Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 2135–2140

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

PRACTICAL SYNTHESIS OF ALL INOSITOL STEREOISOMERS FROM *MYO*-INOSITOL

Sung-Kee Chung* and Yong-Uk Kwon

Department of Chemistry, Pohang University of Science & Technology, Pohang 790-784, Korea.

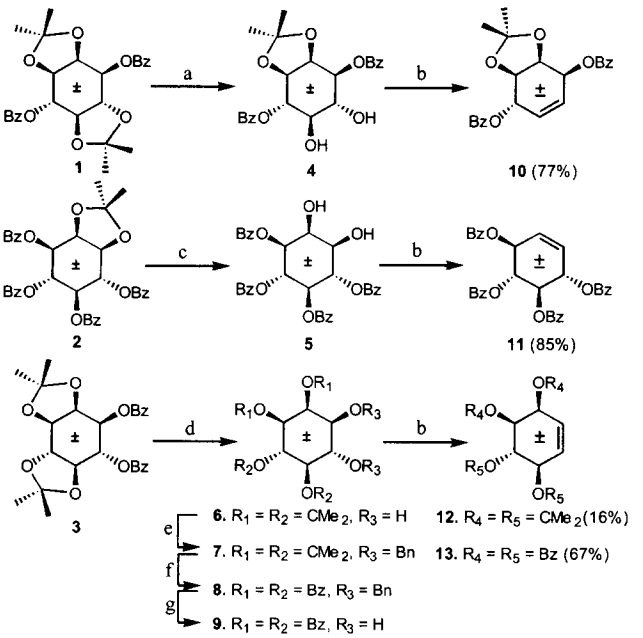
Received 21 April 1999; accepted 9 June 1999

Abstract: Synthesis of six inositol stereoisomers was successfully carried out *via* conduritol intermediates prepared from *myo*-inositol. Dihydroxylation and epoxidation followed by ring opening of the conduritol B, C and F derivatives gave *epi*-, *allo*-, *muco*-, *neo*-, DL-*chiro*- and *scyllo*-inositol. The *cis*-inositol derivative, which may not be prepared by this approach, was synthesized in 5 steps *via* 2-*O*-benzoyl-*myo*-inositol orthoformate as the key intermediate.

The roles of D-*myo*-inositol-1,4,5-trisphosphate [D-I(1,4,5)P_3], various inositol polyphosphates, and phospholipids in the intracellular signal transduction events are now well known.[1] Although the scope of the phosphoinositide-based signalling processes is continually widening, the clear understanding of the molecular mechanisms is still lacking. Thus, much research efforts are now being directed toward the structure-activity relationship (SAR) based on various regio- and stereo-isomers of inositol phosphates (IP_n).[2] There exist nine stereoisomers of inositol; *cis*-, *epi*-, *allo*-, *myo*-, *muco*-, *neo*-, D-*chiro*-(+)-, L-*chiro*-(-)- and *scyllo*-. Although they have previously been synthesized in varying efficiencies from halobenzenes,[3] benzene,[4] hexahydroxybenzene,[5] tetrahydroxyquinone,[6] sugars,[7] inositols,[8] and others,[9] there is no report on the general and systematic synthetic approach to all inositol stereoisomers. Because of the desired availability of all stereoisomers of IP_n in connection with SAR studies of the interactions between inositol phosphates and various biomacromolecules, we investigated the practical and divergent synthetic routes to all inositol stereoisomers. We report herein the first general synthesis of inositol stereoisomers *via* conduritols,[10] which are prepared from *myo*-inositol by didehydroxylation.

The first issue in our synthetic scheme for inositol stereoisomers is how to efficiently prepare the key intermediates, conduritol B, C and F derivatives, from the selectively protected *myo*-inositol diols. For the conversion of vicinal diols into olefins, two types of general procedures are known: two-step conversion *via* intermediates with activating groups[11] and one-step conversion.[12] By and large, the two-step methods do not work well on cyclic diols, especially cyclic *trans*-diols. We have examined the Samuelsson conditions for the one-step conversion of the inositol vicinal diols to conduritol.[13]

0960-894X/99/$ - see front matter
PII: S0960-894X(99)00348-0



Scheme 1. Reagents and conditions: a. AcCl (cat.), CH_2Cl_2/MeOH, 75%; b. see Table 1; c. 80% aq. AcOH, 100 °C, quant.; d. NaOMe, MeOH, ↑↓, 95%; e. BnBr, NaH, DMF, 92.6%; f. i) 80% aq. AcOH, 100 °C, ii) BzCl, pyridine, 94%; g. $Pd(OH)_2$/C, H_2 (50 psi), EtOAc/EtOH, 97%.

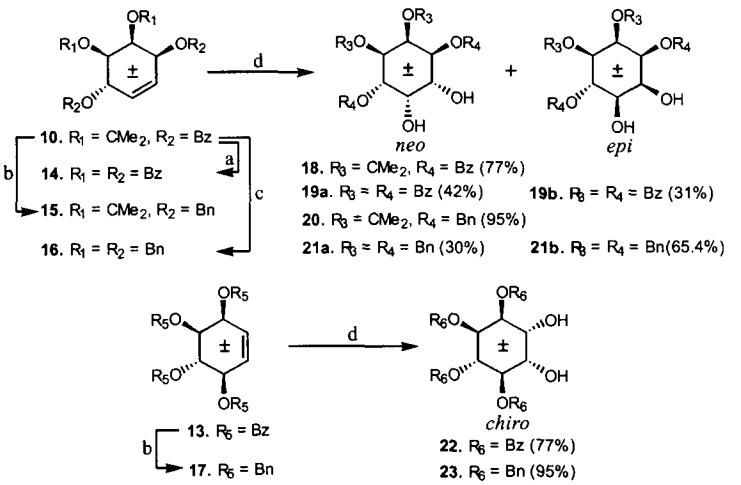
myo-Inositol diols **4**,[14] **5**[15] and **6**[16] were prepared as potential precursors to conduritol B, C and F derivatives from compounds **1**, **2** and **3**, which were in turn obtained in one-pot reactions according to the literature procedures (Scheme 1).[17] The reaction of vicinal *trans*-diol **4** with chlorodiphenylphosphine (2.2 equiv./diol), imidazole (6 equiv./diol), and iodine (2 equiv./diol) in an inert solvent, e.g. toluene resulted in the formation of the corresponding conduritol C derivative **10** in ca. 50% yield (Table 1). We could also isolate and characterize the vicinal iodo-diphenylphosphinate, a possible intermediate and phosphorous-containing conduritols. The use of triphenylphosphine instead of chlorodiphenylphosphine gave a higher yield (77%). Interestingly, the *cis*-diol (**5**) could be converted to tetrabenzoylated conduritol B (**11**) in 79-85% yield under either conditions, which is at variance with literature reports.[13] It is possible that the intermediate, either iodo-phosphinate, or iodo-phosphinium ion, may have the *trans*-relationship, from which a reductive elimination can occur more easily. A similar reaction with *trans*-diol (**6**) protected with diacetonide proceeded very sluggishly to give conduritol F (**12**) in low yield (16%) only under the condition B. Therefore, we prepared *trans*-diol (**9**) by exchanging the acetonide with the benzoyl group to relieve the ring strain, which might be related to the low reactivity observed. Didehydroxylation of **9** with triphenylphosphine proceeded well to furnish the tetrabenzoylated conduritol F (**13**) in 67% yield.

Table 1. Preparation of conduritol derivatives under two different conditions.

Diols	Diol stereochemistry	Yield of conduritol derivatives (%)	
		Condition A[a]	Condition B[b]
4	*trans*	50.2	77
5	*cis*	85	79
6	*trans*	no rxn.	16
9	*trans*	47	67

a. i) $ClPPh_2$, imidazole, I_2, toluene, ↑↓. ii) Zn.
b. i) PPh_3, imidazole, I_2, toluene, ↑↓.

Next, we examined the *cis*-dihydroxylation of the conduritol C and F derivative (**10** & **13**). Compound **10** was reacted with OsO_4 (~5 mol%) and 4-methylmorpholine *N*-oxide (NMO) in aq. acetone to give stereoselectively DL-1,4-di-*O*-benzoyl-2,3-*O*-isopropylidene-*neo*-inositol (**18**), which was isolated in 77% after a flash chromatography (Scheme 2). The observed facial selectivity might be attributed to the steric effect by the acetonide group. In order to obtain the *epi*-inositol derivative by dihydroxylation of a conduritol C derivative, the acetonide group of **10** was removed and the product benzoylated to give **14**. As expected, the reaction of **14** with OsO_4 and NMO in aq. acetone furnished DL-1,2,3,4-tetra-*O*-benzoyl-*neo*-inositol (**19a**) and DL-1,2,3,6-tetra-*O*-benzoyl-*epi*-inositol (**19b**) in 42% and 31% yields, respectively. Similarly, the *cis*-dihydroxylation of the conduritol F derivative (**13**) stereoselectively gave DL-1,2,3,4-tetra-*O*-benzoyl-*chiro*-inositol (**22**) in 77% yield. The origin of the observed stereoselectivity is assumed to be the two neighboring benzoate groups of **13**, which block the *cis* approach.

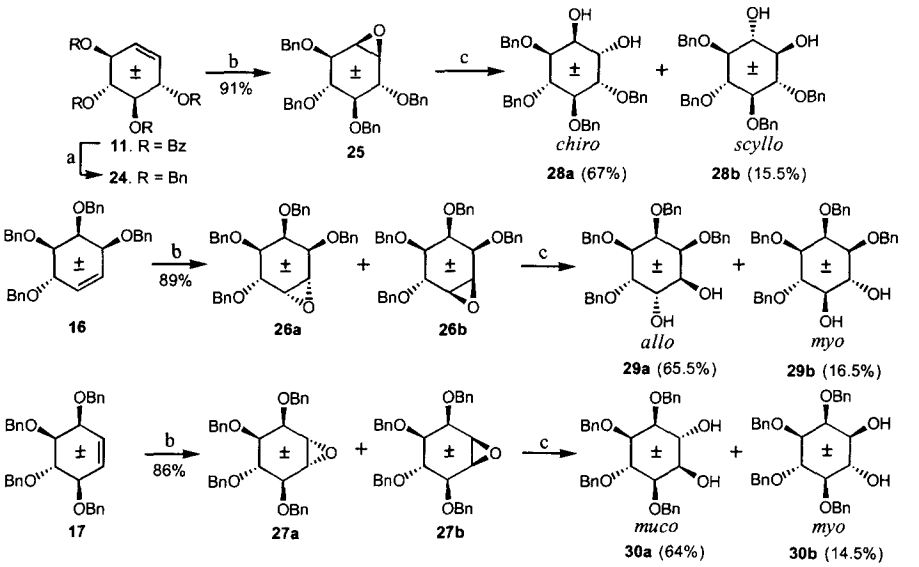


Scheme 2. Reagents and conditions: a. i) 80% aq. AcOH, 100 °C, ii) BzCl, pyridine, 91%; b. i) NaOMe, MeOH, ↑↓, ii) BnBr, NaH, DMF, 90-95%; c. i) 80% aq. AcOH, 100 °C, ii) NaOMe, MeOH, ↑↓, iii) BnBr, NaH, DMF, 87%; d. OsO_4, NMO, aq. acetone.

In the dihydroxylation of the benzoate protected conduritols, practical problems such as the slow reaction rate, the benzoyl group migration, and very low solubility of produced inositols were often encountered, and they were circumvented by changing the protecting group from benzoyl to benzyl. Thus, dihydroxylation of

conduritols **15** and **17** stereoselectively gave DL-1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-*neo*-inositol (**20**) and DL-1,2,3,4-tetra-*O*-benzyl-*chiro*-inositol (**23**) in high yields, respectively. In the dihydroxylation of compound **16,** in contrast to that of **14,** DL-1,2,3,6-tetra-*O*-benzyl-*epi*-inositol (**21b**) (65.4%) was largely produced together with DL-1,2,3,4-tetra-*O*-benzyl-*neo*-inositol (**21a**) (30%). The isomeric inositol products (**21b** and **23**) were fully characterized after acetylation with acetic anhydride in pyridine.

The benzyl protected conduritol B, C and F derivatives (**24**,[7c] **16** & **17**) were epoxidized under several conditions. Conduritol B derivative (**24**) was treated with excess I_2 and Ag_2O to provide epoxide **25** in 91% yield *via* iodohydrin (Scheme 3).[18] Epoxidation of conduritol C and F derivatives (**16** & **17**) under the same conditions produced mixtures (**26a/26b** and **27a/27b**) of the α- and β-epoxide in 89 and 86%, respectively. On the other hand, when the conduritol derivatives were treated with mCPBA and 4,4'-thiobis(6-tert-butyl-*o*-cresol) as a radical inhibitor at 90 °C,[19] the corresponding epoxides were obtained in 55-60% yields. The reaction of conduritol derivatives with I_2, KIO_3 and H_2SO_4 in aq. dioxane[20] followed by the base-promoted cyclization (80-90% yield) of the resultant iodohydrins was found to be most practical in terms of cost and reaction scale.

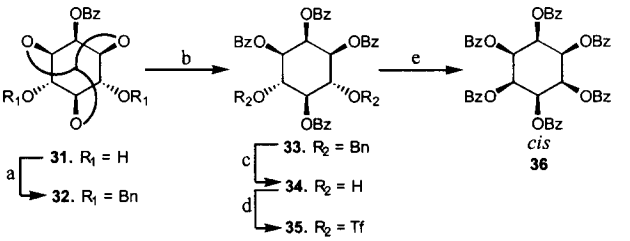


Scheme 3. Reagents and conditions: a. i) NaOMe, MeOH, ↑↓, ii) BnBr, NaH, DMF, 91%; b. I_2, Ag_2O, aq. dioxane, 90 °C; c. CF_3COOH (or H_2SO_4), aq. THF, 50 °C.

Acid-catalyzed ring-opening of epoxide (**25**) with CF_3COOH or H_2SO_4 in aq. THF gave DL-2,3,4,5-tetra-*O*-benzyl-*chiro*-inositol (**28a**) and DL-1,2,3,4-tetra-*O*-benzyl-*scyllo*-inositol (**28b**) in 67% and 15.5% yields, respectively, as expected on the basis of the diaxial opening rule (the Furst-Plattner rule). Similarly, epoxides **26** and **27**, respectively derived from conduritol C and F derivatives, were subjected to th acidic conditions to provide DL-1,2,3,6-tetra-*O*-benzyl-*allo*-inositol (**29a**, 65.5%) and DL-1,2,3,4-tetra-*O*-benzyl-*myo*-inositol (**29b**,

16.5%), and DL-1,2,3,4-tetra-*O*-benzyl-*muco*-inositol (**30a**, 64%) and DL-1,2,5,6-tetra-*O*-benzyl-*myo*-inositol (**30b**, 14.5%), respectively.

Since *cis*-inositol hexabenzoate (**36**) is not readily accessible by the conduritol routes, it was synthesized in 5 steps from 2-*O*-benzoyl-*myo*-inositol orthoformate (**31**)[21] as shown in Scheme 4. Our initial plan to obtain the desired stereochemistry by oxidation and reduction processes was not successful, because the attempted oxidation of **31** was completely unsuccessful under all conditions examined (e.g. pyridinium dichromate, Jones reagent, Swern oxidation, and ruthenium tetroxide). Compound **31** was triflated with trifluoromethanesulfonic anhydride. However, the nucleophilic substitution of the resulting orthoformate triflate with various nucleophiles was unsuccessful. Apparently, rigidity of the orthoformate structure does not allow the transition state geometry necessary for the S_N-2 process. Thus, successive benzylation, hydrolysis, benzoylation, hydrogenolysis, and triflation of **31** were carried out under standard conditions to obtain triflate **35** in good overall yield. Heating **35** with KOBz in DMSO gave the desired *cis*-inositol hexabenzoate (**36**) in 32% yield.



Scheme 4. Reagents and conditions: a. BnBr, NaH, mol. sieve (4Å), DMF, 82%; b. i) TSA, MeOH, ↑↓, ii) BzCl, pyridine, 91%; c. $Pd(OH)_2/C$, MeOH, H_2 (50psi), 96%; d. Tf_2O, CH_2Cl_2/pyridine, -42 °C→rt, 89%; e. KOBz, DMSO, 100 °C, 32%.

In summary, we have successfully charted out general routes for stereoselective synthesis of six inositol stereoisomers *via* conduritol intermediates derived from *myo*-inositol and a separate route to *cis*-inositol on multi-gram scales.[22] We are currently utilizing these inositol stereoisomers in the synthesis of IP_n stereoisomers.

Acknowledgment. This work was supported by the Korea Science & Engineering Foundation/Center for Biofunctional Molecules and the Ministry of Education/Basic Science Research Institute (98-3437).

References and Notes

1. (a) Berridge, M. J. *Nature* **1993**, *361*, 315; (b) Potter, B. V. L.; Lampe, D. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1933, and references therein.
2. (a) Marchant, J. S.; Chang, Y. T.; Chung, S. K.; Irvine, R. F.; Taylor, C. W. *Biochem. J.* **1997**, *321*, 573; (b) Burford, N. T.; Nahorski, S. R.; Chung, S. K.; Chang, Y. T.; Wilcox, R. A. *Cell Calcium* **1997**, *21*, 301; (c) Chung, S. K.; Shin, B. G.; Chang, Y. T.; Suh, B. C.; Kim, K. T. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 659; (d) Cullen, P. J.; Chung, S. K.; Chang, Y. T.; Dawson, A. P.; Irvine, R. F. *FEBS Lett.* **1995**, *358*, 240; (e) Stricker, R.; Chang, Y. T.; Chung, S. K.; Reiser, G. *Biochem. Biophys. Res. Commun.* **1996**, *228*, 596; (f) Choi, G.; Chang, Y. T.; Chung, S. K.; Choi, K. Y. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2709.

3. (a) Brammer Jr., L. E.; Hudlicky, T. *Tetrahedron: Asymmetry* **1998**, *9*, 2011; (b) Desjardins, M.; Brammer Jr., L. E.; Hudlicky, T. *Carbohydr. Res.* **1997**, *304*, 39; (c) Hudlicky, T.; Mandel, M.; Rouden, J.; Lee, R. S.; Bachmann, B.; Dudding, T.; Yost, K. J.; Merola, J. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1553; (d) Mandel, M.; Hudlicky, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 741.
4. (a) Carless, H. A. J.; Busia, K. *Tetrahedron Lett.* **1990**, *31*, 1617; (b) Motherwell, W. B.; Williams, A. S. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2031.
5. Anderson, C.; Wallis, E. S. *J. Am. Chem. Soc.* **1948**, *70*, 2931.
6. Angyal, S. J.; Odier, L.; Tate, M. E. *Carbohydr. Res.* **1995**, *266*, 143.
7. (a) Takahashi, H.; Kittaka, H.; Ikegami, S. *Tetrahedron Lett.* **1998**, *39*, 9707; (b) Chung, S. K.; Yu, S. H. *Bioorg. Med. Chem. Lett.* **1996**, 6, 1461; (c) Watanabe, Y.; Mitani, M.; Ozaki, S. *Chem. Lett.* **1987**, 123.
8. (a) Husson, C.;Odier, L.; Vottéro, P. J. A. *Carbohydr. Res.* **1998**, *307*, 163; (b) Gigg, J.; Gigg, R. *Carbohydr. Res.* **1997**, *299*, 77; (c) Guidot, J. P.; Gall, T. L. *Tetrahedron Lett.* **1993**, *34*, 4647; (d) Tagliaferri, F.; Wang, S. -N.; Berlin, W. K.; Outten, R. A.; Shen, T. Y. *Tetrahedron Lett.* **1990**, *31*, 1105.
9. (a) Kim, K. S.; Park, J. I.; Moon, H. K.; Yi, H. *J. Chem. Soc., Chem. Commun.* **1998**, 1945; (b) Kowarski, C.; Sarel, S. *J. Org. Chem.* **1973**, *38*, 117; (c) Angyal, S. J.; Matheson, N. K. *J. Am. Chem. Soc.* **1955**, *77*, 4343.
10. (a) Yoshizaki, H.; Bäckvall, J. E. *J. Org. Chem.* **1998**, *63*, 9339; (b) Balci, M.; Sütbeyaz, Y.; Seçen, H. *Tetrahedron* **1990**, *46*, 3715, and references therein.
11. (a) Tipson, R. S.; Cohen, A. *Carbohydr. Res.* **1965**, *1*, 338; (b) Albano, E.; Horton, D.; Tsuchiya, T. *Carbohydr. Res.* **1966**, *2*, 349; (c) Marshall, J. A.; Lewellyn, M. E. *J. Org. Chem.* **1977**, *42*, 1311; (d) Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677; (e) Albano, E.; Horton, D.; Tsuchiya, T. *Carbohydr. Res.* **1966**, *2*, 349; (f) Haines, A. H. *Carbohydr. Res.* **1972**, *21*, 99; (g) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 1979; (h) Barrett, A. G. M.; Barton, D. H. R.; Bielski, R.; McCombie, S. W. *J. Chem. Soc., Chem. Commun.*, **1977**, 866; (i) Barrett, A. G. M.; Barton, D. H. R.; Bielski, R. *J. Chem. Soc., Perkin I* **1979**, 2378; (j) Hanessian, S.; Bargiotti, A.; LaRue, M. *Tetrahedron Lett.* **1978**, *8*, 737; (k) Ando, M.; Ohhara, H.; Takase, K. *Chem. Lett.* **1986**, 879; (l) King, J. L.; Posner, B. A.; Mak, K. T.; Yang, N. C. *Tetrahedron Lett.* **1987**, *28*, 3919.
12. (a) Sharpless, K. B.; Flood, T. C. *J. Chem. Soc., Chem. Commun.*, **1972**, 370; (b) McMurry, J. E.; Fleming, M. P. *J. Org. Chem.* **1976**, *41*, 896; (c) Barua, N. C.; Sharma, R. P. *Tetrahedron Lett.* **1982**, *23*, 1365.
13. (a) Garegg, P. J.; Samuelsson, B. *Synthesis* **1979**, 469 and 813; (b) Liu, Z.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1990**, *55*, 4273; (c) Pakulski, Z.; Zamojski, A. *Carbohydr. Res.* **1990**, *205*, 410;.
14. Chung, S. K.; Chang, Y. T. *J. Chem. Soc., Chem. Commun.* **1995**, 11.
15. (a) Chung, S. K.; Chang, Y. T. *Kor. J. Med. Chem.* **1996**, *6*, 162; (b) Garegg, P. J.; Lindberg, B. *Carbohydr. Res.* **1988**, *173*, 205.
16. Chung, S. K.; Ryu, Y. *Carbohydr. Res.* **1994**, *258*, 145.
17. (a) Gigg, J.; Gigg, R.; Payne, S.; Conant, R. *Carbohydr. Res.* **1985**, *142*, 132; (b) Gigg, J.; Gigg, R.; Payne, S.; Conant, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2411; (c)Desai, T.; Femandez-Mayoralas, A.; Gigg, J.; Gigg, R.; Payne, S. *Carbohydr. Res.* **1990**, *205*, 105.
18. Parrilli, M.; Barone, G.; Adinolfi, M.; Mangoni, L. *Tetrahedron Lett.* **1976**, 207.
19. Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama,T.; Goto, T. *J. Chem. Soc., Chem. Commun.*, **1972**, 64.
20. Cornforth, J. W.; Green, D. T. *J. Chem. Soc. (C)* **1970**, 846.
21. (a) Ozaki, S.; Koga, Y.; Ling, L.; Watanabe, Y.; Kimura, Y.; Hirata, M. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1058; (b) Chung, S. K.; Chang, Y. T. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2039.
22. All new compounds gave satisfactory NMR, MS and elemental analysis data, and the stereochemistry of all synthetic inositol isomers has been analyzed on the basis of ^{1}H and ^{1}H-^{1}H homonuclear COSY spectra.