Pergamon

Tetrahedron Letters, Vol. 36, No. 12, pp. 2121-2124, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00188-3

Synthesis of meso-cyclohexa-3,5-diene-1,2-diol derivative from myo-inositol

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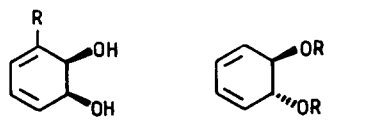
Abstract : Synthesis of (meso)1,2-O-cyclohexylidene-cyclohexa-3,4-diene (**4**) in four steps from myo-inositol and its exclusive conversion to the vinylic epoxide **13** is described.

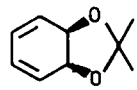
The increasing demand for homochiral compounds has led chemists to look for a variety of approaches to synthesize such molecules. The pioneering work by Gibson[1] has resulted in a practical method for the transformation of achiral aromatic compounds to reactive arene cis-dihydrodiols **1a** with excellent enantiocontrol by bacteria 'Pseudomonas putida'[1,2]. The meso-benzene cis-1,2-dihydrodiol (**1b**) thus obtained from benzene has been used in several enantiospecific syntheses[1,3]. Chiral benzene trans-1,2-dihydrodiol (**2a**) also has been prepared in 50% optical purity through mammalian metabolism of benzene[4]. Arene cis-dihydrodiols **1a** thus derived from toluene, chloro-, fluoro- and bromo- benzene have gained utility in the synthesis of homochiral compounds as diverse as conduritols[3], inositolphosphates[5], chiral cyclopentenones for prostagladin targets[6], aminocyclitol[7] (D and L) hexoses[8], tetroses[9], aza-sugars[10], heterocyclic compounds[11] and enantiodivergent products arising biosynthetically from arene oxides. Functionalization of arene cis-dihydrodiols has relied upon electrophilic attack at one of the diene double bonds; presence of bulky cyclic protection has ensured exclusive epoxidation. Epoxidation[12], osmylation[13], cyclopropanation[14], ozonolysis[15] and Diels-Alder reactions[11,16] of arene cis-dihydrodiols by control of appropriate reagents and conditions have been shown to give useful stereo- and chemoselectivity.

Synthetically, racemic trans-cyclohexa-3,5-diene-1,2-diol diacetate (**2b**) has been prepared from benzene via Birch reduction, bromination, trans-hydroxylation, dehydrobromination and acetylation[17]. Likewise, meso-1,2-O-isopropylidene-cyclohexa-3,5-diene (**3**) has also been synthesised from benzene[18].



1 a) R = CH_3, F, Cl, Br
b) R = H

2 a) R = H
b) R = $COCH_3$



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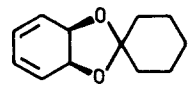

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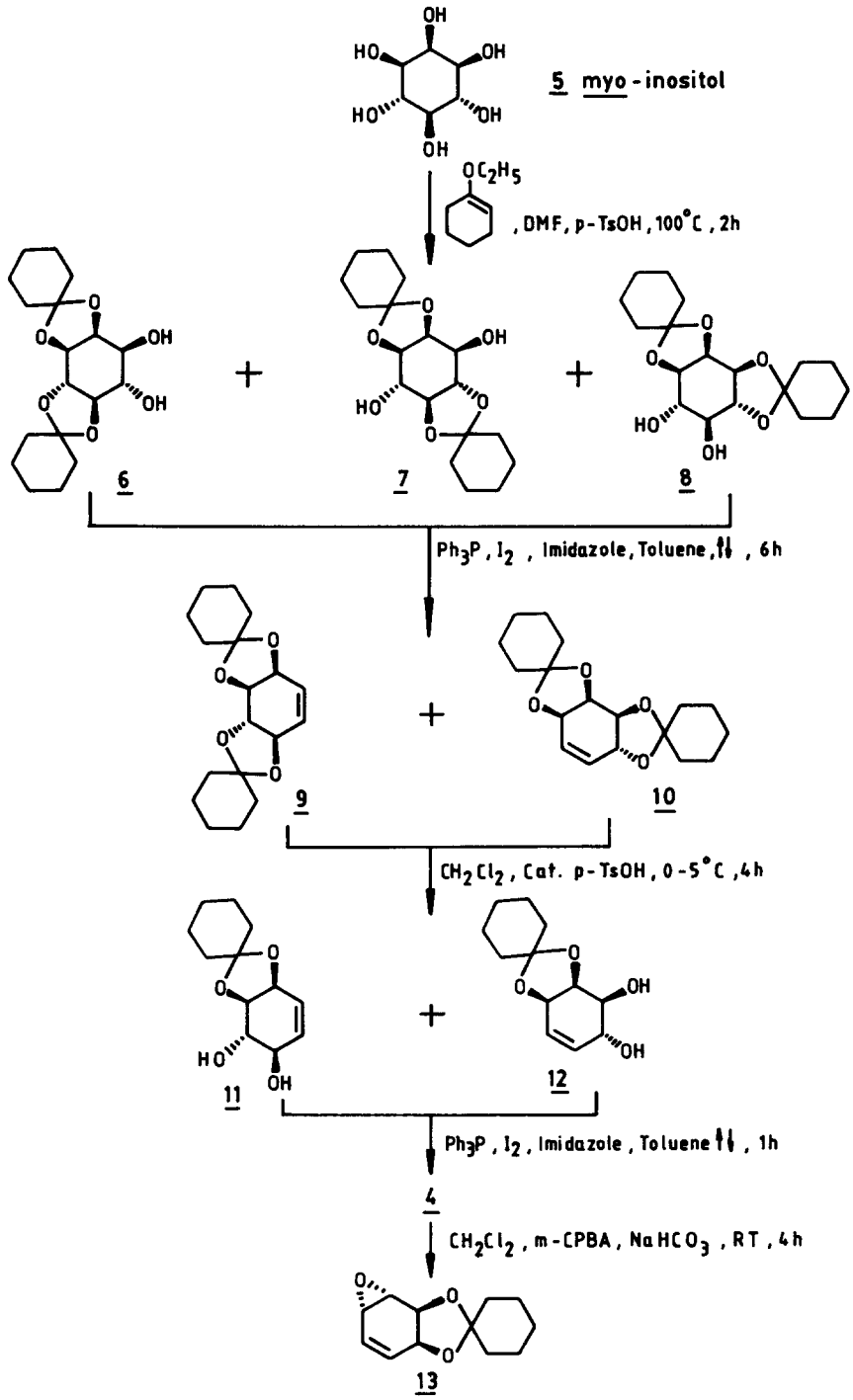
5 myo-inositol
, DMF, p-TsOH, 100°C, 2h
6
7
8
Ph3P, I2, Imidazole, Toluene, , 6h
9
10
CH2Cl2, Cat. p-TsOH, 0-5°C, 4h
11
12
Ph3P, I2, Imidazole, Toluene, 1h
4
CH2Cl2, m-CPBA, NaHCO3, RT, 4h
13

We report here an elegant synthesis of meso-1,2-O-cyclohexylidene-cyclohexa-3,4-diene (**4**) starting from myo-inositol (**5**) in four steps involving transformation of trans-1,2-diols to the olefins as a key step (Scheme). Compound **5** was reacted with ethoxycyclohexene and a catalytic amount of p-toluenesulfonic acid (p-TSA) in DMF at 100°C for 2 h to obtain all three of the bis-cyclohexene ketals **6,7** and **8** in 38, 26 and 19% yields respectively by known method[19]. Compound **7** was separated from the mixture of **6,7** and **8** by fractional crystallisation[19] to leave an oil containing an inseparable mixture of **6** and **8**, which as such was subjected to one-step elimination reaction of the trans 1,2-diols according to the method developed by Garegg[20] by reacting with Ph_3P (3 mole equivalents), imidazole (3 mole equivalents) and iodine (3 mole equivalents) in toluene at reflux for 6 h to yield the cyclohexene bis-ketals **9** and **10** (m.p. 66-68°C) respectively in 74% yield after alkaline workup. **9** and **10** were characterized from the appearence of the double bond protons (2H) between 5.6 and 6.25 in the ^1H NMR spectrum. Regioselective deprotection[21] of the trans-cyclohexene ketals of **9** and **10** was done by reacting it with catalytic amount of p-TSA in dichloromethane strictly at 0-5°C for 4 h to obtain the diols **11** and **12** respectively as solids (m.p. 96-98°C) in 78% yield. The diols **11** and **12** as such were subjected once again to the elimination reaction (Ph_3P/imidazole/I_2)[20] in toluene at reflux for 1 h to obtain after alkaline work up the protected cyclohexadienediol **4** as a syrup in 72% yield. Compound **4** was fully characterised from ^1H NMR, UV and mass spectrum[22,23]. Synthetic utility of **4** was shown by regio- and stereoselective epoxidation with m-chloroperbenzoic acid (m-CPBA/CH_2Cl_2/$NaHCO_3$/RT/2h) to obtain the vinylic epoxide **13**[24] in 92% yield. Exclusive epoxidation of **4** from the opposite side of the cyclohexadiene ring was ensured due to the bulky 1,2-O-cyclohexylidene protection of cis-1,2-diol.

In conclusion a short synthesis of synthetically useful meso-benzene 1,2-dihydrodiol derivative **4** from myo-inositol has been developed. Synthesis of benzene trans-1,2-dihydrodiol derivatives by suitable protection and deprotections is also evident from this protocol.

Acknowledgments: MP thanks University Grants Commission, New Delhi, for financial assistance.

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22. **4** : ^{1}H NMR (200 MHz, δ in ppm, J in Hz, $CDCl_3$): 5.8-6.0 (m, 4H), 4.61 (br.s, 2H), UV (EtOH): λ_{max} (log ε): 262 nm (4700), 252 (4310) : M^+ 192.
23. All the new compounds gave satisfactory elemental analysis.
24. 6,7-Epoxy-3a,6,7,7a-tetrahydro-benzo-2,2-spirocyclohexyl-1,3-dioxolane **13**: ^{1}H NMR (200 MHz, δ in ppm, J in Hz, $CDCl_3$): 5.95 (ddd, 1H, $J_{4,5}$=9.96, $J_{5,6}$=4.0, $J_{3a,5}$ = 1.2, H-5), 5.71 (ddd, 1H, $J_{3a,4}$=2.2, $J_{4,6}$=1.8, H-4), 4.68 (dd, 1H, $J_{3a,7a}$=1.9, $J_{7,7a}$=1.7, H-7a), 4.36 (ddd, 1H, H-3a), 3.48 (dd, 1H, $J_{6,7}$=4.0, H-7), 3.25 (tt, 1H, H-6).

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* Dedicated to Dr A V Rama Rao on the occasion of his 60th birthday.

** IICT Communication No. 3454

(*Received in UK* 12 *October* 1994; *revised* 24 *January* 1995; *accepted* 27 *January* 1995)