286. Asymmetric Induction in *Diels-Alder* Reactions to Acrylates Derived from Chiral *sec*-Alcohols

Preliminary Communication[1])

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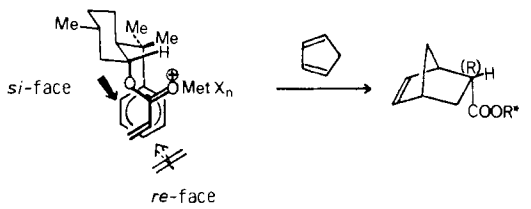
Summary

Starting from the enantiomerically pure monoterpenes (+)-pulegone (**3**), (+)-limonene (**7**), (−)-β-pinene (**9**), (+)- and (−)-camphor (**13**) or (+)-cholestenone (**11**) the chiral alcohols **4**, **5**, **6**, **8**, **10**, **12**, **14**, **15**, **16**, **17** et **18** were prepared; their acrylates **II** underwent a $TiCl_4$-promoted *Diels-Alder* addition to cyclopentadiene *(Scheme 3, Table)* giving in a predictable manner either the (2*R*)- or the (2*S*)-adducts **III** with 63 to 88% asymmetric induction.

Further development of enantioselective C,C-bond-formation by *Diels-Alder* reactions remains a formidable challenge to the organic chemist despite recent progress in this field involving either chiral dienophiles [1] [2], dienes [3][2]), or *Lewis*-acid catalysts [5]. Thus, the acrylate **II** of (−)-8-phenylmenthol (**4**), first reported by *Corey & Ensley* [2a], adds to cyclopentadiene in the presence of $TiCl_4$ to give the (2*R*)-norbornene **III** with ~90% asymmetric induction [6]. By analogy to the model proposed for intramolecular ene-type reactions of 8-phenylmenthyl enoates [7] this

Scheme 1



[1]) Presented by one of us *(W.O.)* at the 11th Northeast Regional Meeting of the American Chemical Society, Rochester, Oct. 19, 1981.

[2]) For an asymmetric intramolecular *Diels-Alder* reaction where the chirality-directing unit is attached to the chain which links the reaction partners see [4].

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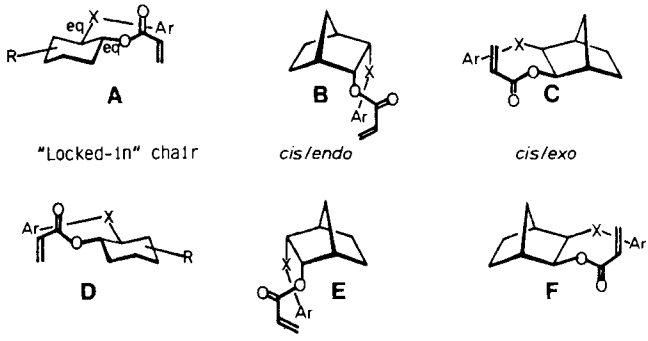
stereochemical control agrees with an acrylate conformation where the ester-carbonyl group is antiplanar with the olefinic C,C-bond and synplanar with the alkoxy-C,H-bond *(Scheme 1)*. Accordingly the phenyl ring of the ester unit shields the C(*α*)-*re* face by π,π-orbital overlap probably even more effectively in the presence of an appropriate *Lewis* acid[3]) thereby directing the diene addition to the dienophile-*si*-face. However, the need to purify the oily auxiliary alcohol (−)-**4** by careful medium-pressure chromatography and the difficult access to the more interesting[4]) enantiomer (+)-**4** seriously limits its applicability in organic synthesis. Nevertheless, the encouraging chiral induction observed with (−)-8-phenylmenthyl acrylate [2a] [6], together with the above rationalisation served as a starting point for the design of more versatile and effective chiral auxiliary alcohols.

As an ultimate goal we aimed at the preparation and use of such alcohols which *1)* lead to quantitative asymmetric induction in addition reactions to their acrylates, *2)* are easily accessible from inexpensive precursors in both antipodal forms or as an equivalent pair of *si*- and *re*-face directing isomers, *3)* may be purified by crystallization and *4)* are recovered easily after induction of chirality has been achieved. Apparent options include cyclohexanols which are locked in a rigid chair conformation with both equatorial hydroxyl group and an *α-trans* positioned aryl-substituted chain, as well as norbornanols carrying these crucial functionalities either in a *cis/endo* or *cis/exo* relationship. Accordingly, the *si*-face directing acrylates **A**, **B** and **C** and their *re*-face directing counterparts **D**, **E** and **F** may be schematically envisaged *(Scheme 2)*. Our first steps towards this goal are sum-

Scheme 2



marized in *Scheme 3* and in the *Table*. To prepare the cyclohexanols **4**, **5**, **6**, **8**, **10**, **12** and the norbornanols **14**, **15** and **18**[5]) the steric position of the aryl-substituted chain was controlled by a base-induced equilibration of the corresponding cyclohexanones which then were reduced with sodium or lithium in 2-propanol [8].

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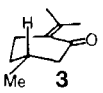
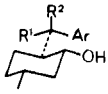
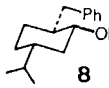
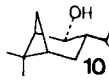
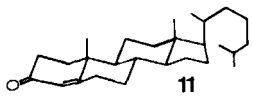
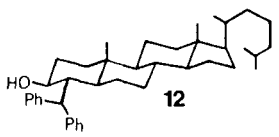
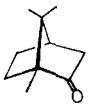
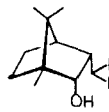
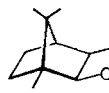
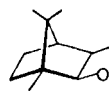
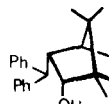
[3]) In the ^{1}H-NMR. spectra the *trans*-H–C(*β*)-signal of 8-phenylmethyl acrylate is shifted upfield by 0.32 ppm in $CDCl_3$, and by 0.85 ppm in $CDCl_3$ containing 1 mol-equiv. of $TiCl_4$, compared to that of menthyl acrylate.

[4]) See for example the enantioselective synthesis of prostaglandins [2a].

[5]) All new compounds were characterized by IR., ^{1}H-NMR. (360 MHz) and mass spectroscopy.

Table. *Preparation of the chiral alcohols* **I** *and asymmetric induction in cycloadditions of their acrylates* **II → III**

Starting material	Preparation	Auxiliary alcohol **I** R*OH, m.p. (°C)	*Endo*-adduct **III** Config.	e.e.%
 **3** (+)-Pulegone	a	 **4** $R^1=R^2$=Me, Ar=Ph **5** $R^1=R^2$=Me, Ar=pOMe-C_6H_4- **6** R^1=H, R^2=Ar=Ph	(*R*) (*R*) (*R*)	89 87 88
	b,c	oils		
 **7** (+)-Limonene	d	 90–91 **8**	(*R*)	63
 **9** (-)-β-Pinene	e,c	 109.5 **10**	(*R*)	85
 **11** (+)-4-Cholesten-3-one	f	 73–75 **12**	(*S*)	84
 (+)-Camphor (+)-**13**	g,h	 **14** R^1=H 47 **15** R^1=Ph 173	(*R*) (*R*)	74 81.5
	i			
— *II* —	g,j	 oil **16**	No Reaction	
— *II* —	k	 oil **17**	(*S*)	88
 (-)-Camphor (-)-**13**	g,h	 173 **18**	(*S*)	82.7

Preparation a. 1) (p-OMe-C_6H_4)$_2$CuLi (1 mol-equiv. CuBr · Me_2S, 2 mol-equiv. (p-OMe-C_6H_4)$_2$Li, prepared from p-OMe-C_6H_4Br and BuLi at −20°) ether, −20°→RT., 48 h, 21%; *2)* slow addition in 8 mol-equiv. 2-propanol to 6 mol-equiv. sodium metal in toluene at reflux, 1 h reflux, 48%.

Preparation b. 1) 8% H_2SO_4 in EtOH/H_2O 2.5:1, reflux 15 h, 65% [9]; *2)* 1.05 mol-equiv. PhCHO, 4% aq. KOH-solution, 3 h, 86% [10]; *3)* 3 mol-equiv. PhLi, 2 mol-equiv. CuBr·Me_2S, Me_2S/ether 1:2, 1.5 h at −20°, 1 h at 0°, 46%.

Preparation c. 5 Mol-equiv. sodium metal, 10 mol-equiv. 2-propanol, toluene, 0.5 h at RT., 46%.

Preparation d. 1) 1 Mol-equiv. MCPBA, CH_2Cl_2, 1.5 h at 5°, 90%; *2)* Pt, 1 atm. H_2, 72% [11]; *3)* 1.4 mol-equiv. diethylaluminium 2,2,6,6-tetramethylpiperidide [12], benzene, 80 min at 0°, 88%; *4)* 1.1 mol-equiv. DMSO, 1.1 mol-equiv. $(COCl)_2$, excess NEt_3, CH_2Cl_2, −78°→RT., 93% [13]; *5)* Ph_2CuLi (2.85 mol-equiv. PhLi, 2 mol-equiv. CuBr, THF, 1 h at −20°), 45 min at −78°, 45 min at −20°, 90 min at RT., 30%; *6)* 0.25N NaOH, EtOH, 70°, 2 h, 93%; *7)* 5 mol-equiv. sodium metal, 1.2 mol-equiv. 2-propanol/toluene, 2 h at reflux, 38%, m.p. 90–91° (pentane).

Preparation e. 1) O_3, −70°, MeOH, Me_2S, 81% [14]; *2)* PhCHO, NaOMe, MeOH, 78% [15]; *3)* Ph_2CuLi (3.7 mol-equiv. CuI, 5.8 mol-equiv. PhLi, THF, 0°, 20 min) −20°→RT., 87%, m.p. 108–109° (hexane/ether); 73%.

Preparation f. 1) 2 Mol-equiv. *t*-BuOK, 1.37 mol-equiv. Ph_2CHCl, *t*-BuOH, reflux, 1 h; *2)* Excess sodium metal, 30 mol-equiv. 2-propanol/ toluene, RT., 28% overall.

Preparation g. 1.1 Mol-equiv. sodium metal, benzene, reflux, 18 h, 1.5 mol-equiv. PhCHO, 4 h at RT., 55% [16]; *2)* 1 Atm. H_2, Pd/C 5%, MeOH, 4 h at RT., 80%; *3)* 1.2N NaOMe, MeOH, 24 h at 80°, 85%.

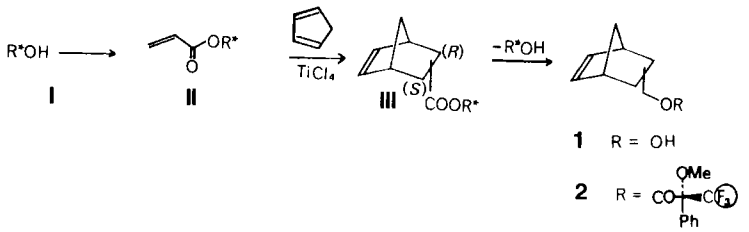
Preparation h. 2.2 Mol-equiv. lithium metal, NH_3/EtOH/Et_2O 6.8:1.8:1, 2 h, 61% [17], m.p. 46–47° (pentane).

Preparation i. 1) 2 Mol-equiv. $CF_3SO_3SiMe_3$, 2.5 mol-equiv. NEt_3, 0°→RT., 2 h, 94% [18]; *2)* 0.9 mol-equiv. Ph_2CHCl, 1 mol-equiv. $TiCl_4$ −78°→RT. [19], 48%, m.p. 132°; *3)* 1 mol-equiv. $LiAlH_4$, ether, 1 h at RT., chromatography (SiO_2), 20%.

Preparation j. 4 Mol-equiv. $LiAlH_4$, ether, reflux, 4 h, 55% overall *(g+j)*.

Preparation k. 1) 1.73 Mol-equiv. SeO_2, Ac_2O, reflux, 6 h, 94% [20]; *2)* H_2, Ra-Ni, 1 atm. H_2, EtOH, 1 h, 86% [21]; *3)* 1 mol-equiv. NaH, 1.3 mol-equiv. $PhCH_2Cl$, DMF, 5 h at −40°, 6 h at RT., 56%; *4)* 1.16 mol-equiv. *L-selectride* [22], THF, 2 h at −78°, 1 h for→RT, 88%.

Scheme 3



After esterification[6]) the acrylates **II** (0.925 mmol) were treated with $TiCl_4$ (1.4 mmol) in dry CH_2Cl_2 (10 ml) at 0° for 45 min. After slow addition of 1.21 M freshly distilled cyclopentadiene in CH_2Cl_2 (2.78 mmol) the mixture was stirred at 0° for 4 h. Work-up gave the cycloadducts **III** which were isolated, purified and analyzed as described previously [6] by conversion to **1** and **2** with recovery of the auxiliary alcohol **I**.

First, the (−)-8-*p*-methoxyphenylmenthol (**5**)[5]) was prepared in close analogy to (−)-**4** from (+)-pulegone (**3**).

We hoped that an increased π-orbital interaction between the *p*-methoxyphenyl and the C(α),C(β)-bond of the enoate moiety in the acrylate of **5** would lead to a

[6]) The esters **II**[5]) were obtained by treatment of the alcohols **I** with acryloyl chloride (2 mol-equiv.), NEt_3 (2 mol-equiv.), *p-N,N*-dimethylaminopyridine (0.14 mol-equiv.) in CH_2Cl_2 at 0° for 1 h in 52 to 93% yield.

higher optical yield; this did not materialize and the adduct **III** was obtained in 87% e.e.[7]).

More encouraging was the induction observed on *Diels-Alder* addition to the acrylate of **6** (88% e.e.) which indicated an equally powerful enoate shielding of the dimethylphenylmethane and the diphenylmethane units. The latter moiety is readily introduced either by phenylcuprate addition to α-benzylidenecyclohexanones or by alkylation of dienolates and of silyl vinyl ethers (in the presence of $TiCl_4$ [19]) with diphenylchloromethane as illustrated by the preparation of the alcohols **6**, **10**, **12**, **15** and **18**. In comparison, a simple benzyl group shields less efficiently, leading to 63 and 74% chiral induction in the addition of cyclopentadiene to the acrylates of **8** and **14**, respectively. However, the alcohols **4**, **5** and **6** display two disadvantages: lack of crystallinity and the commercial availability only of the (+)-enantiomer of the starting pulegone (**3**). By contrast, both antipodes of limonene (**7**) are inexpensive as well as (−)-β-pinene (**9**)[8]).

Thus, the monoterpenes **7** and **9** served as convenient precursors to the crystalline alcohols **8** and **10**; the latter shows a chiral auxiliary capacity comparable to the reference alcohol **4**. Recent access to steroids[9]) renders this rigid skeleton an attractive starting material. For example, cholestenone (**11**) was transformed by two steps into the alcohol **12**; its acrylate gave the (2*S*)-cyclopentadieneadduct **III** with 84% e.e. and thus constitutes the first, readily available '*re*-face directing' acrylate.

For the preparation of the envisaged chiral norbornanols camphor (**13**) is a particularly suitable chiral source for the following reasons: *1)* both pure enantiomers are easily available: (+)-13 commercially and (−)-13 by *Jones'* oxidation [26] of (−)-borneol (*Aldrich, EGA); 2)* substituents may be directed into the more stable *exo*- or into the *endo*-position by means of thermodynamically *vs.* kinetically controlled processes; *3)* derivatives of **13** are frequently crystalline. Thus, the crystalline *endo/cis*-benzyl- and diphenylmethyl-isoborneols **14** and **15**[5]) were obtained from (+)-camphor to afford after esterification[6]) and subsequent *Diels-Alder* reaction the (2*R*)-adducts **III** with 74 and 81.5% asymmetric induction, respectively. The acrylate of the *exo/cis*-benzylborneol afforded no *Diels-Alder* products but led to polymerization under more stringent reaction conditions. On the other hand, the regio- and stereo-selectivity prepared *exo/cis*-benzyloxyborneol **17**[10]) gave an acrylate which yielded smoothly the (2*S*)-adduct **III** in 88% e.e. Accordingly the alcohol **17** constitutes a further efficient '*re*-face directing' auxiliary as well as the norbornanol **18** which was prepared from (−)-camphor.

Presently we are pursuing these leads further to arrive at new chiral acrylates which meet all the requirements for their generally practical use in enantioselective *Diels-Alder*, ene- and 1,4-addition reactions[11]).

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[7]) The electron-donating effect of the *p*-OMe group may be compensated by its association with $TiCl_4$.

[8]) Commercially available (+)-α-pinene may be converted to (+)-β-pinene following established procedures [23]. For stereoselective functionalisations of pinenes see a review [24].

[9]) See for example the fermentation of β-sitosterol [25].

[10]) For a non-selective preparation of **17**, requiring its isolation by HPLC. and for the asymmetric *Diels-Alder* addition of its fumarate to anthracene see [2c].

[11]) For highly enantioselective BF_3-mediated organocuprate additions to enoates derived from (−)-8-phenylmenthol see the subsequent communication [27].

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