262. The Synthesis of Stereoisomers of Arteannuin B

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Die Synthese von Stereoisomeren des Arteannuins B

Zusammenfassung

Wir beschreiben die Synthese von drei rac-Diastereomeren **7A–7C** des Sesquiterpenlaktons Arteannuin B (**I**) auf dem in den *Schemata 2* und *3* zusammengefassten Weg. Als Schlüsselstufe für den Aufbau des Ringsystems **6** wurde eine intramolekulare *Reformatsky*-artige Reaktion verwendet, in der gleichzeitig ein Cyclohexanring und ein α-Methylidenbutyrolaktonring gebildet werden (Schritte 3 und 6). Die Cyclisierung von **5A** bzw. **5B** oder von **9/10** führte vorwiegend zur *cis,cis*-Verknüpfung der drei Ringe A/B/C, wie in **6A** bzw. **6B**. Daneben entstand aus **5B** auch das *trans,cis*-System **6C**. Die Verlängerung der Seitenkette in **1A,B** unter Ausbildung der für die *Reformatsky*-artige Reaktion notwendigen Funktionalität (in **5** bzw. **9/10**) wurde nach zwei Methoden ausgeführt, welche in den Schritten 1, 2 bzw. 5 beschrieben sind. Die Epoxydierung von **6A**, **6B** bzw. **6C** zu **7A**, **7B** bzw. **7C** (Schritt 4) war vollkommen regio- (an C(7′), C(8′)) und stereospezifisch. Die relative Konfiguration an den Zentren C(1′), C(4′), C(4a′) und C(8a′) der drei Diastereomeren **A**, **B** bzw. **C** von **6** und **7** wurde anhand der ^{1}H-NMR-Spektren abgeleitet.

1. Introduction. – The structural features of arteannuin B [1] [2], an epoxy-α-methylidene-butyrolactone of the cadinane type (**I**), isolated from *Artemisia Annua* L. [1], make it an attractive goal for synthetic efforts. Our approach, stimulated by previous experiences in our laboratories [3–6] (see below), is illustrated in *Scheme 1*. The key steps are the introduction of the $CH{=}C(CH_2X)COOR$ functionality (X = Br [5] [7] [8] or $SCH(CH_3)_2$ [7]) (**III** → **II**) and the simultaneous formation of an alicyclic and an α-methylidene-butyrolactone ring [6] [8–10], followed by epoxidation (**II** → **I**). Experience had to be gained with the stereospecificities of these reactions. In this paper we describe the synthesis of three stereoisomers of **I**, all of which, however, are not identical with racemic arteannuin B. The synthetic steps are given in section 2, the relative configurations of the chiral

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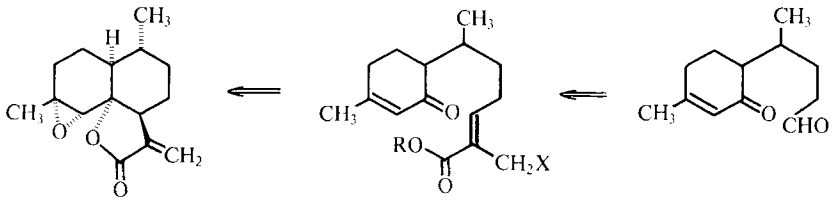
C-atoms are assigned in section 3 and the stereospecificities of the reactions are discussed in section 4.

Scheme 1



I II III

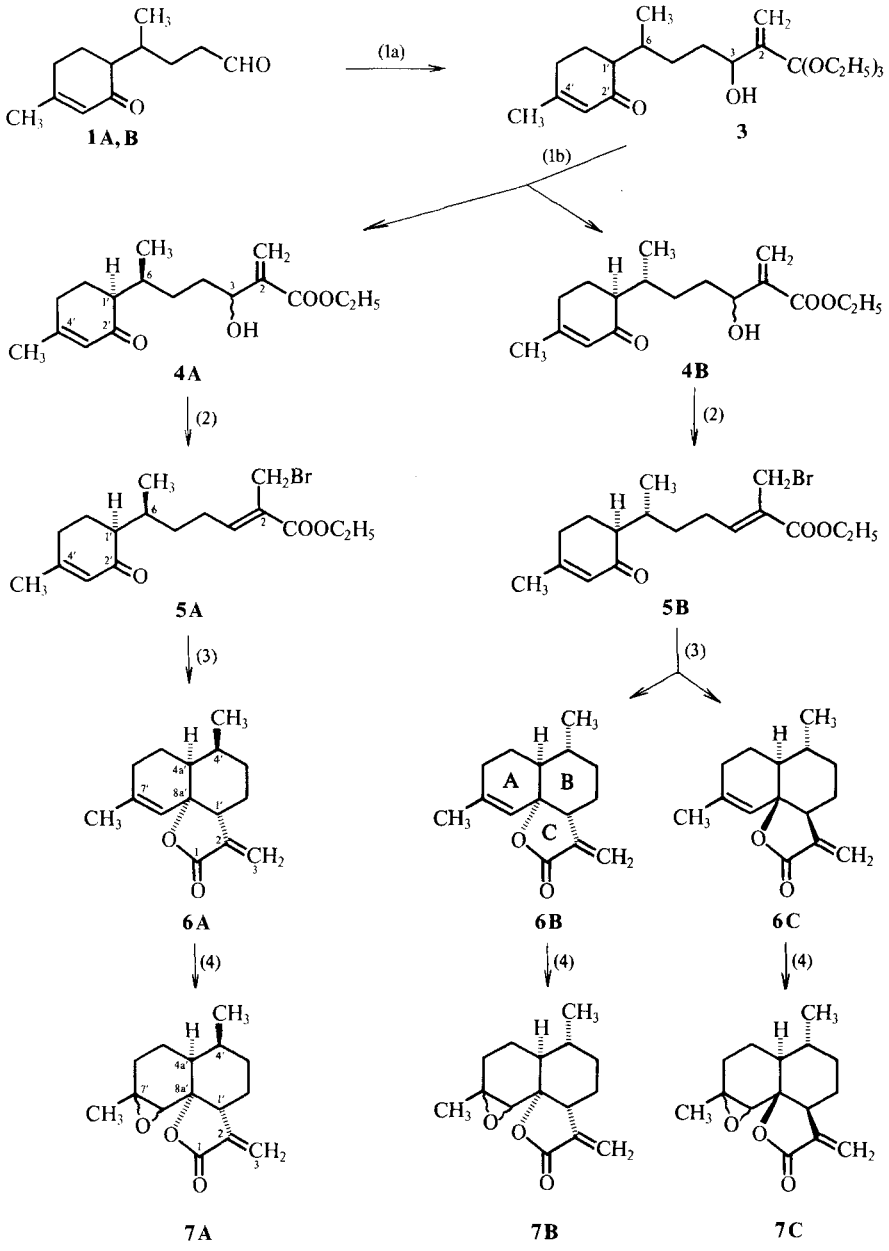
2. Synthetic steps. – Two routes were followed, both according to *Scheme 1*. The first route is illustrated with structural formulae[3]) in *Scheme 2* and the second in *Scheme 3*. In some reactions pure stereoisomers were involved, in others mixtures of stereoisomers were obtained and used. The % figures are isolated yields.

2.1. *Comments to Route 1* (see *Scheme 2*). – *Step 1*. The starting material for this synthesis, the keto-aldehyde **1** [3] [4], was used as a 1:1 mixture of diastereoisomers **A** and **B** because the previously described separation [4] turned out to be difficult on a large scale. The procedure to condense **2** with **1** was analogous to the one described [5]. The hydrolysis of the intermediate hydroxy-keto-orthoester **3** yields a mixture of three or four diastereoisomers of **4**, from which one of the C(3)-epimers of the hydroxy-keto-ester **4A**, was separated (7%). The configuration at C(3) of **4A** and of the other diastereoisomers of **4** was not of importance since the chirality of C(3) disappears in the next step. The remaining mixture (20%) consisted of two or three diastereoisomers, namely the other C(3)-epimer of the hydroxy-keto-ester **4A** and one or both C(3)-epimers of the hydroxy-keto-ester **4B**; the presence of at least two isomers was indicated by two visible doublets for the methyl group at C(6) in the ^{1}H-NMR. spectrum.

Step 2. The substitution of the hydroxyl group of **4** by a Br-atom under the conditions described in [5] [11] involves allylic rearrangement and gives the bromo-keto-ester **5**. Starting with the single diastereoisomer (one C(3)-epimer of **4A**), only the bromo-keto-ester **5A** was isolated (61%); from the mixture of the other diastereoisomers of **4**, on the other hand, a 1:2 mixture of the bromo-keto-esters **5A** and **5B** resulted. The *(Z)*-configuration at C(2) of both **5A** and **5B** is shown by the high δ-value [8] [12] for the H–C(3) triplet in the ^{1}H-NMR.-spectra (7.05 ppm for **5A** and **5A/5B**); the absence of any *(2E)*-isomer is evident from the absence of any signal, in both spectra, between 5.9 (H–C(3′)) and 7.05 ppm. Furthermore, in the ^{13}C-NMR.-spectrum of **5A**, the coupling constant of 7.7 Hz

[3]) The formulae in this paper are meant to represent racemic mixtures (with the exception of **I** for arteannuin B), even though they picture only one enantiomer. When the relative configurations are known, the formulae show the same absolute configuration (*S*) at corresponding C-atoms, namely at C(1′) of **4** and **5** as well as at C(4a′) of **6** and **7**. This configurational standard was also applied to the models given in the *Table* of section 3; it corresponds to the absolute configuration of arteannuin B. A center of unknown configuration (C(3) in **4** and C(7′)/C(8′) in **7**) is shown with a wavy-lined bond; when all configurations are unknown (**1**, **3**, **9** and **10**) only the constitutional formula is used.

Scheme 2



(1a) $CH_2=C(Br)C(OC_2H_5)_3$ (**2**) + butyl lithium,
(1b) Dil. sulfuric acid and ether,
(2) Dimethyl sulfide and *N*-bromosuccinimide,
(3) Zinc/copper couple,
(4) *m*-Chloroperbenzoic acid.

between C(1) and H–C(3) is typical for the vicinal *cis*-arrangement at a double bond [13].

Step 3. The cyclization of the bromo-keto-ester **5** by the intramolecular application [8] [10] of a *Reformatsky*-type reaction [6] [9] gave the desoxy-arteannuin B ring system, namely the lactone **6**, of which eight rac-diastereoisomers are conceivable (see discussion in section 3). From the bromo-keto-ester **5A** only one diastereoisomer of **6**, the lactone **6A**, was isolated (63%). Starting with the 1 : 2 mixture of **5A** and **5B**, a 3 : 4 : 2 mixture of the lactones **6A**, **6B** and **6C** was obtained (67%), from which **6B** could be separated. These ratios and yields show that both **6B** and **6C** were derived from **5B** (45% and 23%, respectively). It was not possible to isolate the lactone **6C** free from **6A**, but those ^{1}H-NMR.-signals of **6C** which were visible in the spectrum of the mixture sufficed to derive its structure.

Step 4. The epoxidation of the lactones **6** under the conditions used here was fully *regio*specific, inasmuch as only the (more highly substituted and non-conjugated) C(7′), C(8)-double bond was attacked, yielding the desired epoxy-lactones **7**. Each of the single diasteroisomers, **6A** resp. **6B**, was converted to a single diastereoisomer, **7A** resp. **7B** (80% and 68%, respectively). The 2 : 1 mixture of the diastereoisomers **6A** and **6B** afforted a 2 : 1 mixture of the diastereoisomers **7A** and **7C** (85%). These ratios and yields indicate that **7C** was derived from **6C**.

Evidently the present epoxidation was also fully *stereo*specific: each of the three lactones **6A**, **6B** and **6C** was attacked by the peracid from only one of the diastereotopic sides of the double bond.

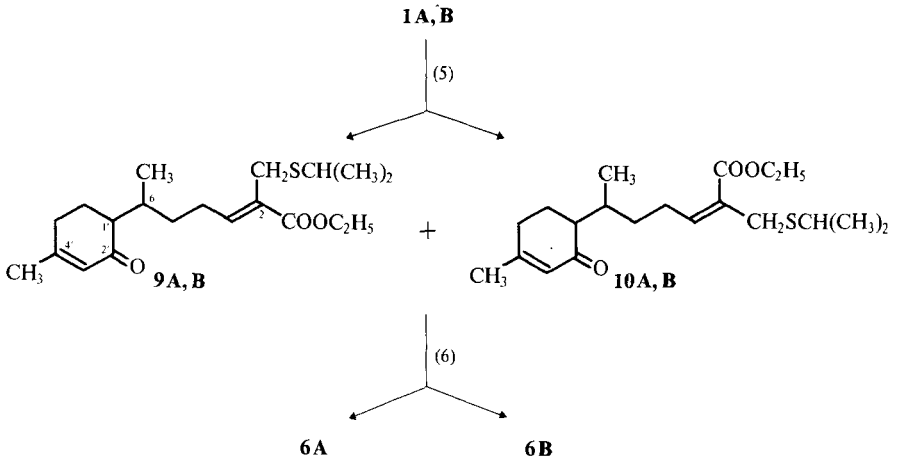
The spectral data of the epoxy-lactones **7A**, **7B** and **7C** did not offer an evident argument for their configuration at the C(7′), C(8′)-double bond, but the high stereospecificity suggests a strongly controlling factor in **6A**, **6B** and **6C**. It is not yet known whether this is the same factor in all three cases. A hypothesis that the lactone O-atom exerts this control appears not to be supported by the results reported in [14]. A purely steric bulk factor favoring attack from the side of the lactone ring can be postulated for **6A** and **6B**, but not, in an evident way, for **6C**.

The 360-MHz ^{1}H-NMR.-spectra of each of the three epoxy-lactones, **7A**, **7B** or **7C**, showed considerable similarity, but also some unmistakable differences, to the one of arteannuin B (**I**, see experimental part and section 3). Clearly neither **7A**, **7B** nor **7C** was racemic arteannuin B.

2.2. *Comments to Route 2* (see *Scheme 3*). *Step 5.* Using NaH in tetrahydrofuran [7], the aldehyde **1A**,**B** was converted to the isopropylthio-keto-ester **9/10** (94%). Chromatography did not separate the stereoisomers, but the ^{1}H-NMR.-signals of H–C(2) in the mixture at δ=6.70 and 5.92 ppm demonstrate the presence of the (2*Z*)-isomer **9** and the (2*E*)-isomer **10** in the ratio of 3 : 1. It was not possible to establish the ratios of the diastereoisomers **A** and **B** in either **9** or **10**, which might have been altered (as compared to the one in **1**) by enolization from C(1′) during the *Wittig* reaction. The ratio of **9** to **10** was not affected by a change of the *Wittig*-reaction conditions (butyl lithium in toluene) in a way as might have been expected by the results of *Semmelhack* [7] [10].

Step 6. Methylation of the mixture of isopropylthio-keto-esters **9/10** at the S-atom and treatment of the crude product with a Zn/Cu couple [8] yielded a separable mixture of the lactones **6A** (24%) and **6B** (58%). These yields suggest

Scheme 3



(5) $CH_2{=}C(COOC_2H_5)PO(OC_2H_5)_2$ (**8**) + $(CH_3)_2CHS^-Na^+(Li^+)$. (6a) FSO_3CH_3. (6b) Zinc/copper couple.

that some epimerization took place at C(1′) along route 2. Since no epimerization had been observed under the *Reformatsky* conditions of route 1 (step 3) it appears likely that it occurred under the *Wittig* conditions of step 5. The configuration of the C(2), C(3)-double bond in **5**, **9** and **10** did not affect the preferred formation of the *cis*-fused lactone moiety during the abnormal *Reformatsky* reaction (steps 3 and 6).

3. Assigment of Relative Configurations. – As mentioned above, neither of the three synthetic epoxy-lactones **7A**, **7B** and **7C** corresponds to racemic arteannuin B (rac-**I**). That none of them differs solely in having the "wrong" configuration of the epoxy-group could be concluded from an analysis of the 360-MHz-^{1}H-NMR. spectra of the isomers of **6** and **7** which show that **7A**, **7B** and **7C** differ from arteannuin B (**I**) in the relative configuration of at least one of the other chirality centers. In fact, certain features of these spectra permitted the deduction of the relative configuration at C(1′), C(4′), C(4a′) and C(8a′) of **7A**, **7B** and **7C**, as well as of **6A**, **6B** and **6C**, utilizing arguments based on the data summarized in the *Table*. This table is subdivided into two parts: part A shows the pertinent ^{1}H-NMR. features of *compounds*, namely the lactones **6A**, **6B**, **6C**, the epoxylactones **7A**, **7B**, **7C** and arteannuin B (**I**); part B shows the corresponding structural aspects and expected properties of diastereoisomer *models* of **6** and **7**.

Three ^{1}H-NMR. criteria were used for the argumentation; they are illustrated in three columns of the *Table*, all of them being based on the *Karplus* relation between coupling constants *(J)* and torsional angles (φ). This was examined: a) between H–C(4′) and three of its vicinal neighbours (H–C(4a′) and 2 H–C(3′)), b) between H–C(1′) and its two vicinal neighbours (2 H–C(2′)), and c) between H–C(1′) and its two allylic neighbours (2 H–C(3)).

Part A of the *Table* shows that the coupling constants – wherever visible – are almost identical in a given lactone (**6A**, **6B** or **6C**) and in the corresponding

Table. *Comparison of some coupling constants observed in the 360-MHz-^{1}H-NMR.-Spectra*[a]) *of the diastereoisomeric lactones* **6** *and epoxy-lactones* **7** (**A**, **B** *and* **C**) *with the ones estimated from models of relatively unstrained conformers of all conceivable diastereoisomers* (**a**–**f**)

A. Compounds	Criterion a: Couplings of H–C(4′) with H–C(4a′) and the two H–C(3′) (Hz)				Criterion b: Couplings of H–C(1′) with the two H–C(2′) (Hz)		Criterion c: Couplings of H–C(1′) with the two H–C(3) (Hz)	
Arteannuin B (**I**)	[b])				3.2	12.5	3.2	3.2
Lactone **6A**	11		4	4	7	8.5	1.8	1.3
Epoxylactone **7A**	11		4	4	7	8.5	1.8	1.3
Lactone **6B**	11.5	11.5	3.5		2	5.5	3.5	3.1
Epoxylactone **7B**	[b])				2	6	3.5	3.1
Lactone **6C**	[b])				[b])	[b])	1.5	1.5
Epoxylactone **7C**	[b])				7	7	1.4	1.4

B. Models	Number of vicinal neighbours of H–C(4′) in the ring		Torsional angle (estimated coupling constant [15]) of H–C(1′) with					
			H(eq)–C(2′)		H(ax)–C(2′)		CH_2=C(2)	
	ap[d])	sc[e])	φ	J(Hz)	φ	J(Hz)	φ	J(Hz)
a	2	1	40°	(6)	160°	(8)	40°	(1–2)
b	0	3	40°	(6)	160°	(8)	40°	(1–2)
c	2	1	60°	(4)	180°	(12)	100°	(3)
d	0	3	60°	(4)	180°	(12)	100°	(3)
	1	2	45°	(6)	165°	(8)	35°	(1–2)
e1	0	3	60°	(4)	60°	(4)	90°	(3)
e2	2	1	60°	(4)	60°	(4)	90°	(3)
f1								
f2	0	3	45°	(6)	165°	(8)	30°	(1–2)

[a]) The chemical shifts of the signals mentioned in this table, as well as the manner in which they were assigned to the protons by selective decoupling, can be found in the experimental description of each compound.
[b]) Signal not separately visible.
[c]) The bond indicated in the formulae with ⟿ is meant to represent a double bond (in **6**) or an oxirane (in **7**).
[d]) ap = antiperiplanar. [e]) sc = synclinal.

epoxylactone (**7A**, **7B** or **7C**). This similarity, together with the configurational identity among the two **A**-isomers, the two **B**-isomers and the two **C**-isomers of **6** and **7**, as demonstrated in section 2, shows that the configuration of the **A**-, the **B**- and the **C**-isomers may be derived from an observation made either on a given lactone **6** or on the corresponding epoxy-lactone **7**, the conclusion always being valid for both.

As candidates for the conformations of the isomers we consider only those in which ring B is in a chair and ring A in a semichair form. The conformational aspects listed in part B of the *Table* were obtained from stereomodels of all these conformations. With the four chirality centers mentioned above, eight rac-diastereoisomers are conceivable. The two ring fusions, namely the A/B- and the B/C-fusion may, in principle, be *trans,trans*, *trans,cis*, *cis,trans* or *cis,cis*. Each of these four doubly ring-fused systems may exist as two C(4′)-epimers.

Inspection of the models shows that two of the diastereoisomers may be eliminated from consideration, namely the two C(4′)-epimers with the *trans/trans* ring-fusion, where a chair/semichair conformation is not possible. The elimination is based on the high strain that would have to be overcome in the lactonization, which *must* be the last stage of the *Reformatsky*-type reaction (steps 3 and 6). Four other diastereoisomers (two C(4′)-epimeric pairs) are characterized by having one *trans* ring fusion (A/B or B/C). Thus, each of them can exist in only one chair/semichair conformation. The four conformers are represented by the models **a**, **b**, **c** and **d**. The remaining two diastereoisomers, **e** and **f** (one C(4′)-epimeric pair), have two *cis* ring fusions and, therefore, may accept two chair/semichair conformations each. They are represented by the models **e1**, **e2**, **f1** and **f2**, with **e1** and **f1** having the methyl group at C(4′) in equatorial and **e2** and **f2** in axial position.

For each of the eight realizable models, part B of the *Table* shows the estimated theoretical values corresponding to the above mentioned three criteria. From criterion a it is immediately evident that the isomers **A** (**6A** and **7A**) correspond to model **e1**, since **e1** is the only model with one ap- (and therefore two sc-) ring neighbour of H–C(4′). The other two criteria agree with this assignment.

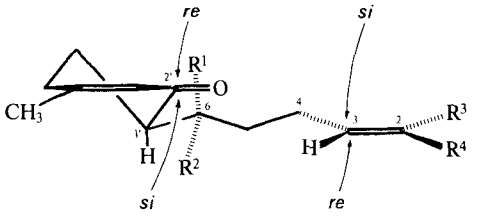
Criterion a, applied to the isomers **B** (visible in **6B**), leaves models **a**, **c** and **f1** as candidates, since they have two antiperiplanar (ap) and one synclinal (sc) ring neighbours of H–C(4′). Criterion b (observed $J = 2$ and 5.5 Hz in **6B** and 2 and 6 Hz in **7B**) confirms the exclusion of model **c** ($J = 4$ and 12 Hz), which had already been assigned to arteannuin B (**I**) [1][2], and also excludes model **a** ($J = 6$ and 8 Hz). Criterion c (observed J with **6B** and **7B** 3.5 and 3.1 Hz) also helps to exclude model **a** ($J = 1$–2 Hz), to which, furthermore, a better assignment is available (see below). Thus **6B** and **7B** correspond to model **f1**. Note that both **6A**/**7A** and **6B**/**7B** exist primarily as the conformers with equatorial methyl groups at C(4′). For the isomers **C** (**6C** and **7C**), only the criteria b ($J = 7$ and 7 Hz, visible in **7C**) and c (observed $J = 1.5$ and 1.5 Hz in **6C** and 1.4 and 1.4 Hz in **7C**) could be used. These values fit only models **a**, **b**, **e1** and **f2**, but the configurations of **e** and **f** have already been assigned (to the isomers **A** and **B**). Of the two remaining models, **a** and **b**, the latter may be excluded, because **6C** is derived from **5B** (see step 3) and thus must have the same configuration at C(4′) as **6B** (model **f1**), which corresponds to **a**, but not to **b**. Thus **6C** and **7C** are represented by model **a**.

The two major synthetic substances, **6A** and **6B**, differ only in the configuration at C(4′) relative (for instance) to that at the angular C-atom (C(4a′)). These two C-atoms are chirality centers already in the precursors, **4** and **5**, where they carry the numbers 1′ and 6, respectively. Since the conversion chains have been established to be **4A** → **5A** → **6A** and **4B** → **5B** → **6B** + **6C**, it can now be concluded that the relative configurations at C(1′)/C(6) of **5A** (also **4A**) and **5B** (also **4B**) correspond to the relative configurations at C(4a′)/C(4′) of **6A** and **6B**, respectively. The configurational conclusions drawn in this section have already been expressed in the formulae of *Scheme 2.*

4. Stereospecificity of the cyclization. – We discuss here the factors which might have influenced the course of steps 3 and 6. Of the six plausible diastereoisomeric lactones with the desoxyarteannuin B constitution **6**, three have been obtained (as racemates) in this work and a fourth one (optically active) corresponds in configuration to natural arteannuin B. All three synthetic isomers, **6A**, **6B** and **6C**, have a *cis*-fused B/C-system, whereas the natural product has this system with a *trans*-fusion. Like the natural product **I**, the two major synthetic substances, **6A** and **6B**, have the A/B *cis*-fusion.

During the cyclization reaction (steps 3 and 6) two new chiral C-atoms are created, namely C(1′) and C(8a′), both being angular C-atoms, the former at the A/B-ring system and the latter at both the A/B- and the B/C-ring system. Since **6A** and **6B** differ only in the relative configuration at C(4′) the preferred cyclization mode is the same in both cases, namely the one leading to *cis*-fusions at both bicyclic systems (A/B and B/C).

The crucial stage of the *Reformatsky*-type reaction controlling the nature of both ring fusions (A/B and B/C) in the product **6** is the bond formation between the olefinic C(3) and the carbonyl C-atom (C(2′)) of the organo-zinc intermediates derived from **5**, **9** or **10**. Each of these two centers, C(3) and C(2′), can participate in bond formation from one of two (locally enantiotopic) sides which we label with *re* and *si* [16] as shown in IV. The four combinations of mutual approach of the two centers, 2′*si*-3*re*, 2′*si*-3*si*, 2′*re*-3*si* and 2′*re*-3*re* lead to the four doubly ring fused systems of **6** with A/B,B/C = *trans*,*trans*, *trans*,*cis*, *cis*,*trans* and *cis*,*cis*, respectively.



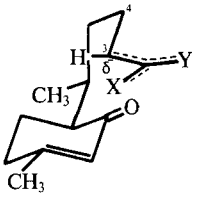
R^1, R^2 = CH_3, H
R^3, R^4 = $COOC_2H_5$, CH_2ZnX

IV

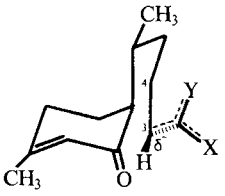
Our results show that C(2′) reacts primarily with the *re*-side, giving the A/B *cis* ring fusion (*cis*-configuration of **6A** and **6B**). Only in the case of the reaction of the bromo-keto-ester **5** (in IV: X = Br) and only with one of its diastereoisomers,

namely **5B** (in IV: $R^1 = CH_3$, $R^2 = H$), does a minor reaction path involve the *si*-side of C(2'), giving the A/B *trans* ring fusion (*trans*-configuration of **6C**). The olefinic C-atom C(3) reacts always with that side, which leads to a product **6** with the B/C *cis*-fusion (*cis*-lactones **6A**, **6B** and **6C**); it is its *re*-side in case of the *re*-attack on C(2'), but the *si*-side in case of the *si*-attack on C(2'). This suggests that the bond formation between C(2') and C(3) takes place *via* a transition state conformation of the C(3), C(4) bond which permits C(2), and the groups R^3, R^4 attached to it, to avoid lying over the cyclohexenone ring. This factor may be the reason that the exclusive *cis*-lactone formation observed in the present case is independent of the configuration at the C(2), C(3) double bond of the starting material (for instance in **9** and **10**). Some *trans*-lactone formation had been reported [8] in the case of an *(E)*-configurated related system.

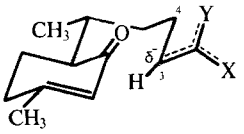
It is of interest to note that the transition states leading to the three observed products **6A**, **6B** and **6C**, when assumed to pass though a pre-chair conformation of the side chain, have the methyl group at C(6) in a pre-equatorial position. This is shown in V to VII.



V



VI



VIII

X, Y = $=CH_2$, $-COOC_2H_5$

This work was supported by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung*. We also thank the *Geigy-Jubiläums-Stiftung* for a fellowship to *J.D.*, *Sandoz AG* for a research grant and *Spectrospin* AG for the high field ^{1}H-NMR.-spectra.

Experimental Part

General remarks. – The abbreviations, notations and instruments used have been described in [17], with the exception of the following modifications or additions: Melting points were determined on a *Mettler*-FP52 apparatus with a microscope. The 360-MHz-^{1}H-NMR. spectra were measured on a *Bruker* HX-360 instrument. The following notation for *selective decoupling* is used here: The numbers [chemical shifts] given in square brackets behind a coupling constant in the description of some ^{1}H-NMR. spectra signify that this coupling was removed on irradiation at the signal of the given chemical shift in ppm. The IR., the 90- and 100-MHz-^{1}H-NMR., the ^{13}C-NMR. and the mass spectra were measured in our laboratories for microanalysis (Mr. *H. Frohofer*), for nuclear magnetic resonance (Prof. *W. von Philipsborn*) and for mass spectrometry (Prof. *M. Hesse*), respectively. The 360-MHz-^{1}H-NMR. spectra were measured at *Spectrospin AG*, Fällanden.

In the title of the following experiments the compounds are named according to IUPAC rules. When the relative configurations are known the R*-convention [18] is used, when it is unknown at a given center no stereochemical descriptor is mentioned there.

1. *Ethyl 3-hydroxy-2-methylidene-6-(4'-methyl-2'-oxo-cyclohex-3'-en-1'-yl)heptanoate* (**4**). To a stirred solution of 2.53 g (10 mmol) of triethyl 2-bromo-orthopropenoate (**2**) in 30 ml of tetrahydrofuran were added, according to the method described in [5], under a N_2-atmosphere, at −75°, 4 ml of ~ 2.5N butyl lithium in hexane (~ 10 mmol). After 30 min, a solution of 1.79 g (9.23 mmol) of 4-(4'-methyl-2'-oxo-cyclohex-3'-en-1'-yl)pentanal (**1**, a 1 : 1 mixture of two diastereoisomers) [4] in 10 ml of tetrahydrofuran was added at the same temperature. After 2.5 h, the solution was allowed to warm up to ambient temperature. Ether and saturated NaCl-solution were added, the aqueous layer was extracted with ether and the combined ethereal solutions were washed with saturated NaCl-solution, dried over $MgSO_4$ and evaporated to give 3.59 g of an oil. According to ^{1}H-NMR. (60 HMz, CCl_4) this oil consisted of *triethyl 3-hydroxy-2-methylidene-6-(4'-methyl-2'-oxo-cyclohex-3'-en-1'-yl)orthoheptanoate* (**3**), contaminated with unreacted keto-aldehyde **1** (a narrow *m* at 9.73 for H–C(1)) and with triethyl orthopropenoate (*m* at 5.4). The available data did not permit an evaluation of the purity of the product **3**, but the following ^{1}H-NMR. signals could be seen: 5.80/br. *s* (H–C(3')); 5.3/*m* (C=CH_2)); 3.45/*qa* (*J* = 7, CH_2 of ethoxy); 1.15/*t* (*J* = 7, CH_3 of ethoxy). The triethyl orthopropenoate and some of the unreacted keto-aldehyde **1** were removed by bulb to bulb distillation at 65°/0.02 Torr, and the residue (3.12 g of crude **3**) was dissolved in 50 ml of ether and stirred with 40 ml of 0.25N aqueous H_2SO_4 during 15 h. The aqueous layer was extracted with ether and the combined ethereal solutions were washed with 5% aqueous $NaHCO_3$-solution followed by saturated NaCl-solution, dried over $MgSO_4$ and evaporated to give 2.66 g of crude **4** as an oil. Column chromatography (silicagel, hexane/ether 2 : 1) yielded a less polar fraction 1, consisting of 190 mg (7%) of one of the C(3)-epimers of the (*1'*R*,*6*R*)-*isomer* **4A** as a colourless oil. – IR. (CCl_4): 3550*w*, 3480*w*, 2960*s*, 2875*m*, 2830*w*, 1715*s*, 1668*s*, 1640*m*, 1380*s*, 1150*s*. – ^{1}H-NMR. (100 HMz, CCl_4): 0.96/*d* (*J* = 7, ~ 3 H, 3 H–C(7)); 1.31/*t* (*J* = 6.5, ~ 3 H, $CH_3$of ethoxy); 1.93/*s* (~ 3 H, H_3C–C(4')); 0.8–2.7/*m* (~ 10 H, 2 H–C(4), 2 H–C(5), H–C(6), H–C(1'), 2 H–C(5') and 2 H–C(6')); 3.2/*m* (1 H, OH); 4.17/*qa* (*J* = 6.5, 2 H, CH_2 of ethoxy); 4.45/*m* (1 H, H–C(3)); 5.76/finely split *s* and 5.83/finely split *s* (2 H, H–C(3') and H(*E*) of methylidene); 6.12/finely split *s* (1 H, H(*Z*) of methylidene). The signals at 5.76 and 5.83 sometimes appear as one multiplet.

The more polar fraction 2 of the chromatography contained 543 mg (20%) of a mixture of two or all of the other three isomers of **4**, including one or both of the C(3)-epimers of **4B**, as a colorless oil. – IR (CCl_4): practically identical to that of **4A**. – ^{1}H-NMR. (CCl_4, 100 MHz): 1.32/*t* (*J* = 7, 3 H, CH_3 of ethoxy); 1.94/*s* (3 H, H_3C–C(4')); 0.7–2.7/*m*, including 0.80/*d* (*J* = 7, 3 H–C(7) of one isomer); 0.95/*d* (*J* = 7, 3 H–C(7) of another isomer); the signal of 3 H–C(7) of the third isomer cannot be seen clearly, 13 H, 3 H–C(7), 2 H–C(4), 2 H–C(5), H–C(6), H–C(1'), 2 H–C(5') and 2 H–C(6'); 3.02/br. *s* (1 H, OH); 4.17/*qa* (*J* = 7, CH_2 of ethoxy) and 4.1–4.6/*m* (H–C(3)) (together 3 H); 5.86/*m* (2 H, H–C(3') and H(*E*) of methylidene); 6.12/br. *s* (1 H, H(*Z*) of methylidene).

2. *Ethyl (2Z)-2-bromomethyl-6-(4'-methyl-2'-oxo-cyclohex-3'-en-1'-yl)-2-heptenoate* (**5**). – a) To a solution of 270 mg (1.5 mmol) of *N*-bromosuccinimide in 2 ml of CH_2Cl_2 was added at 0° a solution of 127 mg (2 mmol) of dimethyl sulfide in 2 ml CH_2Cl_2, followed by a solution of 128 mg (0.44 mmol) of the hydroxy-keto-ester **4A** (as obtained in fraction 1 of experiment 1) in 6 ml of CH_2Cl_2. The mixture was allowed to warm up, stand at RT. for 10 h, diluted with hexane and poured into saturated NaCl-solution. The organic phase was dried over $MgSO_4$ and evaporated to give 185 mg of an oil. Thick plate chromatography (ether/hexane 5 : 4) afforded 95 mg (61%) of the ^{1}H-NMR.-pure (*1'*R*,*6*R*)-*isomer* **5A** as a colourless oil. – IR. (CCl_4): 3040*w*, 2985*m*, 2965*m*, 2940*m*, 2880*m*, 2830*w*, 1720*s*, 1673*s*, 1645*m*, 1280*s* br., 1210*s*, 1178*s* sh, 1162*s*. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 1.03/*d* (*J* = 7, ~ 3 H, 3 H–C(7)); 1.33/*t* (*J* = 7.5, 3 H, CH_3 of ethoxy); 1.98/*s* (~ 3 H, H_3C–C(4')); 1.1–2.8/*m* (~ 10 H, 2 H–C(4), 2 H–C(5), H–C(6), H–C(1'), 2 H–C(5') and 2 H–C(6')); 4.27/*qa* (*J* = 7.5, CH_2 of ethoxy) and 4.27/*s* (CH_2Br) (together 4 H); 5.88/finely split *s* (1 H, H–C(3')); 7.05/*t* (*J* = 7.5, 1 H, H–C(3)). – ^{13}C-NMR. 200.1/*s* (C(2')); 165.3/*s* (C(1)); 161.0/*s* (C(4')); 147.8/*d* (C(3)); 129.2/*s* (C(2)); 126.9/*d* (C(3')); 60.9/*t* (CH_2 of ethoxy); 51.0/*d* (C(1')); 31.2/*d* (C(6)); 24.4/*t* (CH_2Br); 24.1/*qa* (H_3C–C(4')); 17.1/*qa* (C(7)); 14.2/*qa* (CH_3 of ethoxy); further signals at 31.6/*t*, 30.9/*t*, 27.3/*t* and 23.4/*t* corresponded to C(4), C(5), C(5') and C(6') but were not assigned individually. – Irradiation at 4.27 ppm (CH_2Br and CH_2O) converted the signal at 165.3 into *d*, *J* = 7.7. Thus *J*(C(1)/H–C(3)) = 7.7.

b) When the reaction was carried out under the same conditions with 330 mg (1.12 mmol) of the mixture of diastereoisomers of the hydroxy-keto-ester **4** (as obtained in fraction 2 of experiment 1, probable three isomers), 180 mg of a ^{1}H-NMR.-pure 1 : 2 mixture of the (*1'*R*,*6*R*)-*isomer* **5A** and

the (*1'R*,6S**)-*isomer* **5B** was obtained as a colourless oil. This mixture could not be separated on TLC. (ether/hexane 5 : 4). – IR. (CCl_4): practically identical to that of the isomer **5A**. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 0.88/*d* (*J* = 7, 3 H–C(7) of isomer **B**); 1.02/*d* (*J* = 7, 3 H–C(7) of isomer **A**) (together 3 H, ratio 2 : 1); 1.35/*t* (*J* = 7.5, ~3 H, CH_3 of ethoxy); 1.98/*s* (~3 H, H_3C–C(4')); 1.1–2.8/*m* (~10 H, 2 H–C(4), 2 H–C(5), H–C(6), H–C(1'), 2 H–C(5') and 2 H–C(6')); 4.28/*qa* (*J* = 7.5, CH_2 of ethoxy) and 4.28/*s* (CH_2Br) (together 4 H); 5.93/br. *s*, (1 H, H–C(3')); 7.05/*t* (*J* = 7.5, 1 H, H–C(3)).

3. *2-(4',7'-Dimethyl-1',2',3',4',4a',5',6',8a'-octahydro-1'-naphthyl)propen-8a'-olid* (**6**) *from the bromo-keto-ester* **5**. – a) To a solution of 85 mg (0.24 mmol) of the bromo-keto-ester **5A** (as obtained in experiment 2a) in 12 ml of dry THF was added 250 mg of freshly prepared Zn/Cu couple [19]. The mixture was stirred under a N_2-atmosphere during 14 h, filtered through *Celite* and the filtrate was evaporated. The residue was taken up with 20 ml of ether and 10 ml of saturated NH_4Cl-solution. The aqueous phase was extracted with ether and the combined organic solutions were washed consecutively with saturated aqueous NH_4Cl- and NaCl-solutions, dried over $MgSO_4$ and evaporated to give 60 mg of an oil. Thick plate chromatography (hexane/ether 6 : 1) afforded 35 mg (63%) of the ^{1}H-NMR.-pure (*1'R*,4'S*,4a'S*,8a'S**)-*isomer* **6A**, after recrystallization from ether/pentane as a colourless powder, m.p. 86–87°. – IR. (CCl_4): 3015*w*, 2950*s*, 2930*s*, 2870*s*, 2840*m*, 1763*s*, 1675*w*, 1270*s*, 1165*s*, 1140*s*, 970*s*, 938*s*, 915*s*. – ^{1}H-NMR. (360 MHz, $CDCl_3$): 0.96/*d* (*J* = 7.1, 3 H, H_3C–C(4')); 1.17–1.29/*m* (1 H), 1.33–1.46/*m* (3 H) and 1.78–2.12/*m* (6 H), (2 H–C(2'), 2 H–C(3'), H–C(4'), H–C(4a'), 2 H–C(5'), 2 H–C(6')); 1.69/*s* (3 H, H_3C–C(7')); 2.76/*d* × *d* × *d* × *d* (*J* = 8.5, 7, 1.8 and 1.3, 1 H, H–C(1')); 5.19/split *s* (1 H, H–C(8')); 5.47/*d* (*J* = 1.3, 1 H, H–C(3)); 6.10/*d* (*J* = 1.8, 1 H, H–C(3)). – ^{1}H-NMR. (360 MHz, C_6D_6): 0.69/*d* (*J* = 7, 3 H, H_3C–C(4')); 0.78–0.92/*m* (2 H), 0.94–1.15/*m* (2 H); 1.34–1.46/*m* (2 H); 1.48–1.69/*m* (2 H) and 1.80/*d* × *d* × *d* (*J* = 13.5, 3.5 and 3.5, 1 H), (2 H–C(2'), 2 H–C(3'), H–C(4a'), 2 H–C(5'), 2 H–C(6'); 1.39/*s* (3 H, H_3C–C(7')); 1.72/*qa* × *d* × *d* × *d* (*J* = 3 × 7[0.69], 11, 4 and 4, 1 H, H–C(4'); 2.24/*d* × *d* × *d* (*J* = 9, 7, 2 and 1.3, 1 H, H–C(1')); 4.96/*d* (*J* = 1.3[2.24], 1 H, H–C(3)); 5.13/split *s* (1 H, H–C(8')); 6.07/*d* (*J* = 2[2.24], 1 H, H–C(3)). – MS. (70eV): 232 (36, *M*), 217 (5), 204 (12), 189 (11), 188 (24), 187 (6), 176 (23) 173 (18), 171 (6), 161 (18), 160 (17), 159 (13), 147 (13), 146 (10), 145 (17), 137 (60), 135 (12), 134 (14), 131 (16), 128 (10), 123 (13), 122 (36), 119 (17), 117 (13), 115 (11), 111 (10), 110 (100), 109 (26), 107 (12), 105 (21).

$C_{15}H_{20}O_2$ (232.33) Calc. C 77.55 H 8.68% Found C 77.24 H 8.55%

b) To a solution of 176 mg (0.49 mmol) of a 1 : 2 mixture of the diastereoisomeric bromo-keto-esters **5A** and **5B** (as obtained in experiment 2b) in 26 ml of dry THF was added 500 mg of freshly prepared Zn/Cu couple [19]. The mixture was stirred during 14 h and worked up as described in a. The crude oil (122 mg), obtained after evaporation of the ethereal solution, was chromatographed (thick plates, hexane/ether 6 : 1). Elution of the upper part of the less polar band (fraction 1) afforded 20 mg of a 1 : 1 mixture (by ^{1}H-NMR.) of **6A** and the (*1'R*,4'S*,4a'R*,8a'S**)-*isomer* **6C**. – ^{1}H-NMR. (100 MHz, CCl_4): The following signals of **6C** were separately visible: 0.98/*d* (*J* = 7, 3 H, H_3C–C(4')); 1.70/*s* (3 H, H_3C–C(7')); 5.29/split *s* (1 H, H–C(8')); 5.56/*d* (*J* = 1.5, 1 H, H–C(3)); 6.17/*d* (*J* = 1.5, 1 H, H–C(3)). Elution of the lower part of the less polar band (fraction 2) gave 22 mg of a 2 : 1 mixture of **6A** and **6C**. Elution of the more polar band (fraction 3) gave 34 mg (30% of the ^{1}H-NMR.-pure (*1'R*,4'R*,4a'S*,8a'S**)-*isomer* **6B**, after recrystallization from ether/pentane as colourless prisms, m.p. 91–92°. – IR. (CCl_4): 2970*m* sh, 2955*m* sh, 2930*s*, 2875*m*, 2840*w*, 1765*s*, 1670*w*, 1248*s*, 1200*s*, 952*s*, 940*s*, 930*s*. – ^{1}H-NMR. (360 MHz, $CDCl_3$): 0.89/*d* (*J* = 6.6, 3 H, H_3C–C(4')); 1.12/*d* × *d* × *d* × *d* (*J* = 14, 13[1.44], 11.5 and 3.5[2.02], 1 H, H(ax)–C(3')); 1.16–1.21/*m* (1 H) and 1.76–1.97/*m* (4 H), (H–C(4a'), 2 H–C(5'), 2 H–C(6')); 1.28/*qa* × *d* × *d* × *d* (*J* = 3 × 6.6[0.89], 11.5, 11.5 and 3.5[1.44], 1 H, H–C(4')); 1.44/*d* × *d* × *d* × *d* (*J* = 13, 3.5[2.02], 3.5 and 3.5, 1 H, H(eq)–C(3')); 1.69/*d* × *d* × *d* × *d* (*J* = 14[2.02], 14, 5.5[2.80] and 3.5[1.44], 1 H, H(ax)–C(2')); 1.77/*s* (3 H, H_3C–C(7')); 2.02/*d* × *d* × *d* × *d* (*J* = 14, 3.5[1.44], 3.5 and 2[2.80], 1 H, H(eq)–C(2')); 2.80/*d* × *d* × *d* × *d* (*J* = 5.5, 3.5, 3.1 and 2[2.02], 1 H, H–C(1')); 5.25/split *s* (1 H, H–C(8')); 5.43/*d* (*J* = 3.1[2.80], 1 H, H–C(3)); 6.26/*d* (*J* = 3.5[2.80], 1 H, H–C(3)). – MS. (70eV): 232 (73, *M*), 217 (13), 205 (8), 204 (12), 203 (5), 190 (8), 189 (29), 188 (100), 187 (10), 186 (5), 180 (11), 179 (6), 178 (5), 177 (16), 176 (28), 175 (11), 174 (17), 173 (89), 171 (10), 165 (16), 163 (18), 162 (34), 161 (36), 160 (60), 159 (49), 158 (12), 149 (26), 148 (19), 147 (27), 146 (32), 145 (56), 143 (13), 138 (11), 137 (89), 135 (19), 134 (15), 133 (22), 132 (26),

131 (65), 130 (13), 129 (28), 128 (17), 123 (27), 122 (40), 121 (24), 120 (22), 119 (41), 118 (31), 117 (32), 116 (10), 115 (24), 111 (16), 110 (89), 109 (41), 108 (14), 107 (28), 106 (17), 105 (57).

$C_{15}H_{20}O_2$ (232.33) Calc. C 77.55 H 8.68% Found C 77.47 H 8.72%

To summarize experiment 3b, from 59 mg of **5A** and 117 mg of **5B** were isolated 25 mg (22%) of **6A**, 34 mg (30%) of **6B** and 17 mg (15%) of **6C**. Total yield 67%.

4. *2-(7',8'-Epoxy-4',7'-dimethyl-perhydro-1'-naphthyl)propen-8a'-olid* (**7A**). – a) To a solution of 20 mg (0.086 mmol) of the lactone **6A** (from experiment 3a) in 0.5 ml $CDCl_3$ were added 26 mg of *m*-chloro-perbenzoic acid (58% peracid; 0.087 mmol) at RT. Monitoring by ^{1}H-NMR. (signal at 5.19 ppm) showed that the epoxidation was completed after 1 h. The solution was diluted with CH_2Cl_2 and washed consecutively with aqueous 10% $Na_2S_2O_3$-, 5% $NaHCO_3$- and saturated NaCl-solutions, dried over $MgSO_4$ and evaporated to give 22 mg of a colourless solid. Thick plate chromatography (hexane/ether 3 : 1) afforded 17 mg (80%) of the (*1'R*,4'S*,4a'S*,8a'R**)-*isomer* **7A**, after recrystallization from ether/pentane, as colourless powder, m.p. 93–94°. – IR. (CCl_4): 3035*w*, 3020*w*, 2970*s*, 2940*s*, 2880*m*, 2870*m*, 1768*vs*, 1670*w*, 1275*s*, 1150*s*, 980*s*, 948*s*. – ^{1}H-NMR. (360 MHz, $CDCl_3$): 0.90/*d* (*J* = 7.1, 3 H, H_3C–C(4')); 1.05–1.21/*m* (2 H), 1.32–1.47/*m* (3 H), 1.62/*d* × *d* × *d* (*J* = 13, 4 and 4, 1 H), 1.71/*d* × *d* × *d* (*J* = 14.5, 12 and 5, 1 H) and 2.05/*d* × *d* × *d* (*J* = 14.5, 3.5 and 3, 1 H), (2 H–C(2'), H(ax)–C(3'), H–C(4a'), 2 H–C(5'), 2 H–C(6')); 1.36/*s* (3 H, H_3C–C(7')); 1.76/*qa* × *d* × *d* × *d* (*J* = 3 × 7.1[0.90], 11, 4 and 4, 1 H, H–C(4')); 1.93/*d* × *d* × *d* × *d* (*J* = 14, 7[3.17], 5 and 5, 1 H, H(eq)–C(3')); 2.78/*s* (1 H, H–C(8')); 3.17/*d* × *d* × *d* × *d* × *d* (*J* = 8.5, 7, 1.8 and 1.3, 1 H, H–C(1')); 5.60/*d* (*J* = 1.3[3.17], 1 H, H–C(3)); 6.18/*d* (*J* = 1.8[3.17], 1 H, H–C(3)). – MS. (70eV): 248 (15, *M*), 230 (23, $M-H_2O$), 216 (5), 215 (5), 205 (6), 202 (7), 191 (29), 190 (63), 188 (6), 187 (9), 179 (9), 178 (56), 177 (100), 176 (57), 175 (12), 163 (27), 162 (22), 161 (12), 159 (20), 149 (33), 148 (10), 147 (17), 145 (12), 135 (25), 134 (16), 133 (33), 132 (10), 131 (28), 123 (13), 122 (15), 121 (32), 120 (12), 119 (23), 117 (22), 115 (11), 109 (13), 108 (10), 107 (39), 106 (13), 105 (30).

$C_{15}H_{20}O_3$ (248.325) Calc. C 72.55 H 8.12% Found C 72.85 H 8.19%

b) Epoxidation of 11 mg (0.047 mmol) of the lactone **6B** (from fraction 3, experiment 3b) as described in part a of this experiment was completed after 22 h. Thick plate chromatography (hexane/acetone 6 : 11) afforded 8 mg (68%) of the (*1'R*,4'R*,4a'S*,8a'R**)-*isomer* **7B**, after recrystallization from ether/pentane, as colourless needles, m.p. 104–105°. – IR. (CCl_4): 2965*s*, 2940*s*, 2880*m* sh, 1780*vs*, 1672*w*, 1250*s*, 1192*s*, 1143*s*, 1095*s*, 995*s*, 983*s*, 968*s*, 958*s*, 942*s*. – ^{1}H-NMR. (360 MHz, $CDCl_3$): 0.80/*d* (*J* = 6.6, 3 H, H_3C–C(4')); 0,97–1.13/*m* (2 H), 1.49/*d* × *d* × *d* × *d* (*J* = 13.5, 4, 4 and 4, 1 H), 1.54–1.62/*m* (1 H) and 1.65–2.03/*m* (6 H), (2 H–C(2'), 2 H–C(3'), H–C(4'), H–C(4a'), 2 H–C(5'), 2 H–C(6')); 1.37/*s* (3 H, H_3C–C(7')); 2.88/*s* (1 H, H–C(8')); 3.18/*d* × *d* × *d* × *d* (*J* = 6, 3.5, 3.1 and 2, 1 H, H–C(1')); 5.54/*d* (*J* = 3.1, 1 H, H–C(3)); 6.32/*d* (*J* = 3.5, 1 H, H–C(3)). – MS. (70eV): 248 (6, *M*), 231 (11), 230 (50, $M-H_2O$), 220 (6), 219 (9), 215 (18), 205 (8), 203 (6), 202 (21), 201 (6), 191 (20), 190 (52), 189 (5), 188 (12), 187 (19), 185 (6), 179 (8), 178 (44), 177 (55), 176 (32), 175 (15), 174 (13), 173 (11), 172 (8), 171 (6), 164 (11), 163 (52), 162 (100), 161 (14), 160 (15), 159 (33), 150 (36), 149 (37), 148 (11), 147 (25), 145 (22), 144 (18), 136 (11), 135 (42), 124 (24), 132 (23), 131 (33), 129 (12), 124 (18), 123 (18), 122 (29), 121 (15), 120 (30), 109 (11), 108 (13), 107 (43), 106 (13), 105 (33).

$C_{15}H_{20}O_3$ (248.325) Calc. C 72.55 H 8.12% Found C 72.26 H 7.84%

c) Epoxidation of 22 mg of a 2 : 1 mixture of the two diastereoisomeric lactones **6A** and **6C** (from fraction 2 of experiment 3b) (directly the ^{1}H-NMR.-solution) as described in part a of this experiment, was completed after 1 h. (Monitoring by ^{1}H-NMR. showed that **6C** was epoxidized faster than **6A**). Thick plate chromatography (hexane/acetone 6 : 1) afforded 20 mg (85%) of an approximately 2 : 1 mixture of **7A** and the (*1'R*,4'S*,4a'R*,8a'R**)-*isomer* **7C**. – ^{1}H-NMR. (360 MHz, $CDCl_3$): The following signals of **7C** were separately visible: 0.91/*d* (*J* = 7, 3 H, H_3C–C(4')); 1.31/*s* (3 H, H_3C–C(7')); 2.72/*s* (1 H, H–C(8')); 3.01/*d* × *d* × *d* × *d* (*J* = 7, 7, 1.4 and 1.4, 1 H, H–C(1')); 5.65/*d* (*J* = 1.4, 1 H, H–C(3)); 6.25/*d* (*J* = 1.4, 1 H, H–C(3)).

5. *Ethyl* (2Z)- (**9**) *and* (2E)-*2-isopropylthiomethyl-6-(4'-methyl-2'-oxo-cyclohex-3'-en-1'-yl)2-heptenoate* (**10**). To a stirred suspension of 0.42 g sodium hydride (a ~ 57% slurry with mineral oil; ~ 10 mmol) in 75 ml of dry THF was added, under an argon atmosphere, at 0°, 0.76 g (10 mmol) of 2-propanethiol, followed by 2.35 g (10 mmol) of ethyl 2-(diethylphosphono)acrylate (**8**) [7]. After

10 min, a solution of 1.94 g (10 mmol) of the keto-aldehyde **1A,B** (a ~1 : 1 mixture of diastereoisomers **A** and **B**) [4] in 10 ml of THF was added at the same temperature. After 3 h the mixture was allowed to warm up to room temperature and was partitioned between water and ether. The aqueous layer was extracted with ether and the combined ethereal solutions were dried over $MgSO_4$ and evaporated. Bulb to bulb distillation of the residue (180°/0.005 Torr) afforded 3.30 g (94%) of what must be a mixture of four stereoisomers of the thio-keto-ester, namely a pair of (2*Z*)-diastereoisomers, **9A,B**, and a pair of (2*E*)-diastereoisomers, **10A,B**, as a colourless oil. The ^{1}H-NMR.-spectrum was identical to the one of the chromatographed material (see below) and showed a *Z*/*E* isomer ratio of 3 : 1. Chromatography of this distillate over silica gel (ether/chloroform 1 : 1) gave 2.67 g (76%) of the same mixture, without indication of any separation of the stereoisomers. This chromatographed mixture was used for the next reaction and also to determine the following analytical properties. – IR. (film): 2955*s*, 2925*s*, 2865*m*, 2725*w*, 1735–1710*s*, 1667*s*, 1638*m*, 1450*s* br., 1378*s*, 1366*s*, 1324*s*, 1260*s*, 1210*s*, 1094*s*, 1045*s*, 1020*s*, 968*s*. – ^{1}H-NMR. (90 MHz, CCl_4): 1.25/*d* (J = 7, 6 H, $(CH_3)_2CH$); 1.92/*s* (3 H, H_3C–C(4′)); 0.7–1.0/*m* (consisting of several *d* with J = 7, somewhat more than 3 H, probably 3 H–C(7) of 4 isomers); 1.0–2.6/*m* (13 H, 2 H–C(4), 2 H–C(5), H–C(6), H–C(1′), 2 H–C(5′), 2 H–C(6′) and CH_3 of ethoxy); 2.87/*sept* (J = 7, 1 H, $(CH_3)_2CH$); 3.30/split *s* (CH_2–S of (*E*)-isomer), 3.39/br. *s* (CH_2–S of (*Z*)-isomer) (together 2 H, ratio 1 : 3); 4.12/*qa* (J = 7, CH_2 of ethoxy of (*Z*)-isomer), 4.14/*qa* (J = 7, CH_2 of ethoxy of (*E*)-isomer) (together 2 H, ratio 3 : 1); 5.71/br. *s* (1 H, H–C(3′)); 5.92/*t* (J = 7.5, H–C(3) of (*E*)-isomer), 6.70/*t* (J = 7.5, H–C(3) of (*Z*)-isomer) (together 1 H, ratio 1 : 3).

$C_{20}H_{32}O_3S$ (352.54) Calc. C 68.14 H 9.15 S 9.10% Found C 67.69 H 8.81 S 8.65%

Using butyl lithium as base and toluene as solvent and varying the reaction time between 1 and 17 h led to a product, in which **9** and **10** were in the same 3 : 1 ratio, as mentioned above.

6. *2-(4′,7′-Dimethyl-1′,2′,3′,4′,4a′,5′,6′,8a′-octahydro-1′-naphthyl)propen-8a′-olid* (**6**) *from the thio-keto-ester* **9**/**10**. To a solution of 2.04 g (5.78 mmol) of a 3 : 1 mixture of the thio-keto-ester **9** and **10** (obtained from experiment 5) in 80 ml of CH_2Cl_2, under argon, at 0°, in a closed flask, was added 0.67 g (5.86 mmol) of methyl fluorosulfonate all at once. After stirring for 1 h at 0° and 3 h at room temperature, the mixture was concentrated and the residual *S*-methylated product, mixed with 290 ml of THF, was treated with 6.04 g of freshly prepared [19] Zn/Cu couple and stirred under argon at room temperature for 20 h. The mixture was filtered through *Celite*, the filtrate concentrated and the residue partitioned between ether and a saturated NH_4Cl-solution. The organic phase was washed with saturated NaCl-solution, dried over $MgSO_4$ and concentrated to yield 2.00 g of a yellow oil. Fractional column chromatography (for some mixed fractions up to three times) on silicagel with pentane/ether 3 : 1 yielded two fractions, each of which was crystallized in three crops from ether/pentane. From the faster moving fraction was obtained 0.325 g (24%) of the (*1′*R*,*4′*S*,*4a′*S*,*8a′*S*)-*isomer* **6A** as colourless crystals, m.p. 86–87°. The IR.-, ^{1}H-NMR.- and MS.-spectra of this sample were identical with the ones obtained in experiment 3a.

From the slower moving fraction was obtained 0.780 g (58%) of the (*1′*R*,*4′*R*,*4a′*S*,*8a′*S*)-*isomer* **6B** as colourless prisms, m.p. 89–91°. The IR.-, ^{1}H-NMR.- and mass spectra of this sample were identical with the ones obtained in experiment 3b.

7. ^{1}*H-NMR. spectrum of arteannuin B* (**I**) (360 MHz, $CDCl_3$): 0.99/*d* (J = 6, 3 H, H_3C–C(4′)); 1.25/*d*×*d*×*d*×*d* (J = 12.5, 12.5, 12.5 and 3.7[2.06], 1 H, H(ax)–C(3′)); 1.33/*s* (3 H, H_3C–C(7′)); 1.41/*d*×*d*×*d*×*d* (J = 12.5[2.74], 12.5[2.06], 12.5 and 3.2, 1 H, H(ax)–C(2′)); 1.43–1.56/*m* (3 H), 1.63–1.81/*m* (2 H) and 1.84–1.95/*m* (2 H), (H(eq)–C(3′), H–C(4′), H–C(4a′), 2 H–C(5′), 2 H–C(6′)), 2.06/*d*×*d*×*d*×*d* (J = 12.5, 3.7, 3.2[2.74] and 2.5, 1 H, H(eq)–C(2′)); 2.68/*s* (1 H, H–C(8′)); 2.74/*d*×*d*×*d*×*d* (J = 12.5, 3.2, 3.2 and 3.2, 1 H, H–C(1′)); 5.43/*d* (J = 3.2[2.74], 1 H, H–C(3)); 6.15/*d* (J = 3.2[2.74], 1 H, H–C(3)).

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