16. A Novel Entry to the Eremophilane and Valencane Sesquiterpenes *via* a Stereoselective Intramolecular *Diels-Alder* Reaction

Preliminary Communication

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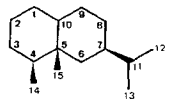
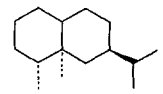
Summary

A general stereoselective entry to racemic eremophilane and valencane sesquiterpenes, *via* a common key intermediate and using an intramolecular *Diels-Alder* reaction, is described.

The main problem of total synthesis of eremophilane/valencane sesquiterpenes[1-4]) is stereochemical: the four chiral centres of the basic saturated skeleton give rise to eight diastereoisomeric pairs of enantiomers. Both eremophilanes and valencanes possess *cis* vicinal methyl groups, and the isopropyl group in the eremophilanes is *cis* relative to the *vic* methyl groups and *trans* in the valencanes. Although the majority of the naturally occurring eremophilanes and valencanes do not have a chiral tetrahedral C(10)-bridgehead, there are examples of the *cis*-decalineremophilanes.



eremophilane



valencane

We now describe a stereoselective route to the key intermediate **8** and demonstrate its usefulness for the total synthesis of either (±)-eremophilane or (±)-valencane sesquiterpenes.

Aldol condensation of ketoacid **3** (obtained from **1** [4] by carbethoxylation and subsequent saponification) with aldehyde **4** [5] (4–5 h at RT., no solvent) gave the expected hydroxyacid (characterized by NMR., configuration unknown)

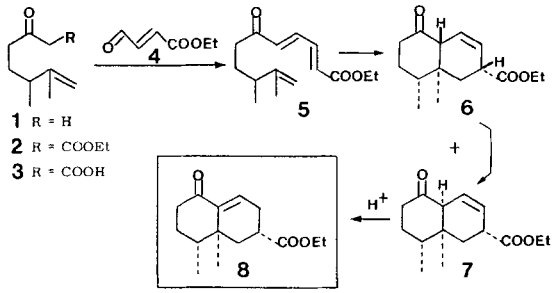
[1]) For the definition of the valencane and eremophilane skeleton used in this paper, see [1].

[2]) For simplicity, the eremophilane/valencane numbering (see first formula) is retained for all decalins throughout the publication.

[3]) For a general account of sesquiterpene total synthesis, see [2].

[4]) For a recent review of eremophilane and valencane sesquiterpenes, see [3].

which was, without purification, directly subjected to decarboxylative dehydration by dimethylformamide dimethyl acetal [6–8] (mixing at 0°, 2 h at 48° in petroleum ether) to furnish the crystalline (*E, E*)-trieneketoester **5**[5]) (39% yield; m.p. 39–40°). On heating (6 h at 250° in toluene), triene **5** underwent an intramolecular *Diels-Alder* reaction to give, depending on the purity of the starting material, either a 1:1 mixture of *trans*-1-oxo-octahydronaphthalene **6**[6]) and his *cis*-isomer **7**[7]), or only *cis*-isomer **7** by very rapid C(10)-epimerization of the unstable primary *Diels-Alder* product **6**. The combined yield of **6**+**7** varied with dilution, ranging from 54% (10% solution) to 93% (0.6% solution). Subsequent acid-catalyzed isomerization (~0.2% TsOH · H_2O in toluene, 3 h under reflux) of **7** (or **6**+**7**, 1:1 mixture) afforded the key intermediate **8**[8]) (90% yield).



The observed stereoselectivity of the intramolecular *Diels-Alder* reaction is fully reconciled by assuming transition state **A** (leading to **6**) being preferred to **B** or other alternatives. In both **A** and **B** the secondary methyl groups are in the more stable, equatorial position, the alternative, axial position leading to unfavourable, 1,3-diaxial H/CH_3 interactions. The preference of transition state **A** over **B** is not well understood at the moment; steric crowding at the transition state may account for it. The exclusive formation of a *trans*-isomer in a comparable intra-

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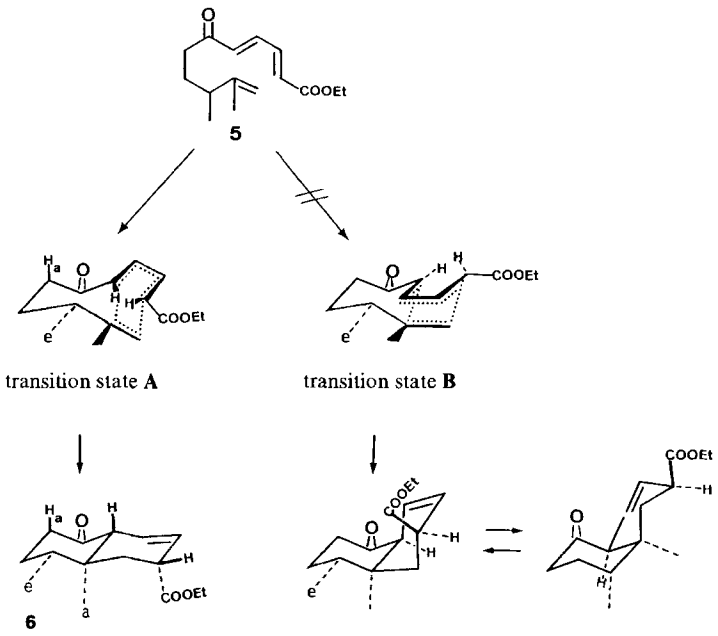
5) IR. (neat): 3060, 1715, 1690, 1595, 997, 890 cm^{-1}. – ^{1}H-NMR. (360 MHz, $CDCl_3$): δ=1.04 (*d*, *J*=7 Hz, CH–CH_3); 1.32 (*t*, *J*=7.5 Hz, O–CH_2–CH_3); 1.65 (*s*, =C–CH_3); 1.68 (*d*×*t*, J_1=7 Hz, J_2=7.5 Hz, CH_2); 2.19 (*t*×*qa*, J_1=7.0 Hz, J_2=7.5 Hz, CH_2–CH–CH_3); 2.53 (*t*, *J*=7.5 Hz, CH_2–CH_2–CO–); 4.24 (*qa*, *J*=7.5, O–CH_2–CH_3); 4.69 and 4.73 (2*s*, =CH_2); 6.23 (*d*, *J*=15 Hz, CH=CHCOO, *trans*); 6.44 (*d*, *J*=15 Hz, CH=CHCO, *trans*); 7.16 (*d*×*d*, J_1=15 Hz, J_2=11 Hz, CH=CH–CH=); 7.31 (*d*×*d*, J_1=15 Hz, J_2=11 Hz, =CH–CH=CH) ppm.

6) For characterization by ^{13}C-NMR., see *Table*.

7) IR. (neat): 1730, 1710 cm^{-1}. – ^{1}H-NMR. (360 MHz, $CDCl_3$): δ=0.88 (*s*, $\geqslant$C–CH_3); 0,94 (*d*, *J*=7 Hz, CH–CH_3); 1.29 (*t*, *J*=7.5 Hz, O–CH_2–CH_3); 2.74 (narrow *m*, =CH–CH–CO–); 3.17 (broad *m*, =CH–CHCOO–); 4.18 (*qa*, *J*=7.5 Hz, O–CH_2–CH_3); 5.48 (*m*, =C(8)–H); 5.94 (*m*, =C(9)–H) ppm. Irrad. at 0.94 ppm → 2.03 (*d*×*d*, $J_{a,a}$=13 Hz, $J_{a,e}$=4 Hz, C(4)–H_a) ppm. – ^{13}C-NMR.-data, see *Table*. – MS.: *m/e*=250 (45, *M*), 177 (100), 204 (83), 93 (79), 43 (75).

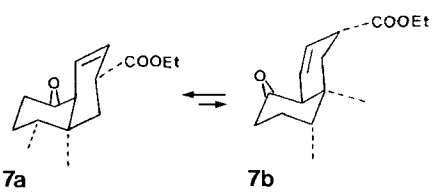
8) IR. (neat): 1725, 1688 cm^{-1}. – ^{1}H-NMR. (360 MHz, $CDCl_3$): δ=0.88 (*s*, $\geqslant$C–CH_3); 0.98 (*d*, *J*=6.5 Hz, CH–CH_3); 1.28 (*t*, *J*=7 Hz, O–CH_2–CH_3); 4.15 (*qa*, *J*=7 Hz, O–CH_2–CH_3); 6.26 (*d*×*d*, J_1=3 Hz, J_2=5 Hz, =CH–) ppm. – Irrad. at 0.98 ppm → 1.89 (*d*×*d*, $J_{a,a}$=12 Hz, $J_{a,e}$=4 Hz, C(4)–H_a) ppm. – ^{13}C-NMR.-data, see *Table*. – MS.: *m/e*=250 (48, *M*), 177 (100), 31 (58), 43 (43), 121 (34).



molecular *Diels-Alder* reaction, leading to eudesmane sesquiterpenes[9]), was recently reported by *Wilson & Mao* [9].

The primary *Diels-Alder* product, *trans*-isomer **6**, however, is not stable under our reaction conditions for the 1,3-interaction of the angular methyl group with the ester substituent, and epimerizes at the most acidic position, C(10)–H, to the more stable *cis*-isomer **7**.

The configuration of **8** (and its precursors **6** and **7**) was established by spectroscopic methods and chemical connections with two independent, known products (**9a** [10] and **10a** [11]). ^{13}C-NMR.-data of **6**, **7** (conformation **7a** preferred) and **8** (see *Table*) allowed the relative configuration at the centres C(4), C(5) and C(10) to be assigned, the main argument being (1) the shift differences $\Delta\delta = 15{,}7$ ppm for the methyl group between *cis*- and *trans*-methyldecalin, (2) the γ-gauche-effect imposed by the C(4)-methyl upon C(3) (9 ppm) [17]. The *cis*-configuration of the *vic* methyl groups in **7** (preferred configuration **7a**) was further corroborated by the 360 MHz ^{1}H-NMR. spectra showing, after irradiation



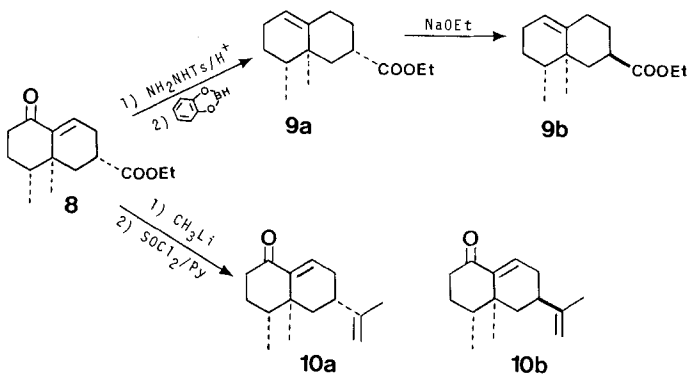
9) 

Table. ^{13}C *shifts* (at 90.55 MHz, in ppm rel. to TMS) of **6**, **7** and **8** (~20% in $CDCl_3$) [12][2])

	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	C(11)	C(14)	C(15)
6	209.1	40.7	31.4	41.2	39.8	35.7	38.9	(123.6)[a])	(124.5)	56.1	174.9	14.6	11.3
7	212.7	39.3	30.1	30.1	38.1	35.6	39.5	(126.1)	(126.4)	59.7	173.5	14.8	20.8
8	203.4	39.9	28.5	38.4	39.0	36.9	36.3	26.9	128.7	146.5	174.9	15.4	19.8

[a]) Similar values in parantheses may be inversed.

at H_3C–C(4), the typical couplings for an axial hydrogen at C(4) ($J_{a,a}$ = 13 Hz; $J_{a,e}$ = 4 Hz). Since the spectra did not allow conclusive configurational assignment of centre C(7) in **6**, **7** and **8**, key intermediate **8** was linked with two independent intermediates of known configuration. Firstly, **8** was selectively transformed *via* its tosylhydrazone into *Coates*'s all-*cis*-ester **9a** [10] (55% yield based on **8**) using *Kabalka*'s catecholborane reduction of tosylhydrazones [13]. Our sample of **9a** was identical in all respectes with the original sample kindly provided by Prof. *Coates*. As the all-*cis*-ester **9a** underwent complete isomerization (NaOEt/ETOH, 45 min at 80°) into the more stable C(7)-epimer **9b** [10], the *cis*-relationship between the substituents at C(5) and C(7) in **8** and its progenitors **6** and **7** is firmly proved.



Secondly, **8** upon treatment with 5 equiv. of methyllithium, followed by dehydration ($SOCl_2$/pyridine, 15 min at 0°) of the alcohol intermediates (not characterized) gave, as main product, *Ziegler*'s compound **10a** [11] together with a little of its C(7)-epimer **10b** [11] (~50% yield of **10a/b** based on **8**). Since the less stable isomer **10a** with its isopropyl group *cis* to the *vic* methyl groups, was formed as main product, the starting ester must be assigned configuration **8**.

Our new, stereoselective route to **8**, a compound already stereoselectively transformed by *Coates et al.* [10] into racemic eremoligenol, eremophilene, valerianol, and valencene, therefore offers a new stereoselective total synthesis of these sesquiterpenoids. In addition, our new access to *Ziegler*'s eremophilone intermediate **10a** also opens an alternative (±)-eremophilone total synthesis.

The authors are much indebted to Professor *F.E. Ziegler*, Yale University, for copies of the ^{1}H-NMR. spectra of **10a** and **10b**, and to Professor *R.M. Coates*, University of Illinois, for a sample of **9a** and for the spectra of **9a** and **9b**. We should also like to acknowledge the courtesy of Dr. *W. Hoffmann, BASF AG*, Ludwigshafen, for providing us with a generous sample of 5,6-dimethyl-6-hepten-2-one (**1**), our starting material.

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