $CDCl_3$, ketone:enol = 63:37) δ(ketone) = 0.80 (s, 3H, CH_3), 0.81 (d, *J* = 7.0 Hz, 3H, iPr CH_3), 0.99 (d, *J* = 7.0 Hz, 3H, iPr CH_3), 1.05 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.26 (s, 3H, ketal CH_3), 1.43 (s, 3H, ketal CH_3), 1.50-1.85 (m, 6H), 1.98 (s, 3H, Ar-CH_3), 2.00-2.28 (m, 3H), 2.34 (s, 3H, Ar-CH_3), 2.40-2.60 (m, 2H), 3.05 (ddd, *J* = 11.5, 10.9 and 10.2 Hz, 1H, 6'-H), 3.57 (d, *J* = 11.5 Hz, 1H, 1'-H), 3.92 (d, *J* = 13.7 Hz, 1H, CH_2O), 4.08-4.68 (m, 4H, 3-H, CH_2O), 5.08 (d, *J* = 10.2 Hz, 1H, =CH-), 5.43 (d, *J* = 8.6 Hz, 1H, 2-H), 5.67 (s, 1H, NAr 2-H), 6.82 (s, 1H, NAr 4-H), 7.14 (s, 1H, NAr 6-H), 7.28-7.43 (m, 4H, SO_2ArH), 7.50 (m_c, 1H, SO_2ArH); δ(enol, separated signals) = 0.80 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.87 (d, *J* = 7.1 Hz, 3H, iPr CH_3), 0.97 (d, *J* = 6.4 Hz, 3H, iPr CH_3), 1.05 (s, 3H, CH_3),

1.33 (s, 6H, ketal CH_3), 3.80 (d, J = 8.3 Hz, 1H, 6'-H), 4.81 (d, J = 14.5 Hz, 1H, CH_2O), 5.37 (d, J = 8.3 Hz, 1H, =CH–), 5.67 (s, 1H, NAr 2-H), 5.68 (d, J = 8.6 Hz, 1H, 2-H), 6.85 (s, 1H, NAr 4-H), 7.21 (s, 1H, NAr 6-H), 12.68 (s, 1H, =C–OH).^{13}C NMR (75 MHz, $CDCl_3$, ketone:enol = 67:33) δ(ketone) = 21.74 (CH_3), 24.11 (CH_3), 98.41 (ketal C) ; δ(enol) = 22.28 (CH_3), 23.64 (CH_3), 98.94 (ketal C); for further signals see Table 2 Anal. Calcd for $C_{41}H_{55}NO_7S$: C, 69.76; H, 7.85; N, 1.98. Found C, 69.58; H, 7.60; N, 1.89.

(1S,5R,6S)-Methyl-6(2,2-dimethyl-1,3-dioxan-5-ylidene)-methyl-2-oxo-5-isopropyl-cyclohexanecarboxylate (10)

9n (705 mg, 1.0 mmol) was dissolved in methanol (20 ml), Et_3N was added (300 mg, 3.0 mmol) and the mixture was heated in an autoclave at 130 °C for 20 h. Then the solvent was evaporated at reduced pressure and the auxiliary was recovered by crystallization from methanol to give **2n** (260 mg, 91%). Kugelrohr distillation of the filtrate afforded **10** (240 mg, 75%), colourless oil, bp 130 °C/0.02 mbar. $[\alpha]_D^{20}$ = + 89.95 (c = 1.094, $CDCl_3$, ketone:enol = 57:43). ^{1}H NMR (300 MHz, $CDCl_3$, ketone:enol = 75:25) δ(ketone) = 0.76 (d, J = 6.8 Hz, 3H, iPr CH_3), 0.97 (d, J = 7.1 Hz, 3H, iPr CH_3), 1.40 (s, 6H, CH_3), 1.50-1.83 (m, 2H), 1.87-2.04 (m, 2H), 2.20-2.59 (m, 2H), 2.88 (ddd, J = 11.8, 10.9 and 10.0 Hz, 1H, 6-H), 3.19 (d, J = 11.8 Hz, 1H, 1-H), 3.73 (s, 3H, OCH_3), 4.13-4.58 (m, 4H, CH_2O), 4.93 (d, J = 10.9 Hz, 1H, =CH–); δ(enol, separated signals) = 0.87 (d, J = 6.6 Hz, 3H, iPr CH_3), 0.95 (d, J = 7.1 Hz, 3H, iPr CH_3), 1.43 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.24 (dd, J = 10.2 and 4.7 Hz, 1H, 6-H), 3.75 (s, 3H, OCH_3), 5.03 (d, J = 10.2 Hz, 1H, =CH–), 12.28 (s, 1H, =C–OH). ^{13}C NMR (75 MHz, $CDCl_3$, ketone:enol = 70:30) δ(ketone) = 23.44 (CH_3), 24.47 (CH_3), 99.09 (ketal C) ; δ(enol) = 23.76 (CH_3), 24.34 (CH_3), 98.92 (ketal C); for further signals see Table 2. Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found C, 66.83; H, 8.93.

(1R,2R,3S,4S)-{3-[N-Benzenesulfonyl-N-(3,5-dimethylphenyl)-amino]-2-bornyl}-(1S,5R,6S)-6(3-hydroxy-2-hydroxymethyl-prop-1-enyl)-2-oxo-5-isopropyl-cyclohexane-carboxylate (11n)

9n (106 mg, 0.15 mmol) was dissolved in methanol (20 ml), hydrochloric acid was added (1.5 ml, 2 M) and the mixture was stirred at 20 °C for 1 h. Then a solution of $NaHCO_3$ (10 ml, 5%) was added, the mixture was extracted with CH_2Cl_2 (3x25 ml), the organic layer was dried (Na_2SO_4) and the solvent distilled off *in vacuo*. Purification of the residue by flash chromatography (10 g, silica gel, hexane/EtOAc = 1:1) gave **11n** (90 mg, 90%), colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.74 (d, J = 7.0 Hz, 3H, iPr CH_3), 0.70-1.14 (m, 4H), 0.79 (s, 3H, CH_3), 0.95 (d, J = 7.0 Hz, 3H, iPr CH_3), 1.03 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.54 (m_c, 1H), 1.62 (t, J = 3.8 Hz, 1H, 4-H), 1.67-1.82 (m, 2H), 1.92 (m_c, 1H), 1.96 (s, 3H, Ar–CH_3), 2.35 (s, 3H, Ar–CH_3), 2.50-2.63 (m, 2H), 2.85 (s, br., 2H, OH), 3.34 (ddd, J = 11.7, 10.8 and 10.2 Hz, 1H, 6'-H), 3.68 (d, J = 11.7 Hz, 1H, 1'-H), 3.87 (d, J = 12.6 Hz, CH_2O), 3.96 (d, J = 14.4 Hz, CH_2O), 4.25 (d, J = 14.4 Hz, CH_2O), 4.26 (dd, J = 8.3 and 3.8 Hz, 1H, 3-H), 4.53 (d, J = 12.6 Hz, CH_2O), 5.41 (d, J = 10.2 Hz, 1H, =CH–), 5.44 (d, J = 8.3 Hz, 1H, 2-H), 5.63 (s, 1H, NAr 2-H), 6.84 (s, 1H, NAr 4-H), 7.15 (s, 1H, NAr 6-H), 7.28-7.34 (m, 4H, SO_2ArH), 7.50 (m_c, 1H, SO_2ArH). ^{13}C NMR (75 MHz, $CDCl_3$) see Table 2. Anal. Calcd for $C_{38}H_{51}NO_7S$: C, 68.54; H, 7.72; N, 2.10. Found C, 68.29; H, 7.73; N, 1.98.

(1S,5R,6S)-Methyl-6-(3-hydroxy-2-hydroxymethyl-prop-1-en-1-yl)-2-oxo-5-isopropyl-cyclohexanecarboxylate (12)

9n (1.41 g, 2.0 mmol) was dissolved in methanol (20 ml) and the mixture was heated in an autoclave at 130 °C for 20 h. Then the solvent was evaporated at reduced pressure. After the main fraction of **2n** (368 mg, 45%) was removed by crystallization from MeOH the residue was separated by flash chromatography (60 g, silica gel, hexane/EtOAc = 3:7) to give **2n** (378 mg, 46%, R_f = 0.92) colourless crystals from MeOH and **12** (400 mg, 71%, R_f = 0.26) colourless crystals from hexane/EtOAc, mp 61-65 °C. $[\alpha]_D^{20}$ = + 24.5 (c = 0.97, $CDCl_3$,

ketone:enol = 79:21). ^{1}H NMR (300 MHz, $CDCl_3$, ketone:enol = 79:21) δ(ketone) = 0.72 (d, *J* = 6.9 Hz, 3H, iPr CH_3), 0.96 (d, *J* = 7.1 Hz, 3H, iPr CH_3), 1.43-1.68 (m, 2H), 1.82 (m_c, 1H), 2.03 (m_c, 1H), 2.23 (m_c, 1H), 2.43 (m_c, 1H), 2.57 (m_c, 1H), 2.75 (m_c, 1H), 3.15 (dt, *J* = 11.8 and 10.5 Hz, 1H, 6-H), 3.33 (d, *J* = 11.8 Hz, 1H, 1-H), 3.72 (s, 3H, OCH_3), 3.93-4.54 (m, 4H, CH_2O), 5.26 (d, *J* = 10.5 Hz, 1H, =CH-); δ(enol, separated signals) = 0.88 (d, *J* = 6.7 Hz, 3H, iPr CH_3), 0.97 (d, *J* = 6.6 Hz, 3H, iPr CH_3), 3.24 (dd, *J* = 10.1 and 4.1 Hz, 1H, 6-H), 3.73 (s, 3H, OCH_3), 5.36 (d, *J* = 10.1 Hz, 1H, =CH-), 12.12 (s, 1H, =C-OH). ^{13}C NMR (75 MHz, $CDCl_3$, ketone:enol = 80:20) see Table 2. Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found C, 63.64; H, 8.71.

(1S,5R,6S)-Methyl-6-[3-*tert*-butyldimethylsilyloxy-2-(*tert*-butyldimethylsilyloxy)methyl-prop-1-en-1-yl]-2-oxo-5-isopropyl-cyclohexanecarboxylate (13)

A solution of **12** (1.14 g, 4 mmol) in CH_2Cl_2 (20 ml) was cooled to 0 °C. Then $tBuMe_2SiCl$ (1.24 g, 8.2 mmol) , Et_3N (2.49 g, 24.6 mmol) and DMAP (98 mg, 0.8 mmol) were added. After stirring for 1 h at 0 °C the mixture was allowed to warm up to 20 °C and stirring was continued for 16 h. Then the reaction mixture was washed with cold HCl (1M, 16 ml) and a solution of $NaHCO_3$ (5%, 10 ml), the organic layer was dried (Na_2SO_4) and the solvent distilled off *in vacuo*. Purification of the residue by flash chromatography (80 g silica gel, hexane/EtOAc = 95:5) gave **13** (1.78 g, 87%), colourless oil. $[\alpha]_D^{20}$ = + 63.5 (*c* = 1.00, $CDCl_3$, ketone:enol = 53:47). ^{1}H NMR (300 MHz, $CDCl_3$, ketone:enol = 45:55) δ = 0.01-0.12 (m, 24H, Si-CH_3), 0.88 (s, 9H, tBu CH_3), 0.89 (s, 9H, tBu CH_3), 0.90 (s, 9H, tBu CH_3), 0.91 (s, 9H, tBu CH_3), 1.16 (m_c, 2H), 1.50-2.05 (m, 6H), 2.15-2.58 (m, 4H), 4.02-4.42 (m, 8H, CH_2O); δ(ketone, separated signals) = 0.74 (d, *J* = 6.8 Hz, 3H, iPr CH_3), 0.96 (d, *J* = 6.6 Hz, 3H, iPr CH_3), 3.06 (ddd, *J* = 11.5, 10.3 and 10.1 Hz, 1H, 6-H), 3.20 (d, *J* = 11.5 Hz, 1H, 1-H), 3.64 (s, 3H, OCH_3), 5.18 (d, *J* = 10.3 Hz, 1H, =CH-); δ(enol, separated signals) = 0.87 (d, *J* = 6.6 Hz, 3H, iPr CH_3), 0.94 (d, *J* = 7.0 Hz, 3H, iPr CH_3), 3.44 (dd, *J* = 9.8 and 4.4 Hz, 1H, 6-H), 3.66 (s, 3H, OCH_3), 5.27 (d, *J* = 9.8 Hz, 1H, =CH-), 12.23 (s, 1H, =C-OH). ^{13}C NMR (75 MHz, $CDCl_3$, ketone:enol = 47:53) δ(ketone) = -5.61 ($SiCH_3$), 18.08 (tBu C), 25.80 (tBu CH_3); δ(enol) = -5.51 ($SiCH_3$), 18.27 (tBu C), 25.80 (tBu CH_3); for further signals see Table 2. Anal. Calcd for $C_{27}H_{52}O_5Si_2$: C, 63.23; H, 10.22. Found C, 63.32; H, 10.27.

REFERENCES AND NOTES

1. Hagenbach, A. *Diss. Eidgenössischen Technischen Hochschule, Zürich, Switzerland, Prom. N.* **1971**, 4674. Arigoni, D. *Pure and Appl. Chem.* **1975**, *41*, 219-245.
2. Itoh, Y.; Kodama, K.; Furuya, K.; Takahashi, S.; Haneishi, T.; Takiguchi, Y.; Arai, M. *J. Antibiot.* **1980**, *33*, 468-473.
3. Sankyo Co., Jpn. Kokai Tokkyo Koho 81 77281, *Chem. Abstr.* **1981**, *95*, P185.559s.
4. Endo, A.; Hasumi, K.; Sakai, K.; Kanbe, T. *J. Antibiot.* **1985**, *38*, 920-925.
5. Danishefsky, S. J.; Mantlo, N. *J. Am. Chem. Soc.* **1988**, *110*, 8129-8133.
6. Helmchen, G.; Wegner, G. *Tetrahedron Lett.* **1985**, *26*, 6051-6054.
7. Urban, E.; Riehs, G. *Tetrahedron* **1996**, *52*, 1221-1230.
8. Structures were resolved by MULTAN 78 and refined by SHELX 93.
9. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.
10. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 3775-3778.
11. Kozikowski, A. P.; Isobe, K. *Tetrahedron Lett.* **1979**, *20*, 833-836.
12. Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945-948.
13. Urban, E.; Riehs, G.; Knühl, G. *Tetrahedron* **1995**, *51*, 11149-11164.

(*Received in Germany* 15 *March* 1996; *accepted* 30 *April* 1996)