Pergamon

Tetrahedron Letters, Vol. 38, No. 24, pp. 4215-4218, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00859-9

Isonucleosides by Michael Addition of Pyrimidine Bases on 2,6-Disubstituted 2*H*-Pyran-3(6*H*)-ones

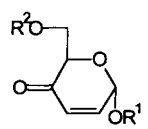
Natacha Prévost and Francis Rouessac*

Laboratoire de Synthèse Organique, associé au CNRS, Faculté des Sciences Université du Maine
Avenue O. Messiaen, F-72085 Le Mans CEDEX 9

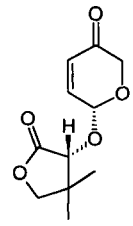
Abstract : A short, stereocontrolled convergent synthesis of pyranosyl isonucleosides, based on a Michael type addition between a silylated pyrimidine base and an unsaturated pyran-3(6H)-one is described. Diastereomeric ratio are of 90/10 up to 100/0, providing a straightforward way to prepare new nucleosides analogues.

In recent years, there has been a growing interest in 2'3'-dideoxynucleosides (*e.g.* AZT, ddI, ddC, D4T) as reverse transcriptase inhibitors of HIV-1 infections. These compounds are prepared by structural modification of naturally occuring nucleosides (linear route) or through glycosylation reactions[1] (convergent synthesis), the last strategy allowing structural variations in the nucleobase moiety and in the carbohydrate part, to be achieved. In order to control the stereoselectivity to obtain the more biologically active β-anomers, authors have investigated different routes as, for instance, fixation at position 2' of a group able to provide the well known anchimeric assistance, and could be eliminated or reductively removed.[2]

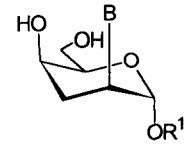
As part of our continuing work on the synthesis of optically active furyl-alkylcarbinols[3], we were interested in the behaviour of pyran-3-(6*H*)-ones, from which they are suitable precursors.[4] Pyranones **1-3** seemed to us key intermediates for synthesis of *iso*-deoxynucleosides of type **I**, a rather rare class of nucleosides showing significant and selective anti-HIV activity[5] as well as appearing upstream precursors of interesting related nucleotides[6]. Feringa *et al.*[7] have particularely shown that for pyran-3-one **4**, the 6-alkoxysubstituant exerts complete stereocontrol in π face selective additions of butadiene (Diels-Alder) or nitroethane (Michael) to this enone. Also of interest in this area, Horton's[8] and Herradon's[9] groups have discussed the total facial stereoselectivity induced by γ substituents present on neighbouring unsaturated lactones.



1 R^1 = Et R^2 = TBDMS (13)
2 R^1 = Et R^2 = Piv (14)
3 R^1 = i-Pr R^2 = TBDMS



4



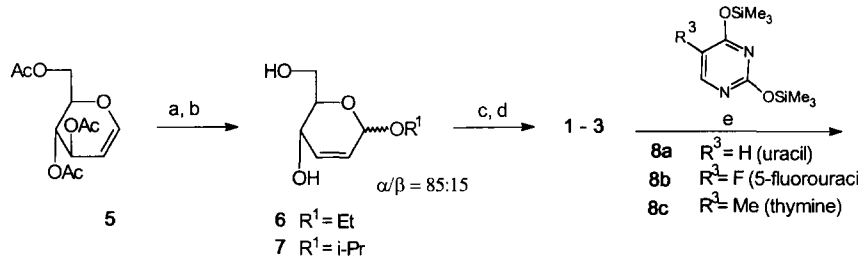
B, nucleobase
type I

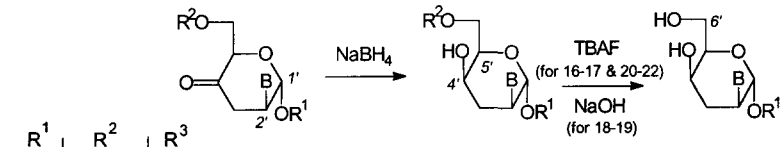
*Fax : (33) 02 43 83 33 66 ; e-mail : rouessac@lola.univ-lemans.fr

Consequently we studied the diastereoselective conjugate addition of *bis*-silylated-uracil, -5-fluorouracil and -thymine to enantiomerically pure α-anomers of pyran-3-ones **1-3** as Michael acceptors, to yield isonucleosides of type **I** that have not been reported previously.

Optically pure pyran-3-ones **1-3** (alkyl *(6-0-protected)*-2,3-dideoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulo-ses) were obtained from tri-*O*-acetyl-D-glucal **5** *via* the Ferrier rearrangement[10] as the key reaction. Thus **5** was converted into ethyl (or isopropyl) pyranosides **1-3** in four steps involving : a) iodine-catalyzed glycosylation of ethyl (or i-propyl) alcohol by the method of Koreeda[11], b) hydrolysis[12] into **6** (or 7), c) selective 6-OH protection with *tert*-butyldimethylsilyl group (TBDMSCl, Et_3N/cat. DMAP)[13] or as a pivalate (PivCl, py.)[14] and d) pyridinium dichromate (PDC) oxidation[14] of 4-OH (sugar nomenclature). α–Anomers of these pyran-3-ones **1-3** (overall yield a →d 55-60%) were purified by silicagel column chromatography.[15]

When pyranones **1-3** were allowed to react in the presence of trimethylsilyl triflate-catalysis as a Lewis acid with *bis*-silylated nucleobases **8a-c** (prepared *in situ* with an excess of *N,O*-bis(trimethylsilyl) acetamide in dry MeCN[16] the Michael adducts **9-15** were formed (Table 1).



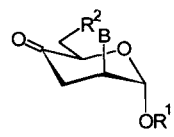


R^1	R^2	R^3			
Et	TBDMS	H	9	16	23
Et	TBDMS	Me	10	17	24
Et	Piv	H	11	18	23
Et	Piv	Me	12	19	24
i-Pr	TBDMS	H	13	20	25
i-Pr	TBDMS	F	14	21	26
i-Pr	TBDMS	Me	15	22	27

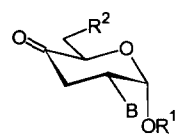
The results displayed in Table 1 show that the d.r.'s of the adducts **9-15** are within the range 89-100 %. TMSOTf[17] allows extremely mild nonbasic Vorbrüggen reaction conditions[18] that gave in each case a very large excess of the diastereomer with the attached base *trans* with respect to the aglycon.[19] An attack by the α side leading to the thermodynamically more stable *cis*-isomer cannot be ruled out as the cause of its appearence in variable proportions in the crude products. The separation of diastereomers (for **10/10'**, **11/11'** and **13/13'**) was complicated by the tendency to give sometimes extensive retro-Michael decomposition on chromatography supports (Merck silica gel 60).

Table 1 — Michael addition of silylated bases on pyran-3-ones **1–3**.

Entry	Pyran-3-one	Silylated base	Adduct*	Yield	d.r. %**
1	**1**	**8a**	**9**	62	100/0
2	**1**	**8c**	**10 (+10')**	83	94/6
3	**2**	**8a**	**11 (+11')**	72	90/10
4	**2**	**8c**	**12**	64	100/0
5	**3**	**8a**	**13 (+13')**	94	89/11
6	**3**	**8b**	**14**	66	100/0
7	**3**	**8c**	**15**	58	100/0



9 - 15



10' 11' 13'
(minor isomers)

* reactions were carried out under 1-3 mmol scale, sugar/base = 1:1 (see ref.20 for a typical procedure)
**diastereomeric ratio based on ^{1}H NMR analysis — see ref. 29 for selected data.

Crude **9-15** were therefore used as such in the subsequent step. Reduction of the carbonyl group with $NaBH_4$ of these adducts furnished a high d.e. in favour of the *cis*-C-4'/C-5' isomer, as revealed by nOe difference spectroscopy.[21] This equatorial reduction to give the axial alcohol predominated in all cases (*cis/trans*-C-4'/C-5' ~ 85/15)[22], thus leading to an inversion at C-4' when comparing to **5**, giving so alkyl 2'3'-dideoxy-2'-pyrimidyl-α-D-*lyxo*-hexopyranosides. Isolated yields of **16-22** after column chromatography range from 45 to 80 %. Cleavage of the silyl-group by tetrabutylammonium fluoride[23] or pivalate by hydroalcoholic sodium hydroxide[24] gave, *in fine*, almost quantitatively, **23-27**.

In summary, this strategy (seven synthetic steps from a commercially available compound) compares well with the few other diastereoselective syntheses[25-28] that give nucleosides mimics with a C-2'/N-1 bond.

Acknowledgment. *We are grateful to Pr. F. Huet for helpful discussions and NMR studies.*

REFERENCES AND NOTES

1. Dueholm, K.L. ; Pedersen, E.B. *Synthesis* **1992**, 1-22.
2. Diaz, Y.; El-Laghdach, A.; Matheu, I.; Castillón, S. *J. Org. Chem.* **1997**, *62*, 1501-1505.
3. Girodier, L. C.; Rouessac, F. P. *Tetrahedron : Asymmetry* **1994**, *5*, 1203-1206.
4. a) Georgiadis, M.P.; Albizati, K.F.; Georgiadis, T.M. *Org. Prep. and Procedures Int.* **1992**, *24*, 95-118. b) Llera, J.-M.; Trujillo, M.; Blanco, M.-E.; Alcudia, F. *Tetrahedron : Asymmetry* **1994**, *5*, 709-716.
5. a) Bolon, P.J.; Sells, T.B.; Nuesca, Z.M.; Purdy, D.F.; Nair, V. *Tetrahedron* **1994**, *50*, 7747- 7764. b) Huryn, DM.; Slubosky, B.C.; Tam, S.Y.; Todaro, L.J.; Weigele, M. *Tetrahedron Lett.* **1989**, *30*, 6259-6262. c) Konkel, M. J.; Vince, R. *Tetrahedron* **1996**, *52*, 799-808 and references therein.
6. a) Eschenmoser, A.; Dobler, M. *Helv. Chim. Acta*, **1992**, *75*, 218-259. b) Hendrix, C.; Rosemeyer, H.; Verheggen, I.; Seela, F.; van Aerschot, A.; Herdewijn, P. *Chemistry Eur. J.* **1997**, *3*, 110-120.
7. a) Knol, J.; Jansen, J.F.G.A.; van Bolhuis, F.; Feringa, B. L. K *Tetrahedron Lett.* **1991**, *32*, 7465-7468. b) van den Heuvel, M.; Cuiper, A.D.; van der Deen, H.; Kellogg, R.M.; Feringa, B.L. *Tetrahedron Lett.* **1997**, *38*, 1655-1658.
8. Horton, D.; Koh, D.; Takagi, Y. *Carbohydr. Res.* **1993**, *250*, 261-274.
9. Herradon, B.; Fenude, E.; Bao, R.; Valverde, S. *J. Org. Chem.* **1996**, *61*, 1143-1147.
10. a) Ferrier, R.J.; Prasad, N. *J. Chem. Soc.* **1969**, **C**, 570-575. b) Ferrier, R. J.; Vethaviyasar, N.; Chizhov, O.S.; Kadentsav, V.I.; Zolotaref, B. M. *Carbohydr. Res.*, **1970**, *13*, 269-280. c) Fraser-Reid, B. *Acc. Chem. Res.* **1985**, *18*, 347-354.
11. Koreeda, M.; Houston, T.A.; Shull, B.K.; Klemke, E.; Tuinman, R.J. *Synlett* **1995**, 90-92.
12. Marco, J.L. *J. Chem. Research (S)* **1988**, 382.

13. Nemoto, H.; Satoh, A.; Fukumoto, K.; Kabuto, C. *J. Org. Chem.* **1995**, *60*, 594-600.
14. Prasad, J.S.; Clive, D.L.J.; da Silva, G.V.J. *J. Org. Chem.* **1986**, *51*, 2717-2721.
15. The Ferrier reaction favors the obtention of α–anomer, chromatographically less polar than the corresponding 2β-anomer (Doboszewski, B.; Blaton, N.; Herdewijn, P. *Tetrahedron Lett.* **1995**, *36*, 1321-1324). Isopropanol has the advantage to give after hydrolysis the α-anomer as a solid directly purified by recrystallization (mp = 103 °C).
16. Card, P.J. *J. Org. Chem.* **1982**, *47*, 2169-2173.
17. Sweeney, J.; Perkins, G. In *Reagents for Organic Synthesis*; Paquette, L. A. Ed.; John Wiley and Sons, Inc.; Chichester, 1995; pp. 5315-5319.
18. Vorbrüggen, H.; Bennua, B. *Chem . Ber.* **1981**, *114*, 1279-1286.
19. Only N-1 nucleosides were observed without N-3 or *O*-alkylation by-products (Luyten, I.; Herdewijn, P. *Tetrahedron* **1996**, *52*, 9249-9262.)
20. General procedure for the preparation of **9-15** : In a flask (100 mL) equipped with a magnetic stirrer and connected to a nitrogen atmosphere, a mixture of nucleobase (3 mmol) in dry acetonitrile (40 mL) was introduced. *N,O*-bis(trimethylsilyl) acetamide (BSA) (2.48 mL, 10 mmol) was added *via* a syringe and the suspension stirred at r.t. until complete dissolution. Pyran-3-one **1-3** (3 mmol) was added over 2 min followed by TMSOTf (1.3 mL, 7 mmol) *via* the syringe. The resulting solution was stirred for 2 h at R.T., then water (60 mL) was added. After concentration *in vacuo*, the aqueous solution was partitioned with EtOAc. After usual work-up, the residue consisted of crude **9-15**.
21. NOE's observed between H-6 and H-1', H-3" and H-2', H-4' ,H-5', were also supported by 2D-NOESY and (^{1}H,^{13}C)-COSY spectra to establish the the relationship of H-atoms in compounds **23-27.** No racemization at C-5' occurs (Eu shift reagent, det. limit ca. 95 % e.e.).
22. Such selective reductions by $NaBH_4$ have been reported. *see* a) Michael, K.; Kessler, H. *Tetrahedron Lett.* **1996,** *37*, 3453-3456. b) Xu, Y.-M.; Zhou, W.-S. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 741-746.
23. Classon, B.; Samuelson, B. *J. Org. Chem.* **1996**, *61*, 3599-3603.
24. Ogilvie K.K.; Iwacka, D.J. *Tetrahedron Lett.* **1973,** 317-319.
25. Kim, J. C.; Dong, E-S.; Kim, S-H.; Park, J-I.; Kim, S-H. *Korean J. Med. Chem.* **1994**, *4*, 111-118.
26. Kakefuda, A.; Shuto, S.; Nagahata, T.; Seki, J.; Sasaki, T.; Matsuda, A. *Tetrahedron* **1994**, *50*, 10167-10182.
27. Ohrui, H.; Waga, T.; Meguro, H. *Biosci. Biotech. Biochem.* **1993**, *57*, 1040-1041
28. Arango, J. H.; Geer, A.; Rodriguez, J.; Young, P. E.; Scheiner, P. *Nucleosides Nucleotides* **1993,** *12*, 773-784.
29. *selected data for one compound of each category* : **9,** oil ; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.71 (br s, 3-H), 7.79 (d, J= 8;2 Hz, 6-H), 5.74 (d, J = 8 Hz, 5-H), 5.11 (dd, J = 8.3, 3.8 Hz 2'-H), 4.95 (s, 1'-H), 4.17 (dd, J = 10.8, 2.9 Hz, 6'-H), 4.15 (m, 5-H), 3.93(dd, J = 10.7, 1.9 Hz, 6"-H), 3.89 (dq, J = 11.7, 7.1 Hz, 7'-H), 3.62 (dq, J = 11.7, 7.1 Hz, 7"-H), 3.1 (dd, J = 17.9, 8.5 Hz, 3"-H), 2.56 (dd, J = 17.9, 3.9 Hz, 3'-H), 1.27 (t, J = 7.1 Hz, Me), 0.9 (s, $SiCMe_3$), 0.1 (s, $SiMe_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.9, 162.8, 150.6, 141.9, 102.9, 97.2, 76.5, 63.9, 62.6, 53.5, 39.3, 25.6, 18.3, 14.5, -5.6. HRMS Found M^+-CMe_3, 341.1167. $C_{14}H_{21}O_6N_2Si$ requires 341.1169. **16** M.p. 170-172°C ; $[\alpha]_D$ = + 101 (c = 0.8, acetone) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.31 (s, 3-H), 8.3 (d, J = 8.2 Hz, 6-H), 5.56 (d, J = 8.2 Hz, 5-H), 4.93 (s, 1'-H), 4.53 (d, J = 4.5 Hz, 2'-H), 4.04 (d, J = 6.8 Hz, 4'-H), 3.99 (dd, J = 11.1, 4.1 Hz, 6'-H), 3.94 (dd., J = 11.0, 3.9 Hz, 6"-H), 3.82 (m, 5'-H), 3.78 (dq, J = 9.6, 7 Hz, 7'-H), 3.53 (dq, J = 9.7, 7 Hz, 7"-H), 2.22 (m, 3'-H), 2.11 (d, J = 15.6 Hz, 3'-H), 1.23 (t, J = 7.1 Hz, 8'-Me), 0.93 (s, $SiCMe_3$), 0.1 (s, $SiMe_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.8, 151.2, 144.6, 100.4, 97.6, 68.8, 65.1, 65, 63, 49.8, 29.8, 25.7, 18.1, 14.9, -5.6. HRMS Found M^+-OEt, 355.1674. $C_{16}H_{27}O_5N_2Si$ requires 355.1689. Analysis : Found : C, 53.96; H, 7.92; N, 7.08%. Calcd for $C_{18}H_{32}N_2O_6Si$: C, 53.98; H, 8.05; N, 6.99%. **27** M.p. 99-100°C ; $[\alpha]_D$ = + 118 (c = 0.4, acetone) ; ^{1}H NMR (400 MHz, DMSO-*d6*) δ = 11.18 (s, 3-H), 7.97 (s), 5.02(d, J= 2.3 Hz, 1'-H), 4.87 (d, J = 2.9 Hz, OH), 4.59 (t, J = 5.7 Hz, OH), 4.2 (m, 2'-H), 3.92 (sept. J = 6.2 Hz, 7'-H), 3.76 (m, 4'-H and 5'-H), 3.58 (m, 6'-H and 6"-H), 2.0 (m, 3"-H), 1.84 (dt, J = 14.6 and 4.2 Hz, 3'-H), 1.73 (s, Me). ^{13}C NMR (100 MHz, DMSO-*d6*) δ = 163.6 (C4), 150.7 (C2), 139.8 (C6), 106.6 (C5), 94.3 (C1'), 71.7 (C5'), 67.8 (C$\underline{H}$$Me_2$), 62.1 (C4'), 59.9 (C6'), 50.6 (C2'), 30.3 (C3'), 22.8 & 20.9 (Me/Me), 12.0 (C7'). HRMS Found M^+-Me_2CHOH, 254.0902. $C_{11}H_{14}O_5N_2$ requires 254.0903. Analysis : Found : C, 53.29; H, 7.06; N, 8.83%. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.05; N, 8.91%.

(*Received in France* 1 *April* 1997; *accepted* 2 *May* 1997)