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IRIDOIDS : THE STRUCTURE ELUCIDATION OF SPECIONIN BASED ON CHEMICAL EVIDENCE AND ^{1}H NMR ANALYSIS

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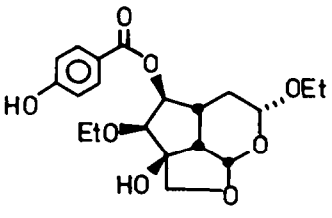
Abstract : The iridoid specionin is an effective antifeedant against the Eastern spruce budworm. Previous synthetic work has shown that the proposed structure was incorrect. Presently the total synthesis of the revised structure 2C is described. The structure elucidation, with special emphasis on the anomeric C-3 configuration, is based on chemical evidence and ^{1}H NMR analysis.

INTRODUCTION

In 1983, the iridoid specionin has been isolated from the leaves of Catalpa speciosa Warder[3]. It has been shown to be an effective antifeedant against the Eastern spruce budworm which infests North American fir and spruce forests in May, inflecting huge damage to the lumber industry. Based on spectral data specionin has been given structure 1[3]. In a previous paper[4] we have reported the synthesis of substance 1 and found it not to be identical with the natural material. Comparison of the spectral data led us to propose structure 2C, with however unspecified configuration at C-3. In a preliminary note we have confirmed this structure (3-OEt unspecified) by total synthesis[5]. This synthesis afforded a mixture of isomers which could be separated by HPLC. One of the isomers was identical with an authentic sample of specionin. The relative stereochemistry shown for centers 1, 5, 6, 7 and 9 is based on NOE enhancements described by Chang and Nakanishi[3]; at that moment the configuration at C-3 could not be determined.



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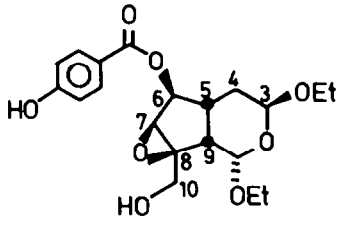
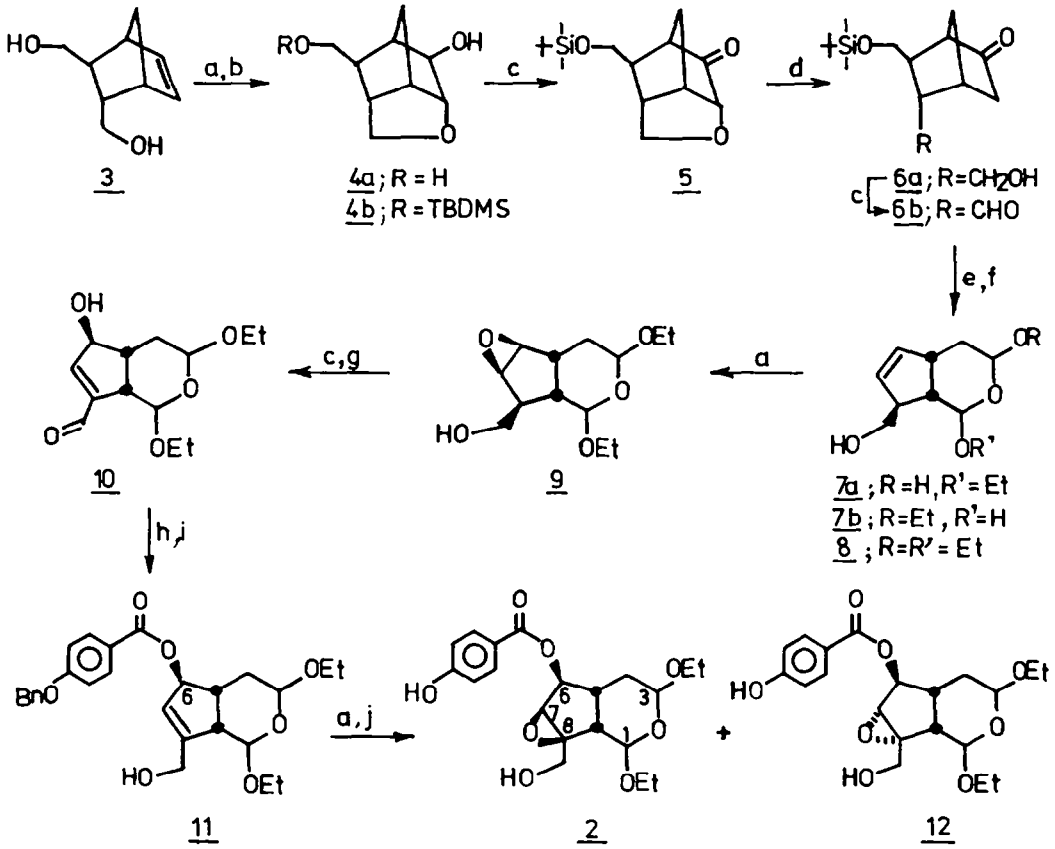


2C

As already mentioned the synthetic material was produced together with isomers which were originally thought to be diastereoisomers at the anomeric positions C-1 and C-3. Reinvestigation of the synthesis has revealed that also isomers 12 (scheme 1) with a 7,8-α-oriented epoxide were formed. Although this is an unattractive aspect from the synthetic point of view it allowed complete configurational assignment of specionin as 2C. Indeed only an extensive comparative study of the ^{1}H NMR spectra of the isomers 12, coupled with chemical evidence allowed us to prove the β-orientation of the 3-ethoxysubstituent, while confirming the correctness for the other stereocenters.

Synthesis of specionin and of its isomers

The synthesis is based on a previously described strategy which allows a general entry into different subclasses of the iridoids via a Norrish I type fragmentation of suitably substituted norbornanone precursors[6].



a) mCPBA, CH_2Cl_2, r.t.; b) t.$BuMe_2SiCl$, DBU, CH_2Cl_2, r.t.; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60°C; d) Al-Hg, EtOH, THF, r.t.; e) irradiation at 254 nm, EtOH; f) PTSA, EtOH, r.t.; g) DBU, CH_2Cl_2, r.t.; h) p.$BnOC_6H_4COCl$, Et_3N, CH_2Cl_2, r.t.; i) $NaBH_4$, EtOH, THF, 0°C; j) Pd-C, H_2, EtOH

SCHEME 1

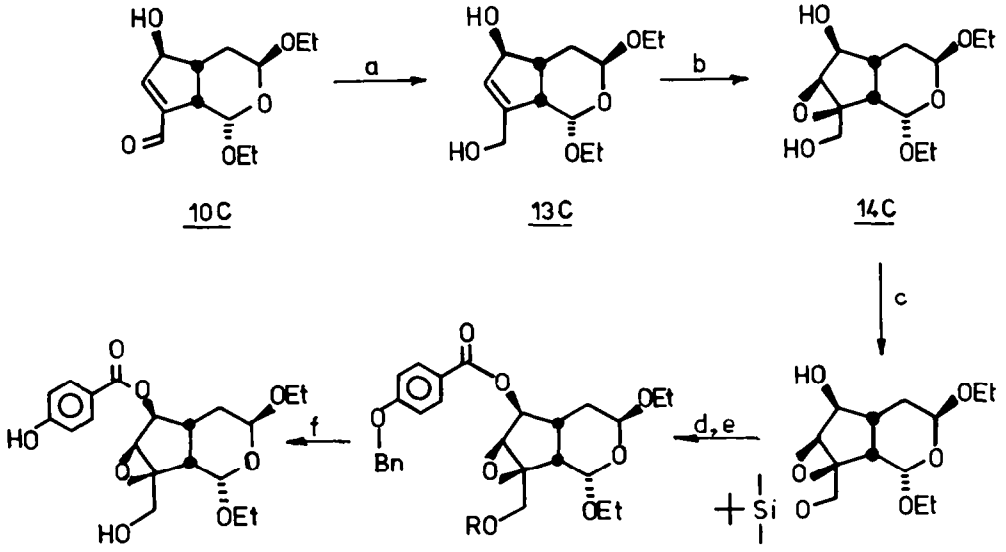
The starting material is the known norbornene 3[7] (Scheme 1). The keto-function in 6a is regioselectively introduced via a three step procedure with additional intermediate protection of the primary alcohol group in 4a. m.Chloroperbenzoic acid induced cyclization of 3, via the elusive exo-epoxide, to 4a (96 %) followed by selective silyl ether[8] formation afforded 4b (81 %). Swern[9] oxidation to 5 (77 %) and successive reductive cleavage of the α-ether bond led to 6a (89 %). Swern oxidation of the hydroxyl function in 6a yielded 6b (89 %), the substrate for the Norrish I type fragmentation. Irradiation of a carefully degassed ethanolic solution of 6b gave smooth fragmentation (TLC monitoring) of the norbornane framework. Most probably a diastereoisomeric mixture of 7a and 7b was formed as no aldehyde function could be detected. These intermediates could not be isolated as they are destroyed upon complete evaporation of the solvent. Therefore the ethanolic solution was treated with p.toluenesulfonic acid in order to perform the acetalization; concomitant silyl ether cleavage yielded directly a mixture of the four diastereoisomers 8 (64 %). The isomers could be separated by preparative HPLC; the ratio for 8C, 8A, 8D and 8B (for configurations see table 3) is 1:4:1:4 (order of elution). The relative configuration of the respective isomers 8 could not be determined unambiguously at this moment[5,10]. Structural confirmation was only possible after transformation of each separate diastereoisomer into the final products 2 and 12 (vide infra).

The stage is now set for the functionalization of the cyclopentene ring. In order to prove the gross planar structure 2 proposed for specionin[4], we decided to carry, in a first approach, the mixture of isomers 8 through the final steps. Epoxidation of 8 from the least hindered exo face gave 9 (94 %). Swern oxidation at -60°C (higher temperature as well as alternative pyridinium chlorochromate oxidation led to the formation of side products) followed by DBU mediated epoxide opening yielded the rather unstable aldehyde 10 (80 %). Formation of the 6-(p-benzyloxy)benzoate and reduction of the aldehyde function led to 11 (50 % overall). Finally

epoxidation of the isomers 11 (81 %) and deprotection of the phenolic function (100 %) gave a mixture of eight isomers (for the ratio see experimental part), consisting of two sets of compounds 2 and 12 with respectively a β- and α-oriented epoxide ring. This result shows that the last epoxidation step is not stereoselective; due to steric hindrance of the C-6 exo oriented ester group also epoxidation from the endo face has occurred.

HPLC separation allowed the isolation of synthetic (±)-specionin which was identical (^{1}H NMR spectroscopy, HPLC and GC retention times on co-injection) with a sample of the natural material kindly provided by Professor Nakanishi. This proves the gross planar structure for specionin; anticipating on the ^{1}H NMR analysis (vide infra) the natural product possesses the configuration 2C.

We now faced the configurational assignment at the anomeric position C-3 and to a lesser extent at C-1. It should be stressed that, with the ^{1}H NMR spectrum of specionin only (or any other individual isomer 2 or 12) in hand unambiguous structural determination of this conformationally flexible ring system is impossible. Evidently, the unselective epoxidation step is not attractive from the synthetic viewpoint, however it eventually allowed complete structural assignment of specionin (vide infra).



a) $NaBH_4$, EtOH, 0°C; b) mCPBA, CH_2Cl_2, r.t.; c) t.BuMe$_2$SiOTf, Et_3N, CH_2Cl_2, 0°C; d) p.BnOC$_6$H$_4$COCl, Et_3N, CH_2Cl_2, r.t.; e) HF, n.Bu$_4$N$^+$F$^-$, H_2O, THF, r.t.; f) Pd-C, H_2, EtOH

SCHEME 2

Inspection of the ^{1}H NMR spectra of the isomers 2 and 12 indeed suggested that the configurations at the anomeric positions could be proven when also chemical evidence was taken into account. Therefore the four isomers 8 were taken separately through the reaction sequence shown in scheme 1. This allowed a classification of the isomers 2 and 12 in four pairs, each of them consisting of a β- and α-epoxide with identical configuration at the anomeric positions C-1 and C-3. For the sake of consistency the four isomers of intermediates 9, 10 and 11 and of the final products 2 and 12 are also indicated as A, B, C and D (see table 3). The same results were found as starting from the isomeric mixture 8, except for 8B (1- and 3-OEt, β oriented) which upon epoxidation led to a mixture of 9B and the isomeric 6,7-α-epoxide[11] (ratio 3:1).

Obviously, the formation of the isomers 12 is due to the steric hindrance exerted by the C-6 ester function in 11. A stereoselective transformation of 8C to specionin (2C) is possible via epoxidation of the allylic alcohol[12] 13C (scheme 2). Reduction of the aldehyde 10C gave the diol

Table 1 : ^{1}H NMR data of the isomers 2 and 12 (in $CDCl_3$ and C_6D_6 solution[a], TMS internal) : δ-values (360 MHz)[b]

	12A		12B		12C		12D		2A		2B		2C		2D
H	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$
1	5.09	5.19	4.89	4.92	5.17	4.91	4.90	4.60	4.74	4.58	4.51	3.87	5.06	4.90	5.04
3	4.86	4.62	4.99	4.75	5.00	4.74	4.53	4.26	5.02	4.67	4.67	4.36	4.89	4.77	4.76
4α[c]	1.75	1.98	1.84	1.72	1.77	2.04	1.92	2.26	1.81	1.69	1.83	1.79	2.00	2.10	2.16
4β[c]	2.15		2.01	-	2.01	1.65		1.85	1.87	1.48	1.73	1.70	1.87	1.99	2.07
5	2.48	2.36	2.86	-	2.69	2.63	2.39	2.08	2.44	2.51	2.51	2.49	2.45	2.67	2.35
6	5.06	5.02	5.07	5.12	5.07	5.07	5.07	5.01	5.59	5.89	5.26	5.26	5.37	5.61	5.29
7	3.71	3.46	3.68	3.49	3.56	3.38	3.57	3.31	3.79	3.66	3.72	3.51	3.77	3.64	3.83
9	2.60	2.60	2.70	2.71	2.69	2.38	2.68	2.37	2.47	2.47	2.51	2.44	2.81	2.84	2.69
10a	4.11	3.89	4.09	3.82	4.11	4.00	4.10	3.91	4.10	3.87	4.07	3.81	4.02	3.74	3.99
10b	3.77	3.63	-	3.55	3.78	3.83	3.85	3.77	3.63	3.58	3.65	3.56	3.74	3.40	-
OCH_2CH_3[d]	3.97	3.79	3.98	-	4.10	3.85	4.08	3.87	4.05	3.82	4.06	3.84	3.87	3.79	-
"	3.89	3.79	3.85	-	3.75	3.54	3.96	3.84	3.75	3.49	3.95	3.77	3.85	3.58	-
"	3.63	3.30	3.58	-	3.59	3.19	3.59	3.31	3.56	3.14	3.59	3.30	3.51	3.22	-
"	3.54	3.26	3.48	-	3.51	3.15	3.52	3.23	3.49	3.13	3.54	3.13	3.48	3.11	-
OCH_2CH_3[d]	1.29	1.12	1.26	1.09	1.31	1.06	1.30	-	1.31	1.04	1.30	1.13	1.24	1.08	-
"	1.23	1.03	1.19	1.08	1.21	1.02	1.23	-	1.24	1.01	1.23	1.02	1.21	0.93	-
arom	7.92	8.00	7.98	7.93	7.89	8.04	7.90	-	7.96	8.09	7.97	8.09	7.98	8.09	-
	6.86	6.49	7.00	6.46	6.85	6.63	6.86	-	6.86	6.50	6.87	6.48	6.87	6.43	-

[a] For each compound the spectrum in C_6D_6 or in $CDCl_3$ solution afforded a complete set of coupling constants by simple first order measurements, thus avoiding very complex simulations in case of degeneration of the spin system.

[b] Data not measured are indicated by -.

[c] Where possible, an assignment of the α- or β-position of the H-4 proton is made.

[d] No efforts were undertaken for assignment of the position of the OCH_2CH_3 groups.

Table 2 : ^{1}H NMR data of the isomers 2 and 12 (in $CDCl_3$ and C_6D_6 solution[a], TMS internal) : J-values (360 MHz)[b]

	12A		12B		12C		12D		2A		2B		2C		2D
	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$
$^3J(1,9)$	7.7	7.7	7.4	7.3	3.7	4.0	4.3	4.9	8.8	8.6	8.4	8.4	4.0	3.7	3.1
$^3J(3,4\alpha)$[c]	9.0	8.7	3.8	3.8	-	4.4	-	9.7	1.4	1	2.7	2.8	[3.0	[2.8	[3.7
$^3J(3,4\beta)$[c]	6.0	6.3	2.4	2.8	-	1.2	-	3.7	4.4	4.5	9.2	9	[6.9	[5.7	[9.6
$\lvert^2J(4\alpha,4\beta)\rvert$	13.9	-	13.9	13.8	-	13.4	-	12.5	14.8	14.5	14.1	13.9	13.9	13.8	13.3
$^3J(4\alpha,5)$[c]	14.4	14.4	12.3	12.3	-	13.2	-	13.3	1.6	1	1.9	2.7	[5.1	[6.1	[9.4
$^3J(4\beta,5)$[c]	5.8	5.5	6.1	-	-	7.1	-	5.5	6.1	6.5	5.9	6.1	[7.2	[7.7	[9.9
$^3J(5,6)$	<1	<1	2.3	2.3	<1	<1	<1	<1	8.9	8.9	9.1	8.9	8.4	8.1	6.7
$^3J(5,9)$	10.1	10.0	10.7	10.7	-	7.8	8.1	8.3	7.6	8.5	-	8.4	8.2	8.3	9.2
$^3J(6,7)$	<1	<1	<1	<1	<1	<1	<1	<1	1.3	1.2	1.3	1.3	1.4	1.1	1.5
$\lvert^2J(10a,10b)\rvert$	13.1	12.9	13	12.8	12.6	12.7	12.2	12.5	13.4	13.3	13.4	14	12.5	12.5	13.0
$\lvert^2J(O\underline{CH}_2,\underline{CH}_3)\rvert$	9.6	9.5	9.5	-	9.2	9.2	9.3	9.4	9.3	9.2	9.4	9.6	9.4	9.2	-
"	9.6	9.5	9.5	-	9.7	9.7	9.4	9.4	9.7	9.7	9.4	9.4	8.5	9.7	-
$^3J(O\underline{CH}_2,\underline{CH}_3)$	7	7	7	7	7	7	7	7	7	7	7	7	7	7	-
"	7	7	7	7	7	7	7	7	7	7	7	7	7	7	-
arom	8.8	8.7	9	8.7	8.8	8.8	8.8	8.8	8.8	8.8	8.8	8.8	8.8	8.7	-

[a] For each compound the spectrum in C_6D_6 or in $CDCl_3$ solution afforded a complete set of coupling constants by simple first order measurements, thus avoiding very complex simulations in case of degeneration of the spin system.

[b] Data not measured are indicated by -.

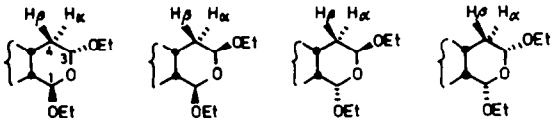
[c] Where possible, an assignment of the α- or β-position of the H-4 proton is made.

13C (60 %) which upon epoxidation provided a single product 14C (51 %). Protection of the primary alcohol function in 14C led to 15C (67 %) next to the disilylated product (26 %)[13]. The alcohol 15C was transformed into the 6-(p-benzyloxy)benzoate 17C (60 %) via esterification to 16C and silyl ether cleavage[14]. Finally hydrogenolysis of the benzyl ether led to specionin 2C (100 %).

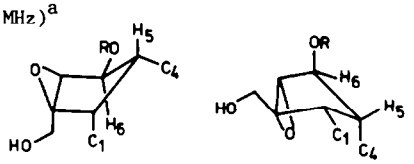
Comparative ^{1}H NMR study of specionin and its isomers

Assignment of the orientation of the epoxide ring was straightforward and is based on the value of the coupling constant (table 2 and scheme 3) between H-5 and H-6. The four isomers 12 display a small $^3J(5,6)$ value (< 1 - 2.3 Hz) which indicates a tortional angle of ca 90°. Knowing the 6-oxy function is β oriented (chemical evidence), this angle is obtained when this substituent and an α-epoxide oxygen atom are at maximum distance (electrostatic repulsion). For the β-epoxides 2, with an equatorially oriented 6-oxy function, the large $^3J(5,6)$ values of 6.7-8.9 Hz are in agreement with the antiperiplanar positions of H-5 and H-6. It should be mentioned that all naturally occurring 7,8-epoxy-iridoids display a β-epoxide function; it is thus logical to find specionin amongst the isomers 2.

Table 3 : ^{1}H NMR ^{3}J values of the intermediates ($CDCl_3$; 200 MHz)[a]



A B C D



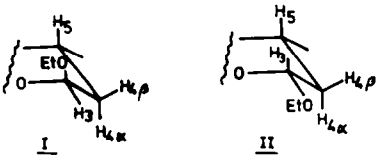
2 12

R = p.BnOC$_6$H$_4$CO

SCHEME 3

Product 8	A	B	C	D
(1,9)	7.5	5	3.3	4
(3,4α)	[5.5	[7.8	[4.5	[2.5
(3,4β)	[9	[3.8	[4.3	[9.5
(4α,5)	[5.5	[6.5	[6.3	[6
(4β,5)	[-	[5	[8	[-

Product 9				
(1,9)	3	2.5	3	3
(3,4α)	9.3	[5.5	4	[2.3
(3,4β)	3.8	[4	1.5	[9.5
(4α,5)	13	[6.5	12.5	[-
(4β,5)	5.5	[8	5.8	[-



I II

Product 10				
(1,9)	5	2	4	5
(3,4α)	[4	5	[4.8	9.5
(3,4β)	[4	9	[3.3	5
(4α,5)	[6.5	3	[7.5	13
(4β,5)	[5.8	5	[7	6.5

	12B	12C	12A	12D
$^3J(4\alpha,5)$	12.3	13.2	14.4	13.3
$^3J(4\beta,5)$	6.1	7.1	5.5	5.5
$^3J(3,4\alpha)$	3.8	4.4	8.7	9.7
$^3J(3,4\beta)$	2.8	1.2	6.3	3.7

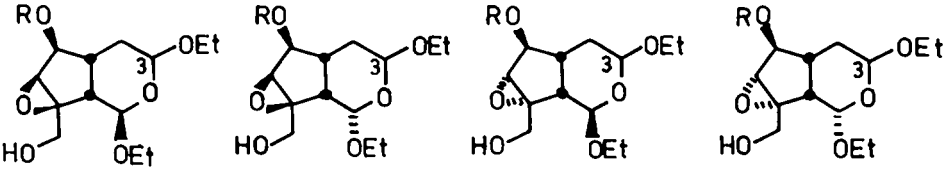
Product 11				
(1,9)	8	6.5	4	5
(3,4α)	[5.5	[5.3	[4.8	9.5
(3,4β)	[7	[5.3	[6	4
(4α,5)	[5.5	[-	[6.5	13
(4β,5)	[10.5	[-	[6	5.8

SCHEME 5

[a] Assignment of the H-4 α and H-4β was only possible for compounds 9A, 9C, 10D and 11D.

Considering the $^3J(1,9)$ values (table 2) the isomers 2 and 12 can be divided into two groups; A and B with large values (7.3-8.6 Hz) and C and D with smaller values (3.1-4.9 Hz). The large coupling constant is only plausible when H-1 and H-9 take an antiperiplanar position, thus

with a 1β-ethoxy substituent (isomers 2A, 2B, 12A and 12B). An analogous situation is observed for 2-deoxy-D-aldopentopyranoses or aldohexopyranoses[15]; for e,e or e,a dispositions the $^3J(1,2)$ values vary between 2 and 4 Hz while for an a,a situation values of ca 9 Hz are found. On the other hand considering a 1α-ethoxy group, for the isomers displaying the large J values, would necessitate the occurrence of a more energy demanding conformation with H-1 and H-9 close to an eclipsed position. Additional evidence is found in the ^1H NMR spectra (table 3) of the precursors 8 to 11. The isomers C and D invariably show small coupling constants between H-1 and H-9 therefore excluding their antiperiplanar orientation and indicating a 1α-ethoxy group. The C-1 configuration is furthermore supported by (a) the observation[3] of a nuclear Overhauser effect between H-1 and H-9 for the naturally occurring isomer 2C; (b) an independant synthesis[16] of isomers 2A and 2B carried out by Prof. D. Curran; the β-orientation of the C-1-ethoxy group being ascertained by the nature of the starting material.



2A ; 3αOEt 2D ; 3αOEt 12A ; 3αOEt 12D ; 3αOEt

2B ; 3βOEt 2C ; 3βOEt 12B ; 3βOEt 12C ; 3βOEt

R = p-BnOC$_6$H$_4$CO

SCHEME 4

With all other stereocenters ascertained (scheme 4) we can now determine the configuration at C-3. It is obvious that as long as the conformation of the heterocyclic ring is unknown the coupling constants between H-3α and H-4β, respectively H-4 cannot be interpreted. Upon comparing the $^3J(4\alpha,5)$ and $^3J(4\beta,5)$ values observed for respectively the isomers 2 and 12 a neat distinction can be made (Table 2). The α-epoxides 12 display one large value, which indicates an antiperiplanar orientation between H-5 and one of the 4-protons. Thus, the heterocyclic part of the four isomers 12 seems to remain close to the extreme conformations I or II (scheme 5); in fact only the C-3, C-4, C-5 part has to be considered for the present discussion. This allows us to determine respectively H-4α and H-4β.

These informations combined with the $^3J(3,4\alpha)$ and $^3J(3,4\beta)$ values (scheme 5) can now be used for deducing the stereochemistry at C-3 for the isomers 12. We have to refer again to the $^3J(1,2)$ values observed for the 2-deoxy-D-aldopentopyranoses and aldohexapyranoses (vide supra)[15]. The large $^3J(3,4\alpha)$ values found for 12A (8.7 Hz) and for 12D (9.7 Hz) indicate a trans diaxial coupling and hence an α-oriented ethoxy group. For the two other isomers 12B and 12C smaller coupling constants between H-4α and H-3 are observed; therefore the 3-ethoxy group has a β-orientation.

Furthermore it is worth noting that a similar analysis of the coupling constants between H-3, H-4 and H-5 (table 2) observed for the β-epoxides 2A and 2B provides additional evidence for respectively a 3α- and 3β-ethoxy substituent; on the contrary no conclusion could be drawn from the ^1H NMR data of 2C and 2D.

However, as each isomer 12 is formed together with a β-epoxide partner 2 when starting from each individual isomer 8 (scheme 1), the structures 2A,B,C and D are also firmly established. In particular 2C (identical to naturally occurring specionin) is obtained together with 12C, thus the ^1H NMR analysis and the chemical evidence unequivocally prove the structure of specionin.

Finally it should be mentioned that analysis of the ^1H NMR data of the intermediates 9A, 9C, 10D and 11D (table 3), as carried out for the compounds 12, also allows unambiguous configurational assignment of the C-3 anomeric center. These results are in complete agreement with those obtained for the α-epoxides 12. In retrospect, the present study leads to a reassignment of the configurations of the isomeric intermediates 8[10].

EXPERIMENTAL

IR spectra were recorded on a Beckmann IR 4230 spectrometer, mass spectra on a AEI MS-50 spectrometer. The ^{1}H NMR spectra were recorded at 200 MHz (WH-Brucker) in $CDCl_3$ unless otherwise stated with TMS as internal standard. Chemical shifts (δ) are expressed in ppm. Rf values are quoted for Merck silica gel 60 GF_{254} plates of thickness 0.25 mm. M.p.s. are uncorrected.
The combined extracts were dried over $MgSO_4$ unless otherwise stated. The solvent was removed from the filtered solution on a rotary evaporator. Column chromatographic separations were performed on silica gel. HPLC separations were performed on RSiL 10 µm silica using a Waters M6000 A pump with a 50 x 0.8 cm column or a Knauer model 64 with a 25 x 2.2 cm column, both with RI-detection.

Diol 4a
To a soln of diol 3 (57 g, 370 mmol) in dry CH_2Cl_2 (1500 ml) mCPBA (76.2 g, 370 mmol) was added in small portions at 0°C. After 20 h, at r.t., dimethylsulfide (6 ml) was added and the solvent was partially evaporated in vacuo. Then 10 % aq. NaOH was added until a pH of ca 10. A sat. aq. NaCl soln was added and the mixture was continuously extracted with Et_2O for several days. Drying and solvent evaporation in vacuo afforded the product 4a (61 g; 96 %) as a white powder. M.p. : 97°C; Rf (EtOAc) : 0.08; IR (KBr) : 3660-3040, 1480, 1420, 1365 cm^{-1}; ^{1}H NMR : 3.98 (dd, 1, J = 5 and 1.5 Hz), 3.81 (dd, 1, ^{2}J = 8 Hz, J = 3.5 Hz), 3.71 (d, 1, ^{2}J = 8 Hz), 3.56 (m, 3), 2.62 (m, 1), 2.12 (m, 1), 1.96 (m, 1), 1.93 (m, 1, ^{2}J = 10 Hz), 1.65 (m, 1, ^{2}J = 10), 1.65 (bs, 2), 1.42 (m, 1, J = 7.5 Hz); MS : m/z 170 (M+˙, 30), 139 (44), 99 (41), 95 (46), 70 (43), 69 (100); HRMS : calc. for $C_9H_{14}O_3$: 170.0923; found : 170.0943.

t.Butyldimethylsilyl ether 4b
To a soln of 4a (10 g, 59 mmol) in CH_2Cl_2 (500 ml) and DBU (10.6 ml, 71 mmol) was added a soln of t.BuMe$_2$SiCl (10.5 g, 70 mmol) in CH_2Cl_2 (110 ml) at r.t.. The reaction mixture was stirred at r.t. for 10 h. After partially removal of the solvent the mixture was poured in water (200 ml). The water layer was extracted with CH_2Cl_2 (4 x 50 ml). The collected organic fractions were washed with brine and dried. Solvent evaporation and column chromatography (hexane/EtOAc 3:1), yielded the product 4b (13.5 g; 81 %). Rf (hexane/EtOAc 7:3) : 0.12; IR (neat) : 3600-3100, 1470, 1460, 1260, 1135 cm^{-1}; ^{1}H NMR : 3.97 (dd, 1, J = 5 and 1.5 Hz), 3.79 (dd, 1, J = 4 Hz, ^{2}J = 7.5 Hz), 3.69 (d, 1, ^{2}J = 7.5 Hz), 3.51 (d, 2, J_2 = 8 Hz), 3.50 (m, 1), 2.58 (m, 1), 2.10 (m, 1), 1.91-1.85 (m, 3, J = 6.5 and 4 Hz), 1.65 (m, 1, ^{2}J = 11 Hz), 1.39 (m, 1, J = 8 Hz), 0.90 (s, 9), 0.05 (s, 6); MS : m/z : 227 (48), 105 (39), 99 (41), 75 (100); HRMS : calc. for $C_{11}H_{19}O_3Si$: 227.1103; found : 227.1091.

Swern oxidation of 4b to the ketone 5
A soln of DMSO (17 ml, 240 mmol) in CH_2Cl_2 (80 ml) was added to a soln of oxalyl chloride (10.4 ml, 119 mmol) in CH_2Cl_2 (170 ml) at -60°C. After 5 min a soln of the alcohol 4b (11.1 g, 39 mmol) in CH_2Cl_2 (140 ml) was added dropwise and the mixture was stirred for 75 min at -60°C. Then Et_3N (71 ml, 509 mmol) was added and the mixture was warmed slowly to -10°C. The solution was poured into 10 % aq. HCl. After extraction with CH_2Cl_2, the combined organic layers were washed with brine, sat. aq. $NaHCO_3$ soln, and brine. Drying (Na_2SO_4), solvent evaporation and column chromatography (hexane/EtOAc 4:1) gave product 5 (8.5 g; 77 %). M.p. : 50°C; Rf (hexane/EtOAc 7:3) : 0.27; IR (KBr) : 1760, 1470, 1460, 1255, 1120, 1100, 1070, 1045 cm^{-1}; ^{1}H NMR : 4.04 (dd, 1, J = 4 Hz, ^{2}J = 8 Hz), 3.89 (m, 1, J = 5.5 Hz), 3.84 (d, 1, ^{2}J = 8), 3.58 (d, 2, J = 7.5 Hz), 3.00 (m, 1), 2.50 (m, 1), 2.33 (m, 1), 2.04 (m, 1, ^{2}J = 11.5 Hz), 1.78 (m, 1, J = 7.5 Hz), 1.70 (m, 1, ^{2}J = 11.5 Hz), 0.89 (s, 9), 0.06 (s, 6); MS : m/z 75 (28), 69 (100); HRMS : calc. for $C_{15}H_{26}O_3Si$: 282.1651; found : 282.1627.

Reductive α-ether cleavage of ketone 5 : formation of 6a
To a susp of freshly prepared aluminum amalgam (from 30 g aluminum) in EtOH (17 ml) and THF (40 ml) was added a soln of 5 (7.5 g, 27 mmol) in EtOH (35 ml) and THF (80 ml) at r.t. The mixture was stirred for 2 h. The solids were centrifugated off and were washed several times with EtOAc. After removal of the solvents of the first extract (THF/EtOH), the collected organic phases were washed with sat. aq. NH_4Cl and with brine. Work-up and column chromatography (hexane/EtOAc 6:4) yielded pure 6a (6.7 g; 89 %). Rf (hexane/EtOAc 6:4) : 0.17; IR (neat) : 1750, 1260, 1120, 1090, 1065 cm^{-1}; ^{1}H NMR : 3.75 (dd, 1, J = 5.5 Hz, ^{2}J = 9.3 Hz), 3.67 (ddd, 1, J = 6 and 6 Hz), ^{2}J = 10 Hz), 3.50 (ddd, 1, J = 9 and 2.5 Hz, ^{2}J = 10 Hz), 3.42 (dd, 1, J = 9.3 Hz, ^{2}J = 9.3 Hz), 2.71 (m, 2), 2.43 (m, 1), 2.13 (ddd, 1, J = 3.8 and 1 Hz, ^{2}J = 18.3 Hz), 2.10 (m, 1), 1.98 (m, 1, ^{2}J = 18.3), 1.85 (m, 1, ^{2}J = 10.8 Hz), 1.71 (m, 1, ^{2}J = 10.8 Hz), 1.70 (m, 1), 0.91 (s, 9), 0.09 (s, 6); MS : m/z 227 (6), 209 (14), 107 (23), 105 (29), 75 (100); HRMS : calc. for $C_{11}H_{19}O_3Si$: 227.1103; found : 227.1118.

5-Endo-formyl-6-exo-tert.butyldimethylsilyloxymethylbicyclo[2.2.1]heptan-2-one (6b)
To a soln of oxalyl chloride (0.740 ml, 8.5 mmol) in CH_2Cl_2 (20 ml) at -60°C was added a soln of DMSO (1.170 ml, 1.65 mmol) in CH_2Cl_2 (4 ml). After 2 min a soln of the alcohol 6a (1 g, 3.5 mmol) in CH_2Cl_2 (4 ml) was added dropwise. The mixture was stirred for 15 minutes at -60°C and then Et_3N (5.8 ml, 41.5 mmol) was added. The reaction mixture was stirred for 1 h at -60°C. The mixture was poured into water, separated and extracted with CH_2Cl_2. The combined organic layers were washed with cold 10 % aq. HCl, sat. eq. $NaHCO_3$ and brine. Work-up and column chromatography (hexane/EtOAc 8:2) yielded 6b (0.95 g; 96 %). Rf (hexane/EtOAc 8:2) : 0.22; IR (neat) : 1750, 1720, 1250, 1110, 1090 cm^{-1}; ^{1}H NMR : 9.83 (d, 1, J = 1 Hz), 3.70 (dd, 1, J = 6 Hz, ^{2}J = 10 Hz), 3.58 (dd, 1, J = 6.5 Hz, ^{2}J = 10 Hz), 3.06 (m, 1), 2.81 (ddd, 1, J = 6, 4 and 1 Hz), 2.56 (m, 1), 2.38 (dddd, J = 6.5, 6, 6 and 1.3 Hz), 2.05 (m,2), 1.99 (m, 1, ^{2}J = 10.5 Hz), 1.76 (m, 1, ^{2}J = 10.5 Hz), 0.88 (s, 9), 0.053 (s, 3), 0.048 (s, 3); MS : m/z 225 (13), 207 (4), 183 (26), 105 (17), 91 (21), 75 (100); HRMS : calc. for $C_{11}H_{17}O_3Si$: 225.0947; found : 225.0908.

Norrish type I fragmentation of 6b and subsequent acetalization to 8

A soln of 6b (200 mg, 0.71 mmol) in carefully degassed EtOH (100 ml) was irradiated for 4 h at r.t. (Ultraviolet Products PCQ-X1 photochemical reactor; 253.7 nm). Then a catalytic amount of PTSA was added and the mixture was stirred for 24 h. After adding sat. aq. $NaHCO_3$ (30 ml) the EtOH was removed in vacuo at 25°C. The water phase was extracted with Et_2O (3 x). Work-up and column chromatography (hexane/EtOAc 6:4) afforded a mixture of the four isomers 8 (A, B, C and D, ratio 4:4:1:1) (110 mg; 64 %). The isomers were separated by HPLC using (hexane/EtOAc/acetone 8:1.5:0.5) leading to pure C, a mixture of A + D and pure B (order of elution). A further separation of A and D was performed with (hexane/EtOAc 8:2).

8A : Rf (hexane/EtOAc 6:4) : 0.22; IR (neat) : 3600-3100, 1145, 1100, 1055, 1000, 970 cm^{-1}; ^1H NMR : 5.76 (ddd, 1, J = 5.5, 2.5 and 2.5 Hz), 5.57 (ddd, 1, J = 5.5, 1.5 and 1.5 Hz), 4.97 (dd, 1, J = 9 and 5.5 Hz), 4.84 (d, 1, J = 7.5 Hz), 3.92 (dq, 1, J = 9.5 and 7 Hz), 3.58 (dq, 1, J = 9.5 and 7 Hz), 3.56 (dq, 1, J = 9.5 and 7 Hz), 3.45 (dd, 1, J = 8.5 Hz, ^2J = 10.5 Hz), 2.88 (m, 2), 2.12 (ddd, 1, J = 7.5, 7.5 and 9 Hz), 2.04 (ddd, 1, ^2J = 14 Hz, J = 5.5 and 5.5 Hz), 1.30 (m, 1), 1.26 (t, 3, J = 7 Hz), 1.23 (t, 3, J = 7 Hz); MS : m/z 242 ($M^{+\cdot}$, 1), 241 (2), 197 (13), 96 (100); HRMS : calc. for $C_{13}H_{21}O_4$: 241.1440; found : 241.1444.

8B : Rf (hexane/EtOAc 6:4) : 0.19; ^1H NMR : 5.72 (ddd, 1, J = 5.5, 1.8 and 1.8 Hz), 5.72 (ddd, 1, J = 5.5, 2 and 2 Hz), 4.75 (ddd, 1, J = 8, 3.8 and 0.8 Hz), 4.60 (d, 1, J = 5 Hz), 3.93 (dq, 1, J = 9.5 and 7 Hz), 3.90 (dq, 1, J = 9.3 and 7 Hz), 3.65 (dd, 1, J = 5.5 Hz, ^2J = 10.5 Hz), 3.56 (dd, 1, J = 6.5 Hz, ^2J = 10.5 Hz), 3.48 (dq, 1, J = 9.3 and 7 Hz), 3.50 (dq, 1, J = 9.5 and 7 Hz), 3.23 (m, 1), 2.81 (m, 1), 2.25 (ddd, 1, J = 9, 5 and 2.5 Hz), 2.10 (ddd, 1, J = 8 and 6.5 Hz, ^2J = 13.8 Hz), 1.73 (ddd, 1, J = 5 and 3.8 Hz, ^2J = 13.8 Hz), 1.23 (t, 3, J = 7 Hz), 1.22 (t, 3, J = 7 Hz).

8C : Rf (hexane/EtOAc 6:4) : 0.24; ^1H NMR : 5.79 (ddd, 1, J = 5.5, 2.5 and 2.5 Hz), 5.55 (m, 1, J = 5.5 Hz), 5.10 (d, 1, J = 3.3 Hz), 4.93 (dd, 1, J = 4 and 4 Hz), 4.00 (dq, 1, J = 9.5 and 7 Hz), 3.83 (dq, 1, J= 9.5 and 7 Hz), 3.59 (dq, 1, J = 9.5 and 7 Hz), 3.49 (dq, 1, J = 9.5 and 7 Hz), 3.16 (m, 2), 2.19 (ddd, 1, J = 8.7and 3.3 Hz), 1.82 (ddd, 1, J = 6.3 and 4.5 Hz, ^2J = 14 Hz), 1.52 (ddd, 1, J = 8 and 4.3 Hz), ^2J = 14 Hz), 1.27 (t, 3, J = 7 Hz), 1.23 (t, 3, J = 7 Hz).

8D : Rf (hexane/EtOAc 6:4) : 0.22; ^1H NMR : 5.85 (ddd, 1, J = 5.5, 2.5 and 2.5 Hz), 5.55 (m, 1, J = 5.5 Hz), 4.84 (d, 1, J = 4 Hz), 4.54 (dd, 1, J = 9.5 and 2.5 Hz), 4.07 (dq, 1, J = 9 and 7 Hz), 1.92 (ddd, 1, J = 6 and 2.5 Hz, ^2J = 13 Hz).

The isomers 8 gave almost identical IR, MS and HRMS spectra.

Epoxide 9

A soln of 8 (39 mg, 0.16 mmol) and mCPBA (70 mg, 0.32 mmol) in CH_2Cl_2 (8 ml) was stirred for 5 h at r.t.. Then sat. aq. $NaHCO_3$ and excess dimethylsulfide was added and the mixture was stirred for 10 min. After extraction with Et_2O, the organic layer was washed with sat. aq. $NaHCO_3$ and brine. Work-up and column chromatography (hexane/EtOAc 6:4) yielded 9 (39 mg; 94 %).

9A : Rf (hexane/EtOAc 6:4) : 0.07; IR (neat) : 3600-3100, 1150, 1100, 1050, 1015 cm^{-1}; ^1H NMR : 4.90 (dd, 1, J = 9.3 and 3.5 Hz), 4.82 (d, 1, J = 3 Hz), 3.91 (dq, 1, J = 9.3 and 7 Hz), 3.84 (dq, 1, J = 9.3 and 7 Hz), 3.82 (d, 2, J = 6.3), 3.54 (dq, 1, J = 9.3 and 7 Hz), 3.51 (dd, 1, J = 2.8 and 1.5 Hz), 3.50 (dq, 1, J = 9.3 and 7 Hz), 3.33 (bd, 1, J = 2.8 Hz), 2.67 (ddd, 1, J = 13, 7.5 and 5.5 Hz), 2.22 (ddt, 1, J = 9.5, 1.5 and 6.3 Hz), 1.89 (ddd, 1, J = 5.5 and 3.5 Hz, ^2J = 13 Hz), 1.65 (ddd, 1, J = 9.5, 7.5 and 3 Hz), 1.24 (t, 3, J = 7 Hz), 1.22 (t, 3, J = 7 Hz); MS : m/z 258 ($M^{+\cdot}$, 1), 257 (1), 213 (5), 95 (14), 81 (35), 72 (100); HRMS : calc. for $C_{13}H_{21}O_5$: 257.1389; found : 257.1401.

9B : Rf (hexane/EtOAc 6:4) : 0.07; ^1H NMR : 4.82 (dd, 1, J = 5.5 and 4 Hz), 4.68 (d, 1, J = 2.5 Hz), 3.88 (dq, 1, J = 9.5 and 7 Hz), 3.87 (dq, 1, J = 9.25 and 7 Hz), 3.81 (d, 2, J = 6.3 Hz), 3.56 (dd, 1, J = 2.5 and 1.5 Hz), 3.50 (dq, 1, J = 9.5 and 7 Hz), 3.47 (dq, 1, J = 9.3 and 7 Hz), 3.34 (bd, 1, J = 2.5 Hz), 2.81 (ddd, 1, J = 8.3, 8 and 6.5 Hz), 2.16 (ddt, 1, J = 8.3, 1.5 and 6.3 Hz), 2.02 (ddd, 1, J = 6.5 and 5.5 Hz, ^2J = 13.8 Hz), 1.80 (ddd, 1, J = 8.3, 8.3 and 2.5 Hz), 1.50 (ddd, 1, J = 4 and 8 Hz, ^2J = 13.8 Hz), 1.22 (t, 3, J = 7 Hz), 1.20 (t, 3, J = 7 Hz).

9C: Rf (hexane/EtOAc 6:4) : 0.07; ^1H NMR : 5.05 (d, 1, J = 3 Hz), 4.98 (d, 1, J = 4 and 1.5 Hz), 3.99 (dq, 1, J = 9 and 7 Hz), 3.78 (dq, 1, J = 9.5 and 7 Hz), 3.75 (dd, 1, J = 8 Hz, ^2J = 10.5 Hz), 3.55 (dq, 1, J = 9 and 7 Hz), 3.52 (dq, 1, J = 9.5 and 7 Hz), 3.41 (bd, 1, J = 2.5 Hz), 3.29 (dd, 1, J = 2.5 Hz), 2.79 (ddd, 1, J = 6.3, 6.3 and 12.5 Hz), 2.36 (dddd, 1, J = 9.3, 8, 4 and 1.5 Hz), 1.78 (ddd, 1, J = 9.5, 6.5 and 3 Hz), 1.71 (ddd, 1, J = 5.8 and 1.5 Hz, ^2J = 13.5 Hz), 1.31 (ddd, J = 12.5 and 4 Hz, ^2J = 13.5 Hz), 1.26 (t, 3, J = 7 Hz), 1.24 (t, 3, J = 7 Hz).

9D : Rf (hexane/EtOAc 6:4) : 0.07; ^1H NMR : 4.73 (d, 1, J = 3 Hz), 4.54 (dd, 1, J = 9.5 and 2.3 Hz).

The isomers 9 gave almost identical IR, MS and HRMS spectra.

α-β-Unsaturated γ-hydroxy aldehyde 10

A soln of DMSO (13 µl, 0.182 mmol) in CH_2Cl_2 (0.5 ml) was added to a soln of oxalylchloride (8 µl, 0.093 mmol) in CH_2Cl_2 (0.5 ml) at -60°C. The mixture was stirred for 2 min, then a soln of 9 (10 mg, 0.039 mmol) in CH_2Cl_2 (1 ml) was slowly added. After 25 min at -60°C Et_3N (64 µl, 0.460 mmol) was added and stirring was continued for 45 min. Then water (1.5 ml) and Et_2O (1.5 ml) were added and after stirring for 10 min the product was extracted with Et_2O. The organic layer was washed with brine and dried. After solvent evaporation in vacuo at 25°C, the crude product was taken up in CH_2Cl_2 (3 ml) and DBU (1.7 µl, 0.116 mmol) was added. This mixture was stirred for 2 h at r.t.. Work-up and column chromatography (hexane/EtOAc 6:4 and afterwards EtOAc) yielded pure 10 (8 mg; 80 %).

10A$_1$: Rf (hexane/EtOAc 3:7) : 0.23; UV (MeOH) : λ_{max} = 240 nm; IR (neat) : 3600-3100, 1680, 1625 cm^{-1}; ^1H NMR : 9.82 (s, 1), 6.84 (dd, 1, J = 1.5 and 1.5 Hz), 5.02 (m, 1), 5.00 (dd, 1, J = 4 and 4 Hz), 4.95 (d, 1, J = 5 Hz), 3.84 (dq, 1, J = 9.5 and 7 Hz);, 3.80 (dq, 1, J = 9.5 and 7 Hz), 3.50 (dq, 1, J = 9.5 and 7 Hz), 3.48 (dq, 1, J = 9.5 and 7 Hz), 3.17 (dd, 1, J = 7 and 5 Hz + LR), 2. 51 (dddd, 1, J = 7, 6.8, 5.8 and 6.5 Hz), 2.01 (ddd, 1, J = 6.5 and 4 Hz, ^2J = 14), 1.71

(ddd, 1, J = 5.8 and 4 Hz, ^{2}J = 14 Hz), 1.21 (t, 3, J = 7 Hz), 1.20 (t, 3, J = 7 Hz); MS : m/z 256 ($M^{+\cdot}$, 1), 255 (1), 211 (7), 138 (24), 136 (24), 107 (31), 81 (24), 79 (28), 72 (100).
10B : Rf (hexane/EtOAc 3:7) : 0.18; ^{1}H NMR : 9.80 (s, 1), 6.78 (dd, 1, J = 1.8 and 1.8 Hz), 4.99 (ddd, 1, J = 6,2.3 and 2.3 Hz), 4.83 (dd, 1, J = 5 and 9 Hz), 4.77 (d, 1, J = 2 Hz), 3.90 (dq, 1, J = 9 and 7 Hz), 3.86 (dq, 1, J = 9 and 7 Hz), 3.48 (dq, 1, J = 9.3 and 7 Hz), 3.46 (dq, 1, J = 9.3 and 7 Hz), 3.31 (ddd, 1, J = 8.8, 3.5 aand 2 Hz), 2.52 (dddd, 1, J = 8.8, 6, 5 and 3 Hz), 2.30 (ddd, 1, J = 9 and 5 Hz, ^{2}J = 14 Hz), 2.14 (ddd, 1, J = 5 and 3 Hz, ^{2}J = 14 Hz), 2.00 (bs, 1), 1.22 (t, 3, J = 7 Hz), 1.21 (t, 3, J = 7 Hz).
10C : Rf (hexane/EtOAc 3:7) : 0.33; ^{1}H NMR : 9.77 (s, 1), 6.77 (dd, 1, J = 2 and 1 Hz), 5.08 (d, 1, J = 4 Hz), 4.92 (dd, 1, J = 4.8 and 3 Hz), 4.87 (ddd, 1, J = 7, 2 and 2 Hz), 3.86 (dq, 1, J = 9.5 and 7 Hz), 3.69 (dq, 1, J = 9.5 and 7 Hz), 3.49 (dq, 1, J = 9.5 and 7 Hz), 3.35 (dq, 1, J = 9.5 and 7 Hz), 2.46 (dddd, 1, J = 9, 7, 7 and 7 Hz), 2.16 (ddd, 1, J = 7 and 3 Hz, ^{2}J = 13.5 Hz), 2.06 (ddd, 1, J = 7.5 and 4.8 Hz, ^{2}J = 13.5 Hz), 1.21 (t, 3, J = 7 Hz), 1.05 (t, 3, J = 7 Hz).
10D : Rf (hexane/EtOAc 3:7) : 0.23; ^{1}H NMR : 9.81 (s, 1), 6.74 (dd, 1, J = 2 and 2 Hz), 5.23 (d, 1, J = 5 Hz), 4.83 (dd, 1, J = 9.5 and 5 Hz), 4.76 (m, 1), 3.91 (dq, 1, J = 9.3 and 7 Hz), 3.76 (dq, 1, J = 9.5 and 7 Hz), 3.51 (dq, 1, J = 9.3 and 7 Hz), 3.34 (dq, 1, J = 9.5 and 7 Hz), 2.34 (dddd, 1, J = 13, 9, 6.5 and 3 Hz), 2.15 (ddd, 1, J = 6.5 and 5 Hz, ^{2}J = 13 Hz), 2.00 (ddd, 1, J = 13 and 9.5 Hz, ^{2}J = 13 Hz), 1.22 (t, 3, J = 7 Hz), 1.04 (t, 3, J = 7 Hz).
The isomers 10 gave almost identical UV, IR and MS spectra.

p. Benzyloxybenzoate 11
A soln of 10 (30 mg, 0.117 mmol), Et_3N (65 µl, 0.470 mmol) and p.$BnOC_6H_4COCl$ (58 mg, 0.234 mmol) in CH_2Cl_2 (8 ml) was stirred for 24 h at r.t.. Then an additional equal portion of Et_3N and of the acid chloride were added and stirring was continued for 24 h. EtOH (80 µl) was added and after 2 h the mixture was diluted with Et_2O and washed with sat. aq. $NaHCO_3$ and brine. After drying and solvent evaporation the residue was dissolved in EtOH (2 ml) and THF (2 ml). $NaBH_4$ (17.8 mg, 0.468 mmol) was added and the suspension was stirred for 30 min at 0°C. After addition of sat. aq. NH_4Cl and water (until the salts were dissolved) the mixture was extracted with Et_2O. Work-up and HPLC purification (hexane/EtOAc 7:3) afforded product 11 (27 mg; 50 %).
11A: Rf (hexane/EtOAc 6:4) : 0.23; UV (MeOH) : λ_{max} = 258 nm; IR (neat) : 1705, 1680, 1605, 1580, 1510 cm^{-1}; ^{1}H NMR : 7.96 (d, 2, J = 9 Hz + LR), 7.39 (m, 5), 7.34 (d, 2, J = 9 Hz + LR), 5.87 (m, 1), 5.60 (m, 1), 5.12 (s, 2), 5.00 (dd, 1, J = 7 and 5.5 Hz), 4.74 (d, 1, J = 8 Hz), 4.28 (bs, 2), 3.96 (dq, 1, J = 9.5 and 7 Hz), 3.85 (dq, 1, J = 9.5 and 7 Hz), 3.56 (dq, 1, J = 9.5 and 7 Hz), 3.54 (dq, 1, J = 9.5 and 7 Hz), 3.07 (m, 1, J = 8 Hz), 2.57 (m, 1), 2.19 (ddd, 1, J = 5.5 and 5.5 Hz, ^{2}J = 14 Hz), 1.61 (ddd, 1, J = 10.5 and 7 Hz, ^{2}J = 14 Hz), 1.28 (t, 3, J = 7 Hz), 1.23 (t, 3, J = 7 Hz); MS : m/z 211 (6), 166 (19), 135 (37), 107 (31), 94 (21), 92 (21), 91 (100); HRMS : calc. for $C_{14}H_{11}O_2$: 211.0759; found : 211.0770.
11B : Rf (hexane/EtOAc 6:4) : 0.22; ^{1}H NMR : 7.99 (d, 2, J = 8.8 Hz + LR), 7.40 (m, 5), 6.99 (d, 2, 8.8 Hz + LR), 5.85 (m, 2), 5.13 (s, 2), 4.88 (dd, 1, J = 5.3 and 5.3 Hz), 4.52 (d, 1, J = 6.5 Hz), 4.27 (bs, 2), 3.99 (dq, 1, J = 9.3 and 7 Hz), 3.93 (dq, 1, J = 9.3 and 7 Hz), 3.54 (dq, 1, J = 9.3 and 7 Hz), 3.53 (dq, 1, J = 9.3 and 7 Hz), 2.88 (m, 2), 2.04 (m, 2, J = 5.5 Hz), 1.25 (t, 3, J = 7 Hz), 1.23 (t, 3, J = 7 Hz).
11C : Rf (hexane/EtOAc 6:4) : 0.24; ^{1}H NMR : 7.97 (d, 2, J = 9 Hz + LR), 7.37 (m, 5), 6.97 (d, 2, J = 9 Hz + LR), 5.87 (m, 1), 5.74 (m, 1), 5.12 (s, 2), 5.06 (dd, 1, J = 6 and 4.8 Hz), 5.06 (d, 1, J = 4 Hz), 4.28 (bs, 2), 3.92 (dq, 1, J = 9.5 and 7 Hz), 3.85 (dq, 1, J = 9.5 and 7 Hz), 3.53 (dq, 2, J = 9.5 and 7 Hz), 3.29 (dq, 1, J = 8.5 Hz), 2.74 (dddd, 1, J = 8.5, 6, 6 and 4.5 Hz), 2.20 (ddd, 1, J = 6.5 and 4.8 Hz, ^{2}J = 14.3 Hz), 1.87 (ddd, 1, J = 6 and 6 Hz, ^{2}J = 14.3 Hz), 1.24 (t, 3, J = 7 Hz), 1.22 (t, 3, J = 7 Hz).
11D : Rf (hexane/EtOAc 6:4) : 0.25; ^{1}H NMR : 7.96 (d, 2, J = 9 Hz + LR), 7.39 (m, 5), 6.97 (d, 2, J = 9 Hz + LR), 5.87 (m, 1), 5.46 (m, 1), 5.11 (s, 2), 5.01 (d, 1, J = 5 Hz), 4.75 (dd, 1, J = 9.5 and 4 Hz), 4.28 (m, 2), 3.95 (dq, 1, J = 9.5 and 7 Hz), 3.91 (dq, 1, J = 9.5 and 7 Hz), 3.52 (dq, 1, J = 9.5 and 7 Hz), 3.48 (dq, 1, J = 9.5 and 7 Hz), 2.51 (dddd, 1, J = 13, 7.5, 6 and 1.5 Hz), 2.19 (ddd, 1, J = 6 and 4 Hz, ^{2}J = 13 Hz), 1.88 (ddd, 1, J = 13 and 9.5 Hz, ^{2}J = 13 Hz), 1.22 (t, 3, J = 7 Hz), 1.21 (t, 3, J = 7 Hz).
The isomers 11 gave almost identical UV, IR, MS and HRMS spectra.

Isomers 2 and 12
A soln of 11 (9 mg, 0.019 mmol) and mCPBA (18.5 mg, 0.085 mmol) in CH_2Cl_2 (1.5 ml) was stirred for 24 h at r.t.. Then sat. aq. $NaHCO_3$ (2 ml) and dimethylsulfide (0.5 ml) were added and the mixture was stirred for 10 min. The system was extracted with Et_2O. The organic layer was washed with sat. aq. $NaHCO_3$ and brine. Work-up and column chromatographic purification (hexane/EtOAc 7:3) gave a mixture of α- and β-epoxides (7.5 mg; 81 %). This mixture was taken up in EtOH (0.750 ml) and added to a suspension of prehydrogenated Pd-C in EtOH (0.750 ml) in H_2 atmosphere. After stirring for 40 min at 1 atm solid $NaHCO_3$ was added and the mixture was filtered through a path of celite. Removal of EtOH at 25°C and column chromatography (hexane/EtOAc 6:4) yielded a mixture of 2 and 12 (6 mg; 90 %).
Ratios in each pair of α- and β-epoxide[17] : 2A/12A : 1, 2B/12B : 2, 2C/12C : 0.8, 2D/12D 0.1 (only traces of 2D could be detected). For the reaction leading to the mixture of all isomers a HPLC separation on a reversed phase 25 x 2.2 cm column RSiL-C_{18}-HL-D 10 um ($MeOH/H_2O$ 55:45; 10 ml/min) (UV detection) gave pure samples of isomers 2 and 12 (A, B, C and D).
2C : Retention time : 5.8; UV (MeOH) : λ_{max} = 254 nm; IR (neat) : 1710, 1610, 1590, 1510, 1275 cm^{-1}; ^{1}H NMR : see table 1 and 2; MS : m/z 365 (1), 349 (1), 138 (13), 122 (12), 121 (100), 107 (12); HRMS : calc. for $C_{18}H_{21}O_8$: 365.1236; found : 365.1214.
Retention time of 2A, 4.6; 2B, 2.9; 2D, 4.8; 12A, 5.3; 12B, 5.3; 12C, 6.7 and 12D, 3.9.
The isomers 2 and 12 gave almost identical UV, IR, MS and HRMS spectra.

Diol 13C
To a soln of 10C (20 mg, 0.078 mmol) in EtOH (1 ml) and THF (1 ml), $NaBH_4$ (1.5 mg, 0.039 mmol) was added and the mixture was stirred for 1 h at 0°C. Then sat. aq. NH_4Cl (1.5 ml) and Et_2O (2 ml) were added and after 10 min the mixture was extracted with Et_2O (8 x). The collected organic layers were washed with brine and dried. Evaporation of the solvent and column chromatography (hexane/EtOAc 2:8) afforded 13C (12 mg; 60 %). Rf (hexane/EtOAc 2:8) : 0.11; IR (neat) : 3600-3100, 1375, 1350, 1160, 1120, 1050 cm^{-1}; ^1H NMR : 5.80 (dd, 1, J = 1.5 and 1.5 Hz), 5.02 (d, 1, J = 4 Hz), 4.97 (dd, 1, J = 5 and 5 Hz), 4.62 (bs, 1), 4.24 (bs, 2), 3.90 (dq, 1, J = 10.5 and 7 Hz), 3.85 (dq, 1, J = 10.5 and 7 Hz), 3.52 (dq, 1, J = 9.5 and 7 Hz), 3.52 (dq, 1, J = 9.5 and 7 Hz), 3.21 (m, 1), 2.45 (dddd, 1, J = 8.5, 5.5, 5.5 and 4.5 Hz), 2.06 (ddd, 1, J = 5.5 and 5 Hz, ^2J = 14 Hz), 1.81 (ddd, 1, J = 5.5 and 5 Hz, ^2J = 14 Hz), 1.23 (t, 6, J = 7 Hz); MS : m/z 72 (100).

Epoxide 14C
A soln of 13C (11 mg, 0.043 mmol) and mCPBA (18 mg, 0.085 mmol) in CH_2Cl_2 (2 ml) was stirred for 1 h at r.t.. Then sat. aq. $NaHCO_3$ and excess dimethylsulfide were added and the mixture was stirred for 10 min. After extraction with Et_2O, the organic layer was washed with sat. aq. $NaHCO_3$ and with brine. Drying, solvent evaporation and column chromatography (hexane/EtOAc 3:7) yielded 14C (6 mg, 51 %). Rf (hexane/EtOAc 2:8) : 0.19; IR (neat) : 3600-3100, 1150, 1125, 1100, 1030 cm^{-1}; ^1H NMR : 4.99 (d, 1, J = 4 Hz), 4.83 (dd, 1, J = 6.5 and 2.8 Hz), 4.14 (dd, 1, J = 7.5 and 1.5 Hz), 3.96 (d, 1, ^2J = 12.5 Hz), 3.86 (dq, 1, J = 9 and 7 Hz), 3.81 (dq, 1, J = 9 and 7 Hz), 3.70 (d, 1, ^2J = 12.5), 3.52 (d, 1, J = 1.5 Hz), 3.48 (dq, 1, J = 9 and 7 Hz), 3.46 (dq, 1, J = 9 and 7 Hz), 2.70 (dd, 1, J = 7.3 and 4 Hz), 1.96 (m, 2), 1.21 (t, 3, J = 7 Hz), 1.19 (t, 3, J = 7 Hz); MS : m/z 229 (26), 183 (39), 73 (100); HRMS : calc. for $C_{11}H_{17}O_5$: 229.1075; found : 229.1121.

t.Butyl-dimethylsilyl ether 15C
To a soln of 14C (21 mg, 0.077 mmol) and Et_3N (16.0 µl, 0.115 mmol) in CH_2Cl_2 (1.5 ml) was added dropwise, at 0°C, t.$BuMe_2SiOTf$ (19.3 µl, 0.084 mmol). After stirring for 30 min, brine was added and the mixture was extracted with CH_2Cl_2. Drying, solvent evaporation and column chromatography (hexane/EtOAc 7:3) afforded 15C (20 mg, 67 %) next to 10 mg of the disilylated compound (26 %). Rf (hexane/EtOAc 7:3) : 0.21; IR (neat) : 3600-3100, 1250, 1080, 1020, 990 cm^{-1}; ^1H NMR : 5.05 (d, 1, J = 4), 4.82 (dd, 1, J = 6.5 and 2.5 Hz), 4.13 (m, 1), 4.12 (d, 1, ^2J = 12), 3.86 (dq, 1, J = 9.3 and 7 Hz), 3.80 (dq, 1, J = 9.5 and 7 Hz), 3.54 (d, 1, ^2J = 12 Hz), 3.49 (dq, 1, J = 9.3 and 7 Hz), 3.45 (dq, 1, J = 9.5 and 7 Hz), 3.36 (d, 1, J = 1.5 Hz), 2.74 (dd, 1, J = 7.3 and 4 Hz), 1.92 (3, m), 1.22 (t, 3, J = 7 Hz), 1.19 (t, 3, J = 7 Hz), 0.90 (s, 9), 0.08 (s, 3), 0.06 (s, 3); MS : m/z : 343 (3), 285 (3), 267 (4), 239 (14), 211 (23), 75 (100), 73 (49); HRMS : calc. for $C_{17}H_{31}O_5Si$: 343.1941; found : 343.1949.

Ester 17C
To a soln of 15C (4 mg, 0.010 mmol) in CH_2Cl_2 (1.5 ml) was added Et_3N (5.8 µl, 0.041 mmol) and p.$BnOC_6H_4COCl$ (5.1 mg, 0.021 mmol). The mixture was stirred for 48 h and then a second portion of Et_3N and p.$BnOC_6H_4COCl$ was added. Stirring was continued for 24 h, EtOH (15 µl) was then added and after 2 h the mixture was diluted with Et_2O and washed with sat. aq. $NaHCO_3$ and brine. Drying, solvent evaporation and column chromatography (hexane/EtOAc 9:1) yielded crude 16C (8 mg). Rf (hexane/EtOAc 8:2) : 0.40. To a soln of crude 16C (8 mg) in THF (0.6 ml) was added 1.5 mol equiv. of fluoride as a 1:1 mixture of HF and p.$Bu_4N^+F^-$ [17 µl, 0.020 mmol of a 1.2 M solution of F^-, prepared from 0.35 ml of 1.0 M n.$Bu_4N^+F^-$ in THF and 0.25 ml of 1.4 M HF in THF (prepared from 0.5 ml of 47 % HF and 9.5 ml of THF)]. The reaction mixture was stirred at r.t. for 48 h, diluted with Et_2O and extracted with brine. Drying, solvent evaporation and column chromatography (hexane/EtOAc 7:3) afforded pure 17C (3 mg, 60 %). Rf (hexane/EtOAc 6:4) : 0.14; UV (MeOH) : λ_{max} = 260 nm; IR (neat) : 1710, 1600, 1580, 1505 cm^{-1}; ^1H NMR : 8.03 (d, 2, J = 9 Hz + LR), 7.40 (m, 5), 7.00 (d, 2, J = 9 Hz + LR), 5.37 (dd, 1, J = 8.3 and 1.5 Hz), 5.13 (s, 2), 5.06 (d, 1, J = 4 Hz), 4.88 (dd, 1, J = 6.5 and 3 Hz), 4.00 (d, 1, ^2J = 12 Hz), 3.86 (dq, 1, J = 9.5 and 7 Hz), 3.85 (dq, 1, J = 9.5 and 7 Hz), 3.75 (d, 1, J = 1.5 Hz), 3.72 (d, 1, ^2J = 12 Hz), 3.51 (dq, 1, J = 9.5 and 7 Hz), 3.48 (dq, 1, J = 9.5 and 7 Hz), 2.80 (dd, 1, J = 8 and 4 Hz), 2.44 (dddd, 1, J = 8.3, 8, 7 and 5.5 Hz), 2.01 (ddd, 1, J = 5.5 and 3 Hz, ^2J = 14 Hz), 1.86 (ddd, 1, J = 7 and 7 Hz, ^2J = 14 Hz), 1.24 (t, 3, J = 7 Hz), 1.20 (t, 3, J = 7 Hz); MS : m/z 211 (12), 92 (11), 91 (100), 72 (14); HRMS : calc. for $C_{14}H_{11}O_2$: 211.0759; found : 211.0695.

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17. The mutual ratio of the pairs is the same as indicated for the mixture of isomers 8 (vide supra).