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The orientation of the β-hydroxyl group controls the diastereoselectivity during the hydride reduction and Grignard reaction of inososes

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ABSTRACT

A comparison of the results of the Grignard reaction and the hydride reduction of the carbonyl group of *epi*- and *scyllo*-inososes reveals that the extent of diastereoselectivity of these reactions is decided by the orientation of the β-hydroxyl group (or its derivative). Presence of an axial β-hydroxyl group generally results in the formation of relatively larger amount of the axial alcohol as a result of the reduction of the carbonyl group. The possible reasons for the observed differences in diastereoselectivity between the reactions of these isomeric *epi*- and *scyllo*-inososes have been discussed. The sequence of reactions reported here provides convenient access to C-alkylated inositols, such as *iso*-laminitol and *iso*-mytilitol as well as 2-*O*-methyl *epi*-inositol, an epimer of the naturally occurring ononitol.

1. Introduction

Extensive research to understand the role of phosphoinositols[1] in cellular functions of eukaryotic systems over the past three decades resulted in the synthesis of a wide variety of cyclitols, their derivatives and analogs.[2] Naturally abundant, *myo*-inositol is often used as a starting material for the synthesis of phosphoinositols, diastereomeric cyclitols as well as natural products and their analogs.[3] Regiospecific oxidation of inositol hydroxyl groups to the corresponding inosose is of significance since the latter provides access to isomeric inositol derivatives (by hydride reduction), inosamines (by reductive amination) and *C*-alkyl inositols (e.g., by Grignard reaction). Nucleophilic addition to carbonyl groups is a ubiquitous reaction in organic synthetic protocols. This reaction has been well investigated and attempts have been made to rationalize or predict the observed diastereo- and enantio-selectivities based on molecular properties, such as electronic and steric effects as well as the ability of the substrate molecules to chelate with metal ions present in reagents or catalysts.[4] Crystal structure correlation has also been utilized to understand the geometry of the approach of the nucleophiles to the carbonyl group, during the addition reaction.[5] We recently reported an instance of protecting group directed diastereoselective reduction of an inosose.[6] The present work shows the crucial role played by the orientation of a neighboring hydroxyl group (OH) or its protected derivative (OPG) in controlling the diastereoselectivity during the hydride reduction and Grignard reaction of inososes. We explored these reactions in our endeavor to obtain C-alkylated inositols, which are being tested as agents to intervene in cellular processes to facilitate the development of drugs for various diseases.[7] Reactivity and product selectivity during the reactions of small molecules containing several other functional groups (as in inositols and their derivatives), are expected to be influenced by each other. Knowledge of such effects would be of immense utility in planning synthetic sequences involving heavily functionalized small molecules, since such an understanding often allows the prediction of the structure of the product.

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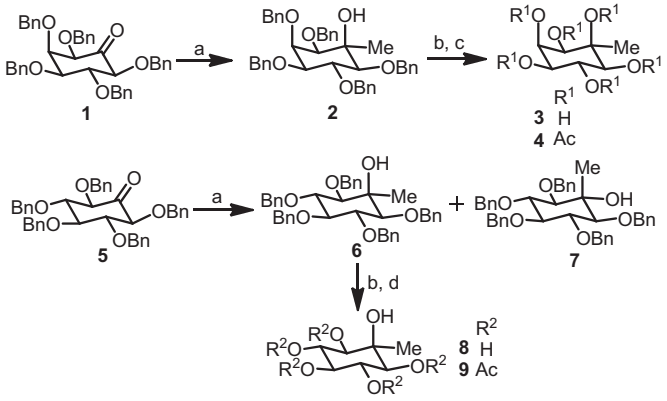
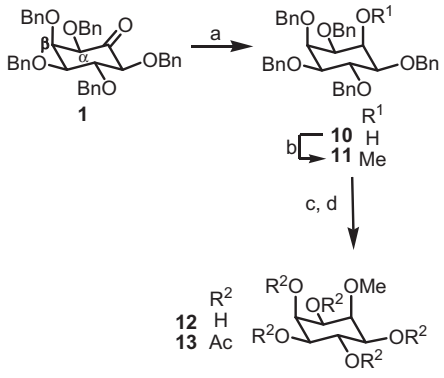
2. Results and discussion

Results of the reaction of *epi*- and *scyllo*-inosose derivatives with methyl magnesium iodide are shown in Scheme 1. Addition of methyl magnesium iodide to the *epi*-inosose **1**[6] was completely selective (to yield **2**) while the addition to *scyllo*-inosose **5** gave a mixture of **6** and **7**. The *C*-methyl inositol derivatives **6** and **7** could be separated by column chromatography. Global deprotection of **2** and **6** gave *iso*-laminitol (**3**) and *iso*-mytilitol (**8**), respectively. Both **3** and **8** were characterized as their acetates **4** and **9**, respectively, and their structure established by single-crystal X-ray diffraction analysis.



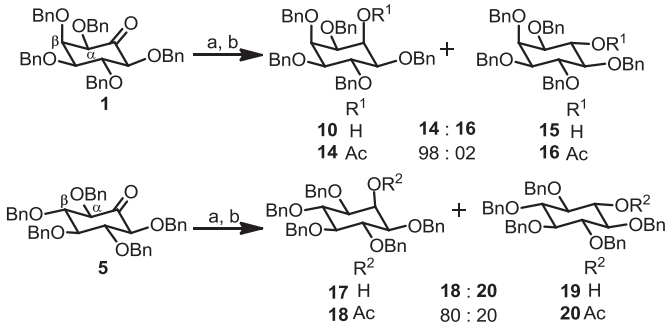
Scheme 1. Reagents and conditions: (a) MeMgI, THF, 0 °C-ambient temp, 93% (for **2**), 76% (for **6**), 18% (for **7**); (b) THF/EtOH/H_2O/TFA, 20% $Pd(OH)_2$/C, H_2 (60 psi); (c) pyridine, DMAP, Ac_2O, reflux, 18 h, 88%; (d) as in (c) at ambient temp, 88%.

Sodium borohydride reduction of the *epi*-inosose **1** gave the *epi*-inositol derivative **10**;[6] O-methylation and global deprotection of **10** gave racemic *iso*-ononitol **12**, which was characterized as its penta acetate **13** (Scheme 2). Structure of **13** was confirmed by single-crystal X-ray diffraction analysis. The synthesis described herein provided racemic 2-*O*-methyl *epi*-inositol (**12**) in an overall yield of 41% in nine steps starting from *myo*-inositol. This represents the first synthesis of 2-*O*-methyl *epi*-inositol (**12**, *iso*-ononitol), which is an epimer of the naturally occurring ononitol.



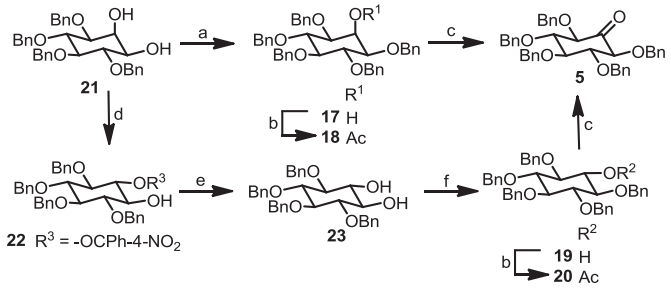
Scheme 2. Reagents and conditions: (a) $NaBH_4$, DCM/MeOH, 0 °C-ambient temp, 30 min, 94%;[6] (b) DMF, NaH, MeI, 96%; (c) THF/EtOH/H_2O/TFA, $Pd(OH)_2$/C, H_2 (60 psi), 20 h; (d) pyridine, Ac_2O, DMAP, reflux, 18 h, 83%. α and β refer to the position of the inositol ring carbon atoms with reference to the carbonyl carbon atom, in these inososes.

Sodium borohydride reduction of the *scyllo*-inosose **5** gave a mixture of the *myo*- and *scyllo*-inositol derivatives **17** and **19**. A comparison of the reduction of the *epi*- and *scyllo*-inososes (Scheme 3) reveals that reduction of the *epi*-inosose **1** is highly selective,[6] while the reduction of the *scyllo*-inosose **5** gives a mixture of diastereomeric inositol derivatives. The ratio of the diastereomeric products estimated by ^{1}H NMR spectroscopy on reduction of the inososes **1** and **5** were, respectively, 98/2 (**14**/**16**) and 80/20 (**18**/**20**). The isolated yield of the products **17** and **19** were 79% and 16%, respectively. This is similar to the outcome of their Grignard reaction (Scheme 1) in that, the C-methylation of the inosose **1** having a β-axial benzyloxy group is more selective than the corresponding inosose **5** having a β-equatorial benzyloxy group.



Scheme 3. Reagents and conditions: (a) $NaBH_4$, DCM/MeOH, 0 °C-ambient temp, 30 min; (b) pyridine, Ac_2O, DMAP, reflux, 20 h.

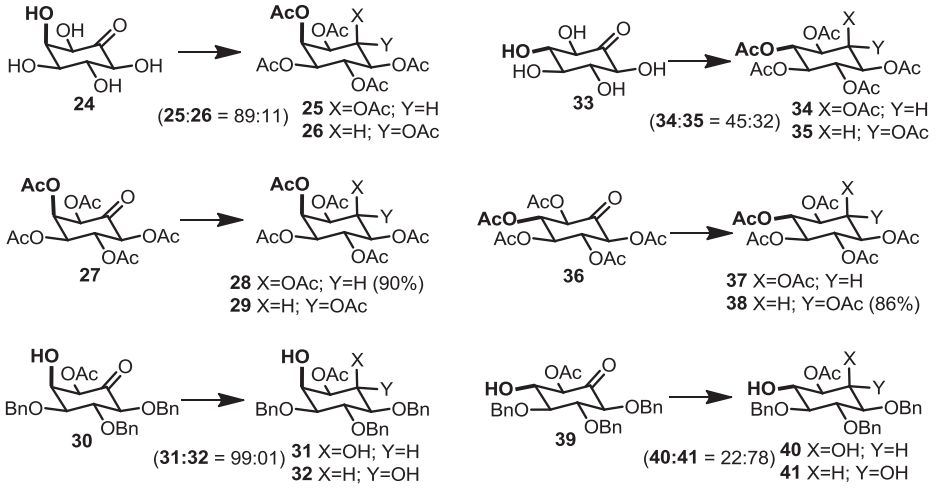
The *epi*-inosose **1** was prepared as reported earlier[6] and the synthesis of *scyllo*-inosose **5** from the known diol **21**[8] is shown in Scheme 4. The *myo*- and *scyllo*-inositol derivatives **17** and **19** were converted to their acetates **18** and **20**, respectively. These acetates were useful for the estimation (by ^{1}H NMR spectroscopy) of the ratio of the diastereomeric inositols formed on reduction of the *scyllo*-inosose **5**, as the two diastereomeric acetates **18** and **20** exhibit characteristic peaks at δ 2.17 and 1.83, respectively, in their ^{1}H NMR spectra.



Scheme 4. Reagents and conditions: (a) benzene, NaH, BnBr, reflux, 1.5 h, 78%; (b) pyridine, DMAP, Ac_2O, reflux, 18 h, 94% (for **18**) and 95% (for **20**); (c) IBX, ethyl acetate, reflux, 6 h, 95%; (d) benzene, TPP, imidazole, 4-NO_2BzOH, 89%; (e) 1% NaOH, THF/MeOH, 98%; (f) DMF, NaH, BnBr, 90%.

A comparison of the structure of the two inososes **1** and **5** shows that they differ only in the orientation of the benzyloxy group at the β-position with respect to the keto group (axial in **1** and equatorial in **5**). We wondered whether the effect of the orientation of the β-OR group on the diastereoselectivity in the reactions shown in Schemes 1 and 3 was real or incidental. Hence we compared the outcome of the reactions of a carbonyl group in molecular systems similar to **1** and **5**, encountered previously in our laboratory as well as elsewhere.

A comparison of the result of the hydride reduction of inososes containing a β-OR group is shown in Scheme 5.[9] The inososes in the left-half of the scheme have a β-OH or OR group in the axial orientation while the inososes in the right-half have the same substituent in the equatorial orientation. Results of the hydride reduction of these pairs of inososes clearly show that the



Scheme 5. Result of sodium borohydride reduction of inososes, which differ only in the orientation of the β-OR group. For the reduction of **27** and **36**, yield of the major product is shown. See Ref. 9 for details.

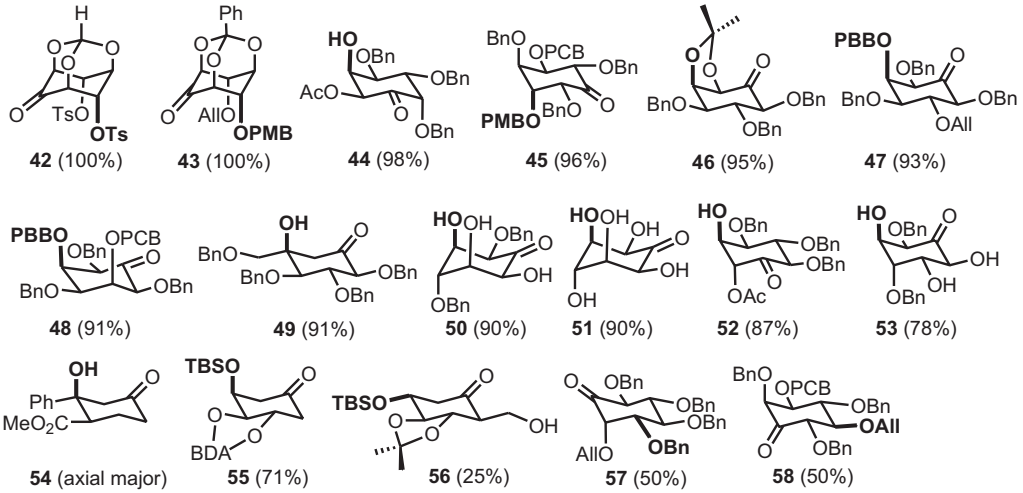
diastereoselectivity for the formation of the axial alcohol is much better when the β-OR group is in the axial orientation.

Scheme 6 shows the result of the reduction of ketones having a β-axial-OR group, for which exact comparison of the corresponding ketone with a β-equatorial-OR group is not available.[9b–d,10] However the last three ketones (**56**–**58**), which have a β-equatorial-OR group exhibit relatively less selectivity during their reduction, reiterating the effect of the orientation of the β-OR group on the diastereoselectivity of addition to carbonyl groups of inososes.

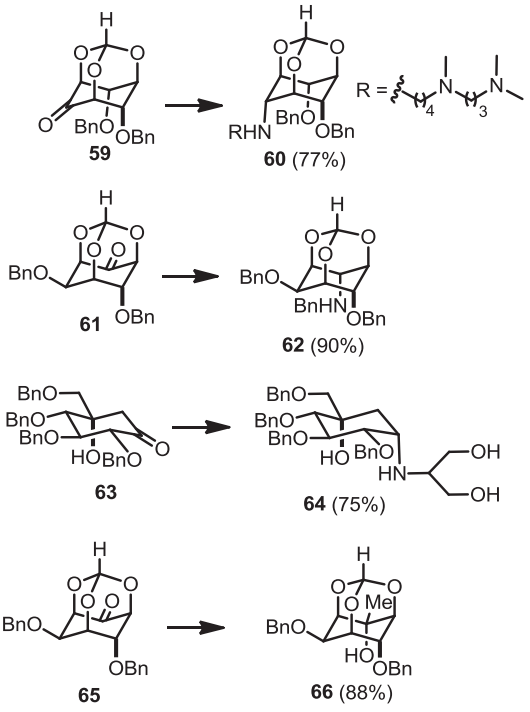
Scheme 7 shows the result of reductive amination of inososes. All the inososes give the corresponding axial amine as the major product.[11] From the results shown in Schemes 5–7, it is clear that the orientation of the β-OR group plays a decisive role in the stereochemical outcome of the addition of nucleophiles to the carbonyl group of inososes.

Higher selectivity during the nucleophilic addition to the carbonyl group in inososes having a β-axial-OR group as compared to inososes having a β-equatorial-OR group could arise due to the steric bulk of the β-axial substituent, which could force the nucleophile to approach the carbonyl group equatorially. However, the degree of selectivity for the formation of the axial alcohol from ketones having β-axial substituent does not correlate with the bulk of the hydroxyl protecting group. For instance, perusal of the literature available[12] on the reduction of silyl ether containing cyclohexanones reveals that the effect of the TBS group is similar to a hydroxyl or a benzyl group (see **54**, **55** in Scheme 6). If the selectivity of reduction was completely dependent on the steric bulk of the β-OR group, the reduction of silyl ether containing ketones (such as **55**) should have resulted in the formation of relatively greater proportion of the axial alcohol, as compared to the inososes carrying smaller groups (such as **54**). This result suggests that although steric bulk of the β-OR group does play a role in deciding the diastereoselectivity, it may not be the sole reason for the observed diastereoselectivity during the reduction of these ketones.

The preferential equatorial approach of the nucleophile (facile formation of the axial alcohol) can also be explained based on the chelation of the metal ions present in the reaction medium leading to the enhanced formation of the 1,3-diaxial diols. Experimental and theoretical investigations[13] on the complexation of metal ions with inositols had revealed that cyclitols, which have a sequence of three consecutive hydroxyl groups in the axial–equatorial–axial arrangement form complexes readily with metal ions. The suggestion that the chelation of cations of the reducing agent (hydride or

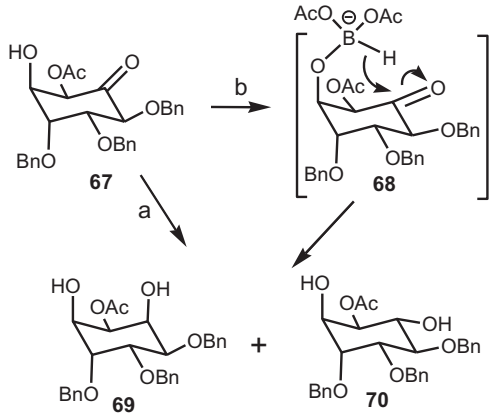


Scheme 6. Ketones, which give axial alcohol as the major product on reduction with sodium borohydride. The extent of the axial alcohol obtained is shown in parenthesis. The last three ketones (**56**–**58**), which lack β-OR group in the axial orientation are shown for comparison. See Refs. 9b–d,10 for details. PMB=CH_2Ph(4-OMe), PBB=CH_2Ph(4-Br), BDA=butanediacetal, PCB=CH_2Ph(4-Cl).



Scheme 7. Reductive amination (amine, $NaBH_3CN$) and Grignard reaction (of **65** with MeMgI) of inososes having a β-OR group in the axial position. Isolated yields are shown in parenthesis. See Ref. 11 for details.

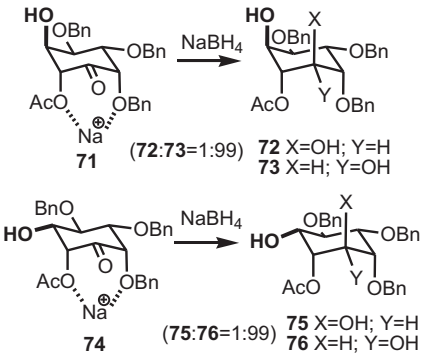
Grignard reagents) could be playing a significant role in the observed stereoselectivity of these reactions is supported by the following observations. (a) The reversal of the observed stereoselectivity of inososes on reduction with sodium borohydride and tetramethylammonium triacetoxyborohydride. The latter reagent gives the equatorial alcohol as the major product since involvement of an intermediate, such as **68** precludes the chelation of the cation between the carbonyl oxygen atom and the β-OR group (Scheme 8).[9c,d,10a]



Scheme 8. Contrast in the reduction of inososes with borohydrides. (a) $NaBH_4$—**69**/**70**=49/1; (b) $Me_4NBH(OAc)_3$—**69**/**70**=1/99. See Refs. 9c,d,10a for details.

(b) Stereoselectivity of the reduction of inososes (such as **71** and **74**, Scheme 9), in which alternate sites for metal ion chelation are available, do not depend on the orientation of the β-OR group. As mentioned earlier, metal ions tend to chelate better with 1,3-diaxial hydroxyl groups.[13]

Furthermore, investigations on the mechanism and diastereoselectivity on sodium borohydride reduction of ketones strongly suggest the possibility of chelation of sodium ion to the ketone and



Scheme 9. Diastereoselectivity of the reduction of ketones (with sodium borohydride), which have alternate sites for metal ion chelation, do not depend on the orientation of the β-hydroxyl group (marked in bold). The ratio of axial:equatorial alcohols formed are shown in parenthesis. See Ref. 9d for details.

the involvement of a transition state with product-like geometry.[14] However, further investigations are required to completely rule out or rule in the involvement of chelation of metal ions during hydride reduction of these inososes.

3. Conclusions

A comparative study of the hydride reduction and the Grignard reaction of inososes reveals the role played by the orientation of the β-OR group on the outcome of the diastereoselectivity of these reactions. An axial orientation of the β-OR group results in better diastereoselectivity during the addition of a nucleophile to the carbonyl group. This comparative study also suggests the possibility of a subtle role of the metal ions on the outcome of the nucleophilic addition to a carbonyl group. We had earlier shown that metal ions play a decisive role in the outcome of O-substitution reactions in partially protected inositol derivatives.[15] Knowledge of such effects is valuable while planning a synthetic scheme and could help to avoid or minimize the formation of undesired isomeric products.

4. Experimental section

4.1. General experimental methods

General experimental methods are as reported earlier.[15] All the asymmetrically substituted *myo*-inositol derivatives reported are racemic; however only one of the enantiomers is shown in schemes for convenience and clarity.

4.2. Experimental procedure and characterization data for compounds

*4.2.1. Racemic 1,3,4,5,6-penta-O-benzyl-2-C-methyl epi-inositol (**2**).* To a stirred solution of penta-*O*-benzyl *epi*-inosose **1**[6] (0.63 g, 1.00 mmol) in THF (7 mL), methyl magnesium iodide (3 M solution in ether, 0.5 mL, 1.5 mmol) was added at 0 °C and the reaction mixture stirred at 0 °C for 15 min then at ambient temperature for 2 h. The reaction mixture was cooled to 0 °C and quenched by adding ethyl acetate (0.5 mL) followed by aqueous ammonium chloride solution (1 mL). The resulting mixture was concentrated under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product was purified by column chromatography (silica gel 100–200 mesh; eluent, ethyl acetate/light petroleum, 3/22, v/v) to get **2** as a colorless solid (0.60 g, 93%); mp 147–150 °C; IR (Nujol): $\bar{\nu}$ 3500–3700 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$): δ 1.21 (s, 3H, CH_3), 2.93 (d, J=2.4 Hz, 1H, Ins H), 3.06 (d, J=9.6 Hz, 1H, Ins H), 3.34–3.45 (dd, J_1=2.5 Hz, J_2=9.8 Hz, 1H, Ins H), 4.12 (t, J=2.5 Hz, 1H,

Ins H), 4.20 (t, J=9.8 Hz, 1H, Ins H), 4.36–4.48 (m, 2H), 4.58–5.03 (m, 9H), 7.19–7.44 (m, 25H, Ar H) ppm; ^{13}C NMR (50 MHz; $CDCl_3$): δ 22.3 (CH_3) 72.0 (CH_2), 73.0 (CH_2), 75.2 (CH_2), 75.8 (CH_2), 76.09 (CH_2), 76.14 (Ins C), 76.8 (Ins C), 77.3 (Ins C), 80.7 (Ins C), 84.2 (Ins C), 127.4 (Ar C), 127.5 (Ar C), 127.6 (Ar C), 127.7 (Ar C), 127.8 (Ar C), 128.0 (Ar C), 128.08 (Ar C), 128.15 (Ar C), 128.2 (Ar C), 128.3 (Ar C), 128.4 (Ar C), 137.3 (Ar C), 137.5 (Ar C), 138.2 (Ar C), 138.3 (Ar C), 138.7 (Ar C); elemental analysis calcd for $C_{42}H_{44}O_6$: C 78.23, H 6.88; found C 78.43; H 6.96%.

*4.2.2. Racemic 1,2,3,4,5,6-hexa-O-acetyl-2-C-methyl-epi-inositol (**4**).* The racemic pentabenzyl ether **2** (0.10 g, 0.16 mmol), THF (2 mL), water (0.50 mL), EtOH (2 mL), and trifluoroacetic acid (TFA, 0.50 mL) were taken in a hydrogenation bottle and 20% $Pd(OH)_2/C$ (0.050 g) was added in one portion. The reaction mixture was stirred in an atmosphere of hydrogen (60 psi) at ambient temperature for 20 h. The reaction mixture was then diluted with aqueous ethanol (1/1, 10 mL) and filtered through a small bed of Celite. The Celite bed was washed with hot water and ethanol (2×5 mL) alternately. The combined filtrate was evaporated under reduced pressure and the residue was co-evaporated with absolute ethanol (2×5 mL) to get crude racemic 2-*C*-methyl *epi*-inositol **3** (0.032 g), which was used in the next step.

A mixture of the crude **3** (0.032 g), pyridine (2 mL), DMAP (0.01 g), and acetic anhydride (0.27 mL, 2.88 mmol) was refluxed for 18 h. The reaction mixture was cooled to ambient temperature and quenched by adding few pieces of ice. The solvent was evaporated under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography (silica gel 100–200 mesh; eluent, ethyl acetate/light petroleum, 1/2, v/v) to get **4** as a colorless solid (0.061 g, 88%); mp 133–137 °C (crystals by slow evaporation of a warm methanol solution); IR (Nujol): $\bar{\nu}$ 1748 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$): δ 1.25 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 4.95–5.07 (m, 2H, Ins H), 5.08–5.18 (dd, J=3.8 Hz, J_2=10.5 Hz, 1H, Ins H), 5.57 (t, J=3.5 Hz, 1H, Ins H), 5.70 (t, J=10.2 Hz, 1H, Ins H) ppm; ^{13}C NMR (50 MHz; $CDCl_3$): δ 19.8 (CH_3), 20.4 (CH_3), 20.5 (CH_3), 20.7 (CH_3), 22.5 (CH_3), 67.9 (Ins C), 68.4 (Ins C), 70.1 (Ins C), 73.7 (Ins C), 82.8 (Ins C-4), 168.8 (CO), 169.4 (CO), 169.6 (CO), 169.7 (CO), 169.8 (CO), 170.0 (CO) ppm; elemental analysis calcd for $C_{19}H_{26}O_{12}$: C 51.12, H 5.87; found C 51.26; H 5.80%.

*4.2.3. 1,2,3,4,5-Penta-O-benzyl-scyllo-inosose (**5**).* To a solution of **17** (2.70 g, 4.28 mmol) in ethyl acetate (30 mL), IBX (3.60 g, 12.8 mmol) was added and the resulting mixture was refluxed for 6 h. The reaction mixture was cooled to ambient temperature and filtered through a bed of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel 230–400 mesh; eluent, ethyl acetate/light petroleum, 3/22, v/v) to get the *scyllo*-inosose **5** (2.56 g, 95%) as a colorless solid; mp 159–162 °C (lit.[16] mp 163–164 °C).

*4.2.4. 1,3,4,5,6-Penta-O-benzyl-2-C-methyl-myo-inositol (**6**) and 1-C-methyl-2,3,4,5,6-penta-O-benzyl-scyllo-inositol (**7**).* To a stirred solution of *scyllo*-inosose **5** (0.13 g, 0.20 mmol) in THF (3 mL), methyl magnesium iodide (3 M solution in ether, 0.10 mL, 0.30 mmol) was added at 0 °C and the reaction mixture stirred at 0 °C for 15 min then at ambient temperature for 2 h. The reaction mixture was cooled to 0 °C and quenched by adding ethyl acetate (1 mL) followed by aqueous ammonium chloride solution. The resulting mixture was concentrated under reduced pressure and the residue obtained was worked up with ethyl acetate. The products obtained were separated by column chromatography (silica gel 100–200 mesh; eluent, ethyl acetate/light petroleum, 3/22, v/v) to get racemic **7** (0.023 g, 18%) and racemic **6** (0.098 g, 76%) as colorless solids. Data for **6**: mp 103–106 °C; IR (Nujol): $\bar{\nu}$ 3557 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$): δ 1.23 (s, 3H, CH_3), 2.12 (br s, 1H, D_2O exchangeable, OH), 3.21 (d, J=9.6 Hz, 2H, Ins H), 3.54 (t, J=9.6 Hz, 1H, Ins H), 3.99 (t, J=9.5 Hz, 2H, Ins H), 4.64 (d, J=10.9 Hz, 2H, CH_2Ph), 4.80–5.03 (m, 8H, CH_2Ph), 7.21–7.40 (m, 25H, Ar H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$): δ 23.0 (CH_3), 75.1 (Ins C-2), 75.78 (CH_2), 75.84 (CH_2), 76.1 (CH_2), 82.88 (Ins C), 82.93 (Ins C), 83.3 (Ins C), 127.52 (Ar C), 127.57 (Ar C), 127.7 (Ar C), 127.8 (Ar C), 128.3 (Ar C), 128.4 (Ar C), 137.9 (Ar C), 138.6 (Ar C) ppm; elemental analysis calcd for $C_{42}H_{44}O_6$: C 78.23, H 6.88; found C 77.81; H 6.97%.

Data for **7**: mp 160–163 °C; IR (Nujol): $\bar{\nu}$ 3500–3600 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.30 (s, 3H, CH_3), 2.18 (br s, 1H, D_2O exchangeable, OH), 3.46 (d, J=9.8 Hz, 2H, Ins H), 3.53 (t, J=9.2 Hz, 2H, Ins H), 3.62 (t, J=9.1 Hz, 1H, Ins H), 4.79–4.94 (m, 10H, CH_2Ph), 7.23–7.38 (m, 25H, Ar H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$): δ 17.6 (CH_3), 75.78 (CH_2), 75.84 (CH_2), 76.0 (Ins C), 76.1 (CH_2), 82.8 (Ins C), 83.5 (Ins C), 84.8 (Ins C), 127.65 (Ar C), 127.69 (Ar C), 127.9 (Ar C), 128.40 (Ar C), 128.43 (Ar C), 138.4 (Ar C), 138.8 (Ar C) ppm; elemental analysis calcd for $C_{42}H_{44}O_6$: C 78.23, H 6.88; found C 77.94; H 6.93%.

*4.2.5. 1,3,4,5,6-Penta-O-acetyl-2-C-methyl-myo-inositol (**9**).* The 2-*C*-methyl-*myo*-inositol **6** (0.92 g, 1.43 mmol), THF (6 mL), ethanol (3 mL), water (1.5 mL), and TFA (1.50 mL) were taken in a hydrogenation bottle and 20% $Pd(OH)_2/C$ (0.75 g) was added in one portion. The hydrogenolysis reaction was carried out as in the preparation of **4**; the crude 2-*C*-methyl-*myo*-inositol (**8**, 0.27 g) obtained was used in the next step.

Crude **8** (0.27 g) was acetylated (at ambient temperature) using pyridine (5 mL), DMAP (0.01 g), and acetic anhydride (2.43 mL, 25.74 mmol) as in the preparation of **4** and purified by column chromatography (silica gel 100–200 mesh; eluent, ethyl acetate/light petroleum, 3/7, v/v) to get **9** as a colorless solid (0.51 g, 88%); mp 133–137 °C (crystals by slow evaporation of a warm methanol solution); IR (Nujol): $\bar{\nu}$ 1746, 3200–3600 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.14 (s, 3H, CH_3), 1.99 (s, 6H, CH_3), 2.01 (s, 3H, CH_3), 2.13 (s, 6H, CH_3), 2.15 (br s, 1H, OH, D_2O exchangeable), 5.05 (d, J=10.0 Hz, 2H, Ins H), 5.22 (t, J=9.8 Hz, 1H, Ins H), 5.53 (t, J=9.9 Hz, 2H, Ins H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$): δ 20.49 (CH_3), 20.52 (CH_3), 22.1 (CH_3), 70.6 (Ins C), 70.7 (Ins C), 73.1 (Ins C), 73.4 (Ins C-2), 169.6 (CO), 169.73 (CO), 169.75 (CO) ppm; elemental analysis calcd for $C_{17}H_{24}O_{11}$: C 50.49, H 5.98; found C 50.26; H 5.66%.

*4.2.6. Racemic 1,3,4,5,6-penta-O-benzyl-2-O-methyl-epi-inositol (**11**).* To a solution of the alcohol **10**[6] (0.063 g, 0.10 mmol) in DMF (2 mL), sodium hydride (0.005 g, 0.12 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then at ambient temperature for 30 min. The reaction mixture was cooled again to 0 °C and methyl iodide (9 μL, 0.15 mmol) was added to it. The reaction mixture was allowed to come to ambient temperature and stirred for 2 h. Few pieces of ice were added and the reaction mixture was concentrated under reduced pressure. The residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography (silica gel, 100–200 mesh; eluent, ethyl acetate/light petroleum, 3/22, v/v) to get the racemic methyl ether **11** (0.062 g, 96%) as a gum. ^{1}H NMR (200 MHz; $CDCl_3$): δ 3.13 (t, J=2.3 Hz, 1H, Ins H), 3.20–3.35 (m, 2H, Ins H), 3.69 (s, 3H, OCH_3), 3.89 (br s, 1H, Ins H), 4.10 (br s, 1H, Ins H), 4.31 (t, J=9.7 Hz, 1H, Ins H), 4.43–4.99 (m, 10H, CH_2Ph), 7.13–7.53 (m, 25H, Ar H) ppm; ^{13}C NMR (50 MHz; $CDCl_3$): δ 61.3 (CH_3), 71.1 (CH_2), 72.6 (CH_2), 73.6 (CH_2), 74.8 (Ins C), 75.8 (CH_2), 78.1 (Ins C), 78.4 (Ins C), 79.2 (Ins C), 80.3 (Ins C), 80.7 (Ins C), 126.8 (Ar C), 127.1 (Ar C), 127.32 (Ar C), 127.35 (Ar C), 127.47 (Ar C), 127.54 (Ar C), 127.6 (Ar C), 127.7 (Ar C), 127.9 (Ar C), 128.1 (Ar C), 128.20 (Ar C), 128.24 (Ar C), 128.3 (Ar C), 137.9 (Ar C), 138.57 (Ar C), 138.63 (Ar C),

139.1(Ar C), 139.5 (Ar C) ppm; elemental analysis calcd for $C_{42}H_{44}O_6$: C 78.23, H 6.88; found C 78.36; H 7.21%.

*4.2.7. Racemic 1,3,4,5,6-penta-O-acetyl-2-O-methyl epi-inositol (**13**).* The racemic pentabenzyl ether **11** (0.134 g, 0.21 mmol) was subjected to hydrogenolysis in a mixture of THF (2 mL), ethanol (2 mL), water (0.50 mL), and TFA (0.50 m L) in the presence of 20% $Pd(OH)_2/C$ (0.050 g) as in the preparation of **4**. The product obtained was co-evaporated with absolute ethanol (2×5 mL) to get racemic 2-*O*-methyl *epi*-inositol **12** (0.039 g).

The crude **12** (0.039 g) was acetylated using pyridine (2 mL), DMAP (0.01 g), and acetic anhydride (0.30 mL, 3.15 mmol) as in the preparation of **4**. The product was purified by column chromatography (silica gel 100–200 mesh; eluent, ethyl acetate/light petroleum, 1/2, v/v) to get **13** as a colorless solid (0.071 g, 83%); mp 131–133 °C (crystals by slow evaporation of a warm methanol solution); IR (Nujol): $\bar{\nu}$ 1747 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ 2.00 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.50 (s, 3H, OCH_3), 3.92 (br s, 1H, Ins H), 4.89–4.95 (dd, J_1=3.3 Hz, J_2=10.3 Hz, 1H, Ins H), 4.98–5.05 (m, 2H, Ins H), 5.54–5.58 (m, 1H, Ins H), 5.72 (t, J=10.3 Hz, 1H, Ins H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$): δ 20.5 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 61.3 (OCH_3), 67.4 (Ins C), 68.4 (Ins C), 68.5 (Ins C), 68.8 (Ins C), 71.3 (Ins C), 77.9 (Ins C), 169.5 (CO), 169.6 (CO), 169.7 (CO), 169.9 (CO), 170.6 (CO) ppm; elemental analysis calcd for $C_{17}H_{24}O_{11}$: C 50.49, H 5.98; found C 50.36; H 5.81%.

*4.2.8. Reduction of 1,2,3,4,5-penta-O-benzyl-scyllo-inosose **5**.* The *scyllo*-inosose **5** (0.063 g, 0.10 mmol) was dissolved in DCM (4 mL)/methanol (1 mL) mixture. To this solution sodium borohydride (0.008 g, 0.20 mmol) was added in one portion at 0 °C and the reaction mixture was stirred at 0 °C for 5 min then at ambient temperature for 30 min. The reaction was quenched by adding saturated solution of ammonium chloride (1 mL). The resulting mixture was concentrated under reduced pressure and the residue was worked up with ethyl acetate and the products were separated by column chromatography (silica gel 230–400 mesh; eluent, ethyl acetate/light petroleum, 3/22, v/v) to get the penta-*O*-benzyl-*myo*-alcohol **17**[16] (0.050 g, 79%) and penta-*O*-benzyl-*scyllo*-alcohol **19**[16] (0.010 g, 16%).

4.2.9. Procedure for the reduction of inosose and estimation of the products. The inosose (0.10 mmol) was dissolved in DCM (4 mL)/methanol (1 mL) mixture. To this solution sodium borohydride (0.20 mmol) was added in one portion at 0 °C and the reaction mixture stirred at 0 °C for 5 min and then at ambient temperature for 30 min. The reaction was quenched by adding aqueous ammonium chloride solution. The resulting mixture was concentrated under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product obtained was acetylated as below.

A mixture of the product obtained above, dry pyridine (2 mL), DMAP (0.01 g), and acetic anhydride (0.20 mmol) was refluxed for 18 h. The reaction mixture was cooled to ambient temperature and quenched by adding few pieces of ice. The solvent was evaporated under reduced pressure and the residue obtained was worked up with ethyl acetate and the diastereomeric acetates were estimated by ^1H NMR spectroscopy. Reduction of **1** (at 0 °C) as above gave **14** and **16** in the ratio 98/2. Reduction of **5** (at 0 °C) as above gave **18** and **20** in the ratio 80/20. Reduction of **5** (at −55 °C) as above gave **18** and **20** in the ratio 92/8.

*4.2.10. 1,3,4,5,6-Penta-O-benzyl-myo-inositol (**17**).* To a stirred solution of the diol **21**[8] (3.01 g, 5.57 mmol) in dry benzene (30 mL) was added sodium hydride (1.81 g, 45.20 mmol) and the mixture was stirred at ambient temperature for 30 min. To this mixture, a solution of benzyl bromide (0.7 mL, 5.86 mmol) in benzene (2 mL) was added and the reaction mixture refluxed for 1.5 h. The reaction mixture was then allowed to come to ambient temperature, a few pieces of ice were added and the solvent was removed under reduced pressure. The residue obtained was worked up with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude product obtained was purified by flash column chromatography (silica gel 230–400 mesh; eluent, ethyl acetate/light petroleum, 3/17, v/v) to get **17** (2.75 g, 78%) as a colorless solid; mp 125–128 °C (lit.[16] mp 125–127 °C).

*4.2.11. 1,3,4,5,6-Penta-O-benzyl-2-O-acetyl-myo-inositol (**18**).* The pentabenzyl ether **17** (0.063 g, 0.10 mmol) was acetylated using dry pyridine (2 mL), DMAP (0.01 g), and acetic anhydride (20 μL, 0.20 mmol) as in the preparation of **4**. The product obtained was purified by column chromatography (silica gel 100–200 mesh; eluent, ethyl acetate/light petroleum, 3/22, v/v) to get **18** as a colorless solid (0.063 g, 94%); mp 107–110 °C (lit.[17] mp 110–111 °C).

*4.2.12. 1,2,3,4,5-Penta-O-benzyl scyllo-inositol (**19**).* To a stirred solution of the diol **23** (2.90 g, 5.36 mmol) in dry DMF (30 mL) was added sodium hydride (0.215 g, 5.37 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min then at ambient temperature for 30 min. The reaction mixture was again cooled to 0 °C and a solution of benzyl bromide (0.65 mL, 5.42 mmol) in DMF (2 mL) was added and the reaction mixture was allowed to come to ambient temperature and stirred for 1 h. The reaction was quenched by adding few pieces of ice and the solvent was removed under reduced pressure. The residue obtained was worked up with ethyl acetate. The crude product obtained was purified by flash column chromatography (silica gel 230–400 mesh; eluent, ethyl acetate/light petroleum, 3/17, v/v) to get **19** (3.03 g, 90%) as a colorless solid; mp 103–106 °C (lit.[16] mp 108–109 °C).

*4.2.13. 1-O-Acetyl-2,3,4,5,6-penta-O-benzyl-scyllo-inositol (**20**).* The pentabenzyl ether **19** (0.063 g, 0.10 mmol) was acetylated using dry pyridine (2 mL), DMAP (0.01 g), and acetic anhydride (20 μL, 0.20 mmol) as in the preparation of **4**. The crude product obtained was purified by column chromatography (silica gel 100–200 mesh; eluent, ethyl acetate/light petroleum, 3/22, v/v) to get **20** as a colorless solid (0.064 g, 95%); mp 118–122 °C; IR (Nujol): $\bar{\nu}$ 1741 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$): δ 1.83 (s, 3H, CH_3), 3.42–3.67 (m, 5H, Ins H), 4.63 (d, J=11.4 Hz, 2H, CH_2Ph), 4.75–4.95 (m, 8H, CH_2Ph), 5.16 (t, J=9.5 Hz, 1H, Ins H), 7.13–7.38 (m, 25H, Ar H) ppm; ^{13}C NMR (50 MHz; $CDCl_3$): δ 20.9 (CH_3), 73.5 (Ins C), 75.5 (CH_2), 76.0 (CH_2), 80.6 (Ins C), 82.7 (Ins C), 82.8 (Ins C), 127.7 (Ar C), 127.8 (Ar C), 128.0 (Ar C), 128.4 (Ar C), 138.2 (Ar C), 138.3 (Ar C), 170.0 (CO) ppm; elemental analysis calcd for $C_{43}H_{44}O_7$: C 76.76, H 6.59; found C 76.69; H 6.56%.

*4.2.14. Racemic 1,2,3,4-tetra-O-benzyl-scyllo-inositol (**23**).* To a stirred solution of **22**[18] (2.14 g, 3.10 mmol) in THF (3 mL) were added methanol (9 mL) and 1% aqueous sodium hydroxide solution (1.5 mL). The reaction mixture was refluxed for 4 h and then allowed to attain ambient temperature. The solvent was removed under reduced pressure. The residue was worked up with ethyl acetate. The crude product was purified by column chromatography (silica gel 60–120 mesh; eluent, ethyl acetate/light petroleum, 1/2, v/v) to get **23** (1.65 g, 98%) as a colorless solid; mp 164–168 °C; IR (Nujol): $\bar{\nu}$ 3200–3350 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ 2.77 (br s, 2H, OH, D_2O exchangeable), 3.38–3.44 (m, 2H, Ins H), 3.47–3.52 (m, 2H, Ins H), 3.56–3.61 (m, 2H, Ins H), 4.80 (d, J=6 Hz, 2H, CH_2Ph), 4.84–4.94 (m, 6H, CH_2Ph), 7.19–7.40 (m, 20H, Ar H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$): δ 73.8 (Ins C), 75.5 (CH_2), 75.8 (CH_2), 82.3 (Ins C), 83.0 (Ins C), 127.7 (Ar C), 127.8 (Ar C), 127.9 (Ar C), 128.4 (Ar C), 128.5 (Ar C), 138.3 (Ar C), 138.4 (Ar C); elemental

Table 1
Single-crystal X-ray diffraction data for crystals of **4**, **9**, **13**, and **22**

Compound no.	**4**	**9**	**13**	**22**
Chemical formula	$C_{19}H_{26}O_{12}$	$C_{17}H_{24}O_{11}\cdot 0.25(H_2O)$	$C_{17}H_{24}O_{11}$	$C_{41}H_{39}O_9N$
M_r	446.40	408.36	404.36	689.73
Temperature (K)	297(2)	297(2)	297(2)	297(2)
Morphology	Plate	Prism	Plate	Plate
Crystal size	0.37×0.27×0.19	0.46×0.41×0.27	0.33×0.26×0.19	0.32×0.06×0.05
Crystal system	Monoclinic	Triclinic	Triclinic	Monoclinic
Space group	$P2_1/c$	$P-1$	$P-1$	$P2_1/c$
a (Å)	10.983(7)	8.5062(7)	10.4171(14)	18.144(4)
b (Å)	32.95(2)	9.5170(8)	13.5098(18)	7.9967(19)
c (Å)	14.886(7)	26.338(2)	15.498(2)	25.775(6)
α (°)	90	98.029(4)	77.756(2)	90
β (°)	112.22(4)	93.690(4)	79.661(2)	100.167(4)
γ (°)	90	100.574(4)	88.350(2)	90
V (Å^3)	4987(5)	2066.6(3)	2096.8(5)	3681.0(15)
Z	8	4	4	4
D_{calcd} (g cm^{-3})	1.189	1.313	1.281	1.245
μ (mm^{-1})	0.100	0.112	0.108	0.088
F(000)	1888	864	856	1456
Absorption correction T_{min}/T_{max}	Multi-scan 0.964/0.981	Multi-scan 0.951/0.971	Multi-scan 0.965/0.980	Multi-scan 0.973/0.996
h, k, l (min, max)	(−13, 13), (−39, 39), (−17, 17)	(−10, 10), (−11, 11), (−31, 31)	(−12, 12), (−16, 16), (−18, 18)	(−21, 21), (−9, 9), (−30, 30)
Reflns collected	28,956	46,382	20,199	34,551
Unique reflns	8744	7276	7361	6496
Observed reflns	4605	6277	5391	4908
R_{int}	0.0955	0.045	0.0328	0.0590
No. of parameters	621	529	526	464
GoF	1.061	1.106	1.070	1.271
$R_1[I>2\sigma(I)]$	0.1032	0.0491	0.1018	0.1028
$wR_2[I>2\sigma(I)]$	0.2679	0.1281	0.2599	0.2064
R_1–all data	0.1732	0.0568	0.1195	0.1347
wR_2–all data	0.3127	0.1327	0.2805	0.2208
$\Delta\rho_{max}$, $\Delta\rho_{min}$(e Å^{-3})	0.20, −0.24	0.59, −0.12	0.96, −0.28	0.22, −0.18
CCDC No.	902249	898796	902247	902248

analysis calcd for $C_{34}H_{36}O_6$: C 75.53, H 6.71; found C 75.36; H 6.81%.

4.2.15. Crystallographic details. Single-crystal X-ray intensity measurements for crystals of **4**, **9**, **13**, and **22** were recorded at ambient temperature on a Bruker SMART APEX single-crystal X-ray CCD diffractometer with graphite-monochromatized (Mo Kα=0.71073 Å) radiation. The X-ray generator was operated at 50 kV and 30 mA. Diffraction data were collected with a ω scan width of 0.3° at different settings of φ (0, 90, 180, and 270°) keeping the sample-to-detector distance fixed at 6.145 cm and the detector position (2θ) fixed at −28°. The X-ray data acquisition was monitored by SMART program (Bruker, 2003).[19] All the data were corrected for Lorentz-polarization effects using SAINT programs.[19] A semi-empirical absorption correction (multi-scan) based on symmetry equivalent reflections was applied using the SADABS program.[19] Lattice parameters were determined from least-squares analysis of all reflections. The structures were solved by direct methods and refined by full matrix least squares, based on F^2, using SHELX-97 software package.[20] Molecular diagrams were generated using ORTEP-32.[21] Geometrical calculations were performed using SHELXTL[19] and PLATON.[22] The crystallographic data are summarized in Table 1. ORTEP diagrams are included in the Supplementary data. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 898796, 902247, 902248, and 902249. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

NMR spectroscopic data for compounds **2**, **4**, **6**, **7**, **9**, **11**, **13**, **20**, **23** and mixture of **18** and **20**; ORTEP diagrams of **4**, **9**, **13**, and **22**. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2013.04.081.

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