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DIASTEREOSELECTIVE SYNTHESIS OF BICYCLO[2.2.2]OCTANES BY DOUBLE MICHAEL ADDITION

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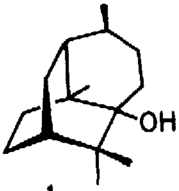
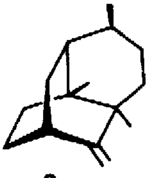
Abstract - Several chiral acrylates (**7b-f**) react with kinetically controlled generated lithium dienolate **6a** to form chiral bicyclo[2.2.2]octanes **4** with modest d.e.. It was found, that the diastereoselection is improved, when the corresponding trimethylsilyl ether **6b** reacts with chiral acrylates under Lewis acid catalysis. The absolute stereochemistry of these bicyclo[2.2.2]octanes was determined by X-ray analysis.

The classical essential oil fragrance Patchouli from Pogostemon spp. contains (-)-patchoulol (**1**) and (-)-seychellene (**2**). These tricyclic sesquiterpenes have been synthesized as racemates from the common intermediate **3**[1], previously made from functionalized bicyclo[2.2.2]octane **4**.



1



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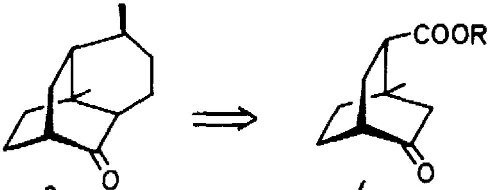
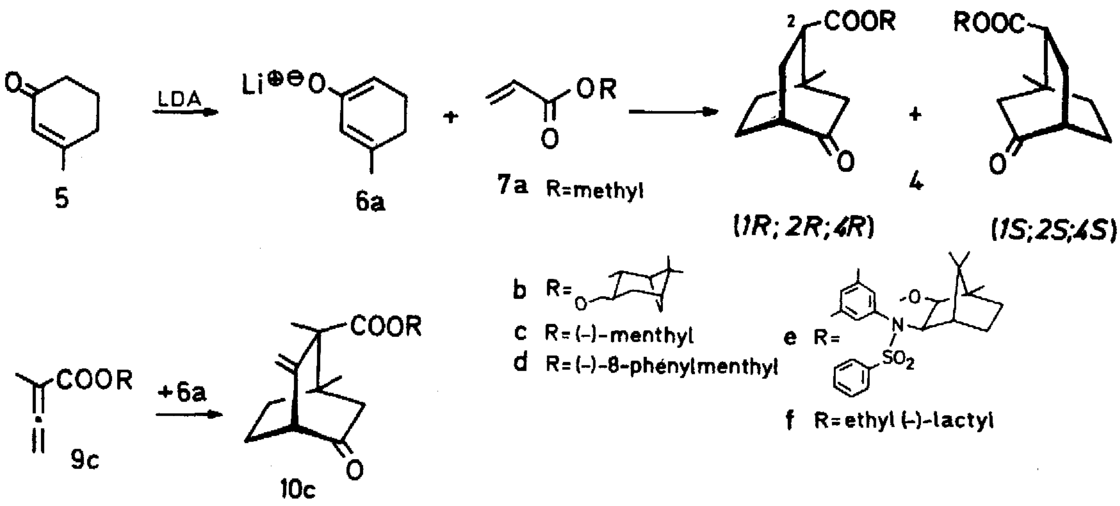


3 **4**

We used the double Michael addition sequence[2] for the construction of this bicyclo[2.2.2]octane. This reaction leads exclusively to endo-**4**. The alternative, thermal [4+2]-cycloaddition of diene **6b** with acrylate **7a** gives invariably 1:1 endo/exo mixtures of **4**. Both methods offer chiral induction by using chiral acrylates.



Chiral acrylates **7b-f** and 2,3-pentadienoate[3] **9c** were prepared by standard literature procedures and reacted with dienolate **6a** to give the expected adducts in good yield (70-90%) and high endo selectivity (>95%) (table 1).

Table 1: Double Michael addition of **6a** with chiral acrylates **7**

Acrylate	bicyclo[2.2.2]octane	yield	endo/exo	d.e.
7b	4b	67	>95/<5	10
7c	4c	71	>95/<5	33
7d	4d	91	>95/<5	50
7e	4e	80	>95/<5	64
7f	4f	90	>95/<5	50
9c	10c	75	>95/<5	0

The diastereomeric excess (d.e.) was estimated by ^{1}H-NMR, but the bicyclo[2.2.2]octanes **4d** and **4e** were separated by chromatography on silica gel (Kieselgel 60, Merck, Darmstadt; mobile phase: pentane - diethylether) directly or after ketalization with ethylene glycol (**4f**). The major diastereomer (1S;2S;4S)-**4d** crystallized from pentane (m.p. 89 °C), and its structural parameters and absolute stereochemistry were determined by X-ray diffraction (Fig. 1).[4]

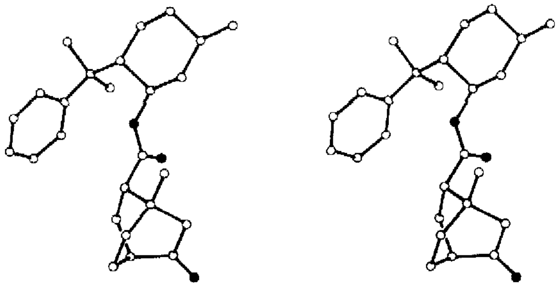
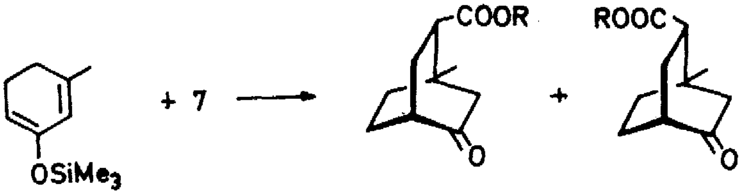


Fig. 1. Stereographical plot of the molecular structure of (1S;2S;4S)-**4d** (space group $P2_1$)

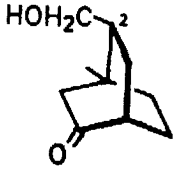
It is worth mentioning that in the crystal the phenyl ring lies on the former *Si* face of the acrylate unit, which may had taken a *cisoid* rather than the energetically more stable *transoid* conformation in the transition state, thus directing the double Michael addition to the *Re* face. The consequence is the (1S;2S;4S) stereochemistry for the major bicyclic adduct **4d**. Protection of the ketone group, reductive removal of the (-)-8-phenylmenthyl[5] group, and acidic work-up gave alcohol (1S;2S;4S)-**8**. This alcohol has a positive optical rotation $[\alpha]_D^{23}$ = + 55.5° (c 0.6, $CHCl_3$). Similarly, the enantiomeric alcohol (1R;2R;4R)-**8** has $[\alpha]_D^{23}$ = - 55° (c 0.5, $CHCl_3$).[6] The camphor derived auxiliar in **7e**[7] gave the best result (d.e. 64 %) which is, however, only marginally better than the (S)-lactate derivative **7f** (d.e. 50 %). Acrylate **7f** forms distinct complexes with the Lewis acids $TiCl_4$ and Et_2AlCl.[8] The topology of the $TiCl_4$-**7f** complex allows the Diels-Alder addition to occur preferentially on the *Si* face of the *cisoid* acrylate unit due to the shielding of the *Re* face by a chlorine atom. We found a similar behavior of these complexes in the double Michael reaction of silyldienolether **6b** with the chiral acrylate **7f** (table 2).



6b

(*endo*)-4

(*exo*)-4



(*1S;2S;4S*)-8

The *endo*/*exo*-**4f** ratio (3:1) was better than in the experiment without catalysts, however generally lower than in the reaction of dienolate **6a** with the same acceptors. The absolute stereochemistry of *exo*-**4f** has not yet been determined.

Table 2: Reaction of Lewis acid-**7f** complexes with **6b**

Et_2AlCl	(2.5 eq.)	76	4/1	47	(1S;2S;4S)
$TiCl_4$	(1 eq.)	85	3/1	83	(1R;2R;4R)

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6. Further experiments are facilitated since the 2,2,2-trifluoroethylurethane of (±)-**8** is easily separated by capillary gas chromatography using XE-60-L-val-(R)-α-pea as a chiral phase. We thank Professor W.A. König, Hamburg, for this experiment (W.A. König "The practice of enantiomer separation by capillary gas chromatography", Heidelberg: Hüthig, **1987**, 48).

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