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Synthesis of cis-Disubstituted Cyclohexane
Synthesis of cis-1-ethenyl-2-hydroxymethyl-cyclohexane

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Abstract□The efficient synthetic routes to cis-1-ethenyl-2-hydroxymethyl-cyclohexane, an useful synthetic intermediate, have been described. Access to the cis-disubstitutd cyclohexane is gained through the Claisen rearrangment and selective DHP protection of diol respectively.

Keywords□cis-1-ethenyl-2-hydroxymethyl-cyclohexane, Claisen rearrangement, iodohexanoic acid, selective DHP protection of diol.

The development of new synthetic methodology for the construction of carbocyclic ring systems has been a long standing goal of synthetic chemists. However many of them has been targeted for a particular size or limited range of sizes[1].

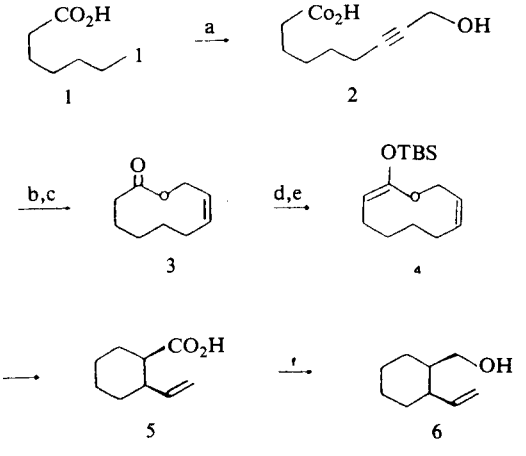
Recently, a series of work for the synthesis of carbocycles was initiated in our laboratory in connection with natural product synthesis. In the course of these studies, we first concentrated on the stereoselective synthesis of cis-disubstituted cyclohexanes as a model study. The cis-relationship of the two substituents is considered as an adequate geometry for the second cyclization which would be applied to the synthesis of the various carbobicycles.

Here we report the useful synthetic routes to the cis-ethenyl-2-hydroxymethyl-cyclohexane which can be utilized as an important synthetic intermediate.

The first approach includes an application of macrolide ring contraction via Claisen rearrangement which has been well developed by Funk *et al*[2]. Scheme 1 describes the improved method for the practical preparation of macrolactone **3** and the synthesis of cis-disubstituted cyclohexane **6**.

6-Iodohexanoic acid **1** is readily available by HI treatment of ε-caprolactone. The yield for the hydroxynonynoic acid was improved by use of 6-iodohexanoic acid[3].

The ketenesilyl acetal **4** was also prepared from lactone **3**[4] by the modified Ireland procedure[5]. It is noticeable that the ester enolate, generated by LDA treatment of the lactone **3** in presence of TBSCl in DMPU as a substitute for the toxic HMPA, could be conveniently trapped as silyl ether in high yield even in multigram scale. The preferential formation of the cis-disubstituted cyclohexane over trans-disubstituted one can be explained by the boat-like transition state

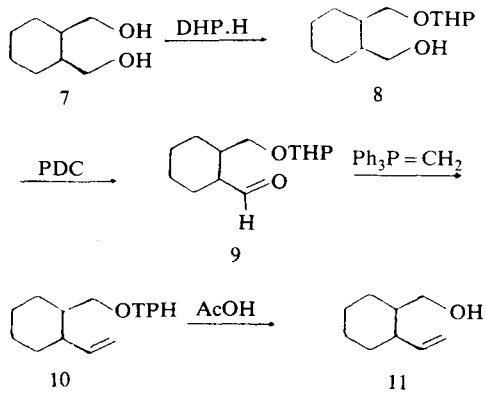


a. i) Li, liq, NH_3, −78°C, 1 h.
ii) Propargyl alcohol, THF, reflux, 2 h.
b. Hydrogen, Pd/$BaSO_4$, quinoline, methanol, rt, 20 min.
c. 2-Chloro-1-methylpyridinium iodide, Et_3N, reflux, 76 h.
d. LDA, TBS-Cl, DMPU, THF, 20 min.
e. HF, CH_3CN, 0°C, 1 h.
f. LAH, THF, rt, 5 h.

Sheme 1

which is more stable than the strained chair-like transition state in this particular case[2]. Finally, reduction of acid **5** with LAH afforded the desired alcohol **6**. The structure of the alcohol **6** was confirmed by spectral properties.

The cis-disubstituted cyclohexane **6** was also derived from diol **7** prepared from cis-1, 2-cyclohexanedicarboxylic anhydride. This second synthetic route summarized in Scheme 2 could be accomplished by a selective DHP protection of one hydroxy group of



Scheme 2

diol **7** as a key feature.

The selectivity relies on the dropping rate of DHP and the amount of the solvent. The selectivity was increased by the slow addition of DHP and the use of large amount of the solvent. Mono-protected alcohol **8** was transformed to the aldehyde **9** by PDC[6] as an appropriate oxidizing reagent. Wittig reaction[7] of aldehyde **9** with methylene triphenylphosphorane provided olefin **10** in 49% overall yield from diol **7**. Finally, deprotection of THP group in AcOH-THF-H_2O (4:2:1) afforded the hydroxyolefin **11** in quantitative yield. The spectral data of the alcohol **12** were well matched with those prepared by the first route.

In summary, cis-ethenyl-2-hydroxymethyl-cyclohexane was synthesized by two efficient routes. Considering hydroxymethyl and vinyl substituents can be converted to the various functional groups, the cis-disubstituted cyclohexane **6(11)** could be utilized as a key synthetic intermediate in the terpene and other carbocycle synthesis[8].

Further applications in this area will be reported in due course.

EXPERIMENTAL

^{1}H-NMR ^{13}C-NMR spectra were recoreded at 80 MHz on a Bruker WP80SY NMR spectrometer with chemical shifts given in scale from TMS as an internal standard for ^{1}H-NMR while for ^{13}C-NMR chemical shifts were calculated from the solvent signals. Infrared spectra were recored on Perkin-Elmer 1710 fourier transform infrared spectrometer and frequencies are given in reciprocal centimeter.

The extent of reaction was checked on thin layer chromatography. Analytical thin layer chromatography was performed on precoated silica gel (0.25 mm, 60G254, Merck) and column chromatography was performed on silca gel (Kiesel gel, 70-230, 230-400 mesh, Merck). All reactions were conducted under atmospheres of nitrogen and all solvents were purified before use.

9-Hydroxy-7-nonyoic acid (2)

To a stirred liquid NH_3 (500 m*l*) was added at $-78°C$ a small piece of lithium metal. After the appearance of a blue color, a catalytic amount of Fe $(NO_2)_3 \cdot 9H_2O$ was added. When the initial blue color faded, the rest of lithium was added in small portions (total 6.94g, 1 mol). After about 60 min, the propargyl alcohol (28g, 0.5 mol) was added to the brown suspension of lithium amide and the mixture was refluxed for 1 hr. After addition of the 6-iodohexanoic acid **1** (12.1 g, 50 mo*l*) in THF (200 m*l*), the mixture was refluxed for 2 hrs, and left to evaporated. 6 N-HCl (50 m*l*) was added and the crude product was extracted with Et_2O, dried with $MgSO_4$ and concentrated in vacuo to afford 8.1g of **2** as a solid (95%). IR (nujol) 3100-3600, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.16 (s, 2H), 4.25 (t, 2H, J = 2 Hz), 2.46-2.1 (m, 4H), 1.75-1.43 (m, 6H).

cis-2-Etheny cyclohexane carboxylic acid (5)

A solution of 1.1 equivalent of LDA in dry THF (5 m*l*) was cooled to $-78°C$. To this rapidly stirred solustion was added 1.0 equivalent of the lactone **3** (30 mg, 0.19 mmol) with t-BuMe_2SiCl (37 mg, 0.25 mmol) in DMPU (1 m*l*). After an additional 2 min at $-78°C$, the reaction mixture was allowed to warm to room temperature during 20 min, and then diluted with 50 m*l* of pentane. The pentane solution was washed with three 10 m*l* portions of ice water, dried ($MgSO_4$), and distilled at atmospheric pressure. The rearrangement product was then hydrolyzed by dissolving the silyl ester in acetonitrille (1 m*l*), cooling the solution to 0°C, and adding a solution of hydrofluoric acid in acetonitrile (2 equivalent of a 3 M-solution in acetonitrile, prepared from 48% HF aq. solution). The disappearance of the silyl ester was monitored by TLC, and the reaction mixture was quenched by addition of 3 M-K_2CO_3 aqueous solution. The aqueous layer was washed with Et_2O, neutralized with conc HCl, and extracted with Et_2O. The organic phase was dried ($MaSO_4$) and the solvents were removed in vacuo to afford the carboxylic acid **5** (21 mg, 70%) of an oil. IR (neat) 3600-3000, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.93 (ddd, 1 H, J = 16, 11, 7.8 Hz), 5.02 (d, 1 H, J = 16 Hz), 4.99(d,1H,J = 11 Hz), 2.75-2.4 (m, 2H), 1.9-1.0 (m, 8H).

cis-1-Ethenyl-2-hydroxymethyl-cyclohexane (6)

A mixture of carboxylic acid **5** (10 mg, 0.06 mmol) and lithium aluminium hydride (5 mg, 0.12 mmol) in 1 m*l* of dry THF was stirred at room temperature for 5 hrs. Work-up with aqueous sodium hydroxide and the residue was chromatographed with 25% EtOAc-hexane to give 9 mg (100%) of alcohol **6.**
IR (neat) 3400 cm^{-1}; ^{1} H-NMR ($CDCl_3$) δ 6.0 (ddd, 1H, J = 16, 11, 7.8 Hz), 5.06 (d, 1H, J = 16 Hz), 5.03 (d, 1H, J = 11 Hz), 3.48 (d, 2H, J = 6.8 Hz), 2.7-2.4 (m, 1H), 1.9-1.0 (m, 9 H),; ^{13} C-NMR ($CDCl_3$) 139.31, 115.05, 65.33, 42.52, 40.99, 30.88, 25.26, 24.89, 22.40.

cis-1, 2-Cyclohexanedimethanol mono THP ether (8)

To a stirred solution of cis- 1, 2-cyclohexanedimethanol **7** (3.36 g, 23.3 mmol) and dihydropyran (2.35g, 28 mmol) in 700 m*l* of CH_2Cl_2 at 0°C was added p-toluenesulfonic acid monohydrate (443 mg, 2.3 mmol), and the mixture was maintained at 0°C with cooling for 2 hrs. The solution was then evaporated and diluted with a solution made of saturated brine (120 m*l*) and water (240 m*l*). The product was chromatographed with 25% EtOAc-Hexane to yield 3.72 g (70%) of **8** as an oil.
IR (neat) 3400 cm^{-1}; ^{1} H-NMR ($CDCl_3$) 4.59 (m, 1 H), 3.4-4.1 (m, 6H), 2.82 (bs, 1H), 1.2-2.3 (m, 10H).

cis-1-Ethenyl-2-hydroxymethyl-cyclohexane (11, alternative route for 6).

To a solution of alcohol **8** (3.72 g, 16 mmol) in 100 m*l* of methylene chloride was added PDC (12.9 g, 34 mmol) and the resulting solution was stirred at room temperature for 24 hrs. The reaction mixture was diluted with ether and water, extracted with ether (3 × 100 m*l*). The organic layer was washed with a solution of saturated sodium bicarbonate, dried over $MgSO_4$, and concentrated. To the uspension of methyltriphenylphosphonium iodide (7.8 g, 19.2 mmol) in dry ether (100 m*l*) was slowly added 1.6 M n-BuLi in hexane (100 m*l*, 16 mmol) at −20°C and the mixture was stirred for 30 min at rt. To the ylide solution was added the crude aldehyde in dry ether through the cannula and the mixture was refluxed for 1 h. After filtration, the filtrate was evaporated and chromatographed on sillica gel (10% EtOAc-Hex) to afford the crude Wittig product (1.8 g, 51% from alcohol **8**) as an oil. ^{1} H-NMR ($CDCl_3$) δ 5.78-6.24 (m, 1H), 4.8-5.05 (m, 2H), 4.53 (m, 1H), 3.05-4.0 (m, 4H), 2.2-2.6 (m, 1H), 1.0-1.9 (m, 9H).

To the Wittig product was added 20 ml of a solution (AcOH:THF:H_2O = 4:2:1) and refluxed for 4 hrs. The solvents were removed by evaporation and the residue was chromatographed with 25% EtOAc-Hexane to yield 1.12 g (95%) of **11** as an oil.
IR (neat) 3400 cm^{-1}; ^{1} H-NMR ($CDCl_3$) δ 6.0 (ddd, 1H, J = 16, 11, 7.8 Hz), 5.06 (d, 1H, J = 16 Hz), 5.03 (d, 1H, J = 11 Hz), 3.48 (d, 2H, J = 6.8 Hz), 2.4-2.7 (m, 1H), 1.0-1.9 (m, 9H); ^{13}C-NMR ($CDCl_3$) 139.31, 115.05, 65.33, 42.52, 40.99, 30.88, 25.26, 24.89, 22.40.

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LITERATURE CITED

1. Ho, T.-L: "Carbocycle Construction in Terpene Synthesis" VCH Publishers, Inc. 1988.
2. Abelman, M.M., Funk, R.L. and Munger, J.D. Jr.: Alicyclic Claisen Rearrangement. A General Carbocycle Synthesis Based on Four-Atom-Ring Contractions of Lactones. *J. Am. Chem. Soc.* **104,** 4030 (1982).
3. Ames, D.E., Covell, A.N. and Goodburm, T.G.; Synthesis of Long-chain Acids. Part V. Synthesis of Some ω -hydroxy-acetylenic Acids. *J. Chem. Soc.,* 5889.
4. Mukaiyama, T., Usui, M. and Saigo, K.: The facile synthesis of lactones. *Chem. Lett.* 49 (1976).
5. Curran, D.P. and Suh, Y.-G.: Selective mono-Claisen Rearrangement of Carbohydrate Glycals. A Chemical Consequence of the Vinylogous Anomeric Effects. *Carbohydrate Res.* **171,** 161 (1987). References cited therein.
6. Corey, E.J. and Schmidt, G.: Useful Procedures for the Oxidation of Alcohols Involving Pyridinium Dichromate in Aprotic Media. *Tetrahedron Lett.* 399 (1979).
7. Fieser, L.F., Fieser, M. "Reagents for Organic Synthesis" John Wiley & Sons vol. 1, 678 (1967).
8. Apsimon, J.: "The Total Synthesis of Natural Products" John Wiley & Sons vol. 5 (1983).