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Ring Expansions of 1-Haloethynyl-2-methylcyclopentanols

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Abstract: 1-Haloethynyl-2-methylcyclopentanols treated with iodine and HTIB ring expand stereoselectively depending on the relative position of the methyl and the hydroxyl groups. The products are *2*-(dihalomethylidene)-3-methylcyclohexanones if the methyls are *cis* to the hydroxyl groups or 2-(dihalomethylidene)-6-methylcyclohexanones if the methyls are *trans* to the hydroxyls.

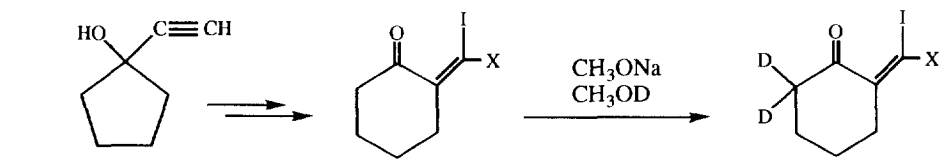
The use of iodonium-producing reagents with haloalkynols to afford β,β-dihaloenones has opened up a synthetic approach to tri- and tetra-substituted ethenes of therapeutic utility such as tamoxifen and clomiphene.[1] The haloenones serve as templates for the preparations of a broad range of such compounds *via* exchanges with organometallic compounds of tin or zinc, catalyzed by palladium complexes.[2] Preferential exchange of iodine over bromine has been noted in these systems.[3] Since the iodine from most iodonium-producing reagents is usually *syn* to the carbonyl, the exchanged products are stereospecifically positioned, unlike the standard preparative modes involving Grignard reactions with ketones followed by dehydration.[4]

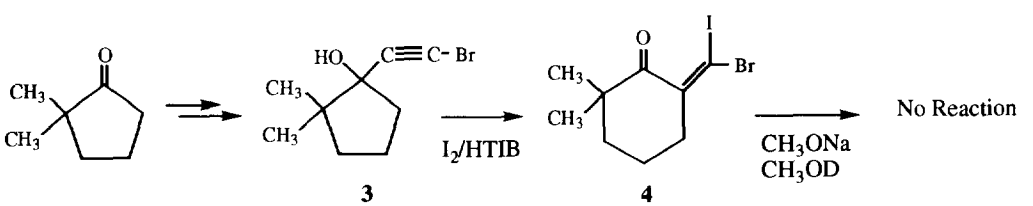
The stereospecific shift reaction has been applied as well to ring expansions. Bromoethynol derivatives of norcamphor, camphor, fluorenone and adamantanone have been converted to their corresponding expanded rings containing *(Z)*-β,β-bromoiodoenones.[5-8]

Initial results of such a reaction for the bromoalkynols of cyclopentanone and the 2-methyl derivatives thereof have also been reported.[9] The reaction of 1-(bromoethynyl)-2-methylcyclopentanol gave a mixture of ketones. Only one ketone was isolated. It is the purpose of this report to present the nature of that mixture and its important implications for ring expansions in general and in shifts to vinyl cations in particular.

An initial consideration was the clarification of ^{1}H-NMR assignments for the cyclohexanones of the series. Of particular interest were the signals of the protons adjacent to the carbonyl and those allylic in the enone grouping. These were not distinguished in a major report on forming such compounds by Wittig-type reactions.[10] For 2-(diiodomethylidene)cyclohexanone (**1a**), whose preparation is given in this paper, the values are δ 2.48 (t, 2H, J = 6.3 Hz) and 2.64 (t, 2H, J = 6.3 Hz). For 2-*(Z)*-(bromoiodomethylidene)cyclohexanone (**1b**), the signals of interest were δ 2.50 (t, 2H, J = 6.6 Hz) and 2.74 (t, 2H, J = 6.2 Hz). Deuterium exchange on **1a** (M^+, 362) afforded **2a** (M^+, 364). The dideuterated **2a**

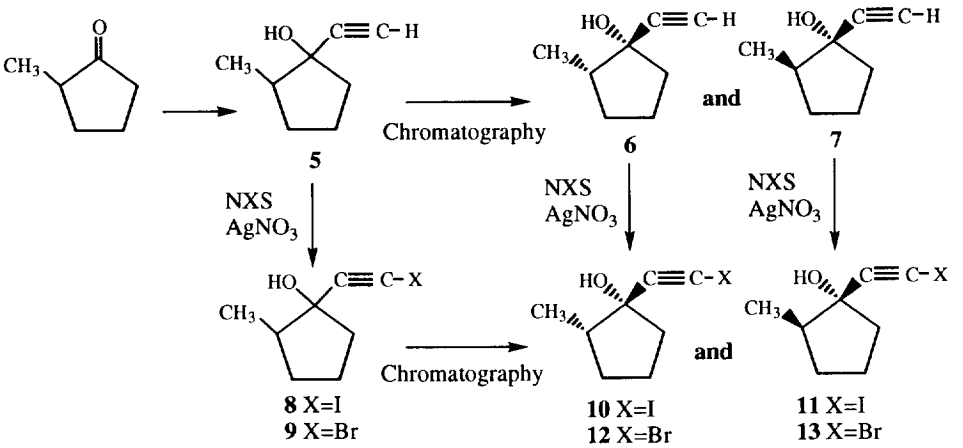
exhibited a triplet at 2.64 ppm and nothing at 2.48 ppm. Deuterium exchange on **1b** (M^+, 316/314) afforded **2b** (M^+, 318/316). The dideuterated **2b** exhibited a triplet at 2.75 ppm and nothing at 2.48 ppm. In the ^{13}C-NMR of **2a** and **2b** absorbances at 43 and 202 ppm present in **1a** and **1b** were absent due to increased relaxation times and the concomitant splitting caused by the deuterium atoms on the C-6 atoms. Thus the higher values in the ^1H-NMR can be used as a diagnostic tool to determine direction of ring expansion of a cyclopentyl alkynol to a β,β-dihalocyclohexenone and the ^{13}C-NMR differences can be used to aid assignments of positions of deuteration. Directly to that point is the case of the reaction of 1-(bromoethynyl)-2,2-dimethylcyclopentanol (**3**) with iodine and [(hydroxy)(tosyloxy)iodo]benzene (HTIB). The ^1H-NMR spectrum of the product cyclohexanone had the multiplet at 2.68-2.76 ppm without any signals between it and a multiplet at 1.75 ppm associated with the four other methylene protons. The assigned structure is *(Z)*-2-(bromoiodomethylidene)-6,6-dimethylcyclohexanone (**4**). The original assignment of the 3,3-dimethyl isomer is incorrect.[9] As further support, the deuterium exchange conditions that were used in the conversions of **1a** and **1b** to **2a** and **2b** did not lead to the incorporation of any deuterium in **4**. If the product were the 3,3-dimethyl isomer with its two protons α to a ketone, there would have been deuterium uptake. Further the reduction product of **4** with $NaBH_4/CeCl_3$ exhibited a singlet at 4.18 ppm for the proton at C-1 rather than a multiplet if it had been the originally proposed isomer.





Since **4** was the chief product, its reaction path would require a shift of the less substituted carbon (C-5) rather than the more substituted carbon (C-2) of **3**. This situation might be applicable to the 2-methyl relatives of **3**. 1-Ethynyl-2-methylcyclopentanol (**5**) was converted to 1-(iodoethynyl)-2-methylcyclopentanol (**8**) by *N*-iodosuccinimide (NIS) and catalytic amounts of silver nitrate in acetone.[10] The corresponding 1-(bromoethynyl) compound (**9**) was prepared similarly with NBS. Compound **9** and its reaction with iodine and HTIB had been studied previously.[9] From that reaction two products were detected and assigned as *(E)* and *(Z)*-2-(bromoiodomethylidene)-3-methylcyclohexanone, but only the latter was isolated. In the present work, ring expansion of 1-(iodoethynyl)-2-methylcyclopentanol (**8**) also gave two products. Since these products could not exhibit *(E)/(Z)* stereochemistry, the products reflected two possible

shifts - one from a tertiary center to give a 3-methylcyclohexanone and one from a secondary center to lead to a 6-methylcyclohexanone. This prompted a renewed search for the missing 6-methyl isomers in the bromoalkynol reaction. Since **8** and **9** should be mixtures of *cis* and *trans* isomers (defined as the relative position of the methyl and the hydroxyl), one isomer might preferentially give rise to one product and the other isomeric alkynol to the second methylcyclohexanone.



5 **6** **7**

8 X=I
9 X=Br

10 X=I
12 X=Br

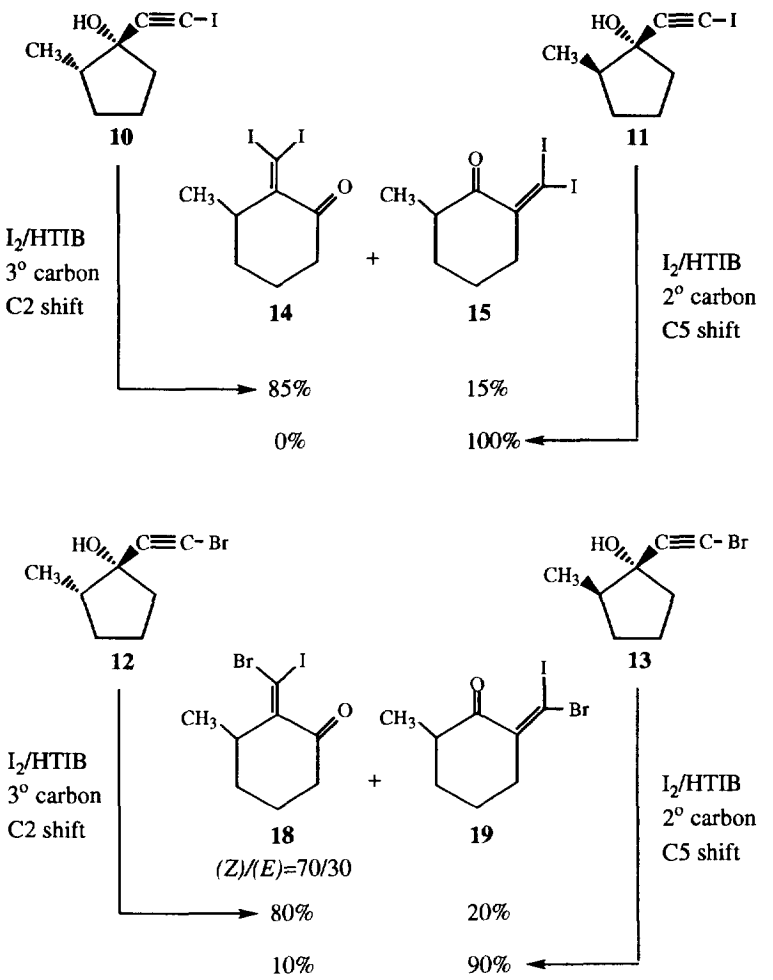
11 X=I
13 X=Br

To test this hypothesis, we separated the *cis* **10** or **12** from the *trans* **11** or **13** by chromatography and then subjected each to ring expansion. Chromatographic separations were successful on the haloalkynols **8** and **9** as well as on the simple unhalogenated alkynol mixture (**5**). A column chromatography on **5** afforded enough of **6** and **7** to react them with the appropriate *N*-halosuccinimide and to relate them with the haloalkynols **10**, **11**, **12** and **13** by the use of ^{1}H-NMR and the retention times on the GC.

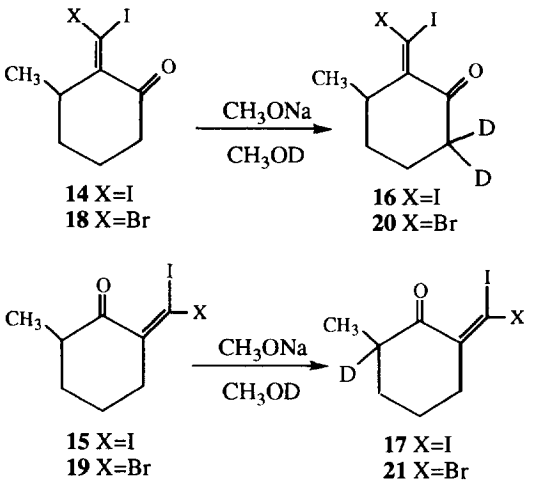
The critical assignments of **6** and **7** were based on the differences in the ^{13}C-NMR spectra for the 2-methyl carbons. One isomer displayed a peak at 12.9 ppm and the other at 16.8 ppm. This difference of about 4 ppm had been noted by Cannone and Bernatchez in their compilation of such values for eight *cis/trans* pairs of 2-methyl-1-susbtituted cyclopentanols.[11] The lower values were associated with those isomers wherein the OH and the CH_3 were *cis* to one another. The extensions to the 1-alkynyl mixture **5** would be that the isomer with the 12.9 ppm signal would be the *cis* or the *(1RS,2SR)* compound designated as **6**. Then the isomer with the 16.8 ppm peak is **7**, the *trans* or *(1RS,2RS)* structure. Consonant with this effect are the following 2-methyl values for the components of **8** and **9** : 13.1 (**10**), 17.1 (**11**), 13.0 (**12**), and 17.0 (**13**).

Each isomer gave one major product (80% to 100% of the product mixture) as shown in the scheme. The *trans* alkynols **11** and **13** were converted chiefly to **15** and **19**, respectively. The *cis* alkynols **10** and **12**, which featured shifts of tertiary carbons, afforded the principal products **14** and **18**, respectively.

As a check that such shifts were not restricted to the I_2/HTIB system, the reaction of bromoalkynol **13** was carried out with *N*-iodosuccinimide and catalytic amounts of *p*-toluenesulfonic acid (NIS/TsOH) in aqueous (5%) acetonitrile. The same values for the ring-expanded products **19** (90%) and **18** (10%) were obtained.



The proofs of structure of the products came from deuterium exchange experiments. The ketones **14** and **18** exchanged two hydrogens for deuteriums to give compounds **16** and **20**. The ketones **15** and **19** exchanged a single hydrogen for deuterium to give compounds **17** and **21**. The *cis* isomers shifted from the more substituted (C2) carbon to give 3-methylketones; the *trans* isomers shifted from the less substituted carbon (C5) to give 6-methylketones.



14 X=I
18 X=Br

16 X=I
20 X=Br

15 X=I
19 X=Br

17 X=I
21 X=Br

The ^{1}H-NMR spectra of the deuterated compounds **16** and **20** lacked the two proton multiplets between 2.36 and 2.48 ppm due to protons α to the carbonyls of **14** and **18**. The ^{13}C-NMR spectra of **16** and **20** also featured absences of peaks at 43 and 202 ppm due to increased relaxation times of the carbonyl atoms and those of the dideuterared C-2 positions which had associated splitting by deuterium atoms. For the deuterated forms **17** and **21**, the proton exchanges at the C-6 atoms were apparent by the changes from doublets for the methyl groups in **15** and **19** to singlets in **17** and **21**. The ^{13}C-NMR spectra of **17** and **21** also lacked the C-1 and C-6 signals at 47 and 205 ppm noted for **15** and **19**. The mass spectra were futher confirmants of deuterium uptakes. The parent peaks of interest of related pairs were as follows: **14** (376) and **16** (378); **18** (330, 328) and **20** (332, 330); **15** (376) and **17** (377); **19** (330, 328) and **21** (331, 329).

Product ratios of ketones derived from *cis/trans* mixtures could also be calculated based on the results with the pure isomers. For example, a 45/55 mixture of **10** and **11** was expected to give a 40/60 mixture of **14** and **15**. The experimental ratio was found to be 40/60. A 40/60 mixture of **12/13** was expected to give a 40/60 mixture of **18** and **19**. The experimental ratio was 30/70.

Of interest are the ^{13}C-NMR spectra of the dihaloenones, wherein striking upfield signals are seen for the dihalomethylidene carbon atoms. For the bromoiodomethylidenes of **1b**, **4**, **18**, and **19** the values are δ 54.8, 52.3, 52.8 and 52.2, respectively. The corresponding values of the diiodo form of **1a**, **14**, and **15** are δ 16.5, 14.2 and 13.6, respectively. The iodine atom also exhibits a profound up-field shift for the alkynols. For example, the δ's of alkynyl carbons bearing halogen are as follows: **12**, 43.8; **10**, 0.1; **13**, 46.0; **11**, 2.1. The signals for 1-(bromoethynyl)cyclopentanol and its iodoethynyl analogue are 59.0 ppm and 0.6 ppm.

The rationale of the ring expansions can be found by considering the steric interaction between the methyl and the ethynyl halogen in the transition state. The first step of the reaction is the production of an iodonium ion by the system I_2/HTIB or NIS/TsOH. Such an ion will react with the alkyne to form a vinylic iodonium bridge. In order for the ring expansion to proceed, the iodonium bridge has to be *anti* to the shifting bond. Such an array requires that during the shift the ethynyl halogen will be moving towards the side of the shifting group to accommodate the new sp^2 geometry. When the methyl and the haloalkynyl are *syn*, steric interactions retard a tertiary carbon (C2) shift and favor a secondary carbon (C5) shift. (Fig. 1)

Reinforcement of this explanation can be seen by comparing iodoalkynol **11** and bromoalkynol **13**. Since iodine is larger than bromine, the steric effects of the *syn* arrangements should be more severe for an iodoalkynol *versus* a bromoalkynol. Such is the case. The iodoalkynol shifts are exclusively from the C5 whereas the bromo shifts are 90%. In the case of the *cis* isomers wherein the methyls and the haloethynyl groups are *anti*, no similar steric effects exist. Therefore the shifts occur largely from the more substituted carbon (C2) regardless of the type of halogen. In the shifts of the secondary carbons interactions between the bridging iodonium ions and the adjacent methyls are minimized as the iodine atoms move parallel and away from the methyl groups as sp^2 bondings increase. In the light of these results, we can now understand why the 1-bromoethynyl-2,2-dimethylcyclopentanol shifted only from C5. Whatever the orientation of the alkynyl fragment, it will still be *cis* to a methyl group (Fig. 1) and should behave as **11** or **13**.

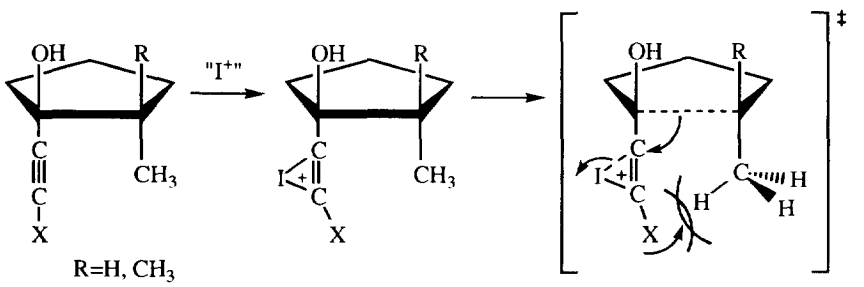


Fig. 1

These results provide guide rails for possible extensions to other ring sizes and groups other than methyl for cyclopentanols. Applications of the latter would be D-ring expansions of steroids bearing alkynols such as norethisterone and mifepristone. The procedure has already been utilized for the ring expansion of a pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane derivative.[12] These findings can also be coupled with the conversion of β,β-dihaloenones with base to remove the dihalomethylidene portion of the ring-expanded dihaloenones as shown by Djuardi.[5] This would be a final step in a sequence that could lead to a general procedure for the homologation of ketones. Thus in this simple application, a 2-methylcyclopentanone could be converted into either 2-methylcyclohexanone or 3-methylcyclohexanone through steps of haloalkynylation, stereospecific ring expansion to a dihaloenone and dihalomethylidene removal. As shown in this report the first two steps proceed in high yield and efforts are afoot to improve and expand the last step.

EXPERIMENTAL SECTION

Melting points are uncorrected and were taken on a Hoover-Thomas melting point apparatus. IR spectra were obtained with a Polaris FTIR Mattson Instruments spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian Gemini 200 operating in the Fourier Transform mode at 200 MHz. GC and MS analyses were carried out on a Hewlett Packard GC/MS HP5890 with a HP-5 column (95% methyl silicone, 0.25 mm x 30 m). Elemental analyses were performed by the E+R Microanalytical Laboratory, Corona, New York and the

Schwartzkopf Microanalytical Laboratory, Woodside, New York.

Ketones, ethynylmagnesium bromide and methanol-d were obtained from the Aldrich Chemical Co. Methylene chloride, chloroform, tetrahydrofuran, acetonitrile and sodium methoxide were obtained from Fisher Scientific. Ethynylcyclopentanol was obtained from Farchan Laboratories. THF was freshly distilled from sodium benzophenone ketyl. HTIB was prepared from (diacetoxyiodo)benzene (purchased from Lancaster Synthesis) using the procedure of Neiland and Karele.[13] All chromatographies were carried out on J. T. Baker silica gel (40-140 mesh) except when noted otherwise.

2-(Diiodomethylidene)cyclohexanone (1a)

1-Ethynylcyclopentanol (2.28 g, 20.75 mmol) was reacted with NIS (4.92 g, 21.88 mmol) and silver nitrate (363.9 mg, 2.14 mmol) in 75 mL of acetone following the procedure of Hofmeister[10] to give a white solid (3.85 g, 79%) of 1-(iodoethynyl)cyclopentanol: mp 43-44 °C; ^{1}H-NMR ($CDCl_3$) δ 1.71-1.92 (m, 8H), 2.25 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 0.6(C-I), 24.0, 43.0, 76.6, 98.7; IR (neat) 3350(s), 2980(s), 2870(s), 2180(w), 1210(s), 1075(m), 1000(s) cm^{-1}; MS *m/z* (rel. int.) 208(19, M^+-18), 207(46), 194(24), 178(40), 126(20), 109(25), 81(100), 79(70). Anal. Calcd. for C_7H_9IO: C, 35.58; H, 3.85. Found: C, 35.90; H, 3.60.

1-(Iodoethynyl)cyclopentanol (2.62 g, 11.12 mmol) was dissolved in 150 mL of acetonitrile. A single portion of iodine (2.87 g, 11.31 mmol) and HTIB (4.36 g, 11.13 mmol) was added to the solution which was protected from light and stirred overnight. The reaction mixture was diluted with ether (200 mL). The organic phase was washed three times with saturated sodium thiosulfate (50 mL) and twice with brine (25 mL) and dried over magnesium sulfate. After evaporation of the solvents under reduced pressure, the residue was chromatographed with hexanes/methylene chloride (1/1) to afford a yellow solid (2.54 g, 63%) of 2-(diiodomethylidene)cyclohexanone: mp 52-54 °C; ^{1}H-NMR ($CDCl_3$) δ 1.76-1.98 (m, 4H), 2.46 (t, 2H, *J* = 6.6 Hz), 2.63 (t, 2H, *J* = 6.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 16.5(CI_2), 25.7, 26.7, 42.9, 43.1, 153.9, 202.3; IR (neat) 2940(s), 2860(m), 1690(s), 1560(m), 1250(s), 1230(s), 1140(s), 1120(s), 750(s) cm^{-1}; MS *m/z* (rel. int.) 362(100, M^+), 334(21), 235(35), 165(49), 127(16), 108(18), 80(98), 79(71). Anal. Calcd for $C_7H_8I_2O$: C, 23.23; H, 2.23. Found: C, 23.26; H, 2.25.

2-(Diiodomethylidene)cyclohexanone-6,6-d_2 (2a)

2-(Diiodomethylidene)cyclohexanone (**1a**) (78.8 mg, 0.218 mmol) was dissolved in 5 mL of methanol-d. To the solution was added sodium methoxide (100 mg, 1.85 mmol). The reaction was stirred overnight under a nitrogen atmosphere. The reaction mixture was quenched with acetic acid-d4 (1 mL) and evaporated to dryness. The residue was dissolved in ether (30 mL), washed with brine (2x5 mL) and dried over magnesium sulfate. After removal of the solvents under reduced pressure, a residue was chromatographed with hexanes/methylene chloride (20%) as eluant to yield a white solid (44.7 mg, 56%) of **2a** : mp 52-53 °C ^{1}H-NMR ($CDCl_3$) δ 1.76-1.95 (m, 4H), 2.64 (t, 2H, *J* = 5.8 Hz); ^{13}C-NMR ($CDCl_3$) δ 16.4(CI_2), 25.7, 26.5, 43.1, 153.9; IR(neat) 2940(m), 2870(w), 2230(w), 1700(s), 1565(w), 1460(w), 1450(w), 1440(w), 1265(w), 1255(m), 1155(w), 1120(m), 1005(w) cm^{-1}; MS *m/z* (rel. int.) 364(100, M^+), 336(18), 237(31), 179(11), 165(60), 127(21), 110(19), 82(99), 81(88), 80(35).

(Z)-2-(Bromoiodomethylidene)cyclohexanone-6,6-d_2 (2b)

(Z)-2-(Bromoiodomethylidene)cyclohexanone **(1b)** (35 mg, 0.11 mmol) was reacted with sodium methoxide (50 mg, 0.93 mmol) in 5 mL of methanol-d and purified as above to give a yellow liquid (22 mg, 63%) of **2b** : ^{1}H-NMR ($CDCl_3$) δ 1.75-1.95 (m, 4H), 2.75 (t, 2H, J = 6.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 25.1, 25.8, 37.0, 54.7(CBrI), 148.2; IR(neat) 2930(m), 2860(m), 2845(w), 1700(s), 1560(m), 1505(m), 1255(m), 1120(m), 765(m) cm^{-1}; MS *m/z* (rel. int.) 318(21, M$^+$), 316(21, M$^+$), 290(16), 288(16), 165(13), 127(25), 119(17), 117(16), 81(100).

(Z)-2-(Bromoiodomethylidene)-6,6-dimethylcyclohexanol

(Z)-2-(Bromoiodomethylidene)-6,6-dimethylcyclohexanone **(4)** (43.0 mg, 0.125 mmol) was dissolved in 10 mL of methanol. Cerium trichloride (52.0 mg, 0.211 mmol) was added and allowed to stand for 5 mn. Sodium borohydride was then added until the reaction was complete as shown on TLC. The reaction mixture was diluted with 50 mL of ether and washed three times with 5 mL of brine. After a drying over $MgSO_4$, a removal of solvents under reduced pressure and chromatography with hexanes/methylene chloride (1/1), a yellow liquid (23.3 mg, 54%) of *(Z)*-2-(bromoiodomethylidene)-6,6-dimethylcyclohexanol was obtained: ^{1}H-NMR ($CDCl_3$) δ 0.88 (s, 3H), 1.06 (s, 3H), 1.40-1.60 (m, 3H), 1.74 (dt, 2H, J = 4.8 Hz, J = 13 Hz), 2.18 (dt, 1H, J = 5.7 Hz, J = 13.1 Hz), 2.94 (dt, 1H, J = 1.3 Hz, J = 13.1 Hz), 4.18 (s,1H); ^{13}C-NMR ($CDCl_3$) δ 22.6, 23.4, 27.9, 30.0, 33.0, 38.0, 50.9, 83.3, 112.8; IR(film) 3420(s), 2935(s), 2875(s), 1590(w), 1460(m), 1035(s), 910(s) cm^{-1}; MS *m/z* (rel. int.) 346(M$^+$, 10), 344(M$^+$, 10), 265(6), 219(25), 217(26), 138(100), 137(79), 119(37), 109(57), 41(38).

***(1RS, 2SR) / (1RS, 2SR)*-1-Ethynyl-2-methylcyclopentanol (5)**

2-Methylcyclopentanone (500 mg, 5.1 mmol) was dissolved in 20 mL of THF and a solution of ethynylmagnesium bromide (60 mL, 0.5 M, 30 mmol) was added under nitrogen. The solution was kept strirring for 30 mn. The reaction mixture was diluted with 300 mL of ether which was washed twice with 25 mL of brine. After a drying over magnesium sulfate and removal of the solvents under reduced pressure, a yellow liquid (360 mg, 55%) of **(5)** was obtained.

***(1RS, 2 SR)*-1-Ethynyl-2-methylcyclopentanol (6) and *(1RS, 2 RS)*-1-ethynyl-2-methylcyclopentanol (7)**

Chromatography of the *cis/trans* mixture **5** with hexanes/methylene chloride (10%) as eluant, afforded first **6** and then **7.** The spectral data for **6** are as follows: ^{1}H-NMR ($CDCl_3$) δ 1.07 (d, 3H, J = 6.7 Hz), 1.37-2.06 (m, 8H), 2.43 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 12.9, 21.9, 31.3, 42.1, 46.7, 71.6, 76.1, 87.6; IR(neat) 3430(s), 3310(s), 2960(s), 2875(s), 1460(m), 1375(m), 1335(m), 1290(m), 1205(m), 1150(m), 1075(m), 1030(m), 1010(m), 995(m), 950(s), 915(m), 850(m), 650(s), 625(s) cm^{-1}; MS *m/z* (rel. int.) 123(18, M$^+$-1), 109(55), 96(40), 95(69), 91(27), 81(100), 68(84), 67(41). The spectral data for **7** are as follows: ^{1}H-NMR ($CDCl_3$) δ 1.04 (d, 3H, J = 6.7 Hz), 1.22-1.42 (m, 2H), 1.65-2.77 (m, 6H), 2.53 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 16.8, 21.0, 31.5, 41.4, 46.1, 74.3, 78.8, 86.0; IR (film) 3380(s), 3300(s), 2960(s), 2870(s), 2129(w), 1460(m), 1380(m), 1310(m), 1200(m), 1080(s), 1040(s), 990(m), 950(m), 910(m), 650(s), 620(s) cm^{-1}; MS *m/z* (rel. int.) 123(19, M$^+$-1), 109(56), 96(41), 95(66), 91(26), 81(100), 68(89), 67(37).

(*1RS,2SR*)-1-Iodoethynyl-2-methylcyclopentanol (10) and (*1RS,2RS*)-1-iodoethynyl-2-methylcyclopentanol (11)

Cis/trans-1-ethynyl-2-methylcyclopentanol (**5**) (360 mg, 1.44 mmol) was dissolved in 75 mL of acetone. NIS (750 mg, 3.33 mmol) and silver nitrate (80 mg, 0.47 mmol) were added and the solution was protected from light. After a stirring of 1 h the acetone was evaporated and the residue was dissolved in 200 mL of ether, which was washed with twice with 25 mL of saturated sodium thiosulfate and twice with brine. After a drying over $MgSO_4$ and solvent removal a yellow liquid of **8** (640 mg, 90%) was obtained.

Chromatography of the *cis/trans* mixture **8** with hexanes/methylene chloride (5%) as eluant afforded first **10** and then **11**. The spectral data for **10** are as follows: ^{1}H-NMR ($CDCl_3$) δ 1.07 (d, 3H, J = 6.8 Hz), 1.37-1.51 (m, 1H), 1.60-2.09 (m, 6H), 1.73 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 0.1(C-I), 13.1, 22.0, 31.3, 42.2, 46.9, 78.0, 98.1; IR(neat) 3560(m), 3420(s), 2960(s), 2870(s), 1455(m), 1380(m), 1335(m), 1290(m), 1210(s), 1150(m), 1090(m), 1030(s), 1010(m), 990(m), 945(s), 915(m), 845(m) cm^{-1}; MS *m/z* (rel. int.) 232(15, M$^+$-18), 217(3), 207(17), 194(33), 179(49), 127(42), 105(16), 103(15), 95(100), 79(27), 77(27), 67(53). Anal. Calcd for $C_8H_{11}IO$: C, 38.42; H, 4.43. Found: C, 38.40; H, 4.84. The analytical data for **11** are as follows: ^{1}H-NMR ($CDCl_3$) δ 1.05 (d, 3H, J = 6.5 Hz), 1.29-1.46 (m, 1H), 1.65-2.17 (m, 6H), 2.22 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 2.1(C-I), 17.1, 21.1, 31.6, 41.4, 46.7, 80.7, 96.8; IR(neat) 3600-3100(s), 2960(s), 2930(s), 2870(s), 2175(w), 1640(w), 1630(w), 1455(m), 1380(m), 1365(m), 1315(m), 1195(m), 1150(w), 1080(s), 1030(m), 995(m), 955(m) cm^{-1}; MS *m/z* (rel. int.) 232(50, M$^+$-18), 217(9), 207(20), 194(38), 179(51), 127(69), 105(30), 103(35), 95(100), 79(52), 77(52), 67(52). Anal. Calcd for $C_8H_{11}IO$: C, 38.42; H, 4.43. Found: C, 38.36; H, 4.32.

(*1RS,2SR*)-1-Bromoethynyl-2-methylcyclopentanol (12) and (*1SR,2RS*)-1-bromoethynyl-2-methylcyclopentanol (13)

Cis/trans-1-ethynyl-2-methylcyclopentanol (**5**) (2.42 g, 19.52 mmol), NBS (3.5 g, 19.77 mmol) and silver nitrate (770 mg, 4.53 mmol) were reacted in 200 mL of acetone and purified as above to give a yellow liquid of **9** (3.43 g, 87%) was obtained.

Chromatography of the *cis/trans* mixture **9** with hexanes/methylene chloride (5%) as eluant afforded first **12** and then **13.** The spectral data for **12** are as follows: ^{1}H-NMR ($CDCl_3$) δ 1.06 (d, 3H, J = 6.8 Hz), 1.42 (dt, 1H, J = 6 Hz, J = 10.7 Hz), 1.61-1.91 (m, 4H), 1.95-2.07 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ 13.0, 22.0, 31.2, 42.0, 43.8(CBr), 46.7, 77.3, 83.5; IR(neat) 3440(m), 2960(s), 2880(m), 1460(m), 1370(m), 1300(m), 1210(m), 1040(m), 1015(m), 995(s), 830(s) cm^{-1}; MS *m/z* (rel. int.) 186(5, M$^+$-18), 184(5, M$^+$-18), 161(23), 159(23), 148(51), 146(51), 133(29), 131(29), 105(12), 95(100), 79(24). Anal. Calcd for $C_8H_{11}BrO$: C, 47.32; H, 5.46. Found: C, 47.80; H, 5.74. The corresponding data for **13** are as follows: ^{1}H-NMR ($CDCl_3$) δ 1.03 (d, 3H, J = 6.6 Hz), 1.25-2.15 (m, 7H), 2.29 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 17.0, 21.1, 31.6, 41.2, 46.0(CBr), 46.5, 80.1, 82.2; IR (neat) 3360(s), 2960(s), 2880(s), 2210(m), 1460(m), 1380(m), 1200(m), 1035(m), 960(m) cm^{-1}; MS *m/z* (rel. int.) 186(6, M$^+$-18), 184(6, M$^+$-18), 161(16), 159(16), 148(31), 146(33), 133(34), 131(36), 119(50), 95(100), 79(31). Anal. Calcd for $C_8H_{11}BrO$: C, 47.32; H, 5.46. Found: C, 47.75; H, 5.77.

2-(Diiodomethylidene)-3-methylcyclohexanone (14) and 2-(diiodomethylidene)-6-methylcyclohexanone (15)

A 45/55 mixture of *(1RS,2RS)/(1RS,2SR)*-1-iodoethynyl-2-methylcyclopentanol (165 mg, 0.66 mmol) (**8**), iodine (180 mg, 0.7 mmol) and HTIB (265 mg, 0.67 mmol) were stirred overnight in 15 mL of acetonitrile. The reaction mixture was diluted with 100 mL of ether which was washed twice with 25 mL of saturated sodium thiosulfate and twice with 25 mL of brine. After a drying over magnesium sulfate and removal of the solvents under reduced pressure, a residue was chromatographed on silica gel with hexanes/methylene chloride (1/1) as eluant. A yellow liquid (160 mg, 64%), a 40/60 mixture of **14** and **15** was obtained. Further separation on silica gel (Fisher, 230-400 mesh) using hexanes/methylene chloride 2.5% as eluant, afforded pure samples of first **15** and then **14**.

2-(Diiodomethylidene)-3-methylcyclohexanone (14)

A sample of **10** (30 mg, 0.12 mmol) was reacted with iodine (36.1 mg, 0.142 mmol) and HTIB (52 mg, 0.132 mmol). The product was purified as above to give a brown liquid (27.2 mg, 60%) an 85/15 mixture of **14** and **15**. Further separation as above afforded pure **14** as a yellow solid: mp 108-109 °C; ^{1}H-NMR ($CDCl_3$) δ 1.00 (d, 3H, J = 7.2 Hz), 1.59-1.73 (m, 1H), 1.87-2.13 (m, 3H), 2.40-2.48 (m, 2H), 3.20-3.35 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 14.2(CI_2), 17.3, 22.4, 31.9, 43.2, 47.1, 159.0, 203.5; IR(film) 2965(m), 2945(m), 2870(w), 1695(s), 1650(w), 1455(w), 1245(m), 1125(m), 1080(m) cm^{-1}; MS *m/z* (rel. int.) 376(100, M$^+$), 249(47), 221(14), 179(63), 165(13), 127(46), 122(25), 94(66), 79(86). Anal. Calcd for $C_8H_{10}I_2O$: C, 25.54; H, 2.68. Found: C, 25.85; H, 2.39.

2-(Diiodomethylidene)-6-methylcyclohexanone (15)

A sample of **11** (345.8 mg, 1.383 mmol) was reacted with iodine (370 mg, 1.46 mmol) and HTIB (570 mg, 1.46 mmol). The product was purified as above to give a yellow solid (194.5 mg, 37%) of **15** : mp 96-97 °C; ^{1}H-NMR ($CDCl_3$) δ 1.14 (d, 3H, J = 6.5 Hz), 1.44-1.98 (m, 3H), 2.04-2.19 (m, 1H), 2.29-2.61(m, 2H). 2.91(ddt, 1H, J = 2.3, 4.2, 14.6 Hz) ; ^{13}C-NMR ($CDCl_3$) δ 13.6(CI_2), 15.3, 25.0, 36.0, 43.9, 47.1, 155.8, 205.3; IR(film) 2970(w), 2935(m), 2865(w), 1705(s), 1560(w), 1455(w), 1245(w), 1220(w), 1180(w), 1130(m), 1080(w), 1005(w), 850(w) cm^{-1}; MS *m/z* (rel. int.) 376(M$^+$, 56), 348(18), 254(7), 221(31), 179(17), 165(58), 127(37), 94(75), 79(100). Anal. Calcd for $C_8H_{10}I_2O$: C, 25.54; H, 2.68. Found: C, 25.74; H, 2.44.

2-(Diiodomethylidene)-3-methylcyclohexanone-6,6-d_2 (16)

2-(Diiodomethylidene)-3-methylcyclohexanone (**14**) (80.5 mg, 0.244 mmol) was reacted with sodium methoxide (90 mg, 1.67 mmol) in 5 mL of methanol-d and purified as previously described to give a yellow solid (54.7 mg, 68%) of **16**: ^{1}H-NMR ($CDCl_3$) δ 1.01 (d, 3H, J = 7.2 Hz), 1.59-1.73 (m, 1H), 1.86-2.13 (m, 3H), 3.21-3.34 (m, 1H) ; ^{13}C-NMR ($CDCl_3$) δ 14.2(CI_2), 17.3, 22.2, 31.8, 47.4, 159.0; IR(film) 2960(m), 2945(m), 2930(m), 2870(w), 2855(w), 2230(w), 1695(s), 1555(w), 1465(w), 1450(w), 1380(w), 1260(m), 1165(m), 1115(m), 1030(w) cm^{-1}; MS *m/z* (rel. int.) 378(M$^+$, 100), 251(52), 223(17), 205(10), 179(91), 165(17), 127(75), 95(66), 81(63)

2-(Diiodomethylidene)-6-methylcyclohexanone-6-d (17)

2-(Diiodomethylidene)-6-methylcyclohexanone **(15)** (168.0 mg, 0.447 mmol) was reacted with sodium methoxide (120 g, 2.22 mmol) in 5 mL of methanol-d and purified as previously described to give a white solid (95.7 mg, 57%) **17** : mp 95-96 °C; ^{1}H-NMR ($CDCl_3$) δ 1.11 (s, 3H), 1.45-1.94 (m, 3H), 2.04-2.16(m, 1H), 2.28-2.44 (m, 1H), 2.89 (ddt, 1H, *J* = 2.2, 4.2, 14.6 Hz); ^{13}C-NMR ($CDCl_3$) δ 13.6(CI_2), 15.2, 24.9, 35.8, 43.9, 155.8; IR(film) 2970(w), 2940(m), 2865(w), 2255(w), 1705(s), 1575(w), 1560(w), 1455(w), 1380(w), 1280(w), 1255(w), 1180(w), 1165(w), 1120(m), 995(w) cm^{-1}; MS *m/z* (rel. int.) 377(M^+, 65), 349(24), 292(41), 222(32), 179(23), 165(83), 127(60), 94(94), 80(100).

***(E)/(Z)*-2-(Bromoiodomethylidene)-3-methylcyclohexanone (18) and *(Z)*-2-(Bromoiodomethylidene)-6-methylcyclohexanone (19)**

A 50/50 mixture of *(1RS,2RS)/(1RS,2SR)*-1-bromoethynyl-2-methylcyclopentanol **(9)** (210 mg, 1.034 mmol) was reacted with iodine (260 mg, 1.024 mmol) and HTIB (410 mg, 1.046 mmol). The product was separated as before to give a yellow liquid (160 mg, 47%), a 50/50 mixture of **18** and **19**. Further purification on silica gel afforded pure samples of first **19** and then **18**.

***(E)/(Z)*-2-(Bromoiodomethylidene)-3-methylcyclohexanone (18)**

A sample of **12** (50 mg, 0.246 mmol) was reacted with iodine (67.5 mg, 0.266 mmol) and HTIB (101 mg, 0.257 mmol). The product was purified as above to give a yellow liquid (33 mg, 41%), a 80/20 mixture of **18** and **19** . Further separation afforded **18** (*(Z)/(E)*=70/30): ^{1}H-NMR ($CDCl_3$) δ 0.99 (d, 3H, *J* = 6.8 Hz, *(E)* isomer), 1.03 (d, 3H, *J* = 7.3 Hz, *(Z)* isomer), 1.42-2.14 (m, 1H), 2.30-2.59 (m, 3H), 2.71-2.83 (m, 2H), 3.48-3.62 (m. 0.5H), 3.70-3.77 (m, 0.5H); ^{13}C-NMR ($CDCl_3$) δ 12.8, 17.8, 21.8, 22.1, 31.6, 32.4, 40.2, 41.4, 43.0, 48.1, 52.8(CBrI), 153.8, 203.2; IR(neat) 2965(s), 2945(s), 2880(m), 2865(m), 1695(s), 1565(s), 1445(m), 1245(s), 1130(s), 1080(m), 910(m), 730(s) cm^{-1}; MS *m/z* (rel. int.) 330(17, M^+), 328(16, M^+), 221(16), 173(7), 133(14), 127(21), 93(100), 77(29). Anal. Calcd for $C_8H_{10}BrIO$: C, 29.21; H, 3.06. Found: C, 29.24; H, 2.77.

***(Z)*-2-(Bromoiodomethylidene)-6-methylcyclohexanone (19)**

A sample of **13** (90 mg, 0.443 mmol) was reacted with iodine (128.1 mg, 0.504 mmol) and HTIB (175.5 mg, 0.447 mmol). The product was purified as above to give a white solid (157.1 mg, 62%), a 90/10 mixture of **19** and **18**. Further separation as above afforded pure **19** (60.4 mg, 24%): mp 74-75 °C; ^{1}H-NMR ($CDCl_3$) δ 1.13 (d, 3H, *J* = 6.5 Hz), 1.44-1.98 (m, 4H), 2.04-2.18 (m, 1H), 2.30-2.62 (m, 1H), 3.09 (dt, 0.5H, *J* = 2.2 Hz, *J* = 4.3 Hz), 3.16 (dt, 0.5H, *J* = 2.2 Hz, *J* = 4.2 Hz) ; ^{13}C-NMR ($CDCl_3$) δ 15.5, 24.5, 35.3, 37.9, 46.9, 52.2(CBrI), 150.0, 205.0; IR(film) 2975(m), 2935(m), 2865(m), 1705(s), 1575(m), 1460(m), 1130(m), 770(s) cm^{-1}; MS *m/z* (rel. int.) 330(11, M^+), 328(12, M^+), 133(6), 131(6), 127(18), 93(100), 79(26). Anal. Calcd for $C_8H_{10}BrIO$: C, 29.21; H, 3.06. Found: C, 29.29; H, 2.79.

Compound **13** (46.1 mg, 0.227 mmol), NIS (102.3 mg, 0.455 mmol) and TsOH (10.2 mg, 0.054 mmol) were disssolved in 20 mL of acetonitrile containing 5% water. The solution was set to refluxing for 1.5 h. Upon cooling 75 mL of ether was added. After the usual work-up and chromatography, a mixture (34mg, 45%) of **18** and **19** (10/90) was obtained.

(E)/(Z)-2-(Bromoiodomethylidene)-3-methylcyclohexanone-6, 6-d_2 (20)

(E)/(Z)-2-(Bromoiodomethylidene)-3-methylcyclohexanone (**18**) (90 mg, 0.27 mmol) was reacted with sodium methoxide (120 mg, 2.22 mmol) in 5 mL of methanol-d and purified as previously described to give a yellow liquid (30 mg, 33%) of **20**: ^{1}H-NMR ($CDCl_3$) δ 1.04 (d, 3H, J = 7.2 Hz), 1.57-2.59 (m, 2H), 2.71-3.05 (m, 2H), 3.49-3.62 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 17.8, 21.6, 31.5, 41.6, 41.9, 52.7(CBrI), 153.8; IR(neat) : 2965(s), 2940(s), 2870(m), 2255(w), 2225(w), 2130(w), 2100(w), 1695(s), 1565(m), 1450(m), 1375(w), 1260(s), 1170(s), 1115(s), 1025(m), 910(m), 740(s) cm^{-1}; MS *m/z* (rel. int.) 332(19, M^+), 330(19, M^+), 179(10), 177(11), 175(10), 133(23), 131(23), 127(30), 95(100), 79(23).

(Z)-2-(Bromoiodomethylidene)-6-methylcyclohexanone-6-d (21)

(Z)-2-(Bromoiodomethylidene)-6-methylcyclohexanone (**19**) (23 mg, 0.07 mmol) was reacted with sodium methoxide (30 mg, 0.55 mmol) in 5 mL of methanol-d and purified as above to give a yellow liquid (10 mg, 43%) of **21** : ^{1}H-NMR ($CDCl_3$) δ 1.13 (s, 3H), 1.48-1.96 (m, 3H), 2.05-2.17 (m, 1H), 2.31-2.47 (m, 1H), 3.08 (dt, 0.5H, J = 2.2 Hz, J = 4.3 Hz), 3.15 (dt, 0.5H, J = 2.4 Hz, J = 4.3 Hz) ; ^{13}C-NMR ($CDCl_3$) δ 15.4, 24.5, 35.2, 37.9, 52.2(CBrI), 150.1; IR(nujol) 1695(m), 1460(s), 1375(m), 1130(w), 1005(w), 770(w) cm^{-1}; MS *m/z* (rel. int.) 331(8, M^+), 329(8, M^+), 222(5), 176(8), 165(8), 127(20), 94(100), 80(18).

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