A New Synthesis of Functionalized 6,8-Dioxabicyclo[3.2.1]octanes

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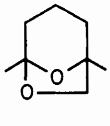
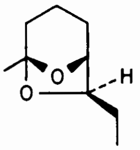
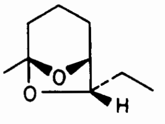
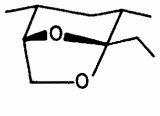
Functionalized 6,8-dioxabicyclo[3.2.1]octanes are prepared efficiently in two steps from aldehydes and methyl vinyl ketone.

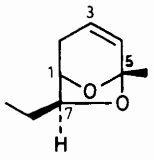
The 6,8-dioxabicyclo[3.2.1]octane moiety constitutes the basic framework of a number of pheromones, *e.g.* frontalin (**1**), *exo*- and *endo*-brevicomin (**2**) and α-multistriatin (**3**). These bicyclic compounds play a decisive role in the chemical signal system of bark beetles and other insects and are used on a large scale in traps for the protection of forests.[1] Recently, the related 3,4-dehydrobrevicomin (**4**) has been identified in urine of the male house mouse and has been shown to be an aggregation pheromone.[2a] Other natural products containing a 6,8-dioxabicyclo[3.2.1]octane skeleton include bullerone[2b] and palytoxin.[2c]


(1) (racemic)


(+)-*exo*-(**2**)


(+)-*endo*-(**2**)


(3)



(4)

We now report an efficient and versatile route to functionalized 6,8-dioxabicyclo[3.2.1.]octanes. Coupling of aldehydes with methyl vinyl ketone (**6**) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) gave the β-ketoallyl alcohols (**7**),[3—5]† which were purified by distillation at reduced pressure and then heated in a high-boiling aromatic hydrocarbon to afford the bicyclic compounds (**9**) in good yields (see Table 1) and in a remarkably clean reaction. On prolonged standing at room temperature, (**9**) was also formed from the neat alcohols (**7**).

Our synthesis of 6,8-dioxabicyclo[3.2.1]octanes involves several bond-making steps, and a possible sequence for the last stage is shown in Scheme 1. Whilst the functionalized THP-ether (**7bα**) (THP = tetrahydropyran-2-yl) did not give (**9b**), the other unprotected allyl alcohols (**7a—e**) did. In these

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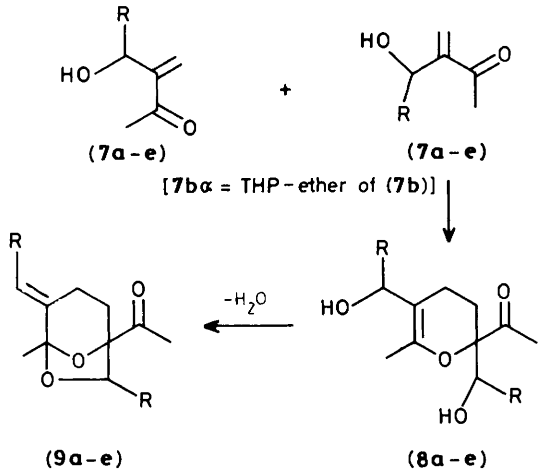
† (**7a**) was obtained from methyl vinyl ketone and paraformaldehyde in tetrahydrofuran, in the presence of a catalytic amount of DABCO at 80 °C. In place of paraformaldehyde, aqueous formaldehyde was also used, at a lower temperature and with better yields.

Table 1. Representative 6,8-dioxabicyclo[3.2.1]octanes (**9a**—**e**) prepared.

	R	Experimental conditions	Epimeric ratio[a]	Isolated yield [%]
(**9a**)	H	Sealed tube, toluene, 120 °C, 10 h		54
(**9b**)[b]	Me	Sealed tube, neat, 140 °C, 10 h	1.7 : 1	69
		benzene, reflux, 5 days	1.5 : 1	62
		xylene, reflux, 2 days	1.5 : 1	85
		room temp., 43 days	1.7 : 1	7
(**9c**)	Et	Benzene, reflux, 6 days	~1.7 : 1	44[c]
(**9d**)	$PhCH_2CH_2$	6—8 °C, 1 yr	2.8 : 1	8
		benzene, reflux, 64 h	2.7 : 1	50[c]
(**9e**)	Me_2CHCH_2	Benzene, reflux, 4 days	3.4 : 1	80
		6—8 °C, 1 yr	3.4 : 1	9

[a] In the major isomer the group R (R ≠ H) at C(7) has the *endo*-configuration. [b] *Spectral data* for (**9b**) ^1H n.m.r. (200 MHz, $CDCl_3$): *endo*-isomer (major): 1.38 (d, *J* 6.5 Hz, 3H, 7-*endo*-Me), 1.62 (d, *J* 7 Hz, 3H, =C–Me), 1.66 (s, 3H, Me), 2.26 (s, 3H, COMe), 1.6—2.7 (m, 4H, 2 CH_2), 3.97 (dq, *J* 1.5 and 6.5 Hz, 1H, 7-H), 5.55 (m, 1H, =CH); *exo*-isomer (minor): 1.1 (d, *J* 6.5 Hz, 3H, 7-*exo*-Me), 1.61 (d, *J* 7 Hz, 3H, =C–Me), 1.67 (s, 3H, Me), 2.27 (s, 3H, COMe), 1.6—2.7 (m, 4H, 2 CH_2), 4.35 (q, *J* 6.5 Hz, 1H, 7-H), 5.55 (m, 1H, =CH). [c] The reaction was halted with recovery of the starting material.



Scheme 1

cases, intermolecular‡ loss of water occurred, presumably *via* a second reactive allylic alcohol such as (**8**). A single configuration was found around the C=C double bond in products (**9b**—**e**). Previous experience with the generation of allylic cations from numerous precursors[6] suggests that this bond has the *E*-configuration.

The other group R at C(7) was found in both the *exo*- and *endo*-configurations. Thanks to the presence of the bridgehead acetyl group, the 400 MHz spectrum for (**9c**) was first order for the C(7)–H proton, as illustrated in Figure 1. The downfield signal due to the *endo*-7 H proton showed two ^3J couplings (2.8 and 10 Hz) from the diastereotopic methylene protons. In contrast, the upfield signal showed ^3J 4 and 9.2 Hz, and also ^4J 1.4 Hz (W-coupling,§ *exo*-7 H, major isomer).

Similarly clear splitting patterns were recorded for the series (**9b**—**e**). The major isomer is therefore the *endo*-substituted epimer, the minor isomer the epimer with *exo*-R group, which eclipses the neighbouring acetyl group.

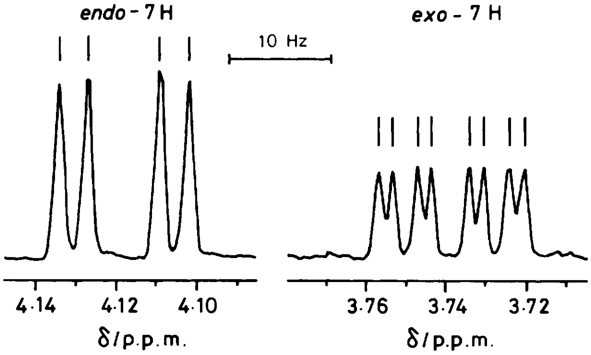


Figure 1. The C(7)–H region of the n.m.r. spectrum of (**9c**).

In conclusion, the new synthesis of functionalized 6,8-dioxabicyclo[3.2.1]octanes *via* intermolecular dehydrative double cyclization of β-ketoallyl alcohols creates a high degree of molecular complexity in two simple stages. Overall, several bonds are being broken, while five σ-bonds and one π-bond are formed. The bicyclic compounds can be built up with a variety of substitution patterns, including functional differentiations of the bridgehead positions.

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‡ For the *intra*molecular dehydration of β-ketoallyl alcohols (**7**) see ref. 3.

§ The ^1H n.m.r. spectrum of the structurally related *endo*-brevicomin [*endo*-(**2**)] is necessarily more complicated, but the signal of the C(7)–H proton also shows long range coupling (^4J ~1 Hz). We thank Professor W. Francke for this information.