Pergamon

Tetrahedron, Vol. 52, No. 4, pp. 1221-1230, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)00952-3

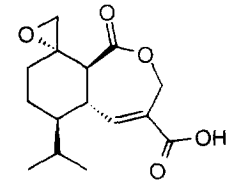
Asymmetric Protected 2-Oxo-5-isopropyl-cyclohexenecarboxylates as Key Intermediates Towards an EPC Synthesis of (+)-Heptelidic Acid

Gerhard Riehs and Ernst Urban*

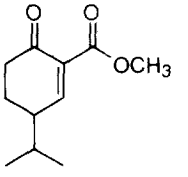
Institut für Pharmazeutische Chemie der Universität Wien,
Althanstraße 14, A-1090 Wien, Austria

Abstract: Asymmetric shielded 2-oxo-5-isopropyl-cyclohexenecarboxylates **3n** and **4n** which are diastereomers at C-5' have been prepared by a five step synthesis and separated by chromatography. Conjugate addition of $(H_2C{=}CH)_2CuLi$ to **3n** and **4n** gave the adducts **13n** (5'R,6'R) and **14n** (5'S,6'R) as single diastereomers, respectively. Finally, the (5'R) configurated enoate **3n** turned out to be valuable as chiral building block for an EPC synthesis of (+)-heptelidic acid.

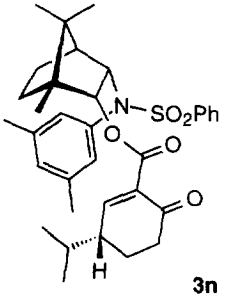
The sesquiterpene lactone (+)-heptelidic acid (**1**) first was isolated by Sankyo scientists[1] from cultures of three different strains of fungi as a part of a screening program for new antibiotics. Structure of **1** was resolved by spectroscopic methods[2] and confirmed by x-ray crystal structure analysis.[3] Research on the biological potency of **1** revealed its specific activity against anaerobic bacteria[4] especially *Bacteroides fragilis* and its ability to lower the blood serum cholesterol level.[5] Recently, **1** was transformed to antitumor agents[6] which underlined the pharmaceutical importance of this natural product. A total synthesis of (±)-heptelidic acid was published by Danishefsky[7] in 1988. Key step of this synthesis was a conjugate addition of a silyl protected side chain fragment to 2-oxo-cyclohexenecarboxylate **2**, which was manufactured *via* cuprates.



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



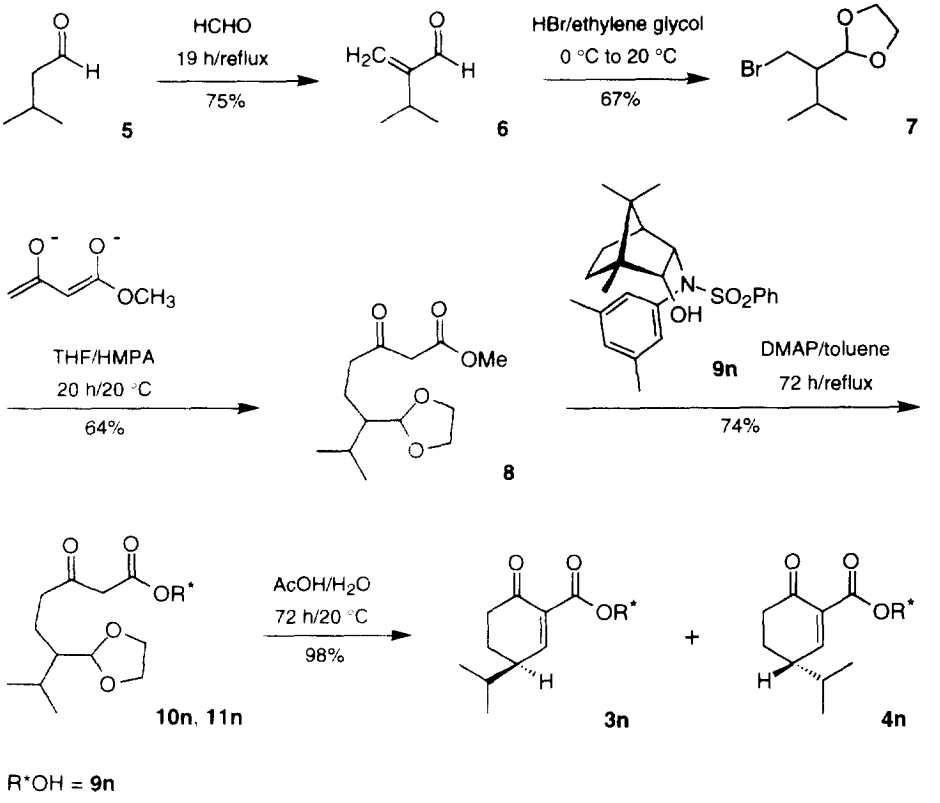
2



3n

Scheme 1

An EPC synthesis of (+)-heptelidic acid (**1**) should in principle be possible by the method of Danishefsky[7] starting from **2** in enantiomerically pure form. But on close examination we recognized **2** as a vinylogous β-ketoester[8] which should easily give arise to racemization *via* its enol form and would be unsuitable as a chiral synthon. Thus we set our hopes to an auxiliary approach to **1** using the asymmetric protected derivative **3n** as starting compound, because we expected considerable advantages from the additional chiral centers of the auxiliary, such as stabilization of the labile asymmetric carbon (C-5'), simplified separation of the undesired C-5' epimer **4n**, and improvement of the diastereoselectivity on conjugate additions.



Scheme 2

We started our synthesis of asymmetric shielded enoates (Scheme 2) from 3-methylbutanal (**5**) which was reacted with formaldehyde to give the aldol condensation product **6**[9] in good yields. Addition of HBr to **6** and subsequent acetalization led to the 2-(2-bromoethyl)-1,3-dioxolane derivative **7**. Following the procedure of Yoshikoshi,[10] **7** was treated with the dianion of methyl acetoacetate to yield the γ-substituted β-ketoester **8**. A DMAP[11] mediated transesterification[12] of the racemic methyl ester **8** with Helmchen's auxiliary **9n**[13] resulted in a mixture of the diastereomeric esters **10n** and **11n**. Finally, hydrolysis and subsequent acid-catalyzed cyclization[10] of **10n** and **11n** gave a mixture of the diastereomeric 2-oxo-5-isopropyl-cyclohexenecarboxylates **3n** and **4n**. After separation by medium pressure chromatography we isolated enoates **3n** (60%) and **4n** (73%) in good yields. Enolization during separation was avoided using an eluent which contained 2% of acetic acid. HPLC analysis revealed a purity of ≥99% for enoates **3n** and **4n**. After crystallization of **3n** and **4n** no peaks of the isomers were detectable.

Indeed, asymmetric shielded enoates **3n** and **4n** proved to be stable and showed no epimerization *via* the enol form **12n**, even on storage over several weeks. However, a complete transformation to enol **12n** proceeded on refluxing hexane solutions of **3n** or **4n** in the presence of triethylamine. Treatment of **12n** with acetic acid resulted in a partial retransformation to **3n** and **4n**, but this method was not practicable for preparative purposes, because unidentified side products were formed too.

Table 1. ^{13}C NMR Shifts ($CDCl_3$, δ in ppm) of Enoates **3n** (5'R) and **4n** (5'S), of Dienol **12n**, and Vinyladducts **13n** (5'R,6'R), **14n** (5'S,6'R), **15n** (5'S,6'S) and *rac*-**16** (5RS,6RS).[a]

	3n	**4n**	**12n**	**13n**[b]		**14n**[b]	**15n**[b]		*rac*-**16**[b]	
				ketone	enol	enol	ketone	enol	ketone	enol
C-1	51.29	51.44	51.04	51.58	51.45	51.26	51.79	51.48	–	–
C-2	76.51	76.57	75.08	77.21	75.83	75.63	78.02	75.82	–	–
C-3	59.06	59.25	58.92	59.38	59.03	59.23	59.12	59.00	–	–
C-4	49.40	49.51	50.16	49.10	49.29	49.59	49.33	49.88	–	–
C-5	19.59	19.57	19.68	19.40	19.40	19.54	19.66	19.59	–	–
C-6	26.93	27.06	27.44	26.86	26.83	26.91	25.65	25.65	–	–
C-7	45.53	45.65	45.44	45.72	45.58	45.46	45.91	45.38	–	–
Ar-CH_3	20.96	21.13	21.07	21.01	21.01	21.15	21.02	21.02	–	–
Ar-CH_3	20.96	21.03	20.97	21.01	21.01	21.15	21.02	21.02	–	–
CH_3	19.48	19.59	19.50	19.52	19.52	19.35	19.61	19.56	–	–
CH_3	19.26	19.39	19.47	19.27	19.27	19.35	19.40	19.40	–	–
CH_3	14.16	14.31	13.84	14.21	14.21	14.07	14.70	14.05	–	–
NAr C-1	136.59	136.71	136.13	136.22	136.22	136.16	136.65	136.65	–	–
NAr C-2	129.15	129.83	128.67	129.87	129.87	127.96	129.43	129.26	–	–
NAr C-3	137.92	138.11	137.72	137.59	137.96	137.87	137.88	137.88	–	–
NAr C-4	129.15	129.33	128.85	129.23	129.23	128.98	128.73	128.73	–	–
NAr C-5	136.85	136.99	137.40	137.14	136.93	136.94	137.88	137.88	–	–
NAr C-6	127.54	127.65	126.50	127.33	127.33	127.57	c	c	–	–
SO_2Ar C-1	138.99	139.06	139.63	139.04	139.04	139.21	139.08	139.43	–	–
SO_2Ar C-2, C-6	128.03	128.27	128.50	128.40	128.40	128.30	c	c	–	–
SO_2Ar C-3, C-5	128.03	128.14	128.09	128.00	128.00	127.96	c	c	–	–
SO_2Ar C-4	132.42	132.53	132.60	132.25	132.49	132.47	132.31	132.52	–	–
–COO–	164.02	163.97	169.20	168.86	172.42	171.92	168.62	171.02	169.39	173.36
C-1'	133.17	133.09	98.80	62.07	98.22	100.39	62.16	98.37	62.81	97.79
C-2'	194.86	195.01	172.30	206.09	172.97	172.83	204.04	172.33	204.67	173.36
C-3'	38.39	38.30	28.53	41.58	26.29	29.55	40.48	25.65	40.81	25.89
C-4'	24.86	24.72	24.18	24.35	18.81	20.30	23.49	19.02	23.90	18.92
C-5'	43.16	43.01	135.67	45.58	44.81	44.94	45.73	44.23	45.27	44.22
C-6'	158.78	159.23	113.00	48.86	38.74	37.39	48.20	38.39	48.89	38.66
iPr CH	31.50	31.70	34.19	27.15	26.97	29.25	27.78	26.73	27.51	26.79
iPr CH_3	19.59	19.78	21.38	21.55	22.45	21.49	21.54	21.47	21.37	21.53
iPr CH_3	19.59	19.64	21.38	14.76	20.09	20.91	15.50	20.77	14.90	20.10
=CH–	–	–	–	137.94	143.97	138.56	139.12	142.82	138.30	142.84
$=CH_2$	–	–	–	117.79	114.19	116.63	117.17	114.85	117.26	113.93

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

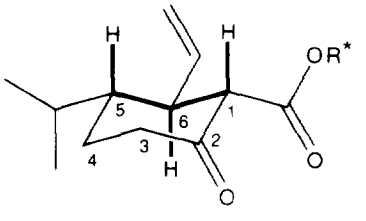
[b] **13n** (ketone:enol = 28:72); **14n** only enol detectable; **15n** (ketone:enol = 42:58); *rac*-**16** (ketone:enol = 55:45).

[c] 128.27, 128.14, 128.07: signals could not be assigned unambiguously.

Recently, we investigated conjugate additions of cuprates to asymmetric shielded 2-oxo-cyclohexene-carboxylates which proceeded with an extremely high level of diastereoselection.[14] Thus the application of this method to **3n** and **4n** was of special interest to us, because influence of the bulky substituent at C-5' to the diastereoselectivity of cuprate addition would elucidate scope and limitations of this reaction.

To get knowledge about the steric course of cuprate addition to **3n** and **4n** we first chose the homocuprate $(H_2C{=}CH)_2CuLi$ as a simple nucleophile instead of the side chain fragment used for the total synthesis of (±)-heptelidic acid by Danishefsky.[7] On conjugate addition of $(H_2C{=}CH)_2CuLi$ to **3n** and **4n** we obtained single diastereomers **13n** (83%) and **14n** (84%) in excellent yields, respectively.

^1H and ^{13}C NMR spectra of **13n** showed both signals of the ketone and the enol forms, while in spectra of **14n** exclusively signals of the enol form were detected (Table 1). Although ^1H NMR spectroscopic studies on the keto form of **13n** revealed coupling constants which indicated that the auxiliary ester moiety, the vinyl group and the isopropyl residue were attached equatorial at the cyclohexanone ring (Scheme 3), we were not quite sure about the relative configuration at C-5' and C-6'.



$J_{1\text{-}6}$ = 11.6 Hz and $J_{5\text{-}6}$ = 11.2 Hz

13n (keto form)

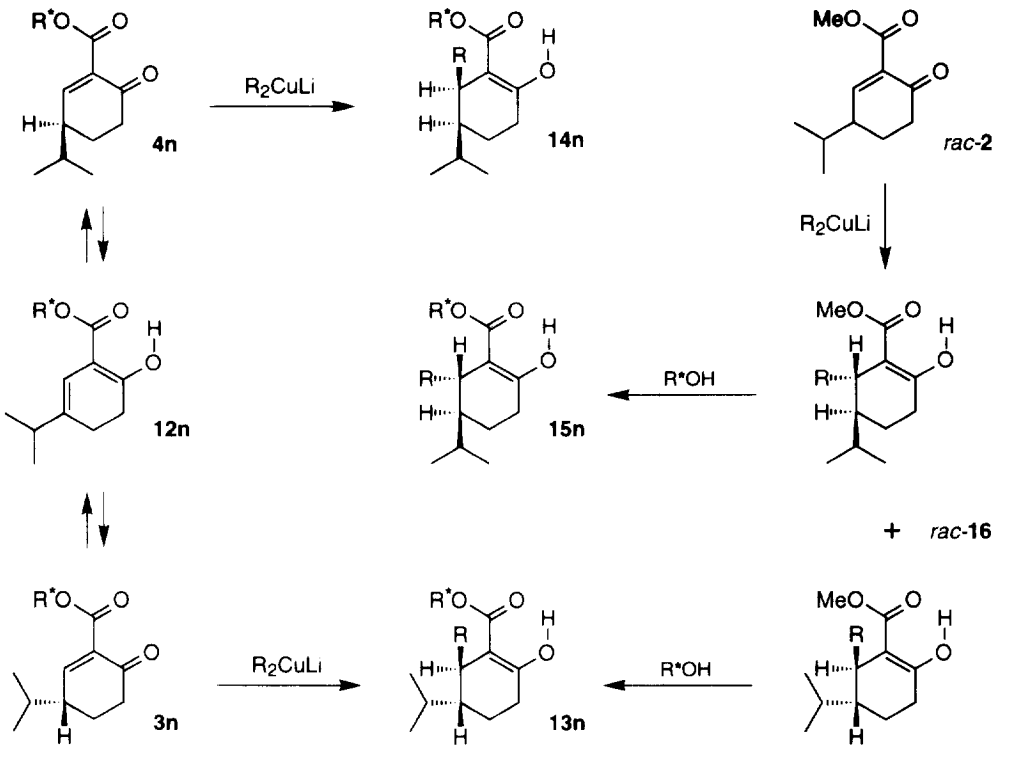
R*OH = **9n**

Scheme 3

Hence we prepared auxiliary esters from the *trans*-configurated methyl ester *rac*-**16** for comparison of spectroscopic data. Course of cuprate addition to the unshielded enoate *rac*-**2** was directed by the isopropyl group at C-5 leading exclusively to the *trans*-configurated adduct *rac*-**16** (5RS, 6RS), as described by Danishefsky.[7] Subsequently, transesterification of *rac*-**16** with **9n** afforded the *trans*-substituted auxiliary esters **13n** and **15n** which were separated by chromatography. Thus we were able to deduct the configuration of **3n** (5'R), **4n** (5'S), **13n** (5'R,6'R), **14n** (5'S,6'R) and **15n** (5'S,6'S) by chemical correlation (Scheme 4), because **13n** was obtained either by cuprate addition to **3n** or by transesterification of *rac*-**16**, while **14n** was achieved by cuprate addition to **4n** and **15n** by transesterification of *rac*-**16**.

Attack of the cuprate reagent to the asymmetric protected enoate **3n** occured from the less hindered half space of the auxiliary ester *trans* to the vicinal isopropyl group giving the *trans*-configurated adduct **13n**. In accordance with our expectations both the shielding effect of the auxiliary and the *trans*-directing effect of the isopropyl group synergistically promoted the formation of **13n** at a very high level of diastereoselection.

Addition of the organocopper compound to the shielded enoate **4n** took place from the less hindered half space of the auxiliary ester *cis* to the vicinal isopropyl group leading to the *cis*-configurated adduct **14n**. Quite obviously shielding effect of the auxiliary was the determinating factor, while steric hinderance by the bulky isopropyl group was tolerated, surprisingly without any detectable decrease of diastereoselectivity.



Scheme 4

In conclusion, **3n** turned out to be a valuable building block for an EPC synthesis of (+)-heptelidic acid, because **3n** was easily available from racemic precursors in diastereomerically pure form and **3n** proved to be stable against epimerisation at C-5'. Conjugate addition of $(H_2C{=}CH)_2CuLi$ to the asymmetric protected enoate **3n** proceeded with high diastereoselection and in excellent yield. Hence we look forward to further investigations aiming at a preparation of (+)-heptelidic acid.

EXPERIMENTAL SECTION

Melting points were determined with a Kofler melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were measured with a Bruker AC 80 or a Varian unity plus 300 spectrometer using TMS as an internal standard. MPLC was performed with a Duramat pump (type 80, 1.4 l/h), a Kronwald column (500x26 mm), a Pharmacia single path monitor (UV-1, 254 nm) and a Pharmacia fraction collector (FRAC-200). The HPLC system consisted of a Shimadzu pump (LC-10AD), a Reodyne injection valve (20 µl), a Merck column (250x5 mm), a Shimadzu UV/VIS detector (SPD-10A, 254 nm), and a Hewlett Packard integrator (3396 A). Microanalyses were determined by J. Theiner (Institute of Physical Chemistry, University of Vienna).

Preparation and separation of enoates **3n** *and* **4n**

A mixture of acetals **10n** and **11n** (36.2 g, 56.6 mmol) was dissolved in acetic acid (290 ml), H_2O (40 ml) was added and the reaction mixture was stirred until no more acetal was detected by TLC (silica gel, hexane:Et_2O = 50:50, **10n** and **11n**: R_f = 0.32, **3n**: R_f = 0.27, **4n**: R_f = 0.20), which took about 72 h. Then CH_2Cl_2 (600 ml) was added, the organic layer was washed with H_2O (3x600 ml) and a solution of $NaHCO_3$ (5%) and dried with Na_2SO_4. Evaporation of the solvent at reduced pressure gave a 1:1 mixture of raw enoates **3n** and **4n** (32.0 g, 98%), discoloured oil. Separation of the raw product (1.7 g) by MPLC (Lichroprep Si 60, 15-25 µm, 95 g, hexane:EtOAc:AcOH = 80:18:2, flow 1.5 l/h) gave **3n** (595 mg, 70%), colourless crystals from nBuOH, mp 118-120 °C and **4n** (670 mg, 79%), colourless crystals from iPrOH, mp 123-125 °C. HPLC analysis (Lichrospher Si 60, 5 µm, hexane:EtOAc:AcOH = 85:13:2, flow 1.0 ml/min, R_t(**12n**) = 5.2 min, R_t(**3n**) = 20.2 min and R_t(**4n**) = 25.7 min) revealed a purity of ≥99% for enoates **3n** and **4n.** After crystallization of **3n** and **4n** no peaks of the isomers were detectable.

(1R,2R,3S,4S)-{3-[N-Benzenesulfonyl-N-(3,5-dimethylphenyl)-amino]-2-bornyl}-(5R)-2-oxo-5-isopropyl-cyclohexenecarboxylate (3n)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.84 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.04 (d, *J* = 6.8 Hz, 3H, iPr CH_3), 1.05 (s, 3H, CH_3), 1.06 (d, *J* = 6.8 Hz, 3H, iPr CH_3), 1.08-1.38 (m, 6H), 1.81 (t, *J* = 3.8 Hz, 1H, 4-H), 1.83-2.00 (m, 2H), 2.05 (s, br., 1H, Ar–CH_3), 2.28 (s, br., 1H, Ar–CH_3), 2.44-2.61 (m, 2H), 4.26 (dd, *J* = 8.7 and 3.8 Hz, 1H, 3-H), 5.47 (d, *J* = 8.7 Hz, 1H, 2-H), 5.94 (s, br., 1H, NAr 2-H), 6.83 (s, 1H, NAr 4-H), 6.92 (s, br., 1H, NAr 6-H), 7.30-7.43 (m, 4H, SO_2ArH), 7.50 (m_c, 1H, SO_2ArH), 7.77 (t, *J* = 2.0 Hz, 1H, 6'-H). ^{13}C NMR (75 MHz, $CDCl_3$) see table 1. Anal. Calcd for $C_{34}H_{43}NO_5S$: C, 70.68, H, 7.50, N, 2.42. Found C, 70.42, H, 7.60, N, 2.40.

(1R,2R,3S,4S)-{3-[N-Benzenesulfonyl-N-(3,5-dimethylphenyl)-amino]-2-bornyl}-(5S)-2-oxo-5-isopropyl-cyclohexenecarboxylate (4n)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.83 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.10 (d, *J* = 6.8 Hz, 6H, iPr CH_3), 1.13-1.35 (m, 4H), 1.77 (t, *J* = 3.8 Hz, 1H, 4-H), 1.83-2.13 (m, 2H), 2.05 (s, br., 1H, Ar–CH_3), 2.28 (s, br., 1H, Ar–CH_3), 2.37-2.70 (m, 2H), 4.27 (dd, *J* = 8.7 and 3.8 Hz, 1H, 3-H), 5.50 (d, *J* = 8.7 Hz, 1H, 2-H), 5.87 (s, br., 1H, NAr 2-H), 6.83 (s, 1H, NAr 4-H), 6.97 (s, br., 1H, NAr 6-H), 7.30-7.43 (m, 4H, SO_2ArH), 7.51 (m_c, 1H, SO_2ArH), 7.93 (s, 1H, 6'-H). ^{13}C NMR (75 MHz, $CDCl_3$) see table 1. Anal. Calcd for $C_{34}H_{43}NO_5S$: C, 70.68, H, 7.50, N, 2.42. Found C, 70.43, H, 7.71, N, 2.37.

2-Isopropyl-acrolein (6)

A mixture of formaldehyde (91.8 g, 36%, 1.10 mol), 3-methylbutanal (86.1 g, 1.00 mol), piperidine (4.3 g, 50 mmol), and HCl (4.2 ml, 6 M, 25 mmol) was refluxed for 19 h. After cooling to 20 °C the mixture was neutralized with HCl (5 ml, 6 M) and the product was removed by steam distillation. Then the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (50 ml) and the combined organic layers were dried (Na_2SO_4). Distillation afforded **6** (74.0 g, 75%), colourless liquid, bp 108-109 °C. ^{1}H NMR (80 MHz, $CDCl_3$) δ = 1.09 (d, *J* = 6.7 Hz, 6H, iPr CH_3), 2.80 (sept, *J* = 6.7 Hz, 1H, iPr CH), 5.95 (s, 1H, =CH_2), 6.24 (s, 1H, =CH_2), 9.53 (s, 1H, HC=O). ^{13}C NMR (20 MHz, $CDCl_3$) δ = 21.07 (iPr CH_3), 25.99 (iPr CH), 131.82 (=CH_2), 156.29 (=C–), 194.28 (C=O). Further analytical data corresponded to previous published values[9].

2-(1-Bromomethyl-2-methyl-propyl)-1,3-dioxolane (7)

A solution of HBr (92 g, 1.14 mol) in ethylene glycol (248 g, 4 mol) was cooled to 0 °C. Then **6** (74 g, 0.75 mol) was added dropwise to the stirred solution at such a rate that temperature maintained at 5-10°C. After 30 min the ice bath was removed and stirring was continued for 3 h. Then the mixture was extracted with hexane (2x500 ml). The organic layer was washed with a solution of $NaHCO_3$ (5%) and filtered through a short column filled with silica gel (100 g). Evaporation of the solvent at reduced pressure and distillation afforded **7** (112 g, 67%), colourless liquid, bp 37 °C/0.1 mbar. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.01 (d, *J* = 6.8 Hz, 3H, iPr CH_3), 1.02 (d, *J* = 6.8 Hz, 3H, iPr CH_3), 1.92 (ddt, *J* = 6.4, 3.4 and 5.0 Hz, 1H, CH), (dsept, *J* = 5.0 and 6.7 Hz, 1H, iPr CH), 3.50 (dd, *J* = 10.3 and 6.4 Hz, 1H, CH_2Br), 3.57 (dd, *J* = 10.3 and 5.0 Hz, 1H, CH_2Br), 3.80-4.10 (m, 4H, CH_2O), 4.94 (d, *J* = 3.4 Hz, OCHO). ^{13}C NMR (20 MHz, $CDCl_3$) δ = 19.49 (iPr CH_3), 20.25 (iPr CH_3), 27.16 (iPr CH), 31.22 (CH_2Br), 49.10 (CH), 64.60 (CH_2O), 64.94 (CH_2O), 104.12 (OCHO). HREIMS: Calcd for $C_8H_{14}BrO_2$ (M^+-H$^\bullet$), 221.0177; Found 221.0179.

Methyl-6-(1,3-dioxolan-2-yl)-7-methyl-3-oxo-octanoate (8)

In an argon atmosphere a dispersion of NaH in mineral oil (5.92 g, 73%, 180 mmol) was suspended in THF (450 ml), HMPA (30 ml) was added, and the mixture was cooled to 0 °C. Then methyl acetoacetate (20.0 g, 172 mmol) was dropped to the above suspension within a period of 20 min and stirring was continued for 30 min. After that nBuLi (108 ml, 1.59 M, 172 mmol) was added dropwise and the reaction mixture was stirred for an additional 30 min. Then bromoacetal **7** (38.4 g, 172 mmol) was added in one lot, the mixture was allowed to warm up to 20 °C and stirring was continued for 20 h. After quenching with a solution of NH_4Cl (5%, 300 ml) the mixture was extracted with ether (3x300 ml), the organic layer was dried (Na_2SO_4) and the solvent was distilled off at reduced pressure. Distillation afforded **8** (28.5 g, 64%), bp 127 °C/0.1 mbar. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.92 (d, *J* = 6.9 Hz, 3H, iPr CH_3), 0.98 (d, *J* = 6.9 Hz, 3H, iPr CH_3), 1.47 (m_c, 1H, 6-H), 1.60-1.72 (m, 2H, 5-H), 1.91 (dsept, *J* = 3.9 and 6.9 Hz, 1H, 7-H), 2.63 (dt, *J* = 17.7 and 7.9 Hz, 1H, 4-H), 2.74 (dt, *J* = 17.7 and 7.4 Hz, 1H, 4-H), 3.47 (s, 2H, 2-H), 3.74 (s, 3H, OCH_3), 3.76-3.99 (m, 4H, CH_2O), 4.76 (d, *J* = 4.4 Hz, OCHO). ^{13}C NMR (20 MHz, $CDCl_3$) δ = 18.57 (iPr CH_3), 18.92 (C-5), 20.14 (iPr CH_3), 28.19 (C-7), 41.96 (C-4), 45.98 (C-6), 48.82 (C-2), 51.90 (OCH_3), 63.91 (CH_2O), 64.65 (CH_2O), 105.93 (OCHO), 167.49 (COO), 202.66 (C-3). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45, H, 8.58. Found C, 60.70, H, 8.85.

(1R,2R,3S,4S)-{3-[N-Benzenesulfonyl-N-(3,5-dimethylphenyl)-amino]-2-bornyl}-(6RS)-6-(1,3-dioxolan-2-yl)-7-methyl-3-oxo-octanoate (10n and 11n)

A solution of **8** (10.33 g, 40 mmol), **9n** (16.54 g, 40 mmol) and DMAP (9.75 g, 80 mmol) in toluene (350 ml) was refluxed in an apparatus equipped with a Dean-Stark trap. Within 3 d the main part of the solvent was distilled off in small portions (25x10 ml, aceotropic removal of MeOH). Then the mixture was evaporated *in vacuo* and the residue dissolved in CH_2Cl_2. The organic layer was washed with 0.2 M HCl and a solution of $NaHCO_3$ (5%), dried (Na_2SO_4) and the solvent removed at reduced pressure. Purification of the residue by flash chromatography (silica gel, 650 g, hexane:EtOAc = 75:25) gave a mixture of diastereomes **10n** and **11n** (18.95 g, 74%), colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, **10n**:**11n** = 1:1) δ = 0.82 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 0.88 (d, *J* = 6.9 Hz, 3H, iPr CH_3), 0.92 (d, *J* = 6.9 Hz, 3H, iPr CH_3), 0.99 (s, 3H, CH_3), 1.15 (m_c, 1H), 1.37-1.51 (m, 2H), 1.57-1.75 (m, 4H), 1.84-1.94 (m, 2H), 2.07 (s, 1H, Ar–CH_3), 2.25 (s, 1H, Ar–CH_3), 2.67 (m_c, 1H, 4'-H), 2.80 (m_c, 1H, 4'-H), 3.38 (d, *J* = 15.8 Hz, 1H, 2'-H), 3.52 (d, *J* = 15.8

Hz, 1H, 2'-H), 3.72-3.84 (m, 2H, CH_2O), 3.84-4.00 (m, 2H, CH_2O), 4.37 (dd, J = 8.6 and 3.6 Hz, 1H, 3-H), 4.75 (d, J = 4.7 Hz, OCHO), 5.32 (d, J = 8.6 Hz, 1H, 2-H), 6.07 (s, 1H, NAr 2-H), 6.81 (s, 1H, NAr 4-H), 6.84 (s, 1H, NAr 6-H), 7.31-7.37 (m, 4H, SO_2ArH), 7.50 (m_c, 1H, SO_2ArH). ^{13}C NMR (75 MHz, $CDCl_3$, **10n**:**11n** = 1:1) δ = 13.98 (CH_3), 18.82 (iPr CH_3), 19.18 (C-5'), 19.40 (CH_3), 19.44 (CH_3), 19.54 (C-5), 20.38 (iPr CH_3), 20.97 (Ar–CH_3), 21.11 (Ar–CH_3), 26.94 (C-6), 28.35 (C-7'), 42.55 and 42.51 (C-4'), 45.58 (C-7), 46.31 and 46.33 (C-6'), 49.35 and 49.40 (C-2'), 49.79 (C-4), 51.10 (C-1), 59.10 (C-3), 64.16 (CH_2O), 64.89 (CH_2O), 76.67 (C-2), 106.19 (OCHO), 127.94 (NAr C-2), 128.16 (NAr C-6), 128.21 (SO_2Ar C-2, C-3, C-5, C-6), 129.19 (NAr C-4), 132.56 (SO_2Ar C-4), 136.65 (NAr C-1), 137.23 (NAr C-3), 138.23 (NAr C-5), 139.51 (SO_2Ar C-1), 169.93 and 169.95 (C-1'), 203.63 (C-3'). Anal. Calcd for $C_{36}H_{49}NO_7S$: C, 67.58, H, 7.72, N, 2.19. Found C, 67.79, H, 7.67, N, 2.48.

(1R,2R,3S,4S)-{3-[N-Benzenesulfonyl-N-(3,5-dimethylphenyl)-amino]-2-bornyl}-2-hydroxy-5-isopropyl-cyclohexa-1,5-diene-carboxylate (12n)

A mixture of **4n** (58 mg, 1 mmol) and Et_3N (1 ml, 7.2 mmol) in hexane (10 ml) was refluxed for 12 h. Then the organic layer was washed with 2 M HCl (10 ml), H_2O (10 ml), a solution of $NaHCO_3$ (5%, 10 ml), dried (Na_2SO_4) and the solvent was distilled off *in vacuo* to give **12n** (52 mg, 90%), colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ = 0.79 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.13 (d, J = 6.8 Hz, 3H, iPr CH_3), 1.15 (d, J = 6.8 Hz, 3H, iPr CH_3), 1.19-1.51 (m, 4H), 1.69-1.87 (m, 2H), 2.10 (s, br., 1H, Ar–CH_3), 2.17 (s, br., 1H, Ar–CH_3), 2.19-2.50 (m, 4H), 4.37 (ddd, J = 8.6, 3.6 and 1.8 Hz, 1H, 3-H), 5.36 (dd, J = 8.6 and 1.5 Hz, 1H, 2-H), 6.13 (qua, J = 1.3 Hz, 1H, 6'-H), 6.40 (s, br., 1H, NAr 2-H), 6.56 (s, br., 1H, NAr 6-H), 6.77 (s, 1H, NAr 4-H), 7.32-7.43 (m, 4H, SO_2ArH), 7.51 (m_c, 1H, SO_2ArH), 12.01 (s, 1H, =C–OH). ^{13}C NMR (75 MHz, $CDCl_3$) see table 1. Anal. Calcd for $C_{34}H_{43}NO_5S$: C, 70.68, H, 7.50, N, 2.42. Found C, 70.46, H, 7.33, N, 2.40.

(1R,2R,3S,4S)-{3-[N-Benzenesulfonyl-N-(3,5-dimethylphenyl)-amino]-2-bornyl}-(5R,6R)-2-hydroxy-5-isopropyl-6-vinyl-cyclohexenecarboxylate (13n)

A suspension of CuI (191 mg, 1.0 mmol) in THF (20 ml) was cooled to -78 °C, a solution of H_2C=CHMgBr (4.0 ml, 0.50 M in THF, 2.0 mmol) was added and the resulting mixture stirred for 1 h at -78 °C. Then a solution of **3n** (289 mg, 0.50 mmol) in THF (10 ml) was added and stirring was continued for 2 h at -78 °C. The reaction mixture was quenched with a solution of NH_4Cl (5%), stirred at 20 °C for 1 h and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent distilled off *in vacuo*. Purification of the residue by flash chromatography (silica gel, 30 g, hexane:EtOAc = 85:15) gave **13n** (250 mg, 83%), colourless crystals from hexane, mp 118-120 °C. ^1H NMR (300 MHz, $CDCl_3$, ketone:enol = 20:80) δ(ketone, separated signals) = 2.86 (ddd, J = 11.6, 11.2 and 9.1 Hz, 1H, 6'-H), 3.67 (d, J = 11.6 Hz, 1H, 1'-H), 4.32 (dd, J = 8.7 and 3.5 Hz, 1H, 3-H), 5.13 (d, J = 17.1 Hz, 1H, =CH_2), 5.19 (d, J = 10.1 Hz, 1H, =CH_2), 5.41 (d, J = 8.7 Hz, 1H, 2-H), 5.62 (ddd, J = 17.1, 10.1 and 9.1 Hz, 1H, =CH–), 5.80 (s, br., 1H, NAr 2-H), 6.81 (s, 1H, NAr 4-H), 6.97 (s, br., 1H, NAr 6-H); δ(enol) = 0.81 (s, 3H, CH_3), 0.82 (s, 3H, CH_3), 1.00 (d, J = 6.7 Hz, 3H, iPr CH_3), 1.03 (s, 3H, CH_3), 1.22 (d, J = 6.4 Hz, 3H, iPr CH_3), 1.24-1.35 (m, 2H), 1.57-1.70 (m, 2H), 1.72-2.40 (m, 13H, 2 Ar–CH_3 and aliphatic H), 3.67 (m_c, 1H, 6'-H), 4.19 (dd, J = 8.7 and 3.7 Hz, 1H, 3-H), 5.01 (d, J = 17.2 Hz, 1H, =CH_2), 5.07 (d, J = 10.3 Hz, 1H, =CH_2), 5.53 (d, J = 8.7 Hz, 1H, 2-H), 5.84 (s, br., 1H, NAr 2-H), 6.00 (ddd, J = 17.2, 10.3 and 6.0 Hz, 1H, =CH–), 6.85 (s,

1H, NAr 4-H), 7.10 (s, br., 1H, NAr 6-H), 7.28-7.43 (m, 4H, SO_2ArH), 7.51 (m_c, 1H, SO_2ArH), 12.45 (s, 1H, =C–OH). ^{13}C NMR (75 MHz, $CDCl_3$, ketone:enol = 28:72) see table 1. Anal. Calcd for $C_{36}H_{47}NO_5S$: C, 71.37, H, 7.82, N, 2.31. Found C, 71.33, H, 8.08, N, 2.28.

(1R,2R,3S,4S)-{3-[N-Benzenesulfonyl-N-(3,5-dimethylphenyl)-amino]-2-bornyl}-(5S,6R)-2-hydroxy-5-isopropyl-6-vinyl-cyclohexenecarboxylate (14n)

A suspension of CuI (191 mg, 1.0 mmol) in THF (20 ml) was cooled to -78 °C, a solution of H_2C=CHMgBr (4.0 ml, 0.50 M in THF, 2.0 mmol) was added and the resulting mixture stirred for 1 h at -78 °C. Then a solution of **4n** (289 mg, 0.50 mmol) in THF (10 ml) was added and stirring was continued for 2 h at -78 °C. The reaction mixture was quenched with a solution of NH_4Cl (5%), stirred at 20 °C for 1 h and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent distilled off *in vacuo*. Purification of the residue by flash chromatography (silica gel, 30 g, hexane:EtOAc = 85:15) gave **14n** (255 mg, 84%), colourless crystals from hexane, mp 132-133 °C. ^1H NMR (300 MHz, $CDCl_3$) δ = 0.80 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 1.00 (d, *J* = 6.4 Hz, 3H, iPr CH_3), 1.04 (s, 3H, CH_3), 1.30 (d, *J* = 6.4 Hz, 3H, iPr CH_3), 1.36-1.62 (m, 2H), 1.79 (m_c, 1H), 1.86-1.97 (m, 2H), 2.06 (s, br., 1H, Ar–CH_3), 2.25 (s, br., 1H, Ar–CH_3), 2.31-2.37 (m, 2H), 3.99 (m_c, 1H, 6'-H), 4.17 (ddd, *J* = 8.7, 3.7 and 1.5 Hz, 1H, 3-H), 5.02 (d, *J* = 17.0 Hz, 1H, =CH_2), 5.16 (d, *J* = 10.4 Hz, 1H, =CH_2), 5.47 (d, *J* = 8.7 Hz, 1H, 2-H), 5.96 (s, br., 1H, NAr 2-H), 5.99 (ddd, *J* = 17.0, 10.4 and 6.4 Hz, 1H, =CH–), 6.81 (s, 1H, NAr 4-H), 6.97 (s, br., 1H, NAr 6-H), 7.28-7.41 (m, 4H, SO_2ArH), 7.48 (m_c, 1H, SO_2ArH), 12.43 (s, 1H, =C–OH). ^{13}C NMR (20 MHz, $CDCl_3$) see table 1. Anal. Calcd for $C_{36}H_{47}NO_5S$: C, 71.37, H, 7.82, N, 2.31. Found C, 71.42, H, 8.03, N, 2.31.

(1R,2R,3S,4S)-{3-[N-Benzenesulfonyl-N-(3,5-dimethylphenyl)-amino]-2-bornyl}-(5S,6S)-2-hydroxy-5-isopropyl-6-vinyl-cyclohexenecarboxylate (15n)

A solution of **2** (672 mg, 3 mmol), **9n** (2.48 g, 6 mmol) and DMAP (1.10 g, 9 mmol) in toluene (100 ml) was refluxed for 18 h. After evaporation of the solvent at reduced pressure the residue was dissolved in CH_2Cl_2, the organic layer was washed with 1 M HCl, dried (Na_2SO_4) and the solvent removed at reduced pressure. Separation of the residue by flash chromatography (silica gel, 200 g, hexane:Et_2O = 83:17) gave **9n** (990 mg, 80%, R_f = 0.31) and **13n** (595 mg, 65%, R_f = 0.26). Further elution (hexane:Et_2O = 50:50) afforded **15n** (420 mg, 46%, R_f = 0.20), colourless crystals from hexane, mp 123-125 °C. ^1H NMR (300 MHz, $CDCl_3$, ketone:enol = 38:62) δ(ketone, separated signals) = 0.84 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.99 (d, *J* = 6.2 Hz, 6H, iPr CH_3), 1.01 (s, 3H, CH_3), 2.99 (ddd, *J* = 10.7, 9.9 and 8.7 Hz, 1H, 6'-H), 3.44 (d, *J* = 10.7 Hz, 1H, 1'-H), 4.29 (dd, *J* = 8.9 and 3.4 Hz, 1H, 3-H), 5.12 (d, *J* = 11.0 Hz, 1H, =CH_2), 5.23 (d, *J* = 16.4 Hz, 1H, =CH_2), 5.36 (d, *J* = 8.9 Hz, 1H, 2-H), 5.75 (ddd, *J* = 16.4, 11.0 and 8.7 Hz, 1H, =CH–), 5.88 (s, 1H, NAr 2-H), 6.85 (s, 1H, NAr 4-H), 7.02 (s, 1H, NAr 6-H); δ(enol) = 0.80 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.96 (d, *J* = 6.2 Hz, 6H, iPr CH_3), 1.03 (s, 3H, CH_3), 1.10-1.50 (m, 3H), 1.55-1.95 (m, 6H), 2.07 (s, 3H, Ar–CH_3), 2.25 (m_c, 1H), 2.30 (s, 3H, Ar–CH_3), 2.72 (m_c, 1H), 3.55 (m_c, 1H, 6'-H), 4.17 (dd, *J* = 8.9 and 3.7 Hz, 1H, 3-H), 5.19 (d, *J* = 17.3 Hz, 1H, =CH_2), 5.31 (d, *J* = 10.3 Hz, 1H, =CH_2), 5.59 (d, *J* = 8.9 Hz, 1H, 2-H), 5.92 (s, 1H, NAr 2-H), 6.17 (ddd, *J* = 17.3, 10.3 and 5.1 Hz, 1H, =CH–), 6.85 (s, 1H, NAr 4-H), 7.08 (s, 1H, NAr 6-H), 7.31-7.49 (m, 4H, SO_2ArH), 7.55 (m_c, 1H, SO_2ArH), 12.04 (s, 1H, =C–OH). ^{13}C NMR (75 MHz, $CDCl_3$, ketone:enol = 42:58) see table 1. Anal. Calcd for $C_{36}H_{47}NO_5S$: C, 71.37, H, 7.82, N, 2.31. Found C, 71.54, H, 8.01, N, 2.29.

Methyl-(5RS,6RS)-2-hydroxy-5-isopropyl-6-vinyl-cyclohexenecarboxylate (*rac*-16)

A suspension of CuI (4.19 g, 22 mmol) in THF (100 ml) was cooled to -78 °C, a solution of H_2C=CHMgBr (80 ml, 0.55 M in THF, 44 mmol) was added and the resulting mixture was stirred for 1 h at -78 °C. Then a solution of *rac*-**2** (2.72 g, 13.9 mmol) in THF (10 ml) was added and stirring was continued for 2 h at -78 °C. The reaction mixture was quenched with a solution of NH_4Cl (5%), stirred at 20 °C for 1 h and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent distilled off *in vacuo*. Purification of the residue by flash chromatography (silica gel, 260 g, hexane:EtOAc:AcOH = 90:9:1) gave *rac*-**16** (2.01 g, 65%), colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ketone:enol = 50:50) δ(ketone, separated signals) = 0.77 (d, *J* = 6.8 Hz, 3H, iPr CH_3), 0.97 (d, *J* = 6.6 Hz, 3H, iPr CH_3), 2.49 (dt, *J* = 14.2 and 3.5 Hz, 1H, 3-H), 2.73 (ddd, *J* = 12.3, 9.8 and 9.2 Hz, 1H, 6-H), 3.24 (d, *J* = 12.3 Hz, 1H, 1-H), 3.68 (s, 3H, OCH_3), 5.05 (d, *J* = 10.0 Hz, 1H, $=CH_2$), 5.07 (d, *J* = 17.2 Hz, 1H, $=CH_2$), 5.54 (ddd, *J* = 17.2, 10.0 and 9.2 Hz, 1H, =CH-); δ(enol) = 0.90 (d, *J* = 7.8 Hz, 3H, iPr CH_3), 0.93 (d, *J* = 7.9 Hz, 3H, iPr CH_3), 1.00-1.30 (m, 1H), 1.40-1.90 (m, 3H), 1.90-2.40 (m, 2H, 3-H), 3.27 (m_c, 1H, 6-H), 3.70 (s, 3H, OCH_3), 4.85 (d, *J* = 17.2 Hz, 1H, $=CH_2$), 4.97 (d, *J* = 10.1 Hz, 1H, $=CH_2$), 5.76 (ddd, *J* = 17.2, 10.1 and 6.1 Hz, 1H, =CH-), 12.32 (s, 1H, =C-OH). ^{13}C NMR (75 MHz, $CDCl_3$, ketone:enol = 55:45) δ(ketone) = 51.56 (OCH_3), δ(enol) = 51.10 (OCH_3); for further signals see table 1. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61, H, 8.99. Found C, 69.75, H, 9.04.

REFERENCES AND NOTES

1. Itoh, Y.; Kodama, K.; Furuya, K.; Takahashi, S.; Haneishi, T.; Takiguchi, Y.; Arai, M. *J. Antibiot.* **1980**, *33*, 468-473.
2. Itoh, Y.; Kodama, K.; Takahashi, S.; Haneishi, T.; Arai, M. *J. Antibiot.* **1980**, *33*, 525-526.
3. Stipanovic, R. D.; Howell, C. R. *Tetrahedron* **1983**, *39*, 1103-1107.
4. Sankyo Co., Jpn. Kokai Tokkyo Koho 81 77281, *Chem. Abstr.* **1981**, *95*, P185.559s.
5. Mitsubishi Chemical Industries Co., Ltd., Jpn Kokai Tokkyo Koho 82 146793, *Chem. Abstr.* **1983**, *98*, P70.338p.
6. Kawashima, J.; Ito, F.; Kato, T.; Niwano, M.; Koshino, H.; Uramoto, M. *J. Antibiot.* **1994**, *47*, 1562-1563.
7. Danishefsky, S. J.; Mantlo, N. *J. Am. Chem. Soc.* **1988**, *110*, 8129-8133.
8. ^{1}H NMR spectra of **2** in $CDCl_3$ indicated the presence of a 13:1 mixture of keto and enol forms.[7]
9. Marvel, C. S.; Myers, R. L.; Saunders, J. H. *J. Am. Chem. Soc.* **1948**, *70*, 1694-1699.
10. Kato, M.; Kamat, V. P.; Yoshikoshi, A. *Synthesis* **1988**, 699-701.
11. Steglich, W.; Höfle, G. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 981.
12. Taber, D. F.; Amedio, J. C.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618-3619.
13. Helmchen, G.; Wegner, G. *Tetrahedron Lett.* **1985**, *26*, 6051-6054.
14. Urban, E.; Riehs, G.; Knühl, G. *Tetrahedron Lett.* **1995**, *36*, 4773-4776.

(*Received in Germany* 13 *October* 1995; *accepted* 30 *October* 1995)