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Formation of a Dimeric Camphor Derivative with an Unusually Stable 3-*exo* Substituent

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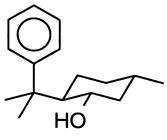
Abstract—The reductive dimerization of *E*-3-benzylidenecamphor with sodium proceeds with homoacyloin regiochemistry to give a complex mixture of products from which two major products have been isolated by chromatography. The major product is formed by dimerization of the *E* radical anion through the *re* face of one radical anion to the *si* face of the other. This compound lacks a true inversion center of symmetry, but the atoms of the 1,2-diphenylethane moiety, as well as the camphor oxygen atoms and C(1)–C(4) and C(10) of the camphor groups, are related by a local inversion center of symmetry. One of the camphor moieties carries an *exo* substituent, but the compound does not readily equilibrate to the epimeric compound where both camphor moieties carry an *endo* substituent.

Introduction

An analysis of several chiral alcohols used as chiral auxiliaries for alkylation of esters, among them Corey's phenmenthol (**1**)[1] and the Oppolzer alcohol (**2**),[2] suggested that successful auxiliaries possessed the following structural features in common: (1) a relatively rigid cyclic carbon skeleton with the hydroxyl oxygen and the steric blocking group in a vicinal relationship on a six-membered ring; (2) a vicinal *trans* relationship between the ester carbinyl oxygen and the steric blocking group; and (3) a short flexible region between the blocking group and the carbinyl oxygen to permit the blocking group to adopt the most effective conformation. Based on this analysis, we hypothesized that the 3-*endo*-benzylisoborneols (**3**) might serve as useful chiral auxiliaries for asymmetric alkylation of lithium ester enolates.

The solid-state conformation of 3-*endo*-(*p*-methoxybenzyl)-isobornyl *p*-nitrobenzoate[3,4] (**4**) tended to support this hypothesis, since the *p*-methoxybenzyl group adopts a conformation where the aryl ring enters into π-stacking with the ester carbonyl group and completely shields the face of the ester group that would correspond to the *si* face of the *E*(*O*) lithium enolate of a straight-chain ester derived from the alcohol prepared from (1*R*)-(+)-camphor.



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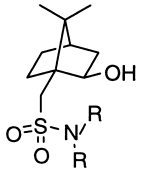

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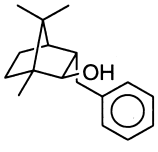

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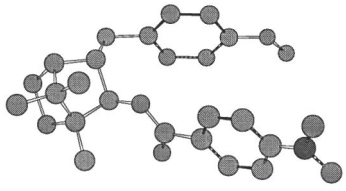

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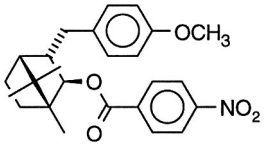

The chemical shifts and coupling constants of the benzyl protons in the ^{1}H NMR spectra of this ester are consistent with the solution conformation being the same as the solid-state conformation. The same protons in the ^{1}H NMR

Keywords: benzylidenecamphor; homoacyloin; local C_i symmetry; stereochemistry; reductive dimerization.

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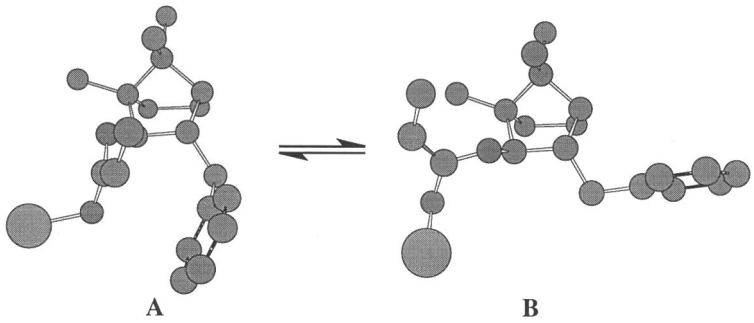


Figure 1. Possible conformational equilibrium in *E*(*O*) enolate of propionate ester of alcohol **3**.

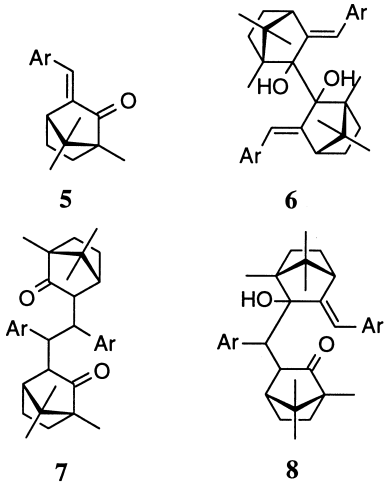
spectra of other esters of this alcohol exhibit the same general pattern. Therefore, it is logical to suggest that most esters of this alcohol assume this conformation in solution.[5] Thus, one would predict that the alkylation of the *E*(*O*) lithium enolate of 3-*endo*-arylmethylisobornyl propionates should lead to very high d.e.'s with the absolute configuration of the new chiral center being the same as that of C-1 of the chiral auxiliary.

We therefore prepared 3-*endo*-(*p*-methoxybenzyl)isobornyl propanoate and studied the alkylation of its lithium enolate. The results of the alkylation experiments, however, were disappointing, with d.e.'s of only 20–40% being obtained. As expected on the basis of the Ireland model,[5] the stereochemistry of the reaction was reversed on changing the solvent for deprotonation from THF to 23% HMPA–THF, suggesting that the predominant enolate geometry in THF is *E*(*O*).[6,7] Moreover, it was the *S* isomer that was obtained as the major product when the (1*R*) auxiliary was used, not the *R* isomer as had been expected.[6] Thus, although one would predict on the basis of the discussion in the preceding paragraph that the aryl ring of the (1*R*) propionate ester would effectively shield the *si* face of the a carbon in the *E*(*O*) lithium enolate, the experimental results make it clear that the *si* face is, in fact, (marginally) *more* accessible to the electrophile. These low d.e.'s have been interpreted in terms of a conformational shift of the acyl and aryl groups on deprotonation of the ester from conformation A to conformation B (Fig. 1); this removes the aryl group as an effective blocking group and makes the C-10 methyl group the major steric controlling group.[6,7]

Results and Discussion

Analysis of the observed results suggested that the major impediment to the success of these auxiliaries for alkylation reactions was the lack of a suitable structural feature at the benzyl carbon to prevent the conformational change of the C-3 substituent on deprotonation of the ester. We expected that by incorporating a branch at the benzyl position of the 3-*endo*-alkyl group, the potential for conformational change would be minimized, and that the d.e.'s would increase. Moreover, we expected that the stereochemical outcome of the reaction would revert to that predicted in the earlier discussion. Although the introduction of branching might be accomplished by adding a suitably large alkyl group at the benzyl carbon, this action has two effects: (1) it increases the molecular weight of the auxiliary above 300 amu – close to the limit of usefulness for many applications; (2) it requires another synthetic step which, unless the two alkyl groups at the benzyl carbon are identical, raises additional stereochemical problems. As an alternative method for introducing branching at the C-3 position, we attempted to prepare C_2-symmetric dimers of the benzylcamphor, with a view to reducing them to the isoborneols. By doing so, the requisite branching at the benzyl carbon is incorporated, but without increasing the effective molecular weight of the auxiliary. Moreover, the symmetry of the system, we anticipated, might help to simplify the stereochemical outcome of the reaction by forcing a preferred stereochemistry on the dimerization reaction. Therefore, we undertook the reductive dimerization of (1*R*)-3-benzylidenecamphor (**5**).

In principle, the reductive dimerization of the 3-benzylidenecamphor can lead to three different regioisomeric dimers: the symmetrical pinacol (**6**), the symmetrical dimeric 1,4-dione (**7**), or the unsymmetrical dimeric γ-hydroxy-δ,ϵ-enone (**8**). Dimerization of cinnamate esters by sodium has been observed to give predominantly symmetrical dimers of the type corresponding to **7** in preference to acyloin-type dimers.[8]

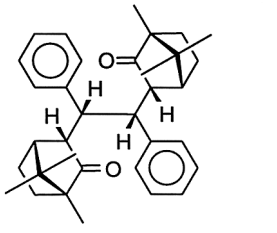


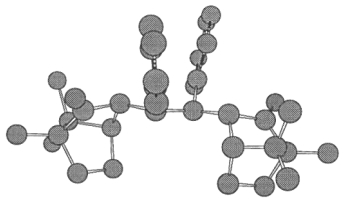
The enone **5** was prepared as optically pure chiral material from (+)-camphor.[9] Dimerization of this compound was attempted under a variety of conditions, including conditions where the dimerization would probably take place on the surface of the metal, and those where there was a reasonable probability that the dimerization of the radical

anions would occur in solution. In order to arrest the reaction immediately after dimerization of the radical anion, the reaction was carried out in the presence of a large excess of trimethylsilyl chloride.[10] The metals initially examined were sodium, magnesium and zinc, all of which are known to lead to pinacol-type dimers of simple saturated ketones.[11–14] To ensure a clean metal surface, the zinc was used as a freshly-prepared zinc–copper couple, the magnesium was activated with ethylene dibromide, and the temperature of the reaction with sodium metal was maintained high enough to ensure that the metal was liquid. Only the reaction with sodium afforded identifiable dimeric products; zinc failed to react and the reaction with magnesium afforded only ill-defined monomeric products.[15]

The enone was reduced with sodium in refluxing toluene,[10] and the crude reaction mixture was treated with ethanolic sodium ethoxide to hydrolyze the enol trimethylsilyl ethers. Flash chromatography of the crude product mixture resulted in the isolation of three crystalline compounds in pure form: two dimeric compounds and recovered starting material. The spectroscopic data showed that dimerization had occurred through the β carbons of the enone systems. This reaction generates four new chiral centers but because the starting enone is chiral the formation of a *meso* compound symmetry-forbidden. In principle, ten diastereoisomeric dimers can be formed in this reaction. One of the dimeric compounds (**9**), isolated in 5% overall yield, clearly possessed C_2 symmetry, but the 200 MHz ^{1}H NMR spectrum did not permit its stereochemistry to be deduced. The other dimeric compound (**10**), isolated in 25% yield, clearly lacked C_2 symmetry; its stereochemistry, likewise, could not be deduced from its 200 MHz ^{1}H NMR spectrum. The stereochemistry of both compounds was elucidated by single crystal X-ray structure analysis.[16]

The stereochemistry of the major product (**10**) as revealed by the X-ray crystal structure analysis corresponds to that expected from dimerization of the *E* radical anion **11** or the corresponding silyl ether **12** through the *exo* (*re*) face of one radical and the *endo* (*si*) face of the other as in the Newman projection **13**.





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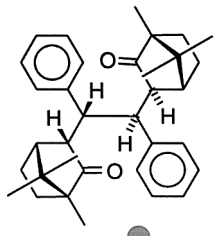

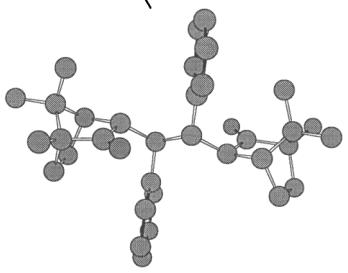

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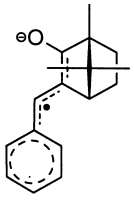
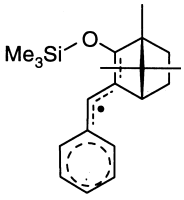
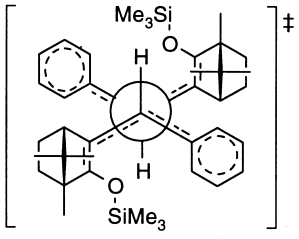




11 **12**



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This is the conformation that minimizes the steric hindrance between the two radical anions and maximizes the distance between the oxyanion centers or the silyl ether groups. Since it would be difficult, at best, to attain this conformation on the surface of the metal, this result may indicate that the dimerization takes place in solution rather than on the metal surface. This dimer possesses local C_i symmetry which relates the atoms of the 1,2-diphenylethane moiety, as well as the camphor oxygen atoms and C(1)–C(4) and C(10) of the camphor groups, but the homochirality of the two camphor moieties (the result of using optically pure D-camphor as starting material) prevents a true center of inversion symmetry having been formed in this molecule. The stereochemistry of the minor product (**9**) corresponds to that expected from dimerization of **11** or **12** through the *endo* face of both radicals with the distance between the oxyanion centers or silyl ether groups maximized. The single crystal X-ray structure of this dimer[16] is strongly reminiscent of that of the *p*-nitrobenzoate of 3-*endo*-(*p*-methoxybenzyl)isoborneol,[6] which suggests that the

corresponding isoborneol may well serve as a useful chiral scaffold for organic synthesis provided that its chemical yield can be improved. We are currently examining the possibility of tethering the two benzylidenecamphors in an effort to force C_2 symmetry on the dimerization reaction.

Unexpectedly, given the work of Richer and Rossi,[17] which would seem to have clearly established that the *endo* isomer is the thermodynamically favored isomer of a 3-alkylcamphor, one of the two constituent 3-benzylcamphor moieties of **10** has the bulky α-alkylbenzyl substituent in the *exo* position of the camphor, although the bond angles at C-3 are distorted to reduce the non-bonded interactions with the 7-*syn* methyl of the bornane ring system. It has been observed that reactions of the enolate of camphor occur through the *exo* face,[18,19] but the isolation of the *exo* product has most often been associated with reactions under kinetic control. It is difficult to reconcile the conditions used to hydrolyze the enol trimethylsilyl ether groups (ethanolic sodium ethoxide) with kinetic control of the stereochemistry of the resultant ketone, although this cannot be rigorously excluded from consideration. This view is reinforced by our attempts to epimerize this product with potassium ethoxide generated from potassium *tert*-butoxide in ethanol. In every case, this reaction achieved conversion to a new compound, detectable by TLC, within 10 min, but this reaction stalled after approximately 30 min at approximately 10% conversion; no further conversion to any other product was observed, even after 48 h at room temperature. This suggested that the reaction achieved equilibrium after approximately 30 min at room temperature. The identity of the major compound present in the mixture after 48 h was established as **10** by ^{1}H NMR spectroscopy. Since the new product could be detected within 10 min, it is clear that deprotonation of **10** occurs at a reasonable rate at room temperature. Therefore, it is difficult to reconcile the observed lack of change after the first 30 min with anything other than isomer **10** being thermodynamically favored over its epimers; were it to be the product of kinetic protonation of the enolate to a non-thermodynamic isomer, one would expect its conversion to the thermodynamically favored epimer with time. We therefore suggest that the isomer **10** may, in fact, possess the thermodynamically favored stereochemistry for this compound. If this is the case, it is a rare example of a thermodynamically favored 3-*exo*-alkylcamphor.

Conclusions

The reductive dimerization of *E*-3-benzylidenecamphor by sodium metal occurs through the *E* radical anion in solution, and is governed by steric and electronic factors. This results in the major product being formed through *re–si* coupling of the radical anion. In this activated complex, the aryl groups are *anti* to each other as are the camphor enolate moieties: steric hindrance and electronic repulsion between the oxyanion sites are both minimized. The product, which contains a camphor moiety bearing an *exo* substituent, appears to be thermodynamically favored with respect to epimerization to the corresponding *endo*,*endo* isomer. Reductive dimerization to the C_2-symmetric dimer proceeds through the *si–ssi* transition state with the aryl groups *gauche* to each other. In order for this isomer to dominate the product mixture, it will be necessary to prevent the aryl groups from adopting the *anti* conformation.

Experimental

General

E-3-Benzylidenecamphor (**5**) was prepared from (1*R*)-(+)-camphor by the literature method;[6] all other reagent chemicals were used as obtained from Aldrich Chemical Company without further purification. Solvents were purified by standard procedures and distilled prior to use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use and collected under dry argon. All reactions involving air- or moisture-sensitive reagents were performed under an atmosphere of argon in oven-dried glassware. Melting points were determined using an electrically heated hot-stage microscope, and are uncorrected. NMR spectra were recorded in $CDCl_3$ solution using a Varian Associates Gemini 200 NMR spectrometer at 200 MHz for ^{1}H and 50 MHz for ^{13}C. Chemical shifts are reported as δ ppm relative to internal Me_4Si. FTIR spectra were recorded by diffuse reflectance (DR) from KBr using an ATI Mattson Genesis Series Fourier Transform Infrared Spectrophotometer. EI mass spectra were recorded at 70 eV using either a Kratos MS25 RFA mass spectrometer at 70 eV or a Hewlett Packard 5890 Gas Chromatograph with a Hewlett Packard 5970 Mass Selective Detector operating at 70 eV. Flash chromatography was performed using 4–20 μ silica gel obtained from Aldrich Chemical Company; column chromatography was performed using 70–230 mesh silica gel obtained from Aldrich Chemical Company; thin layer chromatography (TLC) was carried out on Merck Kieselgel $60F_{254}$.

Dimerization of 3-*endo*-benzylcamphor with sodium

Freshly cut sodium metal (43.6 g, 1.90 mol) was stirred vigorously under refluxing toluene (60 mL) until the metal was fully dispersed. The stirrer speed was reduced, a solution of **5** (4.80 g, 20 mmol) and Me_3SiCl (5.1 mL, 40 mmol) in dry toluene (30 mL) was then added dropwise over 60 min, and the reaction mixture maintained at reflux for a further 24 h. The contents of the flask were cooled and filtered, and the residue was washed with dry toluene. Sodium (15 mg) and ethanol (30 mL) were added to the combined filtrates, the solution was stirred 30 min, and was then neutralized with 1 M aqueous HCl and evaporated to afford an oil. Flash chromatography (hexane–EtOAc, 15:1) of a 5-g sample of this oil afforded three pure compounds which were recrystallized from ethanol. The three products were identified as recovered **5** (0.53 g, 11%), the diketone **9** (0.24 g, 5%), m.304–305°C, and its diastereoisomer **10** (1.2 g, 25%), m. 247–248°C. Slow evaporation of ethanol solutions of both **9** and **10** provided single crystals suitable for X-ray structure analysis.

(1*R*,3*R*,4*R*,1′*R*,2′*R*,1″*R*,3″*R*,4″*R*)-3,3″-(1′,2′-Diphenylethylene)-bis-(1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one (5). ^{1}H NMR ($CDCl_3$, δ): 7.26–6.75 (10H, complex), 3.06 (2H, d, J=11.0 Hz), 2.80 (2H, dd, J=3.8, 11.0 Hz),

2.63 (2H, t, J=3.8 Hz), 1.97–1.24 (8H, complex), 1.06 (6H, s), 0.85 (6H, s), 0.74 (6H, s) ppm. ^{13}C NMR ($CDCl_3$, d): 218.2, 137.3, 130.9, 126.8[1], 59.3, 50.3, 47.1, 45.6, 45.4, 31.0, 20.6, 19.7, 19.4, 9.7 ppm. ν_{max} (KBr, DR): 3032, 2961, 1737, 1452, 1374, 1328, 1032, 981, 775, 702 cm^{-1}. *m/z* (rel. abundance): 482 (37), 370 (17), 330 (37), 241 (65), 212 (100), 116 (39), 52 (27). HREIMS *m/z* Calcd for $C_{34}H_{42}O_2$: 482.3184. Found: 482.3193 (Dev. 1.7 ppm).

(1*R*,3*R*,4*R*,1′*S*,2′*R*,1″*R*,3″*S*,4″*R*)-3,3″-(1′,2′-Diphenylethylene)-bis-(1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one (6). ^{1}H NMR ($CDCl_3$, δ): 7.28–7.23 (10H, br.), 3.70 (1H, t, J=8.7 Hz), 3.04 (1H, dd, J=5.2, 8.7 Hz), 2.69 (1H, t, J=4.3 Hz), 2.04 (1H, t, J=8.7 Hz), 1.85–1.82 (1H, br.), 1.56–0.93 (9H, complex), 0.83 (3H, s), 0.79 (3H, s), 0.75 (3H, s), 0.74 (3H, s), 0.65 (3H, s), 0.46 (3H, s) ppm. ^{13}C NMR ($CDCl_3$, δ): 219.4, 218.9, 142.5, 141.4, 130.4, 129.6, 128.2, 127.6, 127.0, 126.7, 59.6, 57.5, 54.9, 54.0, 52.1, 49.8, 49.2, 46.1, 45.8, 30.2, 29.8, 28.5, 21.7, 21.1, 20.2, 19.1, 19.0, 9.7 ppm. ν_{max} (KBr, DR): 3059, 2954, 1728, 1454, 1374, 1328, 1077, 1001, 942, 706 cm^{-1}. *m/z* (rel. abundance): 482 (29), 369 (11), 330 (26), 241 (42), 210 (100), 116 (45), 52 (28). HREIMS *m/z* Calcd for $C_{34}H_{42}O_2$: 482.3184. Found: 482.3143 (Dev. −8.5 ppm).

Attempted epimerization of the dione 10

The diketone **10** (20 mg) was dissolved in anhydrous ethanol (2 mL) and potassium *tert*-butoxide (20 mg) was added. The solution was allowed to stand at ambient temperature under an argon atmosphere, and was monitored by TLC on SiO_2 (hexane-ethyl acetate, 15:1) for 48 h. Within 10 min, a second spot of lower R_f had appeared, but the TLC plates exhibited no further change after approximately 30 min at room temperature. After 48 h, the reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The ^{1}H NMR spectrum of the recovered solid indicated that it was approximately 90% unaltered starting compound.

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15. The reaction with magnesium afforded, after chromatography (hexane–EtOAc, 40:1; SiO_2), a pale yellow oil consisting of two unstable monomeric compounds which could not be completely characterized or purified, and which reverted to starting material on treatment with ethanolic sodium ethoxide. We suggest that these compounds correspond to the two diastereoisomers of the 1,4-addition product of the enone with trimethylsilyl chloride. The spectroscopic data for these compounds are as follows: *Mixture of isomers* ν_{max} (film): 3033, 2954, 1649, 1324, 1252, 924, 842 cm^{-}1. *m/z* (rel abundance): 314 (35), 313 (79), 312 (88), 297 (82), 207 (70), 129 (26), 91 (23), 73 (100). Repeated chromatography afforded one stereosiomer in approximately 80% stereoisomeric purity, thus allowing the resonances of NMR spectra of the individual isomers to be assigned. *Stereoisomer 1* δ 7.38–6.78 (complex, 5H), 4.23 (s, 1H), 2.42 (d, 1H, J=3.3 Hz), 1.90–0.92 (complex, 4H), 0.77 (s, 3H), 0.64 (s, 3H), 0.25 (s, 9H), 0.15 (s, 3H) ppm. δ 152.1, 143.2, 129.5, 127.4, 124.9, 121.4, 55.1, 53.81, 50.2, 45.3, 32.4, 25.5, 20.3, 19.0, 11.4, 2.1 ppm. *Stereoisomer 2* δ 7.38–6.78 (complex, 5H), 4.38 (s, 1H), 2.35 (d, 1H, J=3.3 Hz), 1.90–0.92 (complex, 4H), 0.91 (s, 3H), 0.81 (s, 3H), 0.30 (s, 9H), 0.21 (s, 3H) ppm. δ 152.6, 143.3, 129.5, 127.3, 124.8, 119.8, 54.5, 53.77, 51.1, 45.1, 32.5, 26.5, 20.6, 20.4, 11.2, 2.3 ppm.
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[1] Accidental equivalence of the *ortho* and *meta* carbons of the phenyl rings.