3-Oxiranylprop-2-enals as Synthetic Building Blocks. A Facile Route to (±)-Aucantene and Other Selectively Functionalized Cyclohexenes

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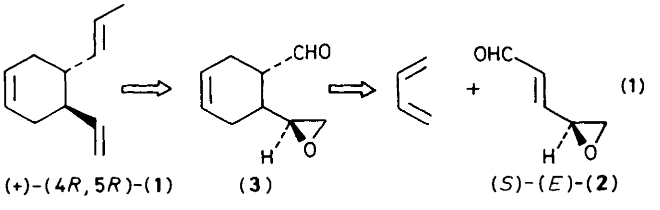
[4 + 2]Cycloadditions of 1,3-dienes to the title compounds lead in one step to functionalized cyclohexenes with predictable stereochemistry, thus providing the basis for a route to (±)-aucantene in three steps with an overall yield of 63%.

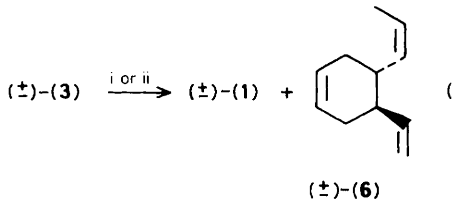
(+)-(4*R*,5*R*)-4-[(*E*)-prop-1-enyl]-5-vinylcyclohexene (+)-(**1**) (aucantene) was isolated several years ago from C_{11}-hydrocarbons produced by the marine brown algae *Cutleria multifida*.[1] Both (±)- and (+)-(**1**) have been synthesized previously in overall yields of 4% and 1%, respectively.[2,3] Owing to incomplete stereocontrol in either the construction of the (*E*)-side chain or the *trans*-substitution pattern on the cyclohexene ring, mixtures of diastereoisomers were always obtained, requiring tedious g.c. separations in the final steps.

Retrosynthetic analysis reveals that the basic skeleton of (+)-(**1**) with correct stereochemistry and a suitable substitution pattern should be accessible in one step by [4 + 2] cycloaddition of (*E*)-3-oxiranylprop-2-enal (*E*)-(**2**) to buta-1,3-diene (equation 1). This also implies that a diastereoselective reaction, using enantiomerically pure (*S*)-(*E*)-(**2**) could lead to the natural enantiomer (+)-(**1**).

Both (±)-(*E*)- and -(*Z*)-(**2**) are readily accessible in multimolar quantities. [4 + 2]Cycloaddition of $^1O_2$ to cyclopenta-1,3-diene produces, by thermal rearrangement of the intermediate endoperoxide, (*Z*)-(**2**), which can be transformed easily into (*E*)-(**2**) by base catalysed isomerisation.[4,5] With three chemically very different functional groups in an array of only five carbon atoms, these molecules are clearly highly attractive synthetic building blocks. Probably owing to difficulties in handling these sensitive compounds, however, their potential has so far been exploited only in a limited number of cases and just three examples of their [4 + 2] cycloadditions are known.[4,5b,c]

We have now found that under carefully controlled conditions a whole series of 1,3-dienes, including buta-1,3-diene





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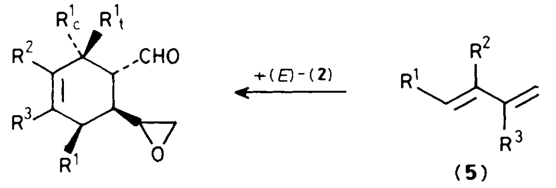
Reagents: i, $Ph_3P{=}CHMe$; KSeCN; *hν*, PhSSPh; ii, Me_3SiI; $Ph_3P{=}CHMe$.

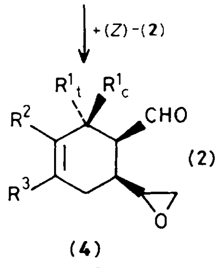


(**3**)

a; R^1, R^2, R^3 = H
b; R^1, R^2 = H, R^3 = Me
c; R^1, R^3 = H, R^2 = Me
d; R^1 = H, R^2, R^3 = Me
e; R^1_t, R^1, R^2, R^3 = H, R^1_c = Me
f; R^1_c, R^1, R^2, R^3 = H, R^1_t = Me
g; R^1_c, R^1_t, R^2, R^3 = H, R^1 = Me

(**5**)

a; R^1, R^2, R^3 = H
b = c; R^1, R^3 = H, R^2 = Me
d; R^1 = H, R^2, R^3 = Me
e = f = g; R^1 = Me, R^2, R^3 = H



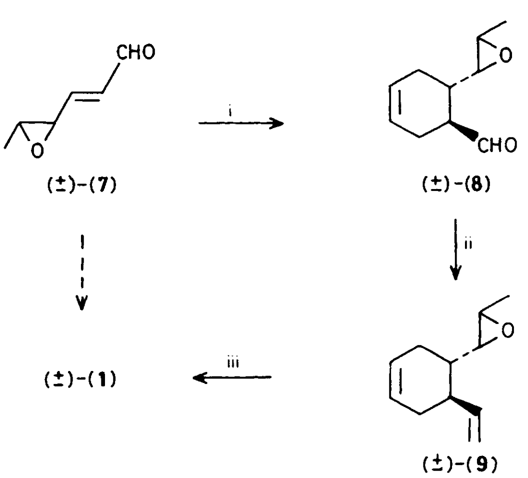
(**4**)

a; R^1, R^2, R^3 = H
b; R^1, R^2 = H, R^3 = Me
c; R^1, R^3 = H, R^2 = Me
d; R^1 = H, R^2, R^3 = Me
e; R^1 = Me, R^2, R^3 = H

Table 1. [4 + 2]Cycloadditions of (*E*)- and (*Z*)-(**2**) to 1,3-dienes[a]

Dienophile	Diene (5)	Method[b]	Product	% D.e.[c]	Yield/%
(*E*)-(**2**)	(**5a**)	A	(**3a**)	0	77
	(**5b**) = (**5c**)	A	(**3b,c**)[d]	0	80
	(**5d**)	A	(**3d**)	0	73
	(**5e**) = (**5f,g**)	A	(**3e**)[e]	0	85
			(**3f**)[e]	23	
			(**3g**)[e]	14	
(*Z*)-(**2**)	(**5a**)	A	(**4a**)	50	70
	(**5b**) = (**5c**)	A	(**4b,c**)[f]	36	76
	(**5d**)	A	(**4d**)	45	70
		B	(**4d**)	55	95
	(**5e**)	A	(**4e**)	33	79
		B	(**4e**)	33	95
		C	(**4e**)	36	88

[a] Since racemic (*E*)- and (*Z*)-(**2**) are used mixtures of diastereoisomers are always produced. [b] A: Neat, 90 °C, 70 h; B: toluene, room temperature, 24 h, 7 kbar; C: toluene, room temperature, 5 h, 7 kbar. [c] % D.e. refers to the excess of one diastereoisomer over the other. [d] (**3b**) : (**3c**) 1.85 : 1. [e] (**3e**) : (**3f**) : (**3g**) 3.4 : 1.5 : 1. [f] (**4b**) : (**4c**) 3 : 1.



Scheme 1. *Reagents and conditions:* i, buta-1,3-diene, sealed tube, 90 °C, 70 h, 92%; ii, Ph$_3$P=CH$_2$, −78 °C, 82%; (iii) Me$_3$SiCl, NaI, MeCN, room temp., 83% (ref. 8).

itself, can be transformed readily and with remarkably good yields into the corresponding cyclohexene derivatives (equation 2).

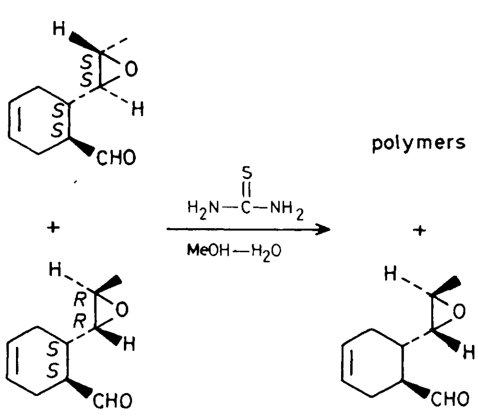
In typical experiments 5 g (51 mmol) of (*E*)- or (*Z*)-(**2**) were mixed with 75 mmol of the corresponding 1,3-diene in a glass ampoule. After addition of 50 mg of hydroquinone the ampoules were sealed and heated in an oil bath at 90 °C for 70 h, after which the products were isolated by distillation. Some representative results are shown in Table 1.

Previous n.m.r. studies had revealed that, in order to minimize side products and polymerisations, the reaction temperature had to be limited to 90 °C with extended reaction times. These times can be shortened considerably by the application of high pressures (7 kbar),[6] leading to near quantitative yields of cycloadducts at ambient temperatures. Typically, 0.5 g (5 mmol) (*E*)- or (*Z*)-(**2**), 7.5 mmol of 1,3-diene, 5 mg hydroquinone, and 0.1 ml toluene were mixed and sealed under argon in a Teflon tube, for pressurization in an autoclave at 7 kbar.[7] This procedure proved to be particularly useful in cycloadditions with the thermally less stable (*Z*)-(**2**).

The obtained cycloadducts are useful starting materials for cyclohexene derivatives and (**3a**) was the obvious choice for the synthesis of (±)-(**1**). Formally, (*E*)-selective construction of the side chain, followed by deoxygenation would lead to (±)-(**1**) in only two steps (equation 3).

All attempts, however, to introduce the (*E*)-side chain 100% stereospecifically [i, Wittig reaction (Ph$_3$P=CHMe), followed by deoxygenation (KSeCN) and photochemical isomerisation (*hν*, PhSSPh); ii, deoxygenation (Me$_3$SiI),[8] (*E*)-directed Wittig reaction[9]] were unsuccessful and at best 3 : 1-mixtures of (±)-(**1**) and the corresponding (*Z*)-diastereoisomer (±)-(**6**) were obtained.

From these results it became clear that the (*E*)-side chain, masked or unmasked, had to be introduced first. This problem was finally solved satisfactorily by employing (*E*)-3-(3-methyloxiranyl)prop-2-enal, (±)-(**7**),† using the same strategy (Scheme 1).



(4)

[4 + 2]Cycloaddition of (±)-(**7**) to buta-1,3-diene, followed by Wittig reaction of (±)-(**8**) and deoxygenation of (±)- (**9**), produced isomerically pure (±)-(**1**) in an overall yield of 63% (compared with the previously obtained 4% yield[2]).

Using racemic starting materials, (±)-(**3a**) (*cf.* Table 1) and (±)-(**8**) are produced as diastereoisomers (*ca.* 1 : 1), one of which can be selectively removed by treatment of the product mixture with thiourea in methanol–water (equation 4). It should therefore also be possible to prepare (+)-(**1**) by employing enantiomerically pure (*S*)-(*E*)-(**7**).

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† Compound (±)-(**7**) was prepared by epoxidation of but-2-enal[10] and subsequent Wittig reaction with Ph$_3$P=CHCHO.[11]