SYNTHESIS OF BICYCLIC DERIVATIVES OF 5A-CARBA-SUGARS: 6-HYDROXYL GROUP CONFORMATIONALLY RESTRICTED 5A-CARBA-D-MANNOPYRANOSE DERIVATIVES

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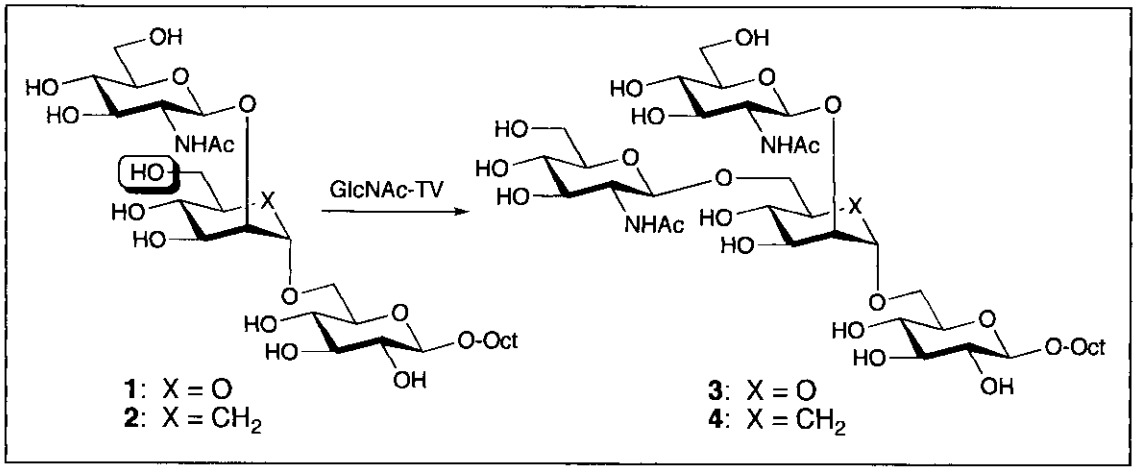
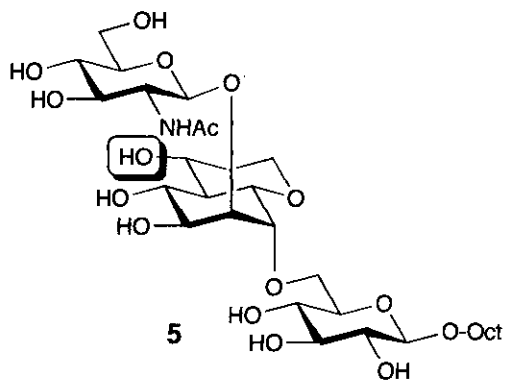
Abstract— Some bicyclic derivatives of 5a-carba-α– and β-D-manno-pyranoses, whose 6-hydroxyl groups are conformationally restricted, have been synthesized in order to provide key components of the trisaccharide mimics designed as inhibitors or substrate analogues useful for elucidation of mechanism and action of GlcNAcT-V.

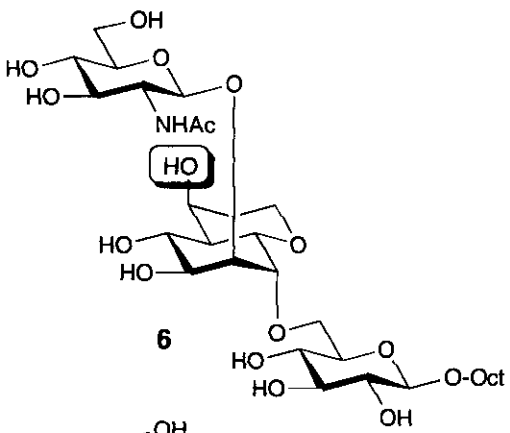
INTRODUCTION

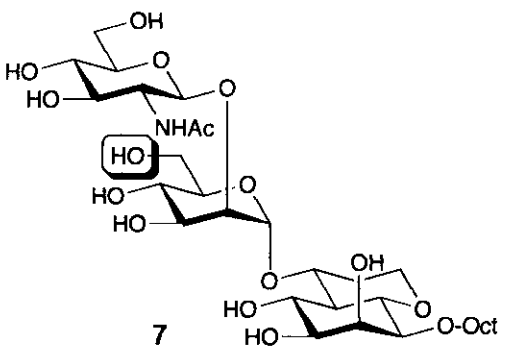
N-Acetylglucosaminyltransferase (GlcNAcT-V) is a key enzyme involved in the biosynthesis of highly branched asparagine-linked oligosaccharides.[1] This enzyme has been focused much attention since, especially, specific increases in the activity of this enzyme have been shown to correlate with the metastatic potential of human and rodent tumor cells.[2,3] Hindsgaul and his coworkers[4] have found that simple synthetic trisaccharide (**1**) is a substrate acceptor for GlcNAcT-V yielding the expected tetrasaccharide (**3**) (Scheme 1). Extensive chemical modification[5] of **1** has so far been carried out both to elucidate mechanism and action of this enzyme, and to develop possible inhibitors of this enzyme. On the other hand, the enzyme has been shown to recognize this acceptor (**1**) in only one of these two accessible conformations (gauche-trans or gauche-gauche rotamer), derived by restriction of rotation about the α-D-Man*p*-(1→6) linkage, on the basis of the study[6] using the substrate analogues, the conformations of which were fixed by linking O4 and C6 with an ethylene bridge.

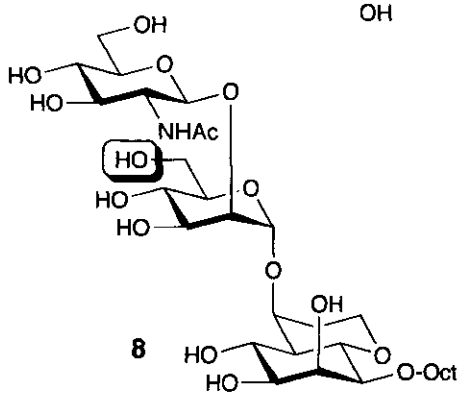
We have previously shown[7] that the trisaccharide mimic (**2**), the central α-D-mannopyranose unit of **1** being replaced with the 5a-carba congener, acts similarly as the effective acceptor for GlcNAcT-V to

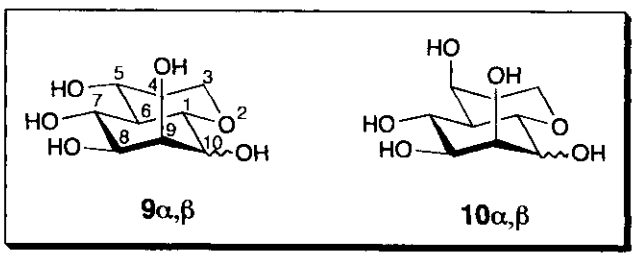




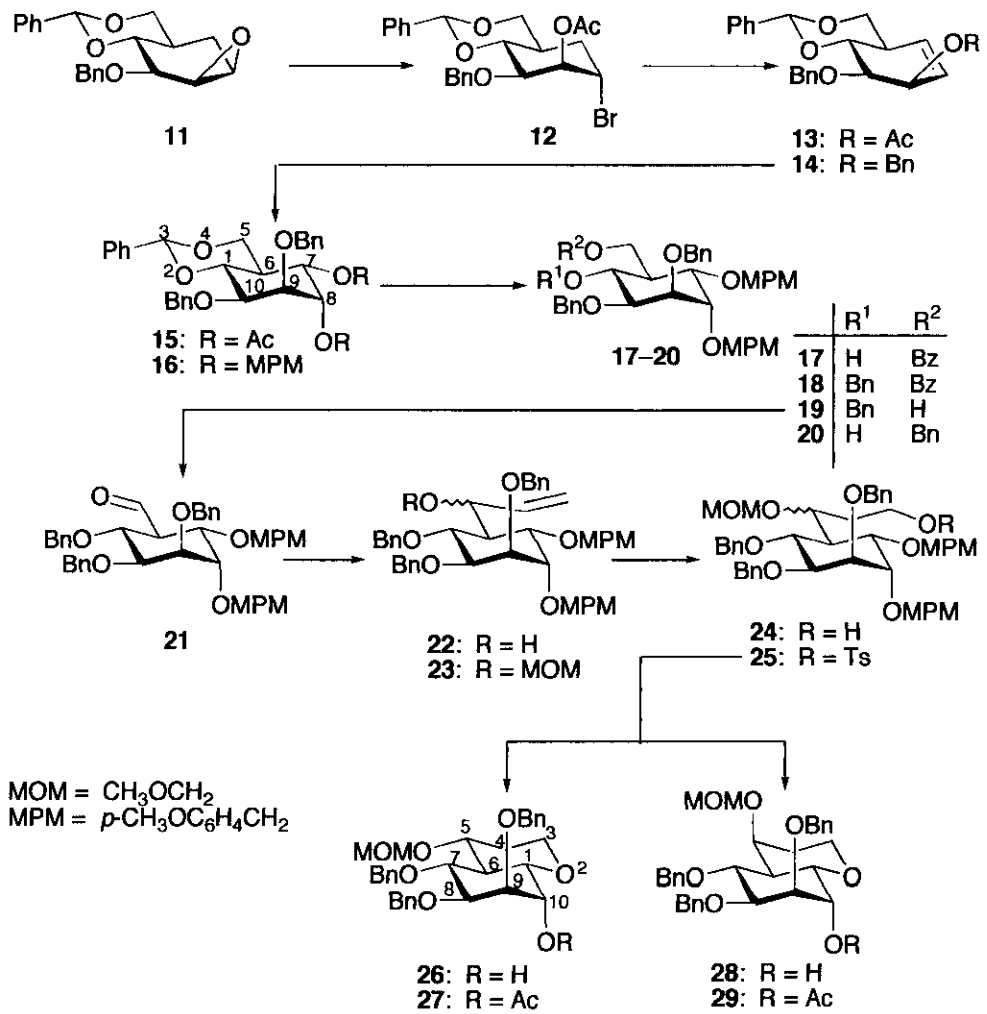




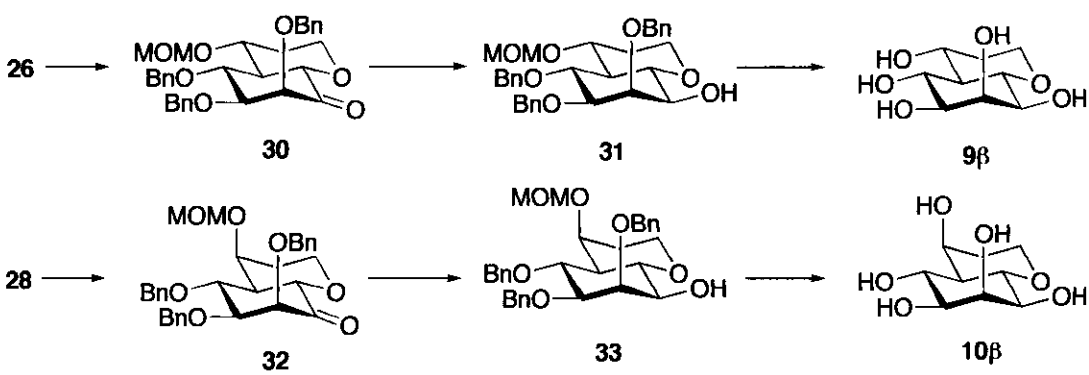




Scheme 1



Scheme 2



Scheme 3

afford the tetrasaccharide (**4**). Therefore, the 6-OH group conformationally restricted derivatives (**9**α) and (**10**α) (gg and gt rotamers) of 5a-carba-D-mannopyranose, 2-oxabicyclo[4.4.0]decane-5,7,8,9,10-pentols, were designed and synthesized, in order to demonstrate whether both the target 5a-carba-trisaccharides (**5**) and (**6**) of gg and gt conformers act as a substrate for GlcNAcT-V or not. Besides **9**β and **10**β may be useful building blocks for preparation of the carba-trisaccharides such as **7** and **8**, in which the possibility for rotation about C-5-C-6 bond of α-D-Man residue are restricted. Compounds (**9**α,β) and (**10**α,β) itself may be applied as D-mannopyranose mimics for certain biochemical studies.

RESULTS AND DISCUSSION

The epoxide[8] (**11**), a versatile intermediate for synthesis of 5a-carba-oligosaccharides, was easily avaliable from optically resolved Diels-Alder endo-adduct of furan and acrylic acid. Treatment of **11** with LiBr and NiBr in THF, followed by acetylation, gave the bromide (**12**) (~100%) (Scheme 2). On treatment with DBU in toluene at 70°C, elimination reaction of **12** underwent smoothly to give the alkene (**13**) (88%), which was converted into the dibenzyl ether (**14**) (87%) by Zemplén *O*-deacetylation and subsequent *O*-benzylation. Treatment of **14** with OsO_4 in the presence of *N*-methylmorpholine in aqueous acetone afforded selectively a single diol, which was isolated as the diacetate[9] (**15**) (~100%). The structure was assigned on the basis of the ^{1}H NMR spectrum. The protecting *O*-acetyl groups of **15** were replaced with *p*-methoxybenzyl (MPM), by *O*-deacetylation and subsequent treatment with NaH and *p*-methoxybenzyl chloride in DMF (→**16**, 90%), being more suitable for the proceeding steps. Compound **16** was then *O*-debenzylidenated with aqueous 80% AcOH. Selective benzoylation of the resulting diol with BzCl in pyridine (–15°C) gave the 6-benzoate (**17**) (87% over-all yield). A solution of **17** in dry DMF was first treated with slightly excess of NaH (~2 molar equiv.) and then with excess benzyl bromide to produce three monobenzyl ethers (**18**) (58%), (**19**) (26%), and (**20**) (11%). Compound (**18**) was readily convertible to the desired **19** by treatment with DIBAH in toluene in 97% yield. Oxidation of **19** with DMSO-oxalyl chloride in CH_2Cl_2 gave the aldehyde (**21**), which was subsequently treated with ethenylmagnesium bromide in THF at –78 °C to give a mixture of the isomeric alcohols (**22**) (80% over-all yield). The mixture was without separation converted into the methoxymethyl ethers (**23**) (92%), which were hydroborated (→**24**, 86%) and then transformed conventionally into the tosylates (→**25**, 85%). The MPM groups were removed with CAN in aqueous CH_3CN and the resulting diols were subjected to basic conditions with methanolic sodium methoxide to give rise to a mixture of

products, which was separated by chromaqtography on silica gel to give two bicyclic compounds[10] (**26**) (39%) and (**28**) (33%). They were further characterized as the acetates (**27**) (73%) and (**29**) (70%), whose structures were fully assigned on the basis of their ^1H NMR spectra. These are the appropriately protected derivatives of **9α** and **10α**, utilizable for further transformation.

Inversion of the configuration at C-10, corresponding to the anomeric position of 5a-carba-D-manno-pyranose derivatives, was carried out by oxidation of the 10-OH group and subsequent reduction (Scheme 3). Thus, treatment of **26** with acetic anhydride in DMSO gave the ketone (**30**) (~100%), which was reduced with L-selectride in THF to afford the β-anomer[11] (**31**) (74%). Removal of the methoxymethyl group with hydrochloric acid in H_2O-THF and successive hydrogenolysis in the presence of 10% Pd/C gave the free carba-sugar derivative (**9β**) (95%), $[\alpha]_D^{21}$ +9.2° (c 0.5, MeOH). Similarly, compound (**28**) was transformed into **10β** (40% over-all yield), $[\alpha]_D^{24}$ +49° (c 0.3, MeOH), through **32** and **33**.[12]

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9. Compound (**15**): $[\alpha]_D^{23}$ –11° (c 2.6, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ = 7.54–7.30 (m, 15 H, 3 × Ph), 5.63 (s, 1 H, 3-H), 5.41 (dd, $J_{7,8}$ = 2.9, $J_{8,9}$ = 3.7 Hz, 1 H, 8-H), 5.09 (dd, $J_{6,7}$ = 11.9, $J_{7,8}$ = 2.9 Hz, 1 H, 7-H), 4.82 (d, J_{gem} = 12.1 Hz, 1 H, PhCH_2), 4.76 (s, 2 H, PhCH_2), 4.61 (d, J_{gem} = 12.1

Hz, 1 H, PhCH_2), 4.25 (dd, $J_{1,6}$ = 11.0, $J_{1,10}$ = 9.2 Hz, 1 H, 1-H), 4.18 (dd, J_{gem} = 11.0, $J_{5eq,6}$ = 4.2 Hz, 1 H, 5eq-H), 3.82 (dd, $J_{1,10}$ = 9.2, $J_{9,10}$ = 2.9 Hz, 1 H, 10-H), 3.80 (dd, $J_{8,9}$ = 3.7, $J_{9,10}$ = 2.9 Hz, 1 H, 9-H), 3.76 (dd, J_{gem} = $J_{5ax,6}$ = 11.0 Hz, 1 H, 5ax-H), 2.43 (dddd, $J_{1,6}$ = $J_{5ax,6}$ = 11.0, $J_{5eq,6}$ = 4.2, $J_{6,7}$ = 11.9 Hz, 1 H, 6-H), 2.03 and 2.02 (2 s, each 3 H, 2 × Me).

10. Compound (**26**): $[\alpha]_D^{23}$ +26° (c 0.4, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 15 H, 3 × Ph), 4.88 (d, J_{gem} = 11.0 Hz, 1 H, PhCH_2), 4.78 (d, J_{gem} = 12.1 Hz, 1 H, PhCH_2), 4.67–4.53 (m, 6 H, MeOCH_2, 2 × PhCH_2), 4.07 (dd, $J_{1,10}$ = 3.1, $J_{9,10}$ = 2.8 Hz, 1 H, 10-H), 4.01 (ddd, J_{gem} = 11.8, $J_{3eq,4ax}$ = 5.1, $J_{3eq,4eq}$ = 1.5 Hz, 1 H, 3eq-H), 3.95 (dd, $J_{7,8}$ = 8.8, $J_{8,9}$ = 2.7 Hz, 1 H, 8-H), 3.93 (dd, $J_{8,9}$ = $J_{9,10}$ = 2.7 Hz, 1 H, 9-H), 3.81 (dd, $J_{6,7}$ = 9.5, $J_{7,8}$ = 8.8 Hz, 1 H, 7-H), 3.71 (ddd, $J_{4ax,5}$ = 10.6, $J_{4eq,5}$ = 4.8, $J_{5,6}$ = 10.1 Hz, 1 H, 5-H), 3.54 (ddd, J_{gem} = $J_{3ax,4ax}$ = 11.8, $J_{3ax,4eq}$ = 2.6 Hz, 1 H, 3ax-H), 3.44 (dd, $J_{1,6}$ = 10.3, $J_{1,10}$ = 3.1 Hz, 1 H, 1-H), 3.30 (s, 3 H, Me), 2.13 (ddd, $J_{1,6}$ = 10.3, $J_{5,6}$ = 10.1, $J_{6,7}$ = 9.5 Hz, 1 H, 6-H), 2.10 (dddd, J_{gem} = 12.8, $J_{3ax,4eq}$ = 2.5, $J_{3eq,4eq}$ = 1.5, $J_{4eq,5}$ = 4.8 Hz, 1 H, 4eq-H), 1.72 (dddd, J_{gem} = 12.8, $J_{3ax,4ax}$ = 11.8, $J_{3eq,4ax}$ = 5.1, $J_{4ax,5}$ = 10.6 Hz, 1 H, 4ax-H).
Compound (**28**): $[\alpha]_D^{23}$ +2.3° (c 1.5, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 15 H, 3 × Ph), 5.05 (d, J_{gem} = 11.0 Hz, 1 H, PhCH_2), 4.79 (d, J_{gem} = 12.1 Hz, 1 H, PhCH_2), 4.71–4.63 (m, 5 H, RCH_2), 4.56 (d, J_{gem} = 11.0 Hz, 1 H, RCH_2), 4.25 (ddd, $J_{4ax,5}$ = 2.2, $J_{4eq,5}$ = $J_{5,6}$ = 2.6 Hz, 1 H, 5-H), 4.07 (ddd, $J_{1,10}$ = $J_{9,10}$ = 3.1, $J_{10,OH}$ = 1.1 Hz, 1 H, 10-H), 3.98–3.88 (m, 5 H, 1-H, 3ax-H, 7-H, 8-H, 9-H), 3.82 (br dd, J_{gem} = 11.1, $J_{3eq,4ax}$ = 4.8 Hz, 1 H, 3eq-H), 3.37 (s, 3 H, Me), 1.96–1.86 (m, 2 H, 4eq-H, 6-H), 1.67 (dddd, J_{gem} = 13.3, $J_{3ax,4ax}$ = 12.5, $J_{3eq,4ax}$ = 5.1, $J_{4ax,5}$ = 2.2 Hz, 1 H, 4ax-H).

11. Compound (**31**): $[\alpha]_D^{23}$ –4.1° (c 1.3, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.41–7.20 (m, 15 H, 3 × Ph), 4.96 (d, J_{gem} = 11.7 Hz, 1 H, PhCH_2), 4.89 (d, J_{gem} = 10.6 Hz, 1 H, PhCH_2), 4.77 (d, J_{gem} = 11.4 Hz, 1 H, PhCH_2), 4.66–4.55 (m, 5 H, RCH_2), 4.08 (dd, $J_{8,9}$ = 2.4, $J_{9,10}$ = 2.7 Hz, 1 H, 9-H), 4.03 (ddd, J_{gem} = 11.8, $J_{3eq,4ax}$ = 5.2, $J_{3eq,4eq}$ = 1.3 Hz, 1 H, 3eq-H), 3.87 (dd, $J_{6,7}$ = 9.9, $J_{7,8}$ = 9.5 Hz, 1 H, 7-H), 3.70 (ddd, $J_{4ax,5}$ = 10.6, $J_{4eq,5}$ = 4.4, $J_{5,6}$ = 10.2 Hz, 1 H, 5-H), 3.57 (dd, $J_{1,10}$ = 9.9, $J_{9,10}$ = 2.7 Hz, 1 H, 10-H), 3.54 (dd, $J_{7,8}$ = 9.5, $J_{8,9}$ = 2.4 Hz, 1 H, 8-H), 3.48 (ddd, J_{gem} = $J_{3ax,4ax}$ = 11.8, $J_{3ax,4eq}$ = 1.4 Hz, 1 H, 3ax-H), 3.34 (dd, $J_{1,6}$ = 10.3, $J_{1,10}$ = 9.9 Hz, 1 H, 1-H), 3.30 (s, 3 H, Me), 2.13 (dddd, J_{gem} = 12.9, $J_{3ax,4eq}$ = $J_{3eq,4eq}$ = 1.3, $J_{4eq,5}$ = 4.4 Hz, 1 H, 4eq-H), 1.76 (dddd, J_{gem} = 12.9, $J_{3ax,4ax}$ = 11.8, $J_{3eq,4ax}$ = 5.2, $J_{4ax,5}$ = 10.6 Hz, 1 H, 4ax-H), 1.67 (ddd, $J_{1,6}$ = 10.3, $J_{5,6}$ = 10.2, $J_{6,7}$ = 9.9 Hz, 1 H, 6-H).

12. Compound (**33**): $[\alpha]_D^{24}$ +2.5° (c 0.9, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.43–7.25 (m, 15 H, 3 × Ph), 5.04 (d, J_{gem} = 12.1 Hz, 1 H, PhCH_2), 5.04 (d, J_{gem} = 11.0 Hz, 1 H, PhCH_2), 4.76 (d, J_{gem} = 12.1 Hz, 1 H, PhCH_2), 4.72–4.61 (m, 4 H, 2 × RCH_2), 4.58 (d, J_{gem} = 11.0 Hz, 1 H, RCH_2), 4.18 (ddd, $J_{4ax,5}$ = $J_{4eq,5}$ = 2.6, $J_{5,6}$ = 2.4 Hz, 1 H, 5-H), 4.09 (dd, $J_{8,9}$ = 2.6, $J_{9,10}$ = 2.7 Hz, 1 H, 9-H), 4.00 (dd, $J_{6,7}$ = 10.7, $J_{7,8}$ = 9.5 Hz, 1 H, 7-H), 3.96–3.80 (m, 2 H, 3-H_2), 3.81 (dd, $J_{1,6}$ = 10.7, $J_{1,10}$ = 9.5 Hz, 1 H, 1-H), 3.52 (dd, $J_{7,8}$ = 9.5, $J_{8,9}$ = 2.6 Hz, 1 H, 8-H), 3.46 (dd, $J_{1,10}$ = 9.5, $J_{9,10}$ = 2.7 Hz, 1 H, 10-H), 3.37 (s, 3 H, Me), 1.93 (dddd, J_{gem} = 13.6, $J_{3ax,4eq}$ = $J_{3eq,4eq}$ = 1.5, $J_{4eq,5}$ = 2.6 Hz, 1 H, 4eq-H), 1.69 (dddd, J_{gem} = 13.6, $J_{3ax,4ax}$ = 11.4, $J_{3eq,4ax}$ = 7.0, $J_{4ax,5}$ = 10.7, $J_{5,6}$ = 2.4 Hz, 1 H, 4ax-H), 1.42(ddd, $J_{1,6}$ = $J_{6,7}$ = 10.7, $J_{5,6}$ = 2.4 Hz, 1 H, 6-H).

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