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REGIO- AND STEREOSELECTIVE GLYCOSYLATION OF 20(S),24(R)-EPOXYDAMMARANE-3,12β,25-TRIOLS WITH CHOLESTERYL (α-D-GLUCOSE ORTHOACETATE). III.

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The glycosylation of 20(S),24(R)-epoxydammarane-3,12β,25-triols under the conditions of the previous formation of an ion pair with a Lewis acid and subsequent treatment with cholesteryl (α-D-glucose orthoacetate) leads to the selective formation with high yields of the corresponding 12-monoglucosides having the trans configuration of the glucosidic bond. The regioselectivity of the direct glycosylation of 20(S),24(R)-epoxydammarane-3,12β,25-triols by orthoesters is determined by the influence of intramolecular hydrogen bonds in the initial triols. Details of the PMR and ^{13}C NMR spectra of the new compounds obtained are given.

The development of methods for both the selective and the exhaustive glycosylation of tetracyclic dammarane polyols of type (I) related to the panaxgenins (Scheme 1) opens up possibilities for obtaining various analogs of ginseng glycosides [1]. We have previously studied the glycosylation of the title alcohols by the orthoester method via the intermediate formation of orthoesters and their subsequent isomerization into the desired glycosides [2].

The isomerization of the 3-monoorthoesters obtained from (I) and (II) led to the anomalous selective formation of the 12-monoglucosides (III) and (V), in view of which the hypothesis was expressed that the isomerization studied takes place in actual fact as the direct intermolecular glycosylation of one molecule of a 3-monoorthoester by another. To confirm this hypothesis, we have investigated the direct glycosylation of tetracyclic dammarane polyols with a number of orthoesters. The nature of the direct glycosylation of the triols (I) and (II) with the orthoesters (XII) and (XIII) depends on the nature of the glycosylating agent and also, to an even greater degree, on the experimental conditions of glycosylation, which is probably connected with the presence of a strong intramolecular hydrogen bond (intra-HB) between the proton of the 12β-OH group and the oxygen atom of the tetrahydrofuran (THF) ring in each of the triols (I) and (II).

In the IR spectra of (I) and (II) in $CHCl_3$ solution (c 37.0 and 34.0 mg/ml, respectively), broad bands of hydroxyl absorption are observed at 3392 and 3401 cm^{-1}, respectively, which did not change their position and intensity when the solutions were diluted 25-fold. In the ^1H NMR spectra ($CDCl_3$) of (I) and (II) broad signals of unit intensity are observed at 5.62 and 5.59 ppm, respectively, which are sensitive to the temperature conditions of recording the spectra and to deuterium exchange. The intra-HBs mentioned may promote the formation of a bipolar ion of type (XIV) or (XV) on the interaction of (I) or (II) with $HgBr_2$ (scheme 2).

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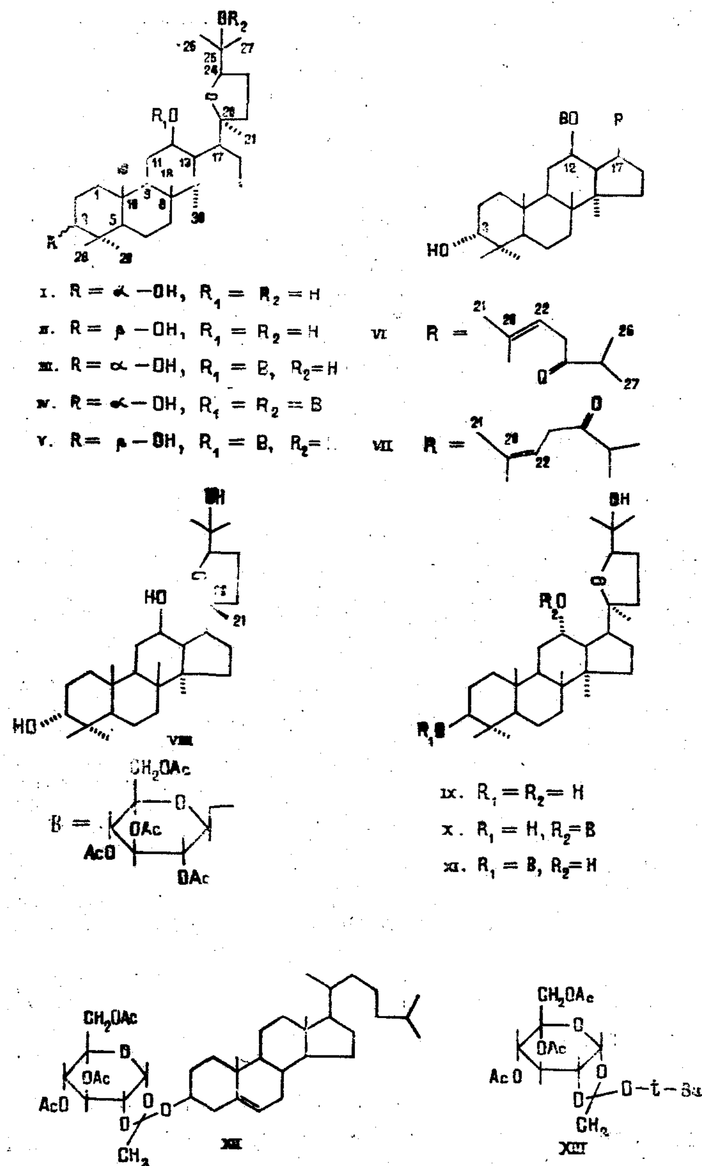


Scheme 1

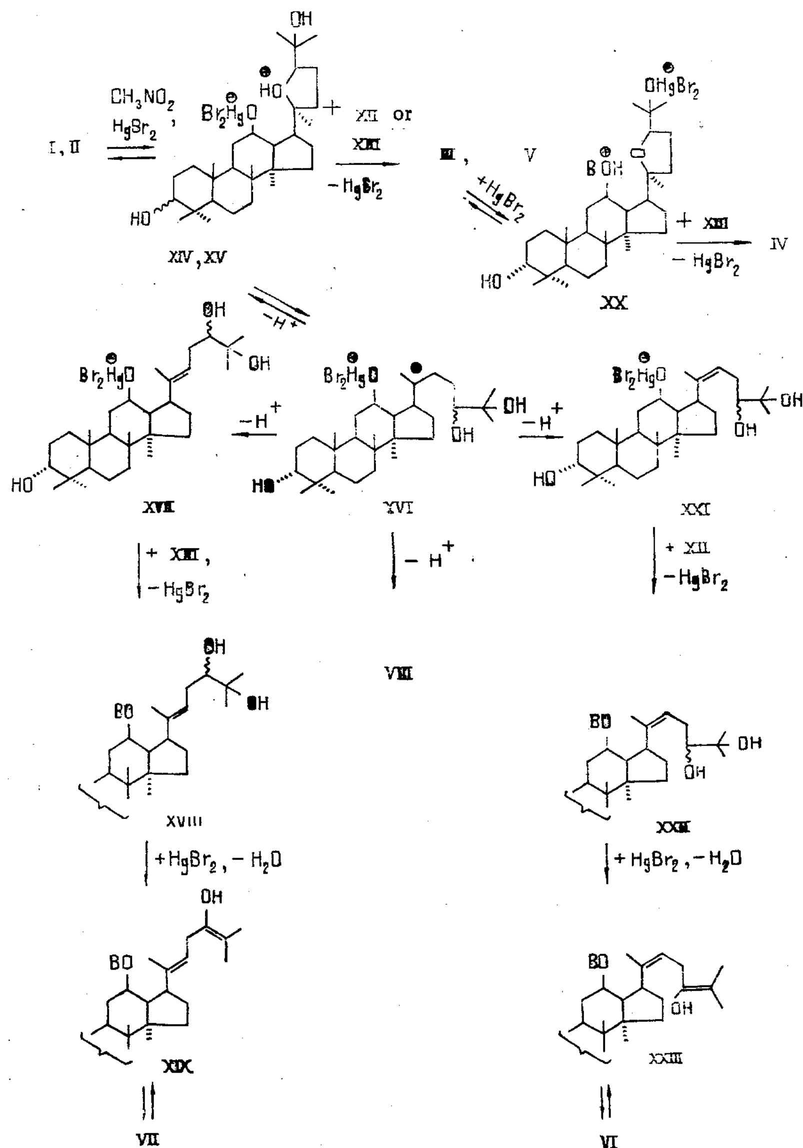
The glycosylation of (I) and (II) under the conditions of the previous formation of the bipolar ion (XIV) or (XV) followed by treatment with cholesteryl (α-D-glucose orthoacetate) (XII) (experiments 1 and 2) led to the regio- and stereoselective formation of the known 12-monoglucosides (III) and (V) [2] (55 and 53% of theoretical, respectively, calculated on the triols (I) and (II) taken, at a conversion of 60%).

It is interesting to note that the bulk of the cholesterol present in the orthoester (XII) separates out from the solution of the reactants in CH_3NO_2 as the reaction proceeds, thereby promoting an increase in the yield of the glycosides (III) and (V) and the avoidance of side glycosylation reactions.

The glycosylation of (I) under the same conditions with α-D-glucose (t-Bu orthoacetate) (XIII) (experiment 3) led to the formation of a mixture of the 12-monoglucoside (III) (22%), the known 12,25-diglucoside (IV) [2] (9%) and "E"-12β-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyloxy)-3α-hydroxydammar-20(22)-en-24-one (VII) (26%).

At the same time, when the triol (I), the orthoester (XII), and $HgBr_2$ were mixed simultaneously (experiment 4), there was the formation only of a mixture of "Z"-12β-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyloxy)-3α-hydroxydammar-20(22)-en-24-one (VI) (27%), and 20R,24(R)-epoxydammarane-3α,12β,25-triol (VII) (16%) – the epimer of the initial triol (I) at C^{20}.

Doublet signals of the anomeric protons of the sugar component at C^{12} in the ^1H NMR spectra of (VI) and



Scheme 2

(VII) appear at 4.48 and 4.46 ppm, respectively. The magnitudes of $J_{1,2}$ (7.7 and 7.1 Hz, respectively) show the trans configurations of the glycosidic bonds in (VI) and (VII).

The structures of (VI) and (VII) and the positions of attachment of the carbohydrate components were established by analysis of the ^{1}H NMR spectra of (VI) and (VII) and a comparison of the ^{13}C NMR spectra of (VI) and (VII) and of (III) (Table 1).

The comparison showed the considerable difference in the chemical shifts (CSs) of the C^{20}–C^{27} atoms in the ^{13}C spectra of (VI) and (VII), on the one hand, and of (III), on the other hand. Consequently, glycosides (VI) and (VII) differ from (III) only by the structure of the side chain. The ^{13}C NMR spectra indicate the presence in the side chain in each of (VI) and (VII) of a carbonyl atom and of a trisubstituted double bond. In the ^{1}H spectrum of (VI), two doublets (J = 7.0 Hz) of Me groups are observed at 1.07 and 1.09 ppm, and a septet (J = 7.0 Hz) of unit intensity at 2.68 ppm, which shows the presence of an isolated isopropyl group in the side chain of (VI). A singlet (3 H) at 1.64 ppm in the ^{1}H spectrum of (VI) relates to the protons of a Me group at a double bond. In the ^{1}H spectrum of (VII), two doublets (J = 7.1 Hz) of Me groups are observed at 1.12 and 1.47 ppm, and a septet (J = 7.1 Hz) of unit intensity at 2.71 ppm, which, as in the case of (VI), shows the presence of an isolated isopropyl group in the side chain of (VII). A singlet (3 H) at 1.51 ppm in the ^{1}H spectrum of (VII) relates to the protons of a Me group at a double bond. Thus, (VI) and (VII) have the same structure of the side chains and differ from one another only by the configuration of the 20(22) double bond.

TABLE 1. ^{13}C Chemical Shifts of Compounds (I), (III), and (VI)-(VIII) (δ, ppm, relative to TMS)

C atom	Compound				
	(I)	(III)	(VI)	(VII)	(VIII)
1	33.7	33.9	33.9	33.9	33.7
2	25.5	25.5	25.3	25.4	25.5
3	75.9	75.8	76.0	76.0	76.0
4	37.5	37.6	37.6	37.6	37.6
5	49.5	49.5	49.5	49.5	49.6
6	18.3	18.3	18.2	18.3	18.3
7	34.8	34.7	34.8	34.9	34.9
8	40.0	39.9	40.2	40.2	40.1
9	50.3	49.9	49.5	49.0	50.6
10	37.3	37.4	37.4	37.5	37.4
11	31.2	27.4	27.1	27.2	30.5
12	71.0	77.6	77.7	77.3	70.7
13	47.9	47.8	47.4	48.2	49.0
14	52.2	52.2	51.1	51.0	51.8
15	31.2	31.7	32.2	32.4	31.4
16	28.6	27.0	27.9	28.9	26.9
17	49.3	49.9	50.2	50.3	49.9
18	16.2	16.1	16.1	16.2	16.1
19	15.4	15.6	15.7	15.7	15.6
20	86.5	86.7	142.6	141.3	86.4
21	26.1	22.2	19.7	13.5	21.3
22	32.6	39.0	114.9	115.7	39.1
23	25.0	26.2	40.5	40.2	26.0
24	85.4	83.5	213.9	213.4	86.5
25	70.1	71.3	39.7	40.2	70.3
26	27.8	27.4	18.5	18.4	27.8
27	27.6	24.2	18.2	18.4	24.7
28	28.4	28.5	28.3	28.3	28.4
29	22.0	22.1	22.0	22.1	22.1
30	18.3	17.9	17.0	17.0	17.1

A comparison of the ^{13}C spectra of (VI) and (VII) showed the CSs of the C_{21} atom (19.7 and 13.5 ppm, respectively). Such a large difference in the CSs of C_{21} and the ^{13}C spectra of (VI) and (VII) is due to the fact that in (VI) the Me at C^{20} has $\gamma_{H,H}$ coupling [3] with H^{22}, while in (VII) such coupling is absent.

On this basis, (VI) was assigned the "Z" configuration of the 20(22) double bond, and (VI) the "E" configuration.

The structure of (VIII) was established by comparing the ^1H and ^{13}C spectra of (VIII) and (I). The ^1H spectrum ($CDCl_3$) of (VIII) showed a broadened signal of unit intensity at 5.61 ppm which was sensitive to the temperature conditions of taking the spectrum and underwent deuterium exchange. Consequently, an intra-HB exists in (VIII) similar to that in (I). The practically identical values of the CSs of the proton of the $C^{12}-OH$ group bound by an intra-HB in the ^1H spectra of (VIII) and (I) (5.61 and 5.62 ppm, respectively) indicate identical spatial and electronic structures of the seven-membered rings formed by these intra-HBs. Since the intra-HBs in (I) and (VIII) stabilize the conformation of the side chains, the spatial directions of the $C^{20}-O$ bonds of the THF rings in (I) and (VIII) must be identical. A comparison of the ^{13}C spectra of (I) and (VIII) shows a considerable difference of the C^{21} and C^{22} CSs, which is obviously due to a difference in the configuration at C^{20}. In the ^{13}C spectrum of (VIII), the C^{21} signal (21.3 ppm) is present in a stronger field than the analogous signal in the spectrum of (I) (26.1 ppm), since in (VIII) the $\gamma_{H,H}$ coupling [3] of the protons of the C^{20} Me group with H^{17} is absent. Conversely, the presence of $\gamma_{H,H}$ coupling of H^{22} with H^{17} in (VIII) leads to the situation that the C^{22} signal in the ^{13}C spectrum of (VIII) is in a weaker field (39.1 ppm) than in the spectrum of (I) (32.6 ppm).

The configuration of the C^{24} asymmetric center in (VIII) had apparently not changed from that of the C^{24} configuration in (I), since, in the first place, the C^{24} signal in the ^{13}C spectrum of (VIII) appears at 86.5 ppm and not at 88.5 ppm, which is characteristic for the "S" configuration of C^{24} in the ^{13}C spectra of dammarane triterpenes of type (I) [4] and, in the second place, the formation of (VI) and (VII) in the glycosylation of (I) (scheme 1) confirms that the THF ring of the bipolar intermediate (XIV) opens without inversion of the C^{24} configuration. The nonstereospecific recyclization of (XVI) gave both the initial triol (I) and the C^{20}-epimer (VIII).

The formation of the 12-monoglucosides (VI) and (VII) obviously takes place in accordance with scheme 2 either as the result of an attack of the anions (XXI) and (XVII) formed from the common intermediate (XVI)

TABLE 2. ^{13}C Chemical Shifts of the Sugar Components of the Glucosides (VI) and (VII) (δ, ppm, relative to TMS)*

Compound	C atom					
	1	2	3	4	5	6
(VI)	97.2	71.5	73.0	68.8	71.5	62.3
(VII)	97.2	71.5	73.2	69.0	71.5	62.4

*The signals of the ^{13}C nuclei of the acetate groups of the sugar components of compounds (VI) and (VII) appear in the 170.0-170.5 and 20.9-21.4 ppm regions.

directly on the glycosidic centers of the orthoester groupings of (XII) and (XIII) or as the result of an attack of the same anions on the glycosidic centers of the acyloxonium ions first formed by the proton-catalyzed decomposition of the orthoesters (XII) and (XIII).

The selective glycosylation of the triols (I) and (II) at C_{12}, leading to the formation of the monoglycosides (III) and (V), and the subsequent glycosylation of (III) at C^{25}, leading to the 12,25-diglucoside (VI) apparently take place through the reaction of the ion pair (XIV) or (XV) with the orthoester (XII) or (XIII) by analogy with a scheme proposed previously [2] for the anomalous catalytic rearrangements of 3-mono- and 3,12-diorthoesters obtained from the triols (I) and (II).

With the aim of checking the idea of the decisive influence of intra-HBs on the regiochemistry of the direct glycosylation of triols (I) and (II) by the orthoesters (XII) and (XIII), we studied the glycosylation of 20(S),24(R)-epoxydammarane-3β,12α,25-triol (IX), in which there is no intra-HB between the proton of the 12α-OH group and the oxygen atom of the THF ring, as a consequence of which the nucleophilicities of the oxygen atoms of all three OH groups are practically comparable. The glycosylation of (IX) by the orthoester (XII) (experiment 5) under the conditions of experiment 1 took place nonselectively and led to the formation, in low yield, of a mixture of the known 3-monoglucoside (XI) (8%) and the known 12-monoglucoside (X) (10%) [5].

Thus, the use of cholesteryl (α-D-glucose orthoacetate) (XII) for the glycosylation of tetracyclic dammarane polyols of types (I) and (II) which have strong intra-HBs, permits this reaction to be performed selectively and with a high yield, and with the simultaneous regeneration of free cholesterol.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker HX-90E spectrometer in the Fourier regime at 30°C using 8% solutions of the substances in $CDCl_3$ at a working frequency of 90.0 MHz for ^{1}H and 22.63 MHz for ^{13}C. TMS was used as internal standard. The chemical shifts are expressed in the δ scale. The accuracy of the measurement was ±0.15 Hz for ^{1}H and ±1.5 Hz for ^{13}C. The assignments of the signals in the ^{13}C spectra were carried out by analogy with our previous investigations [2, 5]. IR spectra were obtained on a IR-75 instrument in $CHCl_3$ solution.

Solvents were prepared as described by Kochetkov et al. [6]. Column chromatography and TC chromatography were performed as described previously [2, 5].

The triterpene (I) was isolated from the leaves of the Far Eastern species Betula platyphylla, (II) was obtained from (I) as described in [1], and (IX) was obtained as described in [5].

Experiment 1. A solution of 333 mg (0.7 mmole) of (I) in 10 ml of CH_3NO_2 was evaporated to 2/3 of its original volume. To the resulting solution was added a solution of 90 mg (0.25 mmole) of $HgBr_2$ prepared by dissolving the substance in 10 ml of CH_3NO_2 and then distilling off 7 ml of the solvent. The mixture was heated at 100-105°C for 30 min, and then 500 mg (0.7 mmole) of (XII) was added and heating was continued at 100-105°C for another 40 min. The mixture was cooled to room temperature, the precipitate (cholesterol) was separated off and washed on the filter with cold CH_3NO_2, and the filtrate was evaporated to dryness. The resi-

due was washed free from $HgBr_2$ with hot water (6 × 20 ml), dried, and chromatographed on a column of SiO_2. This yielded 280 mg (55%) of (III), identical with that obtained previously [2], 30 mg (6%) of cholesterol β-D-glucoside tetraacetate, and 133 mg (40%) of the initial (I).

Experiment 2. Under the conditions of experiment 1, 333 mg (0.7 mmole) of (II), 500 mg (0.7 mmole) of (XII), and 90 mg (0.25 mmole) of $HgBr_2$ yielded 270 mg (53%) of (V), identical with that obtained previously [2], 33 mg (7%) of cholesterol β-D-glucoside tetraacetate, and 135 mg (40%) of the initial (II).

Experiment 3. Under the conditions of experiment 1, 478 mg (1.0 mmole) of (I), 405 mg (1.0 mmole) of (XIII), and 259 mg (0.72 mmole) of $HgBr_2$ yielded 160 mg (22%) of (III), 105 mg (9%) of (IV), identical with that obtained previously [2], 180 mg (26%) of (VII), and 165 mg (24%) of the initial (I).

Compound (VII), $C_{44}H_{68}O_{12}$. ^1H spectrum (δ, ppm): 0.85 (s, 3 H); 0.88 (s, 6 H); 0.94 (s, 3 H); 0.99 (s, 3 H); 1.12 (d, 3 H, J = 7.1 Hz, $C^{25}-CH_3$); 1.14 (d, 3 H, J = 7.1 Hz, $C^{25}-CH_3$); 1.51 (s, 3 H, $C^{20}-CH_3$); 1.97 (s, 3 H, OAc); 2.01 (s, 6 H, 2× OAc); 2.10 (s, 3 H, OAc); 2.71 (septet, 1 H, J = 7.1 Hz, H^{25}); 3.21 (d, 2 H, J = 7.0 Hz, 2× H^{23}); 3.42 (t, 1 H, J = 2.1 Hz, H_e^3); 3.65 (m, 1 H, ΣJ ≃ 24 Hz, H_a^{12}); 4.46 (d, 1 H, J = 7.1 Hz, H_1'); 3.50-5.25 (m, 6 H, H_2', H_3', H_4', H_5', 2× H_6'); 5.35 (doublet of triplets, 1 H, J = 7.0 and 1.6 Hz, H^{22}).

Experiment 4. A mixture of 265 mg (0.55 mmole) of (I), 397 mg (0.55 mmole) of (XII), and 72 mg (0.2 mmole) of $HgBr_2$ in 20 ml of CH_3NO_2 was heated at 100-105°C for 40 min. The resulting precipitate was separated off and was washed with cold CH_3NO_2, and the filtrate was evaporated to dryness. The residue was treated with hot water and was then dried and chromatographed on a column of SiO_2. This yielded 106 mg (27%) of (VI), 42 mg (16%) of (VIII), and 60 mg (23%) of the initial (I).

Compound (VI), $C_{44}H_{68}O_{12}$. ^1H spectrum (δ, ppm): 0.85 (s, 3H); 0.88 (s, 3 H); 0.92 (s, 3 H); 0.95 (s, 3 H); 0.99 (s, 3 H); 1.07 (d, 3 H, J = 7.0 Hz, $C^{25}-CH_3$); 1.09 (d, 3 H, J = 7.0 Hz, $C^{25}-CH_3$); 1.64 (s, 3 H, $C^{20}-CH_3$); 1.99 (s, 3 H, OAc); 2.02 (s, 6 H, 2× OAc); 2.08 (s, 3 H, OAc); 2.68 (septet, 1 H, J = 7.0 Hz, H^{25}); 3.06 (d, 1 H, J = 7.5 Hz, H^{23}); 3.28 (d, 1 H, J = 7.5 Hz, H^{23}); 3.43 (t, 1 H, J = 2.1 Hz, H_e^3); 3.65 (m, 1 H, H_a^{12}); 4.48 (d, 1 H, J = 7.7 Hz, H_1'), 3.50-5.28 (m, 6 H, H_2', H_3', H_4', H_5', 2× H_6'), 5.18 (t, 1 H, J = 7.5 Hz, H^{22}).

Compound (VIII), $C_{30}H_{52}O_4$. ^1H spectrum (δ, ppm): 0.84 (s, 3 H); 0.90 (s, 6 H); 0.94 (s, 3 H); 1.00 (s, 3 H); 1.12 (s, 3 H); 1.15 (s, 3 H); 1.20 (s, 3 H); 3.39 (t, 1 H, J = 2 Hz, H_e^3), 3.56 (sextet, 1 H, J = 5.0 and 10.0 Hz, H_a^{12}); 3.87 (t, 1 H, J = 7.0 Hz, H^{24}); 5.61 (s, 1 H, OH).

Experiment 5. Under the conditions of experiment 1, 159 mg (0.3 mmole) of (IX), 239 mg (0.3 mmole) of (XII), and 40 mg (0.11 mmole) of $HgBr_2$ yielded 25 mg (10%) of (X), 19 mg (8%) of (XI), identical with those obtained previously [5], 48 mg (20%) of cholesterol β-D-glucoside tetraacetate, and 48 mg (30%) of the initial (IX).

SUMMARY

1. The glycosylation of 20(S),24(R)-epoxydammarane-3,12β,25-triols under the conditions of the previous formation of an ion pair with a Lewis acid followed by treatment with cholesteryl (α-D-glucose orthoacetate) leads to the selective formation in high yield of the corresponding 12-monoglucosides with the trans configuration of the glycosidic bond.

2. The regioselectivity of the directed glycosylation of 20(S),24(R)-epoxydammarane-3,12β,25-triols by orthoesters is due to the influence of intramolecular hydrogen bonds in the initial triols.

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