105183-36-6; (±)-**33a**, 105183-37-7; (±)-**34**, 105205-34-3; PhSeCl, 931-59-9; 2-$O_2NC_6H_4SO_2Cl$, 7669-54-7; $PhSeSO_2Ph$, 60805-71-2; 1,3-cyclopentadiene, 542-92-7; 2,4-dinitrobenzenesulfenyl chloride, 528-76-7.

**Supplementary Material Available:** UV, IR, $^{13}C$ NMR, and MS spectral data and elemental analyses of all new compounds (9 pages). Ordering information is given on any current masthead page.

# "Naked Sugars" as Synthetic Intermediates. Total Synthesis of L-Daunosamine[1]

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*Received April 17, 1986*

The "naked sugars" are optically pure synthetic intermediates. Their advantage compared with natural sugars is that they possess a number of unsubstituted carbon atoms that can be substituted stereospecifically through direct procedures. (1*S*,2*R*,4*S*)-2-[(−)-Camphanoyloxy]-7-oxabicyclo[2.2.1]hept-5-ene-2-carbonitrile ((+)-1) is an example of a "naked sugar". Electrophilic reagents add to the C(5),C(6) double bond, giving the corresponding adducts where the electrophile substitutes the exo position of C(6) and the nucleophile the endo position at C(5). This principle was used to prepare (1*R*,4*R*,5*R*)-5-*endo*-chloro-7-oxa-2-bicyclo[2.2.1]heptanone (**13**), which was monomethylated stereoselectively in the exo position at C(3), giving (+)-(1*R*,3*S*,4*R*,5*R*)-5-*endo*-chloro-3-*exo*-methyl-7-oxa-2-bicyclo[2.2.1]heptanone (**14**). The latter was transformed stereospecifically into L-daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose). The (−)-camphanic acid used to engender asymmetry was recovered at an early stage of the synthesis.

Derivatives of 7-oxabicyclo[2.2.1]heptane have been used as starting materials in the synthesis of anthracyclines,[2] nucleosides,[3] muscarine derivatives,[4] prostaglandins,[5] cyclitols derivatives,[6] and other material of biological interest.[7] Some derivatives have also been shown to exhibit antitumor[8] or antiinflammatory activity.[9] We recently reported the preparation of the two optically pure 7-oxabicyclo[2.2.1]hept-5-enes, (+)-1 and (+)-**2**.[10,11] These systems can be seen as "naked sugars" since positions C(3), C(5), and C(6) can be functionalized in a stereospecific fashion by direct procedures, without protection and/or deprotection steps. In the preceding paper[12] we showed that the regioselectivity of the highly stereoselective electrophilic additions of the C(5)–C(6) double bond depends upon the nature of the substituents at C(2). We shall see here that 7-oxa-2-bicyclo[2.2.1]heptanone derivatives can be monoalkylated stereoselectivity at position C(3). Thus, like natural sugars, the naked sugars (+)-1 and (+)-**2** are optically pure molecules; their advantage compared with sugars is that they are already "defoliated" and ready to undergo modifications of the carbon skeleton in a stereoselective, if not stereospecific, fashion. This principle is now illustrated by the total synthesis of L-daunosamine **3** (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose).[13] This important amino sugar is the carbohydrate component of antitumor anthracycline antibiotics such as Adriamycin and Daunomycin.[14] Several ingenious syntheses of **3** have been reported starting from carbohydrate[15] and nonsugar substrates.[16] The technology de-

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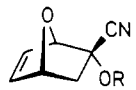
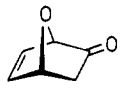
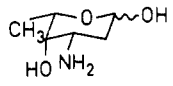
scribed here is highly stereoselective, amenable to large-scale preparation of **3** and of related derivatives. It uses unexpensive starting material; the asymmetry is induced by (−)-camphanic acid, which is recovered during the synthesis. Furthermore, it permits the preparation of the amino sugar in both its furanose and pyranose forms.



(+)-1
4

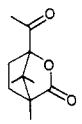


(+)-2



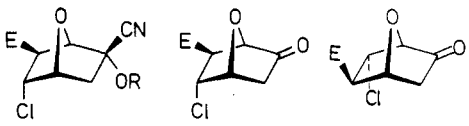
3

R = R* =
R = Ac

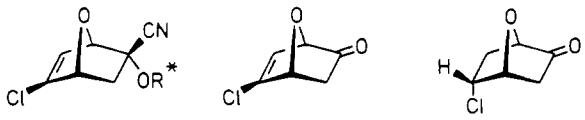


## Results and Discussion

Addition of benzeneselenenyl chloride to (+)-1 gave adduct **5** in 97% yield. Its structure was established by 360-MHz $^1$H NMR spectroscopy.[12] On treatment with a tenfold excess of 30% aqueous $H_2O_2$,[17] **5** was oxidized to **11** (92%). Saponification followed by treatment with formaline yielded the $\beta,\gamma$-unsaturated chloro ketone **12** (99%). The (−)-camphanic acid was recovered at this stage in 85% yield (based on 1); it can be recycled to generate (+)-1.[10a] Quantitative and stereospecific hydrogenation of the chloroalkene **12** to the chloro ketone **13** was achieved with diimide.[18]

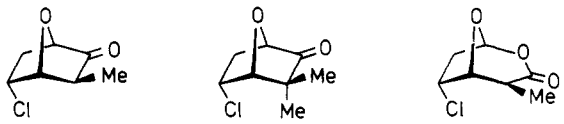


E = PhSe; R = R* **5**
E = PhSe; R = Ac **6** **7** **8**
E = PhS, R = Ac **9** **10**



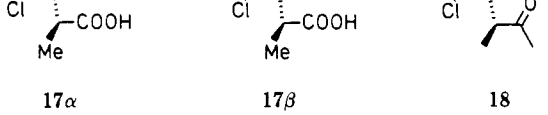
**11** **12** **13**

On addition of a small excess of *t*-BuOK to a mixture of ketone **13** and methyl iodide in anhydrous THF,[19] the monomethylated derivative **14** was obtained in 71% yield. The 360-MHz $^1$H NMR spectrum confirmed the exo position of the methyl group at C(3) (no vicinal $^3J_{H,H}$ coupling constant observed between H-C(3) and H-C(4)). Pure **14** was isolated by crystallization from $CHCl_3$ at −20 °C. HPLC of the mother liquor allowed one to isolate 4–8% of the dimethylated derivative **15**. No trace of the *endo*-monomethyl isomer of **14** could be detected in the reaction mixture.



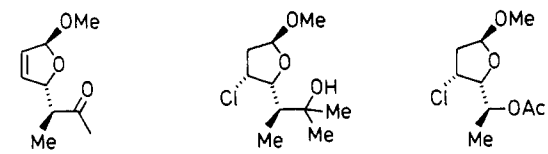
**14** **15** **16**

The Baeyer–Villiger oxidation[16f,20] of ketone **14** with metachloroperbenzoic acid afforded lactone **16** (86%). There was no detectable trace of the product resulting from oxygen insertion between centers C(2) and C(3). On treatment with acidic methanol,[21] **16** was transformed into a 90:4 mixture of the acetal-acids **17**$\alpha$ and **17**$\beta$ (94%).



**17**$\alpha$ **17**$\beta$ **18**

The mixture of **17**$\alpha$ and **17**$\beta$ was treated with 2 equiv of MeLi[22] and gave the methyl ketone **18** (63%). In some reaction runs, less than 10% of the minor products **19** and **20** were visible by $^1$H NMR of the crude reaction mixture and could be isolated by chromatography.



**19** **20** **21**

Baeyer–Villiger oxidation of **18** yielded the desired acetate **21** in 85% yield and with complete retention of configuration at C(5).[23] Attempts to obtain **21** directly from the acids **17**$\alpha$ + **17**$\beta$ through oxidative decarboxylation with $Pb(OAc)_4$[24] gave low yield of mixture of acetates. The chloride **18** was displaced in a $S_N2$ fashion[15e,25] with $NaN_3$ (DMF, 120 °C, 12 h) to give the azide **22** (80%). Catalytic hydrogenation[26] of **22** gave the free-amine **23**

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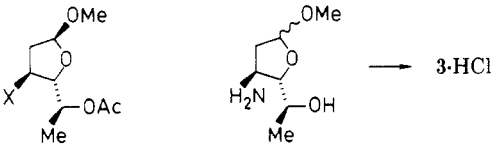
(90%). Ammonolysis[16g] afforded a 9:1 mixture of the methyl 3-amino-2,3,6-trideoxy-*lyxo*-L-hexofuranosides (**24**$\alpha$ and **24**$\beta$) (92%), which was transformed[15d] to the hydrochloride of L-daunosamine. This product was identical with an authentic sample of optically pure **3**·HCl (4:3 mixture of the $\alpha$ and $\beta$ anomers).




X = $N_3$ **22**
X = $NH_2$ **23**

**24**

Hoping to improve or to shorten our total synthesis of L-daunosamine, we explored the following reactions with **6** and **9**, the adducts of the racemic 7-oxanorbornene derivative **4** to PhSeCl and PhSCl, respectively. Saponification of **6** and **9**, followed by treatment with formaline, afforded ketones **7** and **10**, respectively. Treatment of **7** with tributyltin hydride in toluene/benzene (AIBN 1–2%, 80 °C)[27] gave the key intermediate (±)-**13** in 69% yield. Under the same conditions, **10** was reduced to (±)-**13** in 40–45% yield. Raney nickel reduction[28] of **10** afforded (±)-**13** in 50% yield together with 40% of (±)-7-oxa-2-bicyclo[2.2.1]heptanone. However, we found the multistep procedure **5** → **11** → **12** → **13** easier to scale up.

Several intermediates in our synthesis do not have to be isolated. For instance, transformation of **1** into **12** can be carried out in the same pot in 94% yield (see Experimental Section). The reactions **22** → **23** and **23** → **24** can also be done in the same pot in 94.5% global yield.

## Conclusion

The naked sugar **1** has been transformed into methyl 3-amino-2,3,6-trideoxy-*lyxo*-L-hexofuranosides (**24**$\alpha$ + **24**$\beta$), the furanose form of L-daunosamine, in 21.8% global yield. The synthesis required the isolation of eight synthetic intermediates. Many of these are potential starting materials for the preparation of other natural products.[29] On treatment of **24** with HCl, the hydrochloride of L-daunosamine (3·HCl) was isolated in 67% yield.

## Experimental Section

**General Remarks**: see preceding paper. Optical rotations were measured with a Perkin-Elmer 241 polarimeter.

**(1*S*,2*S*,4*R*,5*S*,6*S*)-2-[(−)-Camphanoyloxy]-5-chloro-6-benzeneselenenyl-7-oxabicyclo[2.2.1]heptane-2-carbonitrile (5).** A solution of benzeneselenenyl chloride (12.1 g, 61.2 mmol, 97% pure) dissolved in $CH_2Cl_2$ (130 mL) was added under stirring to the camphanoyloxy carbonitrile (+)-**1** (19.4 g, 61.2 mmol) in $CH_2Cl_2$ (100 mL). The brown mixture was stirred at 20 °C for 3 days until it becomes yellowish. The end of the reaction was checked by TLC (AcOEt/$CH_2Cl_2$ (5:95), $KMnO_4$). The solution was washed with 5% aqueous $Na_2CO_3$ (150 mL, 2 times), then with water (150 mL, 2 times), and finally with brine (150 mL) and dried ($MgSO_4$). After solvent evaporation, 30.2 g (97%) of colorless oil was obtained: $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ 7.62–7.58 (m, 2 H, H-aromatic), 7.39–7.33 (m, 3 H, H-aromatic), 5.03 (br s, 1 H, H-C(1)), 4.76 (br t, $J \simeq 5$, 1 H, H-C(4)), 4.20 (dd, $J$ = 5.0, 4.5, 1 H, H-C(5)), 3.60 (d, $J$ = 4.5, 1 H, H-C(6)), 2.74 (ddd, $J$ = 15.0, 5.0, 1.0, 1 H, $H_{exo}$-C(3)), 2.71 (d, $J$ = 15.0, 1 H, $H_{endo}$-C(3)), 2.41–2.33 (m, 1 H, $CH_2$ of camphanoyl), 2.05–1.90 (m, 2 H, $CH_2$ of camphanoyl), 1.76–1.68 (m, 1 H, $CH_2$ of camphanoyl), 1.14, 1.01, and 0.90 (3 s, 9H, $CH_3$ of camphanoyl); $[\alpha]^{25}_{589}$ +28.37°, $[\alpha]^{25}_{578}$ +29.62°, $[\alpha]^{25}_{546}$ +34.47°, $[\alpha]^{25}_{436}$ +66.51°, $[\alpha]^{25}_{365}$ +137.42° (15.26 g/dm$^3$, $CH_2Cl_2$).

**(1*R*,2*S*,4*R*)-2-[(−)-Camphanoyloxy]-5-chloro-7-oxabicyclo[2.2.1]hept-5-ene-2-carbonitrile (11).** A solution of 30% $H_2O_2$ (65.2 mL, 612 mmol) was added slowly to a stirred solution of **5** (31.1 g, 61.2 mmol) in THF (200 mL) and the temperature was maintained at 0 °C. After stirring for 1 h, the temperature was allowed to reach 20 °C and the mixture was stirred for 12 h. After addition of water (200 mL), the mixture was extracted with $CH_2Cl_2$ (100 mL, 3 times). The extract was washed with a 5% aqueous solution of $Na_2CO_3$ (150 mL), then with $H_2O$ (150 mL), and finally with brine (100 mL) before being dried ($MgSO_4$). The solvent was evaporated in vacuo and the solid residue recrystallized from AcOEt/hexane (1:3) to give 17.0 g (79.1%), white crystals, mp 158–159 °C dec: $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ 6.09 (d, $J$ = 2.0, 1 H, H-C(6)), 5.62 (br s, 1 H, H-C(1)), 4.93 (d, $J$ = 4.5, 1 H, H-C(4)), 2.88 (dd, $J$ = 13.5, 4.5, 1 H, $H_{exo}$-C(3)), 2.41–2.33 (m, 1 H, $CH_2$ of camphanoyl), 2.07–1.90 (m, 2 H, $CH_2$ of camphanoyl), 1.99 (d, $J$ = 13.5, 1 H, $H_{endo}$-C(3)), 1.74–1.67 (m, 1 H, $CH_2$ of camphanoyl), 1.12, 1.06, and 0.98 (3 s, 9 H, $3CH_3$); $[\alpha]^{25}_{589}$ +50.4°, $[\alpha]^{25}_{578}$ +52.0°, $[\alpha]^{25}_{546}$ +61.0°, $[\alpha]^{25}_{436}$ +110.7°, $[\alpha]^{25}_{365}$ +190.3 (12.2 g/dm$^3$, $CH_2Cl_2$).

**(1*R*,4*R*)-5-Chloro-7-oxabicyclo[2.2.1]hept-5-en-2-one (12).** KOH (1, N, 120 mL) was added to a stirred solution of **11** (16.7 g, 47.6 mmol) in THF/$H_2O$ (1:1, 260 mL). After stirring at 20 °C for 30 min, a 37% aqueous solution of formaldehyde (200 mL) was added and the mixture stirred for 15 min at 20 °C, followed by extraction with $CHCl_3$ (300 mL, 3 times). The extract was washed with water (250 mL) and then with brine (250 mL) before being dried ($MgSO_4$). The solvents were removed by distillation (Vigreux column) and the residue was filtered through silica gel ($CH_2Cl_2$/AcOEt, 98:2), yielding after solvent evaporation 6.8 g (99%) of a colorless oil: $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ 6.27 (ddd, $J$ = 2.25, 0.75, 0.75, H-C(6)), 5.06 (ddd, $J$ = 4.25, 0.75, 0.75, H-C(4)), 4.66 (dm, $J$ = 2.25, H-C(1)), 2.33 (ddd, $J$ = 16.0, 4.25, 0.75, $H_{exo}$-C(3)), 2.05 (dd, $J$ = 16.0, 0.75, $H_{endo}$-C(3)); $[\alpha]^{25}_{589}$ +817.5°; $[\alpha]^{25}_{578}$ +862.5°, $[\alpha]^{25}_{546}$ +1030°, $[\alpha]^{25}_{436}$ +2348°, $[\alpha]^{25}_{365}$ −3607° (17.84 g/dm$^3$, $CH_2Cl_2$).

**(1*R*,4*R*,5*R*)-(+)-5-*endo*-Chloro-7-oxa-2-bicyclo[2.2.1]heptanone (13).** A solution of **12** (2 g, 13.83 mmol) in dioxane (10 mL) was added to a stirred suspension of potassium azodicarboxylate (6.51 g, 33.56 mmol) at 20 °C and under Ar atmosphere. Within 1 h glacial acetic acid (10 mL) was added dropwise, at 20 °C and under vigourous stirring. Gaseous evolution was accompanied by a color discharge of the solution and precipitation of AcOK. After complete disappearance (ca. 3 h) of **12** (TLC, $CH_2Cl_2$/AcOEt, 9:1), the precipitate was filtered off and washed with $CHCl_3$ (120 mL). HCl (2 N, 30 mL) was added to the filtrate, and the solution was stirred for 12 h at 20 °C. The organic layer was separated and washed successively with a saturated aqueous solution of $Na_2CO_3$ (150 mL, 3 times), $H_2O$ (150 mL), and brine (80 mL). After drying ($MgSO_4$), the solvent was eliminated by distillation (Vigreux column) and the residue bulb-to-bulb distilled (0.5 torr, 60 °C), yielding 2.01 g (99%) of colorless liquid: $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ 4.81 (dd, $J$ = 6.0, 5.5, H-C(4)), 4.28 (dm, $J$ = 6.75, H-C(1)), 4.27 (dddd, $J$ = 10.3, 5.5, 4.4, 1.25, H-C(5)), 2.78 (d, $J$ = 18.1, $H_{endo}$-C(3)), 2.61 (dddt, $J$ = 14.25, 10.3, 6.75, 1.5, $H_{exo}$-C(6)), 2.43 (ddq, $J$ = 18.1, 6.0, 1.25, $H_{exo}$-C(3)), 1.67 (dd, $J$ = 14.25, 4.4, $H_{endo}$-C(6)); $[\alpha]^{25}_{589}$ +57.4°, $[\alpha]^{25}_{578}$ +59.9°, $[\alpha]^{25}_{546}$ +69.2°, $[\alpha]^{25}_{436}$ +127.2°, $[\alpha]^{25}_{365}$ +229.5° (29 g/dm$^3$, $CH_2Cl_2$).

**(1*R*,3*S*,4*R*,5*R*)-(+)-5-*endo*-Chloro-3-*exo*-methyl-7-oxa-2-bicyclo[2.2.1]heptanone (14).** The ketone **13** (0.44 g, 3 mmol) was dissolved in anhydrous THF (200 mL) under an Ar atmosphere. Methyl iodide (2.2 g, 15.5 mmol) was added and the mixture cooled to 0 °C. Under vigorous stirring a solution of *t*-BuOK (0.4 g, 3.9 mmol) in THF (3 mL) was added dropwise in 15 min. The mixture was allowed to warm to 20 °C and stirred for 2 h (control of the end of the reaction by VPC, capillary column SE-30). Water (150 mL) was added and the mixture neutralized

(27) Kuivila, H. G. *Acc. Chem. Res.* **1968**, *1*, 299–305. Menapace, L. W.; Kuivila, H. G. *J. Am. Chem. Soc.* **1964**, *86*, 3047–3051. Gutierrez, C. G.; Summerhays, L. R. *J. Org. Chem.* **1984**, *49*, 5206–5213. Pang, M.; Becker, E. I. *Ibid.* **1964**, *29*, 1948–1952. Haskell, T. H.; Woo, P. W. K.; Watson, D. R. *Ibid.* **1977**, *42*, 1302–1305.

(28) Pettit, G. R.; van Tamelen, E. E. *Org. React. (N.Y.)* **1962**, *12*, 356. Berson, J. A.; Jones, W. M. *J. Am. Chem. Soc.* **1956**, *78*, 6045–6048. Stork, G.; van Tamelen, E. E.; Friedman, L. J.; Burgstahler, A. W. *Ibid.* **1953**, *75*, 384–392.

(29) For instance, the displacement of the chloride **21** with AcOK ($CH_3CN$, 18-crown-6 ether) gave methyl 3,5-*O*-diacetyl-2,6-dideoxy-*lyxo*-β-L-hexofuranoside, a precursor of 2-deoxy-L-fucose: Durgnat, J.-M.; Warm, A.; Vogel, P., manuscript in preparation.

to pH 7 with 1 N HCl. The mixture was extracted with $Et_2O$ (150 mL, 3 times); the organic extract was washed with water (100 mL) and then with brine (100 mL). After drying ($MgSO_4$), the solvent was evaporated at atmospheric pressure (Vigreux column). The residue was purified by filtration on silica gel (50 g, 230–400 mesh ASTM, $CH_2Cl_2$ or $Et_2O$/petroleum ether 1:4), yielding 0.373 g of an oil containing >92% of **14** (71%) and <8% of **15** (6%). This mixture can be used in the subsequent step or separated by crystallization of **14** from $CHCl_3$ (−20 °C) and isolation of **15** by HPLC (Dupont, Zorbax-sil, 25 cm × 21.2 mm, hexane/AcOMe (95:5) (v/v), 20 mL, min). Characteristics of **14**: $^1H$ NMR (360 MHz, $CDCl_3$) δ 4.44 (d, $J$ = 4.75, H-C(4)), 4.35–4.30 (m, H-C(1) and H-C(5)), 2.86 (q, $J$ = 7.5, H-C(3)), 2.67 (dddd, $J$ = 14.25, 10.5, 6.5, 1.0, $H_{exo}$-C(6)), 1.71 (dd, $J$ = 14.25, 4.25, $H_{endo}$-C(6)), 1.26 (d, $J$ = 7.5, $CH_3$); $[\alpha]^{25}_{589}$ +89.3°, $[\alpha]^{25}_{578}$ +93.5°, $[\alpha]^{25}_{546}$ +108.8°, $[\alpha]^{25}_{436}$ +212.2°, $[\alpha]^{25}_{365}$ +448.1° (15.83 g/dm$^3$, $CH_2Cl_2$).

**(1*R*,4*R*,5*R*)-5-*endo*-Chloro-3,3-dimethyl-7-oxa-2-bicyclo[2.2.1]heptanone (15).** The minor fraction isolated in the above HPLC contained an oil: $^1H$ NMR (360 MHz, $CDCl_3$) δ 4.44 (d, $J$ = 7.0, H-C(1)), 4.36 (ddd, $J$ = 10.3, 6.0, 4.5, H-C(5)), 4.32 (d, $J$ = 4.5, H-C(4)), 2.79 (dddd, $J$ = 13.75, 10.3, 7.0, 1.0, $H_{exo}$-C(6)), 1.77 (ddd, $J$ = 13.75, 6.0, 1.0, $H_{endo}$-C(6)), 1.40 and 1.29 (2 s, $2CH_3$); $[\alpha]^{25}_{589}$ +80.2°, $[\alpha]^{25}_{578}$ +84.0°, $[\alpha]^{25}_{546}$ +98.6°, $[\alpha]^{25}_{436}$ +195.6°, $[\alpha]^{25}_{365}$ +408.8° (12.5 g/dm$^3$, $CH_2Cl_2$).

**(1*S*,4*S*,5*R*,6*R*)-6-*endo*-Chloro-4-*exo*-methyl-2,8-dioxa-3-bicyclo[3.2.1]octanone (16).** A total of 212 mg, (1.04 mmol) of metachloroperbenzoic acid (*m*-CPBA, Fluka, 85% of peracid) was added to a stirred mixture of **14** (152 mg, 0.95 mmol) and $NaHCO_3$ (240 mg) in $CHCl_3$ (15 mmol) at 8 °C and under an Ar atmosphere. The mixture was stirred at 8 °C for 8 h (control of the disappearance of **14** by TLC, $CH_2Cl_2$, vanilin, and phosphomolybdic acid as revelators). The precipitate of 3-$ClC_6H_4COONa$ was filtered off and washed with 3 mL of $CHCl_3$. The solution was concentrated in vacuo (<15 °C). The residue was filtered through Florisil (16 g, 200–300 mesh ASTM, $CH_2Cl_2$/hexane, 1:1) and crystallized from hot hexane, yielding 144 mg (86%) of colorless crystals: mp 83–84 °C (unstable compound, must be stored under Ar at −20 °C or in $CH_2Cl_2$ solution); $^1H$ NMR (360 MHz, $CDCl_3$) δ 5.84 (d, $J$ = 4.9, H-C(1)), 4.51 (ddd, $J$ = 10.25, 6.5, 4.75, H-C(6)), 4.45 (d, $J$ = 6.5, H-C(5)), 3.28 (q, $J$ = 7.5, H-C(4)), 2.90 (ddd, $J$ = 14.8, 10.25, 4.9, $H_{exo}$-C(7)), 2.36 (dd, $J$ = 14.8, 4.75, $H_{endo}$-C(7)), 1.51 (d, $J$ = 7.5, $CH_3$); $[\alpha]^{25}_{589}$ −51.5°, $[\alpha]^{25}_{578}$ −53.8°, $[\alpha]^{25}_{546}$ −61.2°, $[\alpha]^{25}_{436}$ −103.4°, $[\alpha]^{25}_{365}$ −164.2° (17.21 g/dm$^3$, $CH_2Cl_2$).

**Methyl 3-Chloro-2,3,5-trideoxy-5-*C*-methyl-*arabino*-D-α- and -β-hexofuranosiduronic Acids (17α and 17β).** A total of 48 mg (0.5 mmol, 32 μL) of methanesulfonic acid was added to a stirred solution of **16** (87 mg, 0.49 mmol) in anhydrous MeOH (5 mL) at −15 °C under an Ar atmosphere. After stirring for 10 min, $CH_3COONa$ (500 mg, 0.61 mmol) was added to precipitate $CH_3SO_3Na$. After filtration through Celite, the solution was concentrated in vacuo and filtered through silica gel (5 g, 230–400 mesh ASTM, $CH_2Cl_2$/MeOH, 9:1), yielding a colorless oil containing 96% of **17α** and 4% of anomer **17β**. Pure **17α** was obtained on crystallizing the mixture **17α** + **17β** from pentane/$CHCl_3$ (6:1), yielding 96 mg (90%) of **17α**, colorless crystals: mp 90–92 °C; $^1H$ NMR (360 MHz, $CDCl_3$) δ 9.1 (br s, COOH), 5.26 (dd, $J$ = 5.75, 4.0, H-C(1)), 4.47 (ddd, $J$ = 6.0, 3.0, 0.9, H-C(3)), 4.23 (ddd, $J$ = 10.0, 3.0, H-C(4)), 3.37 (s, $CH_3O$), 2.92 (d q, $J$ = 10.0, 7.0, H-C(5)), 2.61 (ddd, $J$ = 15.25, 5.75, 0.9, $H_{syn}$ (with respect to the Cl substituent)-C(2)), 2.42 (ddd, $J$ = 15.25, 6.0, 4.0, $H_{anti}$-C(2)), 1.26 (d, $J$ = 7.0, $CH_3$); $[\alpha]^{25}_{589}$ +104.6°, $[\alpha]^{25}_{578}$ +108.7°, $[\alpha]^{25}_{546}$ +123.4°, $[\alpha]^{25}_{436}$ +204.7°, $[\alpha]^{25}_{365}$ +311.3° (18,7 g/dm$^3$, $CH_2Cl_2$).

**Anomer β (17β)**: $^1H$ NMR (360 MHz, $CDCl_3$) δ 9.5 (br s, COOH), 5.14 (d, $J$ = 6.0, H-C(1)), 4.44 (dd, $J$ = 5.0, 4.5, H-C(3)), 4.21 (dd, $J$ = 10.0, 4.5, H-C(4)), 3.43 (s, $OCH_3$), 3.01 (dq, $J$ = 10.0, 6.5, H-C(5)), 2.61 (ddd, $J$ = 15.0, 6.0, 5.0, $H_{anti}$-C(2)), 2.42 (d, $J$ = 15, $H_{syn}$-C(2)), 1.27 (d, $J$ = 6.5, $CH_3$).

**Methyl 3-Chloro-2,3,5,7-tetradeoxy-5-*C*-methyl-*arabino*-D-α-hept-6-ulofuranoside (18).** A 1.6 M solution of methyllithium in anhydrous $Et_2O$ (5 mL, 8 mmol) was added dropwise to a solution of **17α** + **17β** (787 mg, 3.77 mmol) in anhydrous $Et_2O$ (70 mL) stirred at 0 °C in a Schlenk buret filled with Ar in about 10 min. After stirring at 0 °C for 1 h, the precipitation of lithium carboxylate salt was dissolved by addition of anhydrous THF (ca. 20 mL). After 2 h (the end of the reaction can be controlled by TLC, $CH_2Cl_2$/MeOH (9:1), vanilin as revelator giving a red spot for **18**), the reaction mixture was poured in three portions into a vigourously stirred saturated aqueous solution of $NH_4Cl$ (3 × 200 mL) at 0 °C and under Ar atmosphere. After stirring for 15 min, the organic phase was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (50 g of $SiO_2$, 230–400 mesh ASTM, $CH_2Cl_2$/MeOH, 98:2), yielding 494 mg (63%) of yellowish oil, unstable at 20 °C, must be stored in $CH_2Cl_2$ at −20 °C: $^1H$ NMR (360 MHz, $CDCl_3$) δ 5.2 (dd, $J$ = 5.75, 4.0, H-C(1)), 4.44 (ddd, $J$ = 6.0, 3.0, 1.0, H-C(3)), 4.10 (dd, $J$ = 10.0, 3.0, H-C(4)), 3.33 (s, $OCH_3$), 3.0 (dq, $J$ = 10.0, 7.0, H-C(5)), 2.57 (ddd, $J$ = 15.25, 5.75, 1.0, $H_{syn}$-C(2)), 2.35 (ddd, $J$ = 15.25, 6.0, 4.0, $H_{anti}$-C(2)), 2.27 (s, $H_3$-C(7)), 1.08 (d, $J$ = 7.0, $H_3C$-C(5)); $[\alpha]^{25}_{589}$ +114.5°, $[\alpha]^{25}_{578}$ +119.4°, $[\alpha]^{25}_{546}$ +136.2°, $[\alpha]^{25}_{436}$ +235.9°, $[\alpha]^{25}_{365}$ +395° (16.85 g/dm$^3$, $CH_2Cl_2$).

**Methyl 2,3,5,7-Tetradeoxy-5-*C*-methyl-*erythro*-D-α-hept-2-en-6-osulofuranoside (19).** This oily compound was isolated as a minor fraction (<5%) by chromatography of the above reaction mixture: $^1H$ NMR (360 MHz, $CDCl_3$) δ 6.2 (dt, $J$ = 6.0, 1.25, H-C(2)), 5.85 (ddd, $J$ = 6.0, 1.0, 1.0, H-C(3)), 5.76 (dt, $J$ = 4.0, 1.25, H-C(1)), 5.07 (dddd, $J$ = 8.0, 4.0, 2.0, 1.25, H-C(4)), 3.34 (s, OMe), 2.74 (dq, $J$ = 7.0, 6.0, H-C(5)), 2.21 (s, $H_3C$(7)), 1.03 (d, $J$ = 7.0, $H_3C$-C(5)); $[\alpha]^{25}_{589}$ +68.5°, $[\alpha]^{25}_{578}$ +72.1°, $[\alpha]^{25}_{546}$ +85.6°, $[\alpha]^{25}_{436}$ +187.6° (14 g/dm$^3$, $CH_2Cl_2$).

**Methyl 3-Chloro-2,3,5,7-tetradeoxy-5,6-*C*-dimethyl-*arabino*-D-α-heptofuranoside (20).** The second minor fraction (<5%) in the above chromatographic separation contained the oily **20**: $^1H$ NMR (360 MHz, $CDCl_3$) δ 5.3 (dd, $J$ = 6.0, 4.5, H-C(1)), 4.49 (dd, $J$ = 6.0, 2.75, H-C(3)), 4.01 (dd, $J$ = 10.0, 2.75, H-C(4)), 3.42 (s, OMe), 2.60 (dd, $J$ = 15.25, 6.0, $H_{syn}$-C(2)(with respect to Cl), 2.33 (ddd, $J$ = 15.25, 6.0, 4.5, $H_{anti}$-C(2)), 2.12 (dq, $J$ = 10.0, 7.0, H-C(5)), 1.22 and 1.21 (2s, 2 Me), 0.88 (d, $J$ = 7.0, $CH_3$-C(5)); $[\alpha]^{25}_{589}$ +500°, $[\alpha]^{25}_{578}$ +520°, $[\alpha]^{25}_{546}$ +580°, $[\alpha]^{25}_{436}$ +800°, $[\alpha]^{25}_{365}$ +1440° (10 g/dm$^3$, $CH_2Cl_2$).

**Methyl 5-*O*-Acetyl-3-chloro-2,3,6-trideoxy-*xylo*-L-β-hexofuranoside (21).** Trifluoroacetic anhydride (1.9 g, 1.25 mL, 9.0 mmol) was added to stirred 90% hydrogen peroxide (235 mg, 166 μL, 6.22 mmol) at 0 °C; 0.68 mL (3 mmol) of this 4.4 M solution of $CF_3CO_3H$ was added dropwise during 30 min to a vigorously stirred solution of ketone **18** (306 mg, 1.48 mmol) in $CH_2Cl_2$ (3 mL) containing 1 g of $Na_2HPO_4$. After stirring for 5 h at 20 °C (the end of the reaction was controlled by TLC, $SiO_2$, $CH_2Cl_2$/MeOH (95:5), vanilin as revelator, giving a black spot for **21**), the precipitated salts were filtered off and washed with $CH_2Cl_2$. The solvent was evaporated in vacuo and the residue purified by flash chromatography (5 g of $SiO_2$, 230–400 mesh ASTM, $CH_2Cl_2$/MeOH, 98:2), giving 280 mg (85%) of a slightly yellowish oil: $^1H$ NMR (360 MHz, $CDCl_3$) δ 5.26 (dd, $J$ = 5.75, 4.0, H-C(1)), 5.2 (dq, $J$ = 7.5, 6.5, H-C(5)), 4.42 (ddd, $J$ = 6.0, 3.75, 2.25, H-C(3)), 4.07 (dd, $J$ = 7.5, 3.75, H-C(4)), 3.39 (s, $OCH_3$), 2.56 (ddd, $J$ = 15.0, 5.75, 2.25, $H_{syn}$-C(2)), 2.38 (ddd, $J$ = 15.0, 6.0, 4.0 $H_{anti}$-C(2)), 2.08 (s, $CH_3CO$), 1.3 (d, $J$ = 6.5, $H_3C$(6)); $[\alpha]^{25}_{589}$ +82.7°, $[\alpha]^{25}_{578}$ +86.0°, $[\alpha]^{25}_{546}$ +97.5°, $[\alpha]^{25}_{436}$ +159.5°, $[\alpha]^{25}_{365}$ +238.5° (17.65 g/dm$^3$, $CH_2Cl_2$).

**Methyl 5-*O*-Acetyl-3-azido-2,3,6-trideoxy-*lyxo*-L-β-hexofuranoside (22).** A mixture of **21** (270 mg, 1.21 mmol) and $NaN_3$ (162 mg, 2.5 mmol) in DMF (5 mL) was heated to 120 °C for 12 h (the end of the reaction was controlled by TLC, $SiO_2$, $CH_2Cl_2$/MeOH (95:5), vanilin as revelator, giving a dark-green spot for **22**, about same $R_f$ as for **21**). After cooling to 20 °C, water (25 mL) was added and the mixture extracted with $CHCl_3$ (25 mL, 3 times). The organic extract was washed with water (10 mL, 2 times) and then with brine (20 mL). After drying ($MgSO_4$), it was concentrated in vacuo and the residue filtered through silica gel (5 g, 230–440 mesh ASTM, $CH_2Cl_2$/MeOH, 98:2), yielding 222 mg (80%) of a yellowish liquid: $^1H$ NMR (360 MHz, $CDCl_3$) δ 5.07 (qd, $J$ = 6.5, 4.5, H-C(5)), 5.07 (dd, $J$ = 5.5, 1.25, H-C(1)), 3.96 (dd, $J$ = 5.0, 4.5, H-C(4)), 3.78 (ddd, $J$ = 9.0, 5.0, 3.25, H-C(3)), 3.36 (s, $OCH_3$), 3.22 (ddd, $J$ = 14.25, 9.0, 5.5, $H_{anti}$(with respect to the azido group)-C(2)), 2.07 (s, $CH_3CO$), 2.0 (ddd, $J$ = 14.25, 3.25, 1.25, $H_{syn}$-C(2)), 1.28 (d, $J$ = 6.5, $H_3C$(6)); $[\alpha]^{25}_{578}$ +138.5°, $[\alpha]^{25}_{546}$ +156.8°, $[\alpha]^{25}_{436}$ +257.0°, $[\alpha]^{25}_{365}$ +383.5° (17.1 g/dm$^3$, $CH_2Cl_2$).

**Methyl 5-*O*-Acetyl-3-amino-2,3,6-trideoxy-*lyxo*-L-β-hexofuranoside (23).** The azide **22** (140 mg, 0.61 mmol) was hydrogenated at atmospheric pressure in EtOH (4 mL) stirred with 60 mg of 10% Pd/C. After the end of $H_2$ absorption (ca. 4 h,

control by TLC, $SiO_2$, MeOH/$CHCl_3$ (1:3), revelator, "Fluram" Roche), the mixture was filtered through Celite and evaporated in vacuo. The residue was purified by flash chromatography (3 g of $SiO_2$, 230–400 mesh ASTM, $CH_2Cl_2$/MeOH/$NH_3$ (aqueous 30%), 95:4:1) and yielded 112 g (90%) of a yellowish liquid: $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 5.02 (qd, $J$ = 6.5, 4.0, H-C(5)), 5.01 (dd, $J$ = 5.0, 1.5, H-C(1)), 3.75 (dd, $J$ = 4.5, 4.0, H-C(4)), 3.33 (s, $OCH_3$), 3.18 (m, H-C(3)), 2.60 (br s, $NH_2$), 2.23 (ddd, $J$ = 13.5, 8.25, 5.0, $H_{anti}$(with respect to the amino group)-C(2)), 2.03 (s, $CH_3CO$), 1.74 (ddd, $J$ = 13.5, 3.5, 1.5, $H_{syn}$-C(2)), 1.26 (d, $J$ = 6.5, $H_3C(6)$); $[\alpha]^{25}_{589}$ +92.1°, $[\alpha]^{25}_{578}$ +95.7°, $[\alpha]^{25}_{546}$ +108.2°, $[\alpha]^{25}_{436}$ +175.7°, $[\alpha]^{25}_{365}$ +258.6° (14.0 g/dm$^3$, $CH_2Cl_2$).

**Methyl 3-Amino-2,3,6-trideoxy-*lyxo*-L-α- and -β-hexofuranosides (24α and 24β).** The acetate **23** (85 mg, 0.42 mmol) was dissolved in methanol (5 mL). The solution was saturated with gaseous $NH_3$ at 0 °C (ca. 1 h). The flask was sealed with a septum and allowed to stand at 20 °C for 100 h (control of the end of the ammonolysis by TLC, $SiO_2$, $CHCl_3$/MeOH/$NH_3$ (aqueous 30%), 75:22:3, "Fluram" Roche as revelator). After solvent evaporation in vacuo, the crude mixture of **24α + 24β** was purified by flash chromatography on silica gel (2.5 g, $CHCl_3$/MeOH/$NH_3$ (aqueous 30%, 75:22:3), yielding 56 mg (92%) of a 9:1 mixture of **24β** and **24α**, yellow oil: $^1H$ NMR of **24β** (360 MHz, $CDCl_3$) $\delta$ 5.02 (dd, $J$ = 5.0, 1.0, H-C(1)), 3.73 (dq, $J$ = 6.5, 5.0, H-C(5)), 3.61 (dd, $J$ = 5.0, 4.5, H-C(4)), 3.36 (s, $OCH_3$), 3.27 (ddd, $J$ = 8.5, 4.5, 3.0, H-C(3)), 2.25 (ddd, $J$ = 13.5, 8.5, 5.0, $H_{anti}$-C(2)), 1.92 (br s, $NH_2$), 1.75 (ddd, $J$ = 13.5, 3.0, 1.0, $H_{syn}$-C(2)), 1.25 (d, $J$ = 6.5, $H_3C(6)$); $[\alpha]^{25}_{589}$ +119.5°, $[\alpha]^{25}_{578}$ +124.2°, $[\alpha]^{25}_{546}$ +140.7°, $[\alpha]^{25}_{436}$ +231°, $[\alpha]^{25}_{365}$ +347.4° (12.2 g/dm$^3$, $CH_2Cl_2$).

**Hydrochloride of 3-Amino-2,3,6-trideoxy-*lyxo*-L-hexopyranose (L-Daunosamine·HCl) (3·HCl).** The furanosides **24α + 24β** (30 mg, 0.19 mmol) were heated in 0.2 N HCl (1 mL) to 90 °C for 2 h. After solvent evaporation to dryness, the crude **3**·HCl was dissolved in ethanol (2 mL) and heated with charcoal for 5 min. After filtration (Celite), the solution was concentrated by evaporation in vacuo to 0.5 mL. Addition of acetone (1.5 mL) led to a precipitation of pure **3**·HCl (4:3 mixture of α- and β-anomers, by NMR in $Me_2SO$-$d_6$), yielding 24 mg (67%) of crystalline, white powder, mp 166 °C dec: IR (KBr) 3390, 3000, 2930, 2000, 1600, 1510; $^1H$ NMR of α-anomer (360 MHz, $Me_2SO$-$d_6$) $\delta$ 8.11 (br s, $NH_3Cl$), 6.33 (br s, HO-C(1)), 5.35 (br s, HO-C(4)), 5.13 (br s, H-C(1)), 3.98 (q, $J$ = 6.75, H-C(5)), 3.59 (br s, H-C(4)), 3.42 (br s, H-C(3)), 1.82 (ddd, $J$ = 12.5, 12.5, 3.25, $H_{syn}$(with respect to the amino group)-C(2)), 1.65 (dd, $J$ = 12.5, 4.5, $H_{anti}$-C(2)), 1.08 (d, $J$ = 6.75, $H_3C(6)$); $^1H$ NMR of the β-anomer (360 MHz, $Me_2SO$-$d_6$) $\delta$ 8.17 (br s, $NH_3Cl$), 6.68 (br s, HO-C(1)), 5.43 (br s, HO-C(4)), 4.63 (d, $J$ = 9.0, H-C(1)), 3.53 (q, $J$ = 6.25, H-C(5)), 3.5 (br s, H-C(4)), 3.2 (m, H-C(3)), 1.78 (d, $J$ = 12.5, $H_{anti}$-C(2)), 1.57 (ddd, $J$ = 12.5, 12.5, 9.0, $H_{syn}$-C(2)), 1.13 (d, $J$ = 6.25, H-C(6)); MS (70 eV), $m/z$ (relative intensity) 148 ($M^+$ – 35, 15), 130 (36), 86 (56), 72 (100); $[\alpha]^{25}_{589}$ –60.9°, $[\alpha]^{25}_{578}$ –70.7°, $[\alpha]^{25}_{546}$ –90.2°, $[\alpha]^{25}_{436}$ –131.7° (4.1 g/dm$^3$, $H_2O$). Compare with data in the literature.[13,15b-f]

Anal. Calcd for $C_6H_{13}NO_3$·HCl ($M_r$, 183.63): C 39.24; H 7.68. Found: C 39.21; H 7.78.

**(1*RS*,4*SR*,5*RS*,6*RS*)-5-Chloro-6-benzeneselenenyl-7-oxa-2-bicyclo[2.2.1]heptanone (7).** A 5.4 N solution of MeONa in MeOH (1 mL) was added to a stirred solution of **6** (6.6 g, 17.8 mmol)[12] in anhydrous MeOH (100 mL) under an Ar atmosphere. After stirring at 20 °C for 1 h, a 37% solution of formaline (10 mL) was added. After stirring at 20 °C for 20 min, $H_2O$ (150 mL) was added and the mixture was neutralized (pH 7) with 1 N HCl and extracted with $CH_2Cl_2$ (100 mL, 3 times). The extract was washed with brine (100 mL) and dried ($MgSO_4$). After solvent evaporation, the crude product was purified by flash chromatography on silica gel ($CH_2Cl_2$), yielding 5.1 g (91%) as a colorless solid, mp 49–51 °C: $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.63–7.59 (m, 2 H), 7.39–7.30 (m, 3 H), 4.96 (ddd, $J$ = 5.5, 4.5, 1.0 H-C(4)), 4.36 (ddd, $J$ = 4.5, 4.0, 1.25, H-C(5)), 4.33 (br s, H-C(1)), 3.39 (d, $J$ = 4.0, H-C(6)), 2.83 (d, $J$ = 18.0, $H_{endo}$-C(3)), 2.48 (dddd, $J$ = 18.0, 5.5, 1.25, 1.0 $H_{exo}$-C(3)).

On heating **7** in $CD_3CN$ to 120 °C, slow isomerization to the isomeric product **8**[12] was observed.

**(1*RS*,2*RS*,4*SR*,5*RS*,6*RS*)-2-*endo*-Acetoxy-5-*endo*-chloro-6-*exo*-benzenesulfenyl-7-oxabicyclo[2.2.1]heptane-2-*exo*-carbonitrile (9).** Thiophenol (1.1 g, 1.02 mL, 10 mmol) was added dropwise and slowly (in ca. 10 min) to a vigorously stirred suspension of *N*-chlorosuccinimide (1.36 g, 10.2 mmol) in $CH_2Cl_2$ (10 mL). As soon as the mixture turns orange, the flask must be cooled by an ice–water bath. In a few minutes, *N*-chlorosuccinimide disappears and succinimide then precipites. The mixture was stirred for 30 min at 20 °C and then cooled to –78 °C. The 7-oxanorbornene derivative **4** (1.79 g, 10 mmol) was added portionwise. The temperature should not raise above –65 °C. After complete color discharge, the reaction mixture was allowed to reach 20 °C (control of the end of the reaction by TLC, $SiO_2$, AcOEt/$Et_2O$/petroleum ether, 1:1:3, $KMnO_4$ revealed **4**, and 254 nm UV light revealed **9**). The succinimide was filtered off and the filtrate evaporated in vacuo to dryness, yielding 3.07 g (95%) of colorless crystals: mp 67–68 °C; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.47–7.44 (m, 2 H-aromatic), 7.39–7.33 (m, 3 H-aromatic), 4.97 (s, H-C(1)), 4.72 (m, H-C(4)), 4.08 (t, $J$ = 4.7, H-C(5)), 3.46 (d, $J$ = 4.75, H-C(6)), 2.71–2.62 (m, $H_2C(3)$), 2.09 (s, $CH_3CO$).

**(1*RS*,4*SR*,5*RS*,6*RS*)-5-*endo*-Chloro-6-*exo*-benzenesulfenyl-7-oxa-2-bicyclo[2.2.1]heptanone (10).** The adduct **9** (1 g, 3.08 mmol) was dissolved in MeOH (30 mL). After addition of 0.2 mL of a 30% solution of MeONa in MeOH (ca. 1.08 mmol), the mixture was stirred for ca. 1 h at 20 °C under an Ar atmosphere. The end of the reaction was controlled by TLC ($SiO_2$, $Et_2O$/EtOAc/petroleum ether (1:1:3), 254 nm UV light). The solution contains a mixture of the cyanohydrins of **10**. The latter are transformed into **10** by addition a 37% aqueous solution of formaldehyde. After being stirred at 20 °C for 15 min, the reaction mixture was poured into ice–water and neutralized with 1 N HCl. After extraction with $CH_2Cl_2$ (50 mL, 3 times), the organic extract was concentrated by distillation (Vigreux column) and purified by flash chromatography (20 g of $SiO_2$, $CHCl_3$), yielding 0.75 g (95.3%) of colorless crystals: mp 34–35 °C; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.46–7.43 (m, 2 H-aromatic), 7.38–7.29 (m, 3 H-aromatic), 5.01 (ddm, $J$ = 5.8, 5.0, 1.0, H-C(4)), 4.27 (m, $J \leq 1$, H-C(1)), 4.16 (ddd, $J$ = 5.0, 3.9, 1.0, H-C(5)), 3.46 (d, $J$ = 3.9, H-C(6)), 2.85 (d, $J$ = 18.1, $H_{endo}$-C(3)), 2.53 (ddt, $J$ = 18.1, 5.8, 1.0, $H_{exo}$-C(3)).

**Reduction of 10 with Raney Nickel.** Raney Ni (70 g) in $H_2O$ was centrifugated, decanted, and taken successively with methanol (250 mL, 3×) and ether (250 mL, 3×). The Raney Ni suspended in benzene was added to a solution of **10** (10 g, 39.26 mmol) in anhydrous benzene (200 mL) under vigorous stirring at 10–15 °C. The reaction was monitored either by TLC on silica gel ($CH_2Cl_2$, (2,4-dinitrophenyl)hydrazine to reveal the ketones, vanilin to reveal the alcohols) or by VPC (capillary SE 30 column, 150 kPa, $T_{initial}$ 60 °C, $T_{final}$ 200 °C, 15 °/min). **10** was consumed after ca. 2 h. After filtration on Celite, the filtrate was concentrated by distillation (Vigreux column) at atmospheric pressure. If alcohols were present, the reaction mixture was dissolved in $CH_2Cl_2$ (100 mL) and treated with ca. twofold excess of pyridinium chlorochromate. Flash chromatography (300 g of $SiO_2$, 230–4000 mesh ASTM, $CH_2Cl_2$) yielded 2.9 g (50%) of (±)-**13**, colorless liquid bp 213 °C, and 1.76 g (40%) of (±)-7-oxa-2-bicyclo[2.2.1]heptanone, colorless liquid.

**Simplified Procedure for the Transformation of 1 into 12.** A solution of 7.14 g (36.18 mmol) of PhSeCl in $CH_2Cl_2$ (80 mL) was added to a solution of 11.48 g (36.18 mmol) of **1** in $CH_2Cl_2$ (60 mL). After staying at 20 °C for 4 days, the solvent was evaporated in vacuo and the residue dissolved in THF (100 mL). After cooling to 0 °C, 30% $H_2O_2$ (38.5 mL) was added dropwise in about 10 min. After being stirred at 0 °C for 1 h, the mixture was allowed to warm to 20 °C and stirred for 20 h. After cooling to 0 °C, sodium pyrosulfite (50 g) was added portionwise. After stirring at 20 °C for 5 h, 4 N KOH (150 mL) was added (pH ca. 9). Two hours later, a 37% aqueous solution of formaldehyde (100 mL) was added. After 30 min at 20 °C, the mixture was extracted with $CHCl_3$ (300 mL, 3 times). The extract was washed with brine (150 mL) and dried ($MgSO_4$). The solvent was evaporated at atmospheric pressure (Vigreux column) and the residue purified by flash chromatography on silica gel ($CH_2Cl_2$), yielding 4.92 g (94%) of colorless oil.

**Recovery of (–)-Camphanic Acid.** The aqueous phase obtained above was acidified to pH 2–3 with 2 N HCl and extracted with $CH_2Cl_2$ (300 mL, 4 times). The extract was washed with brine (200 mL) and evaporated in vacuo. The residue was recrystallized from AcOEt/hexane (1:4) (750 mL), yielding 6.1 g (85.1%) of colorless crystals, mp 198–199 °C (lit. 198–200 °C).

**Simplified Procedure for the Transformation of 22 into 24.** **22** (100 mg, 0.44 mmol) in MeOH (3 mL) was hydrogenated ($H_2$, 1 atm) in the presence of 10% Pd/C (20 mg) at 20 °C (ca. 6 h). The mixture was filtered through Celite and then saturated with gaseous $NH_3$ at 0 °C (1 h). After 3 days at 20 °C (stopped flask), the solvent was evaporated and the residue purified by flash chromatography on silica gel ($CH_2Cl_2$/MeOH/ 30% aqueous $NH_3$ 75:22:3), yielding 67 mg (94.5%) of yellowish oil.

**Acknowledgment.** We are grateful to Hoffmann-La Roche and Co., AG (Basel), the Fonds Herbette (Lausanne), and the Swiss National Science Foundation for financial support. We thank Miss D. Fontanella for her technical assistance.

**Supplementary Material Available:** UV, IR, $^{13}C$ NMR, and MS spectral data and elemental analyses of compounds **5**, **7**, and **9–24** (8 pages). Ordering information is given on any current masthead page.

# Asymmetric Synthesis of (5*R*,6*S*)-6-Acetoxy-5-hexadecanolide, the Major Component of the Oviposition Attractant Pheromone of the Mosquito *Culex pipens fatigans*, and Two of Its Stereoisomers

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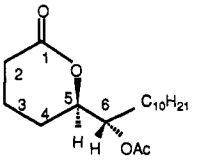
*Received July 3, 1986*

The benzyl derivatives of (*R*)- and (*S*)-2-hydroxydodecanal have been prepared by a previously described asymmetric synthesis based on a chiral 1,3-oxathiane and have been converted into (5*R*,6*S*)-6-acetoxy-5-hexadecanolide, a mosquito oviposition attractant pheromone, and its 5*R*,6*R* and 5*S*,6*R* stereoisomers in highly diastereoselective fashion. The steps involved are Grignard addition of 5-pentenylmagnesium bromide, Mitsunobu inversion for one of the erythro (5*R*,6*S*) isomers and oxidation–hydride reduction for the other, ozonization, oxidation, lactone formation, debenzylation, and acetylation, the overall yield in these steps being 30–42%.

In 1982, Laurence and Picket[2] isolated a substance from the apical droplets that form on the eggs of the mosquito *Culex pipens fatigans* (=*quinquefasciatus*) Wiedemann and identified it as *erythro*-6-acetoxy-5-hexadecanolide (1)

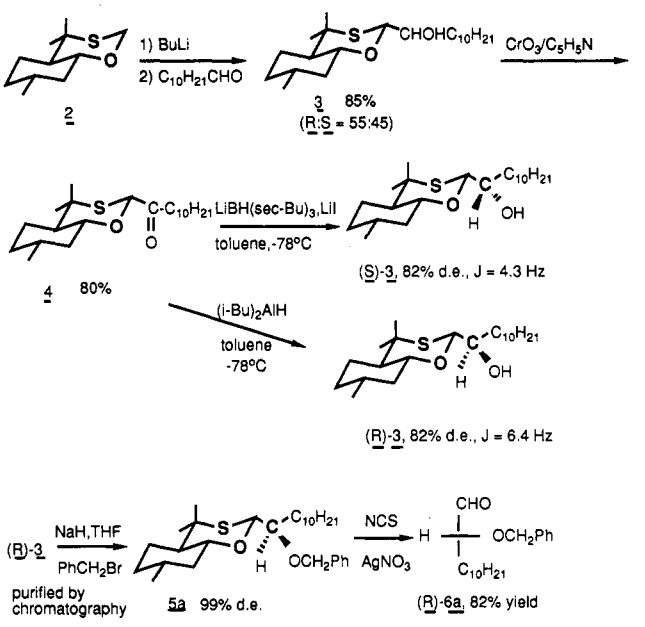


(5R,6S)-1

by mass spectral comparison with a synthetic, racemic sample. The substance acts as an oviposition attractant pheromone in that it attracts other gravid females of the same and some related mosquito species and induces them to oviposit in the same spot where the original eggs are found. Although the natural material is nonracemic, the amount available was too small to determine its optical rotation, and it was only later comparison of pheromonal activity of synthetic specimen of the (5*R*,6*S*)-**1** and (5*S*,6*R*)-**1** enantiomers which proved the former to be the natural substance.[3]

The first synthesis of the two enantiomeric erythro isomers of 1 was reported in 1982.[5] One of the two chiral centers (OH → OAc) was introduced in a chiral precursor (whose chiral center was later destroyed) in a synthesis of low diastereoselectivity (6:4) followed by chromatographic separation of the diastereomers; similarly low diastereoselectivity was encountered in the introduction of the second (lactone) chiral center and chromatography was again resorted to. Although the stereochemical efficiency

**Scheme I**

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