Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 8261–8263

TETRAHEDRON LETTERS

A stereoselective route to bioactive nucleotide phosphonate analogs

Monica Bubenik,* Patrice Préville, Josée Dugas, Giorgio Attardo and Laval Chan

Shire BioChem Inc., 275 Armand-Frappier Blvd., Laval, Québec, Canada, H7V 4A7

Received 8 August 2003; revised 9 September 2003; accepted 10 September 2003

Abstract—Recently we have reported a novel class of tetrahydrofuran phosphonates of which *trans* guanine nucleotide analog **1a** showed potent antiviral activity as well as antitumor activity. In this paper we describe a stereoselective route where the key step involves an iodoetherification of a α-hydroxyphosphonate to generate the *trans* tetrahydrofuran with high stereoselectivity. The same intermediate **2** was also used to access the key intermediate for the *cis* analog **1b**.

Nucleotide phosphonates are widely used therapeutic agents known to have a broad spectrum of antiviral activity, with several reported as having antitumor activity.[1] Upon intracellular conversion to the active mono- and diphosphates by cellular kinases, they are incorporated into DNA during replication, or repair, leading to termination of DNA chain elongation. Recently we have reported a novel class of tetrahydrofuran phosphonates of which the *trans* and *cis* guanine analogs **1a** and **1b**, showed potent HCMV activity[2] and antitumor activity (Fig. 1).[3]

Preliminary work led us to further evaluate the potential of **1a** as an antitumor agent by examining its in vivo activity and characterizing its mechanism of action.[3a] In vivo, phosphonate **1a** was active on a broad panel of human tumor xenografts (Caki-1, HT-29, DU 145, COLO 205, CCRF-CEM). In all tumor models tested, a significant tumor growth inhibition was noted. It was shown that phophonate **1a** exerts its antitumor activity by arresting DNA synthesis and blocking cell division at the S-phase of the cell cycle. In order to further evaluate **1a**, an efficient route for its preparation was required. In earlier work, **1a** and **1b** were prepared by installing the phosphonate moiety via a titanium chloride catalyzed Arbuzov reaction of anomeric acetates with a triakylphosphite resulting in a 1:1 mixture of *cis* and *trans* phosphonates.[2a] Incidentally, we observed that using TMSI as a Lewis acid gave a 2:1 ratio, but in favor of the *cis* isomer.

An elegant approach towards the stereocontrolled construction of *cis*-2,5-disubsituted tetrahydrofurans was described by Bartlett[4], who studied the iodoetherification of olefinic ethers and how electronic effects influenced the selectivity of the reaction. When R^1 is H, the *trans* tetrahydrofuran is preferentially formed, especially when the group adjacent to the hydroxy is large (Scheme 1). The *cis* isomer is highly favoured when R^1

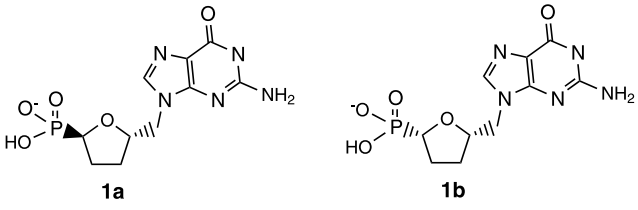
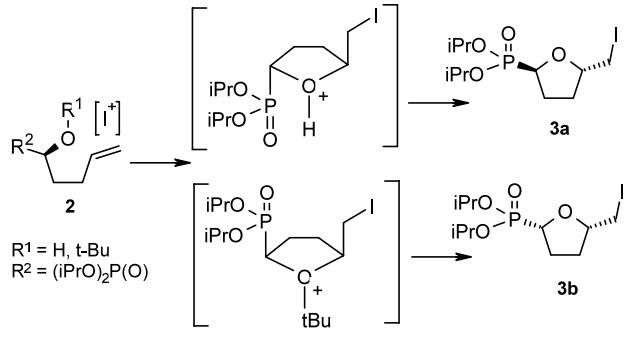


Figure 1.



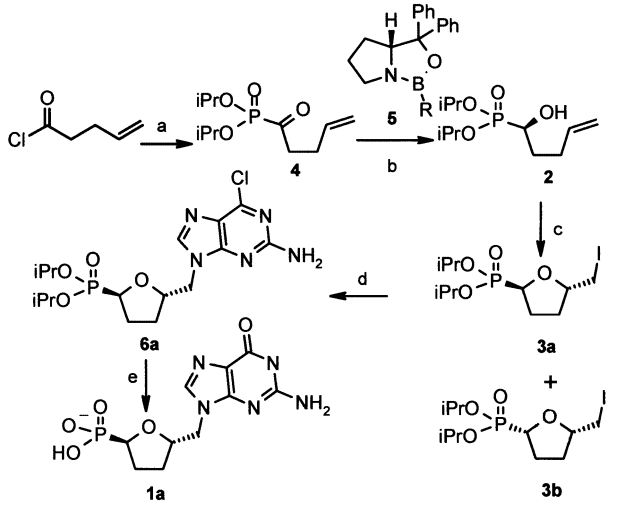
Scheme 1.

* Corresponding author. Tel.: 514-286-1336; fax: 514-956-1473; e-mail: monicabubenik@sympatico.ca

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.071

is a substituted benzyl with the appropriate electronic characteristics to provide optimal stabilization of the oxonium transition state. Subsequent work by Marek and Normant, showed that very high diastereoselectivity for this reaction can also be obtained with a bulky *t*-butyl ether.[5] Similarly, we anticipated that α-hydroxyphosphonate **2** would be a common intermediate for the preparation of both **1a** and **1b** as the phosphonate group (R^2) would provide the bulk to induce the cyclization to the *trans* or *cis* tetrahydrofuran.

The requisite chiral α-hydroxyphosphonate was obtained according to Scheme 2. Ketophosphonate **4** was prepared in 73% yield by Arbuzov reaction of the acyl chloride with triisopropylphosphite.[6] Following the work done by Meier and Laux, the α-hydroxyphosphonate was obtained by an enantioselective reduction of the ketophosphonate by means of catalytic amounts of oxazaborolidine[7] with catecholborane as the reducing agent.[8] By varying the solvent and temperature as shown in Table 1, the highest enantioselectivity and



Scheme 2. *Reagents and conditions*: (a) $P(OiPr)_3$, 73%; (b) catecholborane, **5** (R = Me), toluene, −20°C, 85%; (c) *N*-iodosuccinimide, $ClCH_2CH_2Cl$, 0°C, 71% **3a**, 8% **3b**; (d) 2-amino-6-chloropurine, Cs_2CO_3, DMF, 90°C, 50%; (e) (i) TMSBr, rt. (ii) 10% HCl (aq.), reflux (iii) NH_4OH, 70%.

Table 1. Reductions of ketophosphonate **4** with catecholborane and oxazaborolidine **5**

Catalyst **5** (R)	Solvent	Temp. (°C)	Ratio (*R*:*S*)[a]
Me	Toluene	−20	14:1
Me	Toluene	0	14:1
Me	Toluene	−78	2:1
Me	Toluene	−40	7:1
Me	THF	−20	14:1
Me	THF	0	14:1
Me	Diethyl ether	−20	7:1
Me	DME	−20	14:1
Ph	Toluene	−20	2:1

[a] Determined by chiral GC.

most reproducible yields were observed when **4** was reacted with catecholborane in toluene at −20°C in the presence of 10 mol% of (R)-5,5-diphenyl-2-methyl-3,4-propano-1.3.2-oxazaborolidine **5** (R = Me).[9] The stereochemical outcome of the reduction is consistent with Corey's model, where the phosphonyl group represents the large group and the hydride of the reducing agent attacks the carbonyl from the *si*-face leading to the (R)-configuration at the new stereogenic center.[10] Using oxazaborolidine catalyst **5**, where (R = Ph), no enhancement in the enantioselectivity of the reduction was observed.

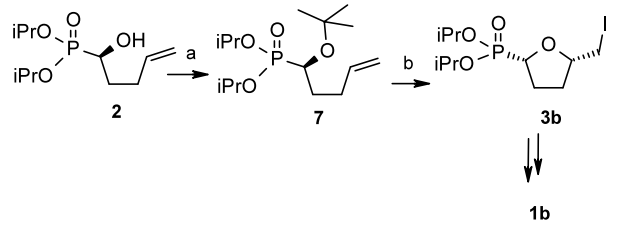
The iodoetherification[4] reaction was performed by reaction with *N*-iodosuccinimide[11] in various solvents (Table 2).[12] This is, to the best of our knowledge, the first example of an iodoetherification of a γ-hydroxyalkene having a heteroatom directly substituted on the carbon bearing the hydroxy group. Iodoetherification proceeded in 1,2-dichloroethane with the highest selectivity. Use of other solvents resulted in poorer selectivities. As shown in Scheme 1, electrophilic addition gives rise to an oxonium ion transition state where the bulky phosphonate prefers to be *anti* to the iodoalkyl moiety so as to minimize steric interaction. Iodide **3a** was then converted to the 6-chloro-purine **6a** and ultimately phosphonate **1a** according to procedures described previously (Scheme 2).[3b] Compound **1a** was identical in all respects to authentic material synthesized previously.[3b]

In order to access the *cis* tetrahydrofuran **3b**, alcohol **2** was converted to the corresponding *t*-butyl ether **7** by reaction with *t*-butyl 2,2,2-trichloroacetimidate in the presence of a catalytic amount of boron trifluoride

Table 2. Iodoetherifications of α-hydroxyphosphonate **2**

Solvent	*trans* (**3a**)/*cis* (**3b**) ratio[a]
THF	4.5:1
EtOAc	4:1
NMP	2.8:1
CH_3CN	2.8:1
Benzene	1.9:1
AcOH	2.2:1
CH_2Cl_2	6.2:1
$CHCl_3$	2:1
$ClCH_2CH_2Cl$	11.4:1

[a] Determined by ^{31}P NMR recorded at 400 MHz in $CDCl_3$.



Scheme 3. *Reagents and conditions*: (a) *t*-Butyl 2,2,2-trichloroacetimidate, $BF_3{\cdot}Et_2O$, cyclohexane, rt, 67%; (b) I_2, CH_3CN, −20°C, 41%.

etherate (Scheme 3).[13] In accordance with the Normant procedure[5], reaction of compound **7** with iodine in acetonitrile gave exclusively the *cis* isomer as determined by ^{31}P NMR.[14] Electrophilic addition of iodine gives an oxonium transition state where the large *t*-butyl group adopts an *anti* orientation to both the phosphonate and the iodoalkyl moiety (Scheme 1).

In summary, we have demonstrated simple access to the *trans* nucleotide phosphonate and a formal synthesis of the *cis* isomer through a common α-hydroxyphosphonate intermediate in a diastereoselective manner. The intermediate is easily obtained from an enantioselective catecholborane reduction of the corresponding ketophosphonate under oxazaborolidine catalysis. The key iodoetherification step represents the first reported for this type of γ-hydroxyalkene.

Acknowledgements

We thank Thérèse Godbout for her help in the preparation of this manuscript.

References

1. (a) Valerianova, M.; Vortuba, I.; Holy, A.; Mandys, V.; Otova, B. *Anticancer Res.* **2001**, *21*, 2057; (b) Pisarev, V. M.; Lee, S.; Connelly, M. C.; Fridland, A. *Mol. Pharmacol.* **1997**, *52*, 63; (c) Elliot, R. D.; Rener, G. A.; Riordan, J. M.; Secrist, J. A.; Bennett, L. L.; Parker, W. B.; Montgomery, J. A. *J. Med. Chem.* **1994**, *37*, 739.
2. (a) Nguyen-Ba, P.; Turcotte, N; Yuen, L.; Bédard, J.; Quimpère, M.; Chan, L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3561; (b) Bédard, J.; May, S.; Lis, M.; Tryphonas, L; Drach, J.; Huffman, J.; Sidwell, R.; Chan, L.; Bowlin, T.; Rando, R. *Antimicrob. Agents. Chemother.* **1999**, *43*, 557.
3. (a) Leblond, L.; Attardo, G.; Hamelin, B.; Bouffard, D. Y.; Nguyen-Ba, N.; Goudreau, H. *Mol. Cancer Ther.* **2002**, *1* (9), 737; (b) Bubenik, M.; Rej, R.; Nguyen-Ba, N.; Attardo, G.; Oeullet, F.; Chan, L. *Bioorg Med. Chem. Lett.* **2002**, *12*, 3063.
4. Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.
5. Marek, I.; Lefrancois, J.-M; Normant, J-F. *Tetrahedron Lett.* **1992**, *33*, 1747.
6. Arbuzov, B. A.; Zoroatrova, V. M.; Tudrin, G. A.; Fuzhenkova, A. V. *Izv. Akad. Nauk S.S.S.R. (Trans.)* **1974**, *23*, 2541.
7. The catalyst was prepared according to procedures descibed in: Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751.
8. Meier, C.; Laux, W. H. G. *Tetrahedron* **1996**, *52*, 589.
9. Typical procedure for preparation of **2**: Catechol borane (12.8 g, 106.5 mmol, 1.1 equiv.; neat diluted to 1 molar in THF) was added slowly over 10 minutes at −78°C to a toluene solution (150 mL) of ketophosphonate **4** (24.0 g, 96.8 mmol, 1.0 equiv.) and oxazaborolidine catalyst **5** (5.0 mL of 1.9 M/toluene, 9.7 mmol, 0.1 equiv.) and the reaction mixture stirred for 10 minutes before warming up to −20°C for 30 minutes and 4.5 hours at −5°C. Methanol (5 mL) was added and diluted with 10% sodium bicarbonate. Solvents were evaporated and diluted with ethyl acetate. The organic layer was washed with 10% sodium bicarbonate, brine and dried over magnesium sulfate, filtered and evaporated to dryness. The crude was purified by flash chromatography (20–75% ethyl acetate in hexane) giving **2** (20.56 g, 85%). ^1H NMR (400 MHz, $CDCl_3$): 5.79 (m, 1H), 5.01 (m, 2H), 4.72 (m, 2H), 3.79 (m, 1H), 2.33 (m, 1H), 2.17 (m, 1H), 1.85–1.70 (m, 2H); ^{31}P NMR (400 MHz, CDCl3): 24.5 ppm.
10. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986.
11. Cyclization with iodine resulted in poor selectivities and yields.
12. Typical procedure for preparation of **3a**: *N*-iodosuccinimide (657 mg, 2.92 mmol, 1.0 equiv.) was added in 4 portions at 0°C to a 1,2-dichloroethane solution (10 mL) of hydroxyphosphonate **2** (730 mg, 2.92 mmol, 1.0 equiv.) and the reaction mixture stirred at 0°C until TLC indicated completion of reaction (approx. 1 h). The solvent was evaporated and crude purified by column chromatography (15–30% acetone in hexane) giving **3a** (767 mg, 71%) and **3b** (86 mg, 8%). **3a**: ^1H NMR (400 MHz, $CDCl_3$): 4.75 (m, 2H), 4.21 (m, 1H), 4.15 (m, 1H), 3.25 (m, 1H), 3.17 (m, 1H), 2.30–2.15 (m, 3H), 1.67 (m, 1H), 1.30 (m, 12H); ^{31}P NMR (400 MHz, $CDCl_3$): 21.8 ppm. **3b**: ^1H NMR (400 MHz, $CDCl_3$): 4.75 (m, 2H), 4.25 (m, 1H), 4.12 (m, 1H), 3.32 (m, 1H), 3.20 (m, 1H), 2.30–2.10 (m, 3H), 2.00 (m, 1H), 1.35 (m, 12H).; ^{31}P NMR (400 MHz, $CDCl_3$): 21.6 ppm.
13. Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483–2486.
14. Compound **3b** was confirmed to be *cis* by spiking a mixture of **3a** and **3b** (11:1 mixture obtained by cyclization of **2**) with **3b** (obtained from cyclization of **7**) and comparing ^{31}P NMR intensities.