Simultaneous Inversion of Configuration of both the Chiral Ring and the Carbinol Carbon in (*E*)-(1*R*,2*R*)-Cyclo-oct-2-en-1-ol

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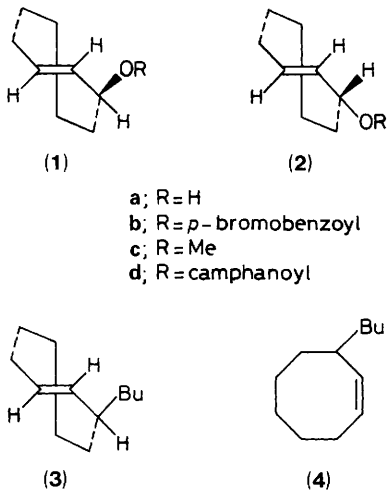
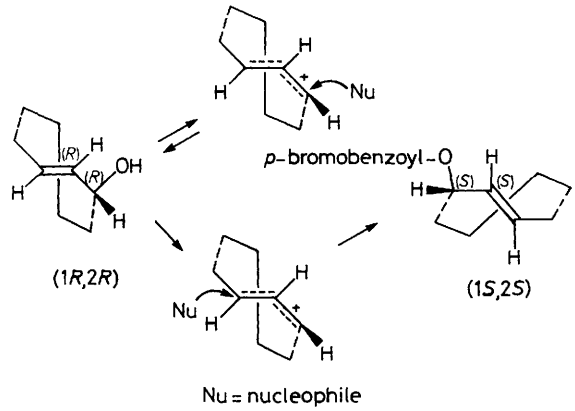
The reaction of (−)-(*E*)-(1*R*,2*R*)-cyclo-oct-2-en-1-ol with *p*-bromobenzoic acid under Mitsunobu reaction conditions yields the corresponding *p*-bromobenzoate with simultaneous inversion of configuration of both the chiral ring and the carbinol carbon.

Derivatives of (*E*)-cyclo-octene constitute an unusual series of molecules which maintain chiral ring structures in the absence of chiral centres.[1] Whitham *et al.*[2] have described the preparation and reactions of both diastereoisomers of (*E*)-cyclo-oct-2-en-1-ol, (**1a**) and (**2a**). They suggested that the conversion of racemic (**1c**) into (**3**), and that of racemic (**2c**) into (**4**) with butyl-lithium proceed *via* S_N2' (bimolecular nucleophilic substitution with allylic rearrangement) displacements but were unable to verify the mechanism. One consequence of the S_N2' mechanism for (**1a**) is that it involves a simultaneous inversion of configuration at the carbinol carbon and the chirality of the cyclo-octene ring. In the





Scheme 1

reaction of (±)-(**1a**) with *p*-bromobenzoic acid under Mitsunobu reaction conditions[3] [triphenylphosphine, diethyl azodicarboxylate, and *p*-bromobenzoic acid in tetrahydrofuran (THF)] we obtained (±)-(**1b**) instead of the anticipated (±)-(**2b**). The structure of the (**1b**) formed was confirmed by base-catalysed hydrolysis to reform (**1a**), and through an independent synthesis of (**1b**) by esterification of (**1a**) with *p*-bromobenzoyl chloride in dichloromethane in the presence of 4-dimethylaminopyridine. Samples of (**2a**) and (**2b**) were prepared by known procedures,[2c] and were readily distinguished by their ^{1}H NMR spectra. The racemic product could have been formed either by retention of configuration at both centres or by an inversion at both centres. In order to distinguish between these possibilities, we used an optically active sample of the starting material in the Mitsunobu reaction and established the configurations of the starting material and the product.

A sample of (−)-(**1a**) [enantiomeric excess (e.e.) 58%] was prepared *via* (**1d**) by fractional crystallization, followed by saponification. Its absolute stereochemistry was determined by isomerizing the double bond (*trans*- into *cis*-) of the (+)-enantiomer of (**1a**) (e.e. 35%), conveniently prepared by hydrolysis of the diastereoisomeric camphanate obtained from mother liquors of the fractional crystallization. The double bond was isomerized by treating the alcohol with silver ions in aqueous dioxane, without affecting the configuration of the carbinol carbon. The identity of the enantiomer present in excess was established by esterification with (−)-camphanoyl chloride and analysing the resulting mixture of diastereoisomers by GC.[4] The major diastereoisomer observed was the ester of (*Z*)-2-cyclo-octen-(1*S*)-ol.[5] Thus, the absolute stereochemistry of (−)-(**1a**) is (1*R*,2*R*).

The reaction product of (−)-(**1a**) (e.e. 58%) with *p*-bromobenzoic acid under Mitsunobu reaction conditions was (+)-(**1b**) (Scheme 1). Saponification followed by re-esterification of the alcohol with (−)-camphanoyl chloride yielded a mixture of diastereoisomers. The retention time of the major diastereoisomer present (e.e. 26%) was identical to that of an authentic sample of (*E*)-cyclo-oct-2-en-(1*S*)-yl camphanate. Thus, the major reaction product is formed with inversion of configuration of the chiral ring and at the carbinol carbon, consistent with an S_N2' mechanism. Inversion solely at the carbinol carbon would have yielded (**2b**). While the Mitsunobu reaction of allylic alcohols normally proceeds without rearrangement,[6] there are recent reports[7] of S_N2' processes for this reaction. The decrease in the e.e. of the product (**1b**) can be accounted for either by: (i) a competative direct esterification of the starting alcohol, and/or (ii) a two-step mechanism for the S_N2' process. The two-step reaction sequence could involve preliminary formation of an ion-pair, followed by reaction primarily, but not exclusively, at one end of the allylic system as a result of shielding by the gegen ion. Bordwell[8] has argued that S_N2' reactions proceed stepwise *via* ion-pair intermediates. Calculations by Dewar[9] show that one-bond mechanisms have activation energies that are approximately half those of analogous two-bond mechanisms.

Cope and Pawson[1b] determined that the half-life for racemization of (*E*)-cyclo-octene at 150 °C was 15 h. Whitham and Wright[2c] interconverted derivatives of (**1a**) and (**2a**) by heating them to approximately 170 °C for 18 h. It is thus remarkable that the (*E*)-cyclo-octene ring is inverted at room temperature under the present reaction conditions (2 h, room temperature). In addition to raising some very interesting questions concerning the mechanism of the reaction, the rearrangement provides a potentially valuable synthetic method for simultaneously inverting two centres in a single facile reaction.

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