

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

Preliminary Communication¹⁾

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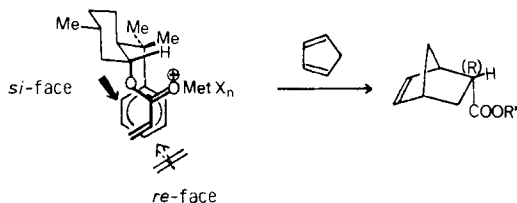
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Summary

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* [2 a], 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

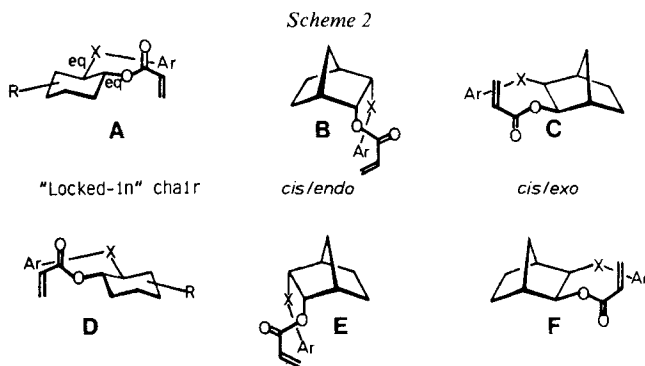


¹⁾ Presented by one of us (*W.O.*) at the 11th Northeast Regional Meeting of the American Chemical Society, Rochester, Oct. 19, 1981.

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].

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 acid³⁾ 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 interesting⁴⁾ 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-



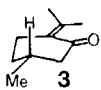
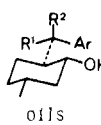
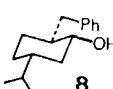
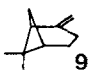
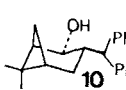
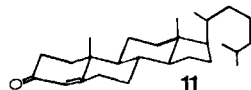
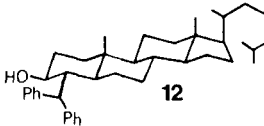
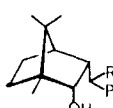
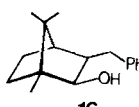
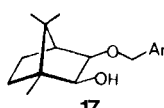
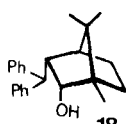
marized in *Scheme 3* and in the *Table*. To prepare the cyclohexanols **4**, **5**, **6**, **8**, **10**, **12** and the norbornanols **14**, **15** and **18**⁵⁾ the steric position of the aryl-substituted chain was controlled by a base-induced equilibration of the corresponding cyclohexanones which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

³⁾ In the ¹H-NMR. spectra the *trans*-H–C(β)-signal of 8-phenylmethyl acrylate is shifted upfield by 0.32 ppm in CDCl₃, and by 0.85 ppm in CDCl₃ containing 1 mol-equiv. of TiCl₄, compared to that of menthyl acrylate.

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

⁵⁾ All new compounds were characterized by IR., ¹H-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.%
 (+)-Pulegone 3	a b, c	 4 R ¹ =R ² =Me, Ar=Ph 5 R ¹ =R ² =Me, Ar=pOMe-C ₆ H ₄ - 6 R ¹ =H, R ² =Ar=Ph oils	(R) 89 (R) 87 (R) 88
 (+)-Limonene 7	d	 8 90-91	(R) 63
 (-)-β-Pinene 9	e, c	 10 109.5	(R) 85
 (+)-4-Cholesten-3-one 11	f	 12 73-75	(S) 84
 (+)-Camphor (+)- 13	g, h j	 14 R ¹ =H 47 15 R ¹ =Ph 173	(R) 74 (R) 81.5
— II —	g, j	 16 oil	No Reaction
— II —	k	 17 oil	(S) 88
 (-)-Camphor (-)- 13	g, h	 18 173	(S) 82.7

Preparation a. 1) (p-OMe-C₆H₄)₂CuLi (1 mol-equiv. CuBr · Me₂S, 2 mol-equiv. (p-OMe-C₆H₄)₂Li, prepared from p-OMe-C₆H₄Br 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 $\text{EtOH}/\text{H}_2\text{O}$ 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. $\text{CuBr} \cdot \text{Me}_2\text{S}$, $\text{Me}_2\text{S}/\text{ether}$ 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. diethylaluminum 2,2,6,6-tetramethylpiperidide [12], benzene, 80 min at 0° , 88%; 4) 1.1 mol-equiv. DMSO, 1.1 mol-equiv. $(\text{COCl})_2$, excess NEt_3 , CH_2Cl_2 , $-78^\circ \rightarrow \text{RT.}$, 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. $90\text{--}91^\circ$ (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) $-20^\circ \rightarrow \text{RT.}$, 87%, m.p. $108\text{--}109^\circ$ (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.

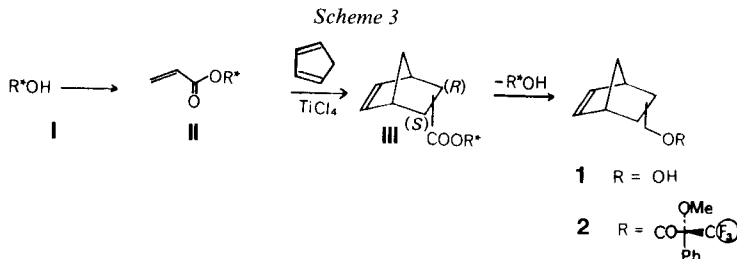
Preparation g. 1.1 Mol-equiv. sodium metal, benzene, reflux, 18 h, 1.5 mol-equiv. PhCHO , 4 h at RT. , 55% [16]; 2) 1 atm. H_2 , Pd/C 5%, MeOH , 4 h at RT. , 80%; 3) 1.2N NaOMe , MeOH , 24 h at 80° , 85%.

Preparation h. 2.2 Mol-equiv. lithium metal, $\text{NH}_3/\text{EtOH}/\text{Et}_2\text{O}$ 6.8:1.8:1, 2 h, 61% [17], m.p. $46\text{--}47^\circ$ (pentane).

Preparation i. 1) 2 Mol-equiv. $\text{CF}_3\text{SO}_3\text{SiMe}_3$, 2.5 mol-equiv. NEt_3 , $0^\circ \rightarrow \text{RT.}$, 2 h, 94% [18]; 2) 0.9 mol-equiv. Ph_2CHCl , 1 mol-equiv. TiCl_4 , $-78^\circ \rightarrow \text{RT.}$ [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 $\rightarrow \text{RT.}$, 88%.



After esterification⁶⁾ 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 steroids⁹⁾ 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 esterification⁶⁾ 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 reactions¹¹⁾.

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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