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Iodocyclization Reactions for the Desymmetrization of Cyclohexa-1,4-dienes

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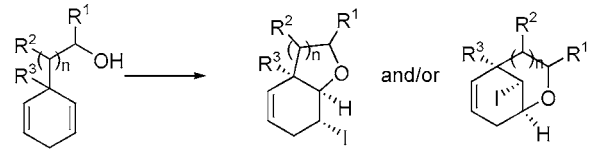
ABSTRACT



n = 0,1,2; R^1 = (functionalized) alkyl, aryl; R^2 = alkyl, aryl; R^3 = CH_2OH, H

Fifteen examples are presented showing that various modes of cyclization (5-*endo*, 5-*exo*, 6-*endo*, 6-*exo*, and 7-*endo*) can be used for the desymmetrization of cyclohexa-1,4-dienes. All take place with complete diastereocontrol and good yield.

Desymmetrization reactions have seen considerable use in organic synthesis.[1] The distinct advantage of these reactions is that a readily accessible symmetrical precursor can be converted in a single step into a stereochemically complex product, often with the formation of several stereogenic centers. Desymmetrization reactions have been applied to many classes of substrate, but cyclohexa-1,4-dienes are among the more prominent and synthetically useful.[2] These compounds are readily prepared by the Birch reduction/alkylation of aromatic compounds,[3] so that the substrate has a quaternary center which will become stereogenic upon discrimination between the cyclohexadiene double bonds.[4] Many different reactions have been used for the desymmetrization of cyclohexa-1,4-dienes, including oxidation,[5] free-radical cyclization,[6] conjugate addition,[7] and other ionic cyclizations[8] and cycloadditions.[9] In our own work, we have reported selective free-radical,[10] Prins,[11] and anionic cyclization reactions[12] onto the diastereotopic double bonds of chiral

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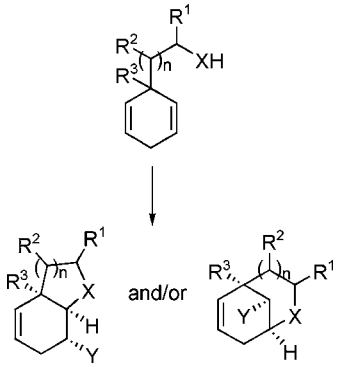
cyclohexadiene derivatives. Iodocyclization reactions permit the formation of a variety of heterocyclic ring sizes under mild conditions, often with excellent stereocontrol.[13] A number of iodocyclization reactions of cyclohexa-1,4-dienes have been reported,[14,15] although the only examples which differentiate between diastereotopic double bonds are those utilizing chiral acetals and aminals reported recently by Fujioka and Kita.[16] The corresponding cyclization reactions in which chirality is present in the tethering chain are unknown, despite their considerable synthetic potential. We can envisage the formation of a range of products via both *exo* and *endo* cyclization modes, to give varying ring sizes and positioning of substituents (Scheme 1).

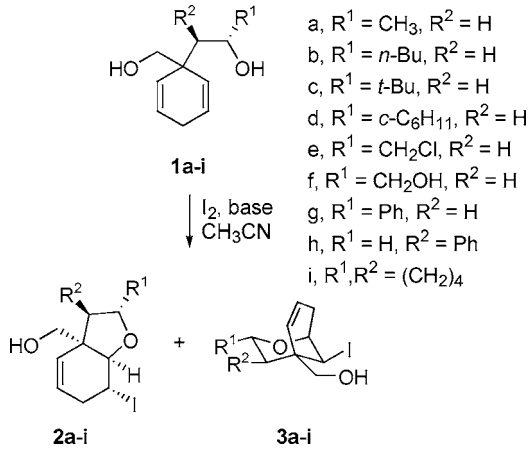
Scheme 1. Desymmetrization of a Cyclohexa-1,4-diene



We now report that 5-*exo*, 5-*endo*, 6-*exo*, 6-*endo*, and 7-*endo* iodocyclization reactions of this type proceed with essentially complete levels of diastereocontrol and good levels of regiocontrol. The requisite substrates for the first phase of the study were prepared in two steps by reaction of the anion derived from methyl cyclohexa-2,5-diene-1-carboxylate[17] with epoxides, cyclic sulfates, acid chlorides, or α-bromoketones, followed in each case by reduction as described in the Supporting Information.

With a stereogenic center adjacent to the oxygen atom (**1a**−**1g**), the cyclization reactions all proceeded smoothly and in high yield under essentially standard reaction conditions (3 equivalents of iodine, sodium carbonate or sodium hydrogen carbonate as base in acetonitrile). These reactions give predominantly the expected 5-*exo* cyclization products **2**, along with small amounts of the 6-*endo* products **3** (Table 1).

Table 1. 5-*exo* and 6-*endo* Iodocyclization Reactions of Compounds **1**



substrate	base	reaction time	ratio **2**:**3**[a]	isolated yields[b]
1a	$NaHCO_3$	30 min	11:1	**2a** (65.5%); **3a** (5.5%)
1b	Na_2CO_3	1 h	20:1	**2b** (65%)
1c	$NaHCO_3$	1 min	>99:1	**2c** (89%)
1d	Na_2CO_3	30 min	30:1	**2d** (44%)
1e	Na_2CO_3	30 min	17:1	**2e** (87%)
1f	$NaHCO_3$	1 min	19:1	**2f** (91%)
1g	Na_2CO_3	30 min	10:1	**2g** (59%); **3g** (4%)
1h	Na_2CO_3	30 min	19:1	**2h** (79%); **3h** (3%)
1i	Na_2CO_3	30 min	10:1	**2i** (62%)
1i	none	24 h	1:8	**3i** (57%)

[a] Ratios of products were determined by integration of two or more peaks in the ^1H NMR spectra of crude reaction mixtures. [b] In most cases, the 6-*endo* product was not isolated in pure form.

Both of these product types are formed by anti-cyclization onto only one of the diastereotopic double bonds, and so the reactions are completely diastereoselective. The regio- and stereochemistry of the products were determined by extensive use of NMR (COSY, NOESY, HMBC, HSQC) along with single-crystal X-ray diffraction on compounds **2c** and **2g**.[18] These reactions are consistent with an envelope transition state, in which the substituent in **1a**−**1g** is as far from the cyclohexadiene ring as possible. This is most easily seen in the Chem3D representation of the cyclizing conformations of iodoniranium ions **4** and **5** (Figure 1). In the latter, the methyl group is close to the cyclohexadiene ring. It is unlikely that coordination of iodine to only one of the double bonds is occurring. Therefore, as with other diastereoselective iodocyclization reactions, rapid reversible iodonium ion

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(18) CCDC Nos. 646880 and 646881 contain the crystallographic data for compounds **2c** and **2g**, respectively. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

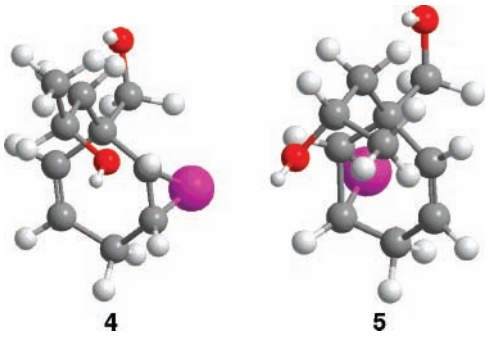


Figure 1. Favored (**4**) and disfavored (**5**) 5-*exo* cyclizations of the iodoniranium ions derived from substrate **1a**.

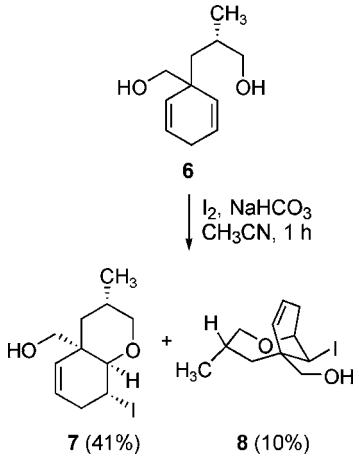
formation[19] is followed by preferential cyclization via one of the two possible transition states.

Moving the stereogenic center one atom further along the tether (substrate **1h**), the reaction is also completely diastereoselective and highly regioselective. Substrate **1i**, with a fused cyclohexane ring, is expected to lead to a particularly rigid transition state and indeed gives a completely diastereoselective and highly regioselective cyclization reaction. In this case, leaving the reaction longer leads to an isomerization reaction to compound **3i**. With the omission of base, compound **3i** becomes the major product. Although complete reversal of the reaction pathway is possible,[20] loss of iodine to form an oxiranium ion, followed by a thermodynamically favored ring opening to give the tetrahydropyran ring, is also conceivable.[21] Some isomerization from 5-*exo* to 6-*endo* was observed with the other substrates, but this was only to the extent of ca. 2% after 24 h and so is not presently synthetically useful. As shown in Table 1, with the exception of compounds **3a**, **3g**, **3h**, and **3i**, the 6-*endo* products were not isolated after chromatographic purification of the crude reaction mixtures.

The competition between 6-*exo* and 7-*endo* cyclization was also investigated. Although the regioselectivity was, as expected, somewhat lower, the diastereocontrol was, once again, complete (Scheme 2).

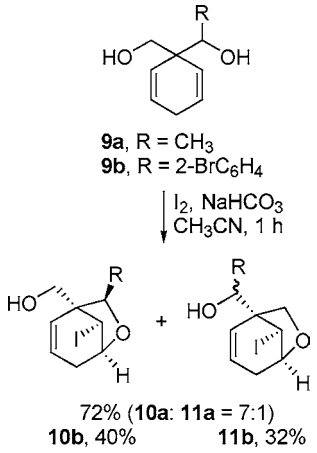
Finally, 5-*endo* cyclization reactions were investigated with substrates **9a** and **9b** (Scheme 3), in which either of the two hydroxyl groups could attack. In the case of substrate **9a**, a very useful 7:1 regioselectivity favoring attack of the secondary alcohol was observed, whereas with compound **9b** a more modest 1.25:1 regioselectivity was observed. However, in all cases, the products were formed as single stereoisomers. Although we might have expected cyclization of the secondary alcohol to proceed with some stereoselectivity, we had not expected high selectivity from cyclization

Scheme 2. Iodocyclization of Compound **6**



of the primary alcohol. Although we have no direct evidence, we presume that hydrogen bonding of the chiral secondary alcohol to the iodonium ion is responsible for the stereocontrol in this instance. The different amounts of cyclization via primary and secondary alcohols between the two compounds **9a** and **9b** are difficult to rationalize in terms of

Scheme 3. Iodocyclization of Compounds **9a** and **9b**



nucleophilicity parameters[22] and must be tentatively ascribed to conformational effects, although more work is required to understand the precise reasons for the difference.[23] Compounds **10a** and **11a** proved difficult to separate, so that only an analytical sample of each of the pure compounds was produced. As with iodolactonization onto cyclohexa-1,4-dienes,[24] we see only the 5-*endo* product and none of the 4-*exo* cyclization.[25]

The ease of preparation of hydroxymethyl-substituted cyclohexadienes stems from the use of methyl cyclohexa-

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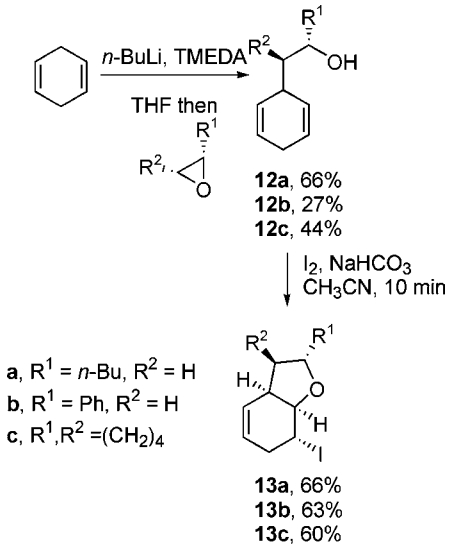
(23) This situation may be more complicated if the rate of I^+ transfer between the faces of the cyclohexa-1,4-diene ring (presumably not a unimolecular process) are comparable with the rates of ring closure.

Scheme 4. Iodocyclization of Compounds **12a**−**c**



2,5-diene-1-carboxylate as a starting material and offers considerable opportunities for further elaboration of the products. However, this is not required for successful iodocyclization, and substrates **12a**−**c** lacking this group were prepared by deprotonation[26] of cyclohexa-1,4-diene followed by reaction with an epoxide. These compounds all undergo a completely diastereoselective iodocyclization reaction to give products **13a**−**c** as shown in Scheme 4. In this case, none of the corresponding 6-*endo* cyclization product was observed.

In summary, the iodocyclization reactions of cyclohexa-1,4-diene derivatives containing a pendant hydroxy group on a chiral tether have been investigated. Essentially complete levels of diastereocontrol were obtained in 5-*endo*, 5-*exo*, 6-*exo*, 6-*endo*, and 7-*endo* cyclization modes.

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Supporting Information Available: Full experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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