Tetrahedron: Asymmetry Vol. 3, No. 3, pp 367-370, 1992
Printed in Great Britain

0957-4166/92 $3.00+.00
Pergamon Press plc

The Conformation of 3-*endo*-Arylmethylisobornyl Esters.

Byung-Ick Seo, Il-Hwan Suh, William P. Jensen and David E. Lewis*
Department of Chemistry, South Dakota State University, Box 2202, Brookings, SD 57007-0896 (U.S.A.)

L. Kevin Wall
Department of Chemistry, Baylor University, Waco, TX 76798 (U.S.A.)

and

Robert A. Jacobson
Ames Laboratory, USDOE and Department of Chemistry, Iowa State University, Ames, IA 50011 (U.S.A.)

(*Received* 30 *January* 1992)

Abstract: The conformation of the benzyl group in 3-*endo*-benzylisobornyl esters depends on the nature of the ester group, and changes into a position close to coplanar with the ester group as the carbonyl group of the ester becomes conjugated. The potential use of these alcohols as chiral auxiliaries in asymmetric synthesis is addressed.

The efforts of synthetic organic chemists over the past two decades have resulted in the discovery of several highly effective chiral auxiliaries for effecting asymmetric transformations. Noteworthy among these are the camphor-derived chiral sultams and sulfonamide auxiliaries developed by Oppolzer,[1a] the camphor-derived chiral alcohols developed by Helmchen,[1b] Corey's phenmenthol,[1c,d] Evans' chiral oxazolidinones,[1e] and Enders' chiral hydrazines.[1f,g] Our analysis of the structural elements of these highly successful chiral auxiliaries led us to conclude that the 3-*endo*-benzylisoborneols (1), a class of alcohols not yet investigated as potential chiral auxiliaries, might function as effective chiral adjuvants for Diels-Alder cycloadditions, Michael additions, and ester enolate alkylations and additions.

In order for the title compounds to function as chiral auxiliaries, they must meet two major requirements: they must be able to exist in a conformation in which one face of the prochiral group is shielded from the approach of the reagent, and they must also be able to adopt a conformation in which the auxiliary can be removed from the product without compromising the stereochemical integrity of the newly-introduced chiral center. In order to gauge their potential as chiral auxiliaries, we have undertaken a study of the conformations of 3-*endo*-benzylisobornyl esters by ^{1}H NMR spectroscopy and X-ray crystallography.

The synthesis of the alcohols was effected by Bouveault-Blanc reduction[2] of the corresponding enones, followed by fractional crystallization[3] of the *p*-nitrobenzoates[4] and base hydrolysis. Esterification of the alcohols was accomplished with the appropriate anhydride [anhydride (1 eq.) / anhydrous pyridine (3 mL per mmol alcohol) / r.t. / 24-72 h] or the appropriate acid chloride [acid chloride (1 eq.) /CH_2Cl_2/ (10 mL per mmol alcohol) / pyridine (1 eq) / r.t. / 24-72 h].[5]

In the ^1H NMR spectrum of the alcohols, the methylene protons of the benzyl carbons are quite distinct (Table 1); the vicinal coupling constants with the proton at C3 indicate that the conformation about the C3–C1′ bond is such that this bond is nearly eclipsed in all the alcohols.

Table 1. Vicinal Coupling Constants of Benzyl Protons in Benzylisoborneols

Alcohol	Substituent	$\delta_{H\text{-}1'a}$	J_{vic}	$\delta_{H\text{-}1'b}$	J_{vic}	$\delta_{H\text{-}3}$
1a	H	2.81	7.4	2.60	8.6	2.37
1b	*p*-OMe	2.78	7.6	2.55	8.6	2.32

During the synthesis of the alcohols, the *p*-nitrobenzoate esters are formed. The ^1H NMR spectra of these esters show a totally different pattern of vicinal coupling constants of the benzyl protons, as shown in Table 2. In contrast to this, the ^1H NMR spectra of the propionate and α-methylbutyrate esters of the same alcohols exhibit chemical shifts and coupling constants little different from those of the parent alcohol. That this effect is the result of the additional conjugation of the ester carbonyl group is borne out by the spectra of the acrylate esters and the crotonate ester of the *p*-methoxy derivative of the parent alcohol.

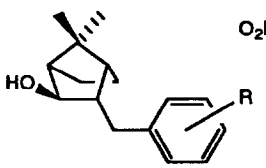
Table 2. Vicinal Coupling Constants of Benzyl Protons in Benzylisobornyl Esters

Ester	Substituent	Acyl Group	$\delta_{H\text{-}1'a}$	J_{vic}	$\delta_{H\text{-}1'b}$	J_{vic}	$\delta_{H\text{-}3}$
2a	H	*p*-O_2N-C_6H_4-CO–	2.96	5.6	2.64	9.8	2.62
2b	*p*-OMe	*p*-O_2N-C_6H_4-CO–	3.00	5.4	2.67	9.1	2.55
3a	*p*-OMe	MeCO	2.86	6.9	2.57	9.0	2.41
3b	H	EtCO–	2.81	7.3	2.54	8.7	2.43
3c	*p*-OMe	EtCO–	2.81	7.3	2.55	8.8	2.36
3d	H	CH_2=CH-CO–	2.99	6.0	2.65	9.8	2.51
3e	*p*-OMe	CH_2=CH-CO–	2.93	5.9	2.59	9.8	2.48
3f	*p*-OMe	CH_3CH=CH-CO–	2.94	5.8	2.57	9.8	2.44
3g	*p*-OMe	EtCH(Me)CO–	2.82 (2.81)*	7.4	2.58	8.7	2.39

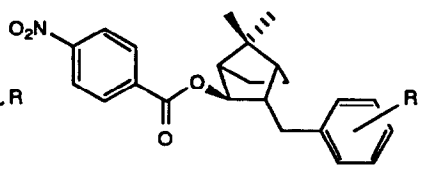
*The spectrum was obtained without separating the diastereoisomers, which appeared as a single spot by t.l.c.

The coupling constants in Table 2 are most consistent with a conformational change about the C3– C1′ bond from nearly eclipsed to staggered induced by the conjugated ester groups such that the aromatic ring, which is nearly eclipsed by the C3 hydrogen in the alcohol moves into a position *antiperiplanar* to C4. As a

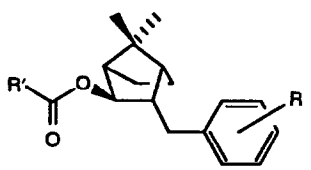
means of confirming the conformation of the C3–C1′ bond, the single-crystal X-ray structure of the *p*-nitrobenzoate of the *p*-methoxy alcohol was determined.[6] The result, shown in Figure 1, clearly shows that the *p*-methoxybenzyl group in the *p*-nitrobenzoate ester adopts a conformation so that the C3–C4 and C1′–C1″ bonds are *anti*. Moreover, the conformation of the *p*-methoxyphenyl ring is such that it is in a good position to effect strong shielding of the *Re* face of the α carbons of the acrylate and crotonate esters, suggesting that this alcohol should be a good chiral auxiliary for Diels-Alder reactions, and even allowing the possibility that these alcohols might be useful auxiliaries for chiral alkylation reactions. Our initial studies of alkylation reactions of the propionate esters [LDA/THF/-78→0°C/20 min; R–X/-78→0°C/18 h] have yielded preliminary 200 MHz ^{1}H NMR evidence that suggests that the d.e.'s to be realized in this reaction are above 95%.[7] The preliminary ^{1}H NMR estimates of d.e.'s obtained in the diethylaluminum-catalyzed Diels-Alder reaction between the acrylate ester of **1a** and cyclopentadiene [Et_2AlCl (1 eq.)/CH_2Cl_2/-78°C] are in the ranges 83-90%.[8]



1a: R = H
1b: R = *p*-OCH_3



2a: R = H
2b: R = *p*-OCH_3



3a: R = H; R′= CH_3
3b: R = H; R′= CH_3CH_2
3c: R = *p*-OCH_3; R′= CH_3CH_2
3d: R = H; R′= $CH{=}CH_2$
3e: R = *p*-OCH_3; R′ = $CH{=}CH_2$
3f: R = *p*-OCH_3; R′= $CH{=}CH{-}CH_3$
3g: R = *p*-OCH_3; R′= $CH_3CH_2CH(CH_3)$

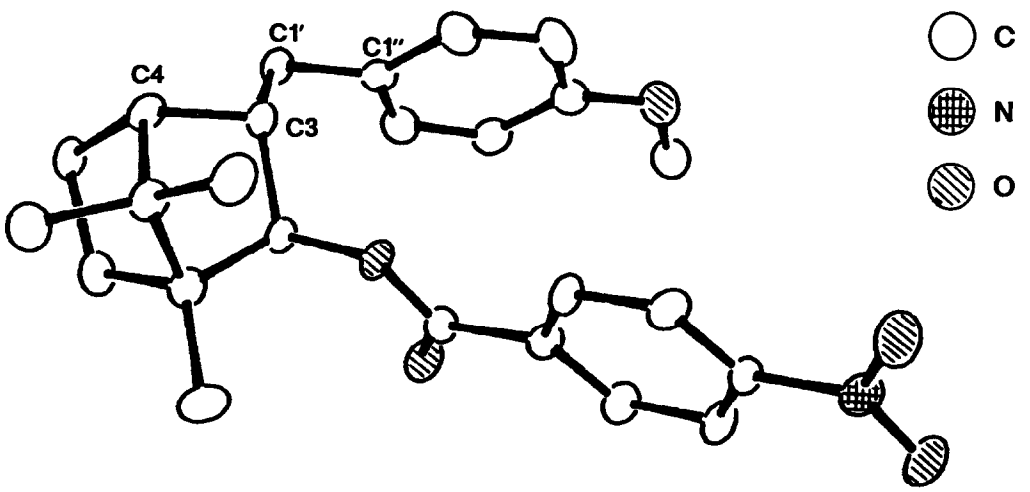


Figure 1. The conformation of 3*endo*-(*p*-methoxybenzyl)isobornyl *p*-nitrobenzoate as determined by single crystal X-ray structure analysis.

Acknowledgements:

The authors gratefully acknowledge the financial support of this work, in part, by the Robert A. Welch Foundation (DEL; Grant #AA-936), the National Science Foundation (DEL; Grant # STI-8902066) and the U.S. Department of Energy, Office of Basic Energy Sciences, Materials Sciences Division, (RAJ; contract W-74-5-Eng-82).

References and Notes:

1. For leading references, see: (a) Oppolzer, W. *Tetrahedron*, **1987**, *43*, 1969, and references cited therein. (b) Helmchen, G.; Wierschokuski, R. *Angew. Chem. Int. Ed. Engl.*, **1984**, *20*, 207. (c) Corey, E.J.; Ensley, H.E. *J. Am. Chem. Soc.*, **1975**, *97*, 6908. (d) Ort, O. *Org. Syn.*, **1987**, *65*, 203, and references therein. (e) Gage, J.R.; Evans, D.A. *Org. Syn.*, **1989**, *68*, 77, 83, and references therein. (f) Enders, D.; Fey, P.; Kipphardt, H. *Org. Syn.*, **1987**, *65*, 173, and references therein. (g) Enders, D.; Kipphardt, H.; Fey, P. *Org. Syn.*, **1987**, *65*, 183, and references therein.

2. Review: House, H.O. *Modern Synthetic Reactions*; 2nd Ed.; (Benjamin: New York, 1972); pp. 152-160.

3. (a) L.K. Wall, M.S. Thesis, Baylor University, 1990. (b) Seo, B.-I.; Wall, L.K.; Lewis, D.E. *Tetrahedron*, in preparation.

4. Richer, J.-C.; Rossi, A. *Can. J. Chem.*, **1972**, *50*, 1376.

5. All new single compounds are homogeneous by t.l.c., and give ^{1}H NMR, ^{13}C NMR, IR and mass spectra in accord with the structures given. Known compounds exhibit properties in accord with published values. ^{13}C NMR (relative to center peak of $CDCl_3$ at 77.0 ppm): **1a:** 141.7, 128.8, 128.4, 125.8, 85.7, 50.9, 49.6, 48.0, 47.3, 37.0, 34.4, 20.6, 20.1, 19.4, 11.3. **1b:** 157.8, 133.7, 129.5, 113.9, 85.7, 55.0, 50.9, 49.6, 47.9, 47.3, 36.0, 34.5, 20.7, 20.0, 19.5, 11.3. **2a:** 164.4, 150.7, 141.0, 136.3, 130.6, 128.8, 128.4, 126.0, 123.6, 87.8, 50.7, 49.0, 48.1, 47.9, 36.5, 34.0, 20.3, 20.1, 19.8, 11.9. **2b:** 164.4, 158.1, 150.7, 136.3, 133.0, 130.6, 129.7, 123.6, 114.9, 87.8, 55.1, 50.3, 49.1, 48.0, 47.9, 35.5, 34.1, 20.3, 20.1, 19.5, 11.5. **3a:** 171.2, 158.3, 133.7, 130.1, 114.1, 86.1, 55.5, 50.1, 49.1, 48.1, 35.8, 34.3, 21.3, 20.6, 20.3, 19.6, 11.7. **3b:** 173.8, 141.3, 128.8, 128.2, 125.7, 85.5, 49.8, 48.7, 48.0, 47.6, 36.5, 34.0, 27.7, 20.2, 20.0, 19.2, 11.2, 8.7. **3c:** 174.0, 157.9, 133.4, 129.7, 113.7, 85.5, 55.1, 49.7, 48.8, 47.8, 47.6, 35.5, 33.9, 27.7, 20.2, 19.9, 19.2, 11.2, 9.0. **3d:** 165.4, 140.8, 129.5, 128.9, 128.5, 128.1, 125.6, 85.7, 49.7, 48.4, 47.5, 47.3, 36.1, 33.7, 20.0, 19.7, 18.9, 11.0. **3e:** 165.9, 157.9, 131.2, 130.0, 129.6, 129.1, 113.7, 86.0, 55.0, 49.9, 48.7, 47.6, 47.5, 35.3, 33.9, 20.2, 19.9, 19.2, 11.3. **3f:** 166.2, 157.8, 143.9, 133.3, 129.6, 123.3, 113.7, 85.5, 55.0, 49.9, 48.8, 47.5, 47.4, 35.3, 33.9, 20.2, 19.8, 19.2, 17.7, 11.3.

6. Suh, I.-H.; Seo, B.-I.; Lewis, D.E.; Jensen, W.P.; Jacobson, R.A. *Acta Cryst. C*, in preparation.

7. 200 MHz ^{1}H NMR analysis of the crude product mixture from the alkylation of **3c** with several alkyl halides (EtBr, *i*-PrI, *n*-BuBr, CH_2=$CHCH_2Br$, $EtOCH_2Cl$, or $PhCH_2Br$) reveals the presence of only one diastereoisomeric product in each case. Seo, B.-I.; Wall, L.K.; Lewis, D.E., manuscript in preparation.

8. The Diels-Alder reaction of **3e** with cyclopentadiene affords an 11:1 mixture of diastereoisomeric *endo* esters, with an *endo:exo* ratio of approximately 6:1. With hexachlorocyclopentadiene ($CHCl_3$/Δ/96 h), two diastereoisomeric products are obtained in a ratio of approximately 2:1. Seo, B.-I.; Lewis, D.E., manuscript in preparation.