4. Thermoconversion of Caryophyllene- to Farnesene-Type Sesquiterpenes. Short Access to the Enantiomers of (6*RS*,7*RS*)- and (6*RS*,7*SR*)-6,7-Epoxy-6,7-dihydro-β-farnesenes

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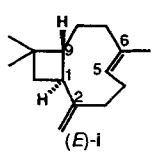
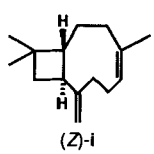
Flash-vacuum thermolysis of the four diastereoisomeric 5,6-epoxy-5,6-dihydro-caryophyllenes **1**–**4** at 500–550°/0.1–0.7 Torr leads to the hitherto unreported enantiomers of (6*RS*,7*RS*)- and (6*RS*,7*SR*)-6,7-epoxy-6,7-dihydro-β-farnesenes ((±)-**5** and (±)-**6**, resp.). In particular, (+)-**5** is formed in 45% yield (*ca.* 90% ee) and is, thus, an attractive chiral building block for natural-product synthesis.

Introduction. – An abundant availability from natural sources [1] and an outstanding propensity for skeletal rearrangement have made caryophyllene ((*E*)-**i** [2]) and its (*Z*)-configurated diastereoisomer, isocaryophyllene ((*Z*)-**i** [3]) highly attractive model compounds for many preparatively useful transformations [4]. In particular, the presence of an α-methylidene-cyclobutane moiety offers direct access to farnesene-type sesquiterpenes (*E*)- and (*Z*)-**ii** *via* thermal cyclobutane fragmentation[1]).



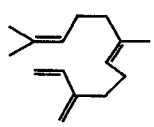
(*E*)-**i**

caryophyllene

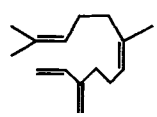


(*Z*)-**i**

isocaryophyllene



(*E*)-**ii**

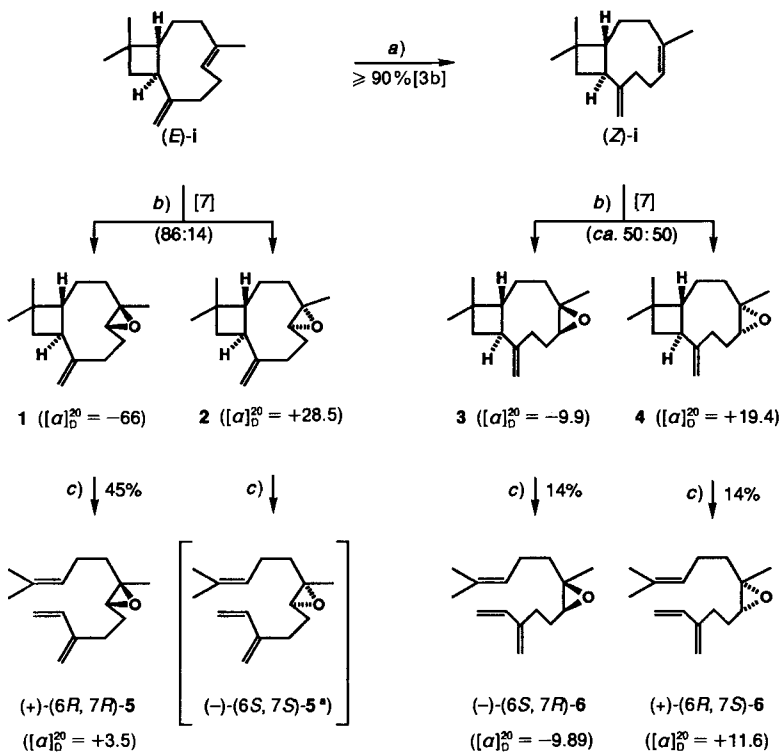


(*Z*)-**ii**

However, previous studies [6] showed that this fragmentation is strongly disfavoured due to the competing, much faster proceeding [3,3]-sigmatropic rearrangement of the 1,5-diene system. *E.g.*, thermolysis of (*E*)- and (*Z*)-**i** at 450° afforded (*E*)- and (*Z*)-**ii** in only 10 and 1% yields, respectively [6]. With a view to improve the synthetic utility of this fragmentation strategy, we now report the thermolysis of the four diastereoisomeric caryophyllene epoxides **1**–**4** (*Scheme*), compounds which are prevented from undergoing [3,3]-sigmatropic rearrangement.

[1]) Formally representing a [2 + 2]-cycloreversion reaction [5].

Scheme



a) Ph_2S_2; toluene, *hv*, N_2. *b*) AcO_2H; CH_2Cl_2, 0°; NaOAc. *c*) Thermolysis conditions according to *Table 1* and *Exper. Part.*

[a]) Obtained together with (+)-**5** (GC analysis) as a 1:1 mixture, since the starting material was **1**/**2** 1:1 and the product had $[\alpha]_D = 0$.

Results and Discussion. – Epoxides **1**, **3**, and **4** were prepared following known procedures [7][2]). The previously unreported epoxide **2**, which was formed together with **1** in a difficultly separable 14:86 mixture [7], was isolated in mg quantities by column chromatography followed by prep. GC, and fully characterized spectroscopically. The thermolyses of **1**, **1**/**2** (1:1), **3**, and **4** were performed employing standard flash-vacuum thermolysis conditions (*ca.* 500–550°, contact time 1–2 s, *cf. Exper. Part*), and the course of reaction was monitored by GC analysis. The results are presented in *Table 1*; product identification was unambiguously effected by spectral analysis. As anticipated, **1**–**4** underwent cyclobutane fragmentation to *β*-farnesene epoxides **5** or **6**, to the exclusion of the alternative pathway involving fragmentation of the cyclobutane ring to 2-methylpropene and 5,6-epoxy-5-methyl-9-methylidenecyclonon-1-ene. Significantly, both **1** and **2** were transformed more efficiently than **3** and **4**. Thus, thermolysis of either **1** or **1**/**2** (1:1)

[2]) Optical purities of *ca.* 90% ee were estimated by comparison with reported values [1].

Table 1. *Flash-Vacuum Thermolysis of Caryophyllene Epoxides* **1–4**

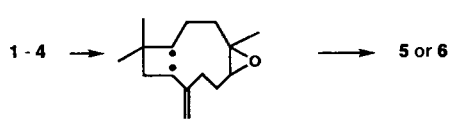
Entry	Starting epoxide	Thermolysis conditions[a])		Yield (total) [%]	Product compositions [%]			
		oven temp. [°C]	number of injections		unreacted epoxide		β-farnesene epoxide	by-products (total)
1	**1**	500	1	96	**1** 75		(+)-**5** 15	6
2	**1**	530	1	92	66		23	11
3	**1**	550[b])	1	89	30		43	27
4	**1**	530	4	74	2		38	60
5	**1/2** (55:45)	500	1	97	**1/2** 35:39		(±)-**5** 20	6
6	**1/2** (55:45)	530	1	94	28:37		26	9
7	**1/2** (55:45)	550	1	90	8:15		46	31
8	**3**	500	1	99	**3** 96		(−)-**6** 1	3
9	**3**	530	1	97	85		6	9
10	**3**	550	1	92	38		20	42
11	**3**	530	4	71	20		20	60
12	**4**	530	3	79	**4** 28		(+)-**6** 18	54

[a]) Contact time *ca.* 1–2 s; internal vacuum 0.1–0.7 Torr.
[b]) Internal vacuum 0.1–2 Torr.

at 500–550°/0.1 Torr (*Entries 1–3* and *5–7*, *Table 1*) afforded respectively epoxides (+)-**5** and (±)-**5** in *ca.* 45% yield, together with several unidentified volatile by-products (*ca.* 25–30% yield[3])). In contrast, under identical conditions, **3** and **4** were incompletely converted (70–80% conversion) to epoxides (+)-**6** and (−)-**6**, respectively, in only 20% yield with increased amounts of by-products (42–60% yield) (*Entries 8–12*, *Table 1*). Complete conversion could be achieved by repeated thermolysis but resulted in a reduced yield.

This decrease in yield was also apparent when thermolysis temperatures exceeded 550°. For this reason, to prepare gram quantities of pure β-farnesene epoxides, the thermolyses were run at 50–60% conversion. Fractional distillation and chromatography then provided samples of (+)-**5**, (−)-**6**, and (+)-**6** in high chemical and optical purity. Isolated chemical yields of (+)-**5** and (±)-**5** attained 45% whilst, in contrast, the yields of (+)- and (−)-**6** never exceeded 14%.

A plausible explanation for the high selectivity with regard to the fragmentation pathway may be due to the additional ring strain caused by the annulated nine-membered ring; thus, the weakened cyclobutane C(1)–C(9) bond preferentially cleaves to generate the intermediate 1,4-diradical **iii**.



iii

[3]) The by-products were not individually analysed. However, spectroscopic examination of several distillation fractions revealed the presence of allyl alcohols, ketones, and aldehydes, evidently originating from isomerisation of the epoxy group [1] [4] [8].

The higher reactivity of **1** compared to **3** is consistent with molecular-mechanics calculations. Thus, the geometrical parameters for the transition state of the conversion of cyclobutane to ethylene, *via* a 1,4-biradical, calculated by *ab initio* methods [9] [10], were added to the MM2* force field of *MacroModel* [11]. In this manner, the strain energies of the two transition states, **1** → (+)-**5** and **3** → (−)-**6**, were estimated. *Table 2* summarises these calculations which show that, whereas the ground state of **3** is more stable than that of **1** by *ca.* 4 kJ/mol, the transition state for **1** → (+)-**5** is 6 kJ/mol lower in energy than the transition state for **3** → (−)-**6**. It follows that the activation energy for the thermolysis of **1** is favoured by *ca.* 10 kJ/mol.

Table 2. *MM2* Energies* [kJ/mol] *of the Ground States of* **1** *and* **3** *and the Transition States Leading to (+)-***5** *and (−)-***6**, *Respectively*

	Ground state	Transition state	Difference
1	229.1	276.5	47.4
3	224.9	282.5	57.6

The same conclusion can also be drawn by inspecting the relative stabilities of *cis*- and *trans*-cyclononene and *cis*- and *trans*-cycloundecene [12]. For cyclononene, the *cis*-isomer is more stable by 16 kJ/mol, whereas this order is reversed for cycloundecene where the *trans*-isomer is marginally favoured by 2.5 kJ/mol. In the thermolysis of **1** and **3** where the transition states partially resemble a 11-membered ring, it is thus logical that the higher release in strain for **1** increases the reactivity of this diastereoisomer.

We are indebted to Dr. *C. Chapuis* and Dr. *B. Maurer* for helpful discussions.

Experimental Part

1. *General.* GC: *Varian 3400*, megabore column *DB-5* (30 m) and *Stabilwax* (30 m); *Hewlett-Packard 5890*, capillary column *Supelcowax* (50 m) and *SPBJ* (30 m). Prep. GC: *Varian Auto 700* (prep.), glass column packed with *Carbowax 20M*, 15% on *Chromosorb W* (3 m). ^{1}H- (360 MHz) and ^{13}C-NMR (90.5 MHz): *Bruker-WH-360* instrument; in $CDCl_3$ solns. with Me_4Si (= 0.00 ppm) as internal standard; *J* in Hz. MS: *Finnigan-MAT* quadrupole instrument coupled with a GC; electr. energy *ca.* 70 eV; fragment ions *m/z* in % of the most abundant peak.

2. *Starting Materials.* Commercially available caryophyllene ((*E*)-**i**; GC purity *ca.* 99%; $[\alpha]_D^{20} = -11$; *Fluka*) was used. Isocaryophyllene ((*Z*)-**i**; GC purity ⩾ 98%; $[\alpha]_D^{20} = -22.6$ (EtOH)) was obtained from (*E*)-**i** by Ph_2S_2-catalysed isomerisation [3b] (yield ⩾ 90%). Known epoxidation of (*E*)-**i** and (*Z*)-**i** [7] [13] gave **1**/**2** (86:14) and **3**/**4** (50:50), resp. Separation by crystallisation (hexane) afforded **1** (m.p. 61°; $[\alpha]_D^{20} = -66$ ($CHCl_3$)) and **3** (m.p. 71°; $[\alpha]_D^{20} = -9.9$ (EtOH)), while GC separation of the mother liquors gave **2** as an oil in mg quantities ($[\alpha]_D^{20} = +28.5$ (EtOH); 80% enriched) and **4** as an oil in g quantities ($[\alpha]_D^{20} = +19.4$ (EtOH); 100% pure). Except for **2**, all epoxides were previously characterised spectroscopically.

Data of (5S,6S)-5,6-Epoxy-5,6-dihydrocaryophyllene (= (1R,5S,6S,9S)-5,6-Epoxy-4,11,11-trimethyl-8-methylidenebicyclo[7.2.0]undecane; (+)-**2**): Oil, *ca.* 80% pure. $[\alpha]_D^{20} = +28.5$ (EtOH). ^{1}H-NMR: 0.97, 1.00, 1.25 (3*s*, 9 H); 3.1 (*dd*, *J* = 2, 12, 1 H); 4.99, 5.11 (2*s*, 2 H). ^{13}C-NMR: 152.7 (*s*); 112.1 (*t*); 61.1 (*d*); 60.8 (*s*); 53.9 (*d*); 47.1 (*d*); 42.3 (*t*); 36.6 (*t*); 36.3 (*t*); 33.1 (*s*); 29.9 (*q*); 29.6 (*t*); 27.7 (*t*); 22.6 (*q*); 21.7 (*q*). MS: 220 (1, M^+), 205 (2), 202 (1), 187 (4), 177 (6), 159 (8), 149 (13), 131 (21), 121 (34), 105 (50), 93 (87), 79 (100), 69 (88), 55 (51), 41 (73).

3. *Flash-Vacuum Thermolysis of Isomeric 5,6-Epoxycaryophyllenes* **1**–**4**. 3.1. *General Procedure.* The thermolysis oven used (model *Firmenich SA*; inner volume 26 × 16 × 45 cm) was equipped with a quartz tube (length 4.2 cm, ∅ 28 mm), a dropping funnel heated to 100°, and an outlet trap cooled to −80° and connected to a vacuum line.

The thermolysis temperature was 500–550° (±1° adjustable) and the inner pressure maintained at *ca.* 0.7 mbar. Retention time *ca.* 1–2 s. The quartz tube was neutralised before use by treatment with a NaH_2PO_4/Na_2HPO_4 1:1 aqueous buffer soln. The caryophyllene epoxide (**1**, **3**, and **4** pure; **2** as a *ca.* 1:1 mixture **1/2**) were introduced dropwise at 100°. The collected thermolysates were chromatographed (silica gel, CH_2Cl_2/petroleum ether (b.p. 30–50°)) and, if necessary, further separated by GC to give the pure *β-farnesene epoxides* (= *6,7-epoxy-7,11-dimethyl-3-methylidenedodeca-1,10-dienes*) (+)-**5**, (±)-**5**, (−)-**6**, and (+)-**6**.

3.2. *(+)-(6R,7R)-6,7-Epoxy-6,7-dihydro-β-farnesene* ((+)-**5**). Thermolysis of **1** (35 g) at 550° yielded a product (30 g) containing (+)-**5** (43% by GC). Chromatographic separation gave pure (+)-**5** (16 g, 45%). $[\alpha]_D^{20} = +3.5$ ($CHCl_3$). ^{1}H-NMR: 1.25 (*s*); 1.61 (*s*, 3 H); 1.68 (*s*, 3 H); 5.03, 5.04 (2*s*, 2 H); 5.07 (*d*, *J* = 10.8, 1 H); 5.24 (*d*, *J* = 18, 1 H); 6.38 (*dd*, *J* = 10.5, 18, 1 H). ^{13}C-NMR: 16.7 (*Me*−C(7)); 17.7 (C(12), *cis* to C(9)); 23.9 (C(5)); 25.7 (*Me*−C(11), *trans* to C(9)); 27.5 (C(9)); 28.2 (C(4)); 38.8 (C(8)); 60.9 (C(7)); 63.3 (C(6)); 113.4 (C(1)); 116.1 (CH_2=C(3)); 123.8 (C(10)); 131.9 (C(11)); 138.9 (C(2)); 145.5 (C(3)). MS: 220 (0, $M^{+\cdot}$), 202 (1), 159 (2), 138 (8), 123 (11), 109 (29), 95 (45), 79 (73), 69 (100), 55 (41), 41 (91).

3.3. *(±)-(6RS,7RS)-6,7-Epoxy-6,7-dihydro-β-farnesene* ((±)-**5**). At 530°, **1/2** 1:1 (5 g) was thermolysed to afford a thermolysate (4.8 g) from which (±)-**5** (2.2 g, 45%) was isolated by chromatography. $[\alpha]_D^{20} = 0$ ($CHCl_3$). Spectra: identical with those of (+)-**5**.

3.4. *(−)-(6S,7R)-6,7-Epoxy-6,7-dihydro-β-farnesene* ((−)-**6**). At 520–530°, **3** (7.6 g) was thermolysed 3 times to give a product (*ca.* 4 g) containing (−)-**6** (*ca.* 20%). Chromatographic and GC purification afforded (−)-**6** (200 mg). $[\alpha]_D^{20} = -9.9$ (EtOH). ^{1}H-NMR: 1.30 (*s*, 3 H); 1.60 (*s*, 3 H); 1.68 (*s*, 3 H); 5.04, 5.06 (2*s*, 2 H); 5.09 (*d*, *J* = 10.8, 1 H); 5.11 (*m*, 1 H); 5.25 (*d*, *J* = 18, 1 H); 6.39 (*dd*, *J* = 10.8, 18, 1 H). ^{13}C-NMR: 17.6 (C(12), *cis* to C(9)); 22.3 (*Me*−C(7)); 24.1 (C(5)); 25.7 (*Me*−C(11), *trans* to C(9)); 27.3 (C(9)); 28.3 (C(4)); 33.0 (C(8)); 61.0 (C(7)); 64.6 (C(6)); 113.4 (C(1)); 116.0 (CH_2=C(3)); 123.8 (C(10)); 132.0 (C(11)); 138.7 (C(2)); 145.6 (C(3)). MS: 220 (0.5, $M^{+\cdot}$), 202 (1), 187 (2), 159 (3), 138 (14), 123 (15), 109 (25), 93 (41), 79 (63), 69 (100), 55 (30), 41 (59).

3.5. *(+)-(6R,7S)-6,7-Epoxy-6,7-dihydro-β-farnesene* ((+)-**6**). At 530°, **4** (11.7 g, purity 87%; $[\alpha]_D^{20} = +19.4$ (EtOH)) was thermolysed 3 times to yield a product (9.3 g) containing (+)-**6** (2.1 g, 18%). A pure sample of (+)-**6** was available by prep. GC: $[\alpha]_D^{20} = +11.6$ (EtOH). Spectra: identical with those of (−)-**6**.

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