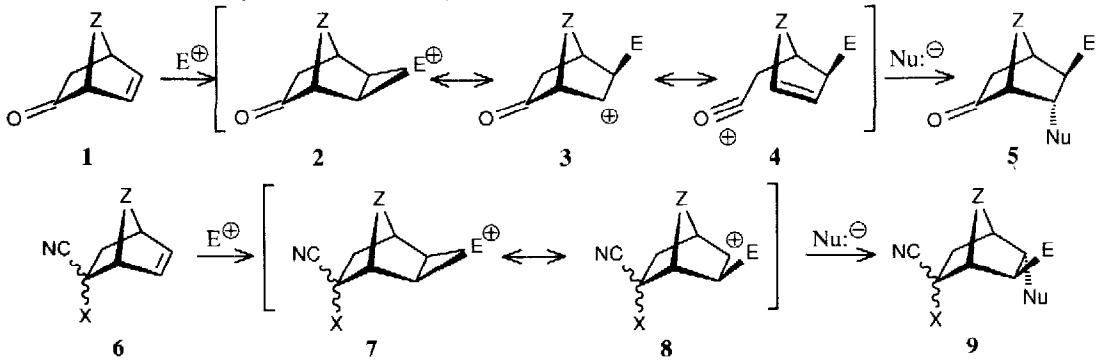
Tetrahedron Letters,Vol.30,No.52,pp 7415-7418,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

THE ELECTRON-RELEASING HOMOCONJUGATED CARBONYL GROUP. APPLICATION TO THE TOTAL SYNTHESES OF 3-DEOXY-, 4-DEOXY-HEXOSE, LIVIDOSAMINE AND DERIVATIVES

Daniela Fattori, Etienne de Guchteneere and Pierre Vogel*
Institut de chimie organique de l'Université, 2, rue de la Barre, CH-1005 Lausanne, Switzerland

Summary. *The regioselective electrophilic addition of benzeneselenyl bromide to (-)-(1S,4S)-7-oxabicyclo[2.2.1]-hept-5-en-2-one were exploited to develop efficient syntheses of methyl 3-deoxy-α-D-*arabino*-hexofuranoside and 4-deoxy-D-*lyxo*-hexopyranose. Similarly, D-lividosamine (3-deoxy-D-glucosamine) was derived from (+)-(1R,4R)-7-oxabicyclo[2.2.1]hept-5-en-2-one.*

In a recent publication on the solvolysis of 3-oxobicyclo[2.2.2]oct-1-yl triflates, Takeuchi and Yoshida[1] claimed to have discovered the first example of the through-bond interaction of the β-carbonyl lone pair with a cationic p orbital. Already in 1982, we reported[2] on the electrophilic additions of enones **1** that give exclusively adducts **5** under conditions of kinetic control. The results were interpreted in terms of electron-releasing homoconjugated carbonyl group (**2** ↔ **3** ↔ **4**) due to favourable n(CO)-σ(C(1),C(2))-πC(6) hyperconjugative interactions that make 6-oxonorborn-2-yl cation more stable than 5-oxonorborn-2-yl cation derivatives.[3] We also found that an acyl group has a greater intrinsic (kinetic) migratory aptitude than an alkyl group in exothermic Wagner-Meerwein rearrangements due to the n(CO) electrons.[4]



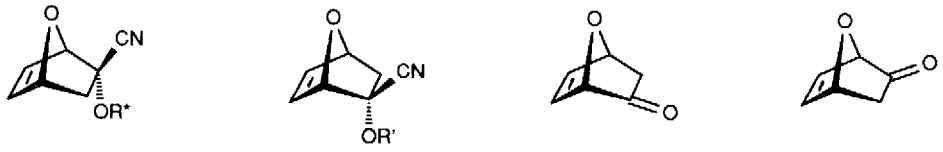
1 **2** **3** **4** **5**

6 **7** **8** **9**

Z= CH_2, CH_2-CH_2 X=Cl, OAc

As expected on the basis of steric or/and electronic factors (favoured limiting structures **7** ↔ **8**) the additions of alkenes **6** (synthetic precursors of enones **1**) to electrophiles E^+Nu^- gave the corresponding adducts **9** with opposite regioselectivity than additions **1** + E^+Nu^- → **5**. This principle[5] has been applied to the development of an efficient, total synthesis of L-daunosamine[6] starting with the "naked sugar" **10**.[7] We wish to report here on the exploitation of the electron-releasing homoconjugated carbonyl group in the development of total syntheses of methyl 3-deoxy-D-*arabino*-furanoside,[8] 4-deoxy-D-*lyxo*-pyranose[9] (Scheme 1) and D-lividosamine[10] (Scheme 2).

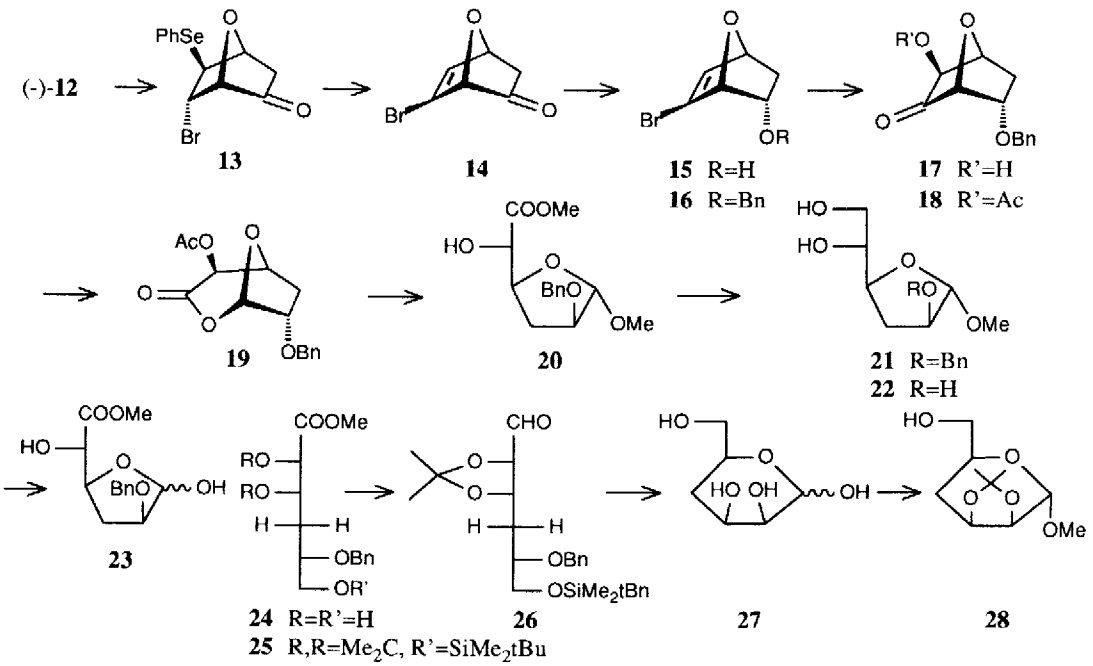
Addition of PhSeBr (CH_2Cl_2, 0°-20°C) to ((-)-**12**) derived from **11**[7] gave **13** (m.p. 72°C, $[\alpha]_D^{25}$ = +34.5 (c = 1.5, CH_2Cl_2)) nearly quantitatively. Treatment with 55% mCPBA (CH_2Cl_2, 20°C, 4 h) afforded **14** (84%, oil,



10 R*=(1S)-camphanoyl **11** R'=(1R)-camphanoyl (-)-**12** (+)-**12**

^{1}H-NMR (250 MHz, $CDCl_3$): δ_H = 6.75 (d, J = 2.0 Hz, H-C(5)); 5.36 (dd, J = 2.0, 4.0, H-C(4)); 4.35 (s, H-C(1)); 2.29 (dd, J = 16.0, 4.0, H_{exo}-C(3)); 2.0 (d, J = 16.0, H_{endo}-C(3))). Reduction of **14** with $NaBH_4$ in MeOH (0-2°C) furnished **15** (95%, oil, $[\alpha]_D^{25}$ = -79.8 (c = 1.5, CH_2Cl_2)) which was benzylated by reaction with NaH (THF, 0°C) and then with Bu_4NI + $PhCH_2Br$[11] to yield **16** (83%, m.p. 84-84.5°C, $[\alpha]_D^{25}$ = -120.9 (c = 1.5, CH_2Cl_2)). Double hydroxylation of **16** with H_2O_2 (30% aq.) and a catalytical amount of OsO_4 ($NaHCO_3$, THF, 0-20°C) gave the 3-*exo*-hydroxyketone **17** (98%, m.p. 88-89°C, $[\alpha]_D^{25}$ = -38 (c = 1.5, CH_2Cl_2)). Baeyer-Villiger oxidation of **17** with mCPBA was low yielded. The alcoholic function was thus protected (Ac_2O, pyridine, DMAP, 20°C, 15 h) as the acetate **18** (94%, oil, $[\alpha]_D^{25}$ = -38.9 (c = 1.5, CH_2Cl_2) and then treated with 85% mCPBA ($NaHCO_3$, CH_2Cl_2, 20°C, 14 h) which led to lactone **19** (85%, m.p. 86°C, $[\alpha]_D^{25}$ = -127.7 (c = 1.57, CH_2Cl_2)). Treatment of a methanolic solution of **19** with $SOCl_2$ (20°C, 3 h) gave methyl uronate **20** (86%, oil, $[\alpha]_D^{25}$ = +49.7 (c = 0.95, CH_2Cl_2)) which was reduced ($LiAlH_4$, Et_2O, 20°C) into methyl 2-0-benzyl-3-deoxy-D-*arabino*-furanoside (**21**, 93%, oil, $[\alpha]_D^{25}$ = +53.3 (c = 1.5, CH_2Cl_2)). Hydrogenolysis of **21** (H_2, 5% Pd/C, MeOH, 20°C, 15 h (afforded the known[8] methyl 3-deoxy-D-*arabino*-furanoside **22** (77%, m.p. 92-93°C (from Et_2O/MeOH), $[\alpha]_D^{25}$ = +99.9 (c = 0.436, H_2O).[12]

Scheme 1

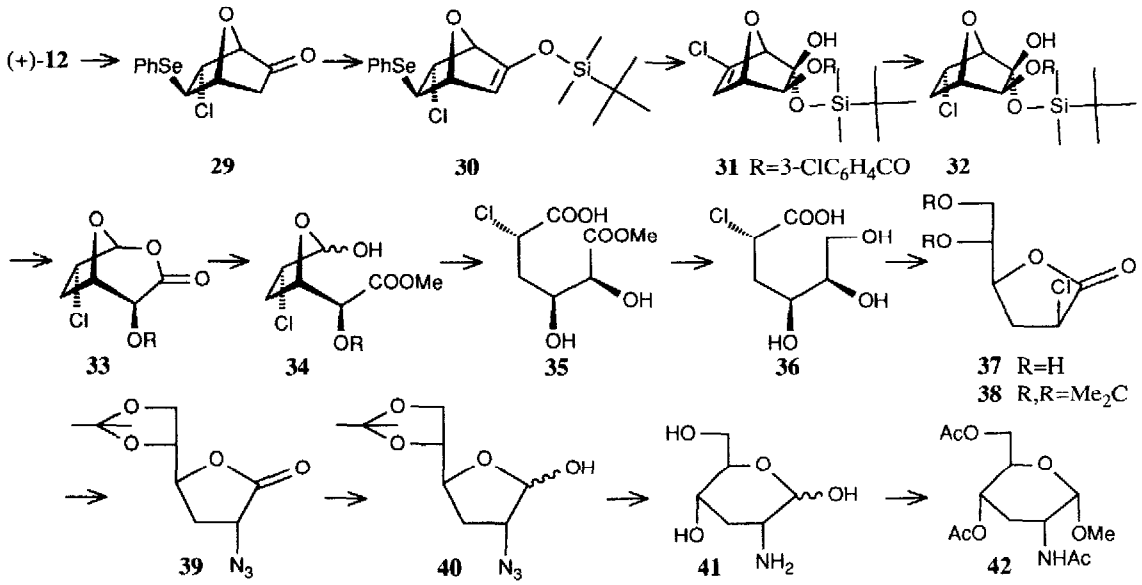


Lactone **19** is also a useful starting material for the synthesis of 4-deoxy-*lyxo*-hexose and derivatives. Treatment of **19** with anh. MeOH and K_2CO_3 (20°C, 5 h) gave methyl uronate **23**. It was reduced with $NaBH_4$ (MeOH, 0°C) into the partially protected methyl 4-deoxy-*lyxo*-hexonate **24** which was further protected by treatment with $Me_2C(OMe)_2$ and $SnCl_2$ in dioxane (20°C, 24 h) and then with $tBuMe_2SiCl$/imidazole (DMF, 0°C)

to yield **25** (72%, oil, $[\alpha]_D^{25}$ = -25 (c = 2.6, CH_2Cl_2)). Reduction of **25** with DIBAH in toluene (-65°C) afforded **26** (91%, oil, $[\alpha]_D^{25}$ = -40 (c = 1.88, $CHCl_2CHCl_2$)) which gave the unprotected pyranose **27**[9] (96%, oil) by hydrogenolysis (H_2/10% Pd/C, MeOH, 25°C, 48 h). **27** was transformed into the known methyl pyranoside **28**[9c] (73%) by treatment with MeOH (Dowex 50 Wx8, 65°C) and then with $Me_2C(OMe)_2/SnCl_2$/THF (20°C).

D-lividosamine[13] (or 3-deoxy-D-glucosamine) is present in lividomycin-A and -B,[14] and in 3'-deoxykanamycin.[15] We show here-below (Scheme 2) how (1R,4R)-7-oxabicyclo[2.2.1]hept-5-en-2-one ((+)-**12**) derived readily from furan and (1S)-camphanic acid[7] can be converted into D-lividosamine (**41**) in 11% overall yield.[10]

Scheme 2



Addition of PhSeCl to (+)-**12** ($CHCl_3$, 0°C, 15 min)[5] gave **29** (m.p. 66-67°C, $[\alpha]_D^{25}$ = -9.5 (c = 1, CH_2Cl_2) nearly quantitatively. Treatment of **29** with N-methyl-N-tertbutyldimethylsilyltrifluoroacetamide[16] (DMF, Et_3N, molecular sieves 4 Å, 40°C, 15 h) gave **30** (95%, oil $[\alpha]_D^{25}$ = -87 (c = 1, CH_2Cl_2)). Oxidation of **30** with 2.5 equiv. of anh. mCPBA (AcONa, anh. CH_2Cl_2, 0-20°C, 30 min) led to **31** (69%, m.p. 97-98°C, $[\alpha]_D^{25}$ = +111.2 (c = 1, CH_2Cl_2)). The process implies oxidative removal of the selenium, epoxidation of the enol ether, followed by ring opening of the corresponding epoxide intermediate induced by 3-$ClC_6H_4CO_2H$ and acyl migration of the resulting adduct.[17] Catalytical hydrogenation (10% Pd/C, Na_2CO_3, AcOEt, 20°C) of the chloroalkene **31** afforded **32** (89%). Treatment with mCPBA ($NaHCO_3$, CH_2Cl_2, 20°C, 66 h) led to lactone **33** (79%, m.p. 160-161°C, $[\alpha]_D^{25}$ = -57.4 (c = 1, CH_2Cl_2). Alkaline methanolysis (anh. MeOH, K_2CO_3, 20°C, 1 h) of **33** gave a mixture of α- and β-furanose **34** which was oxidized with 85% mCPBA (MeOH, 20°C, 3 h) to yield **35** (95.6%, oil, $[\alpha]_D^{25}$ = -15.7 (c = 1, CH_3OH)). Reduction of **35**, with 2 M $LiBH_4$ in THF (20°C), followed by treatment with 1 N aq. HCl (40°C) gave 1,4-manno-lactone **37** (oil) which was protected as its 5,6-0-isopropylidene derivatives **38** (52% based on **35**, oil, $[\alpha]_D^{25}$ = +4.5 (c = 1, CH_2Cl_2)) with $Me_2C(OMe)_2/SnCl_2$/dioxane (50°C, 4 h). Reaction of **38** with Bu_4NN_3 in THF (20°C, 15 h) afforded the known azide **39** (m.p. 60-61°C).[18] Reduction of **39** with DIBAH toluene (-78°C, 1 h), led to a mixture of α- and β-ribofuranose **40** (98%) which was then hydrogenated (H_2, 10% Pd/C, 1 N aq. HCl, 20°C, 4 h) into the hydrochloride of D-lividosamine (**41**·HCl, 94%). **41** was characterized as its methyl N-acetyl-4,6-0-diacetyl-α-D-lividosaminide **42**.[10,19,20]

Our results make use of the electron-releasing carbonyl function and present new applications of our "naked sugars" to the total syntheses of rare sugars. Compared with classical synthetic methods using carbohydrates as starting material,[8-10] our approach presents certain advantages: a) both enantiomers of a targeted compound can be attained with the same ease as both (+)- and (-)-7-oxabicyclo[2.2.1]hept-5-en-2-one are available, the chiral auxiliaries (1S)- and (1R)-camphanic acids, respectively, are recovered at an early stage of the synthesis; b) protected or partially protected polyfunctionnal molecules with different protective groups can be obtained selectively; c) these intermediates are potential precursors for the preparation of several natural products or compounds of biological interest.[21]

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(Received in France 6 October 1989)