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COMMUNICATION

Modular synthesis of 1-α- and 1-β-(indol-2-yl)-2′-deoxyribose *C*-nucleosides†

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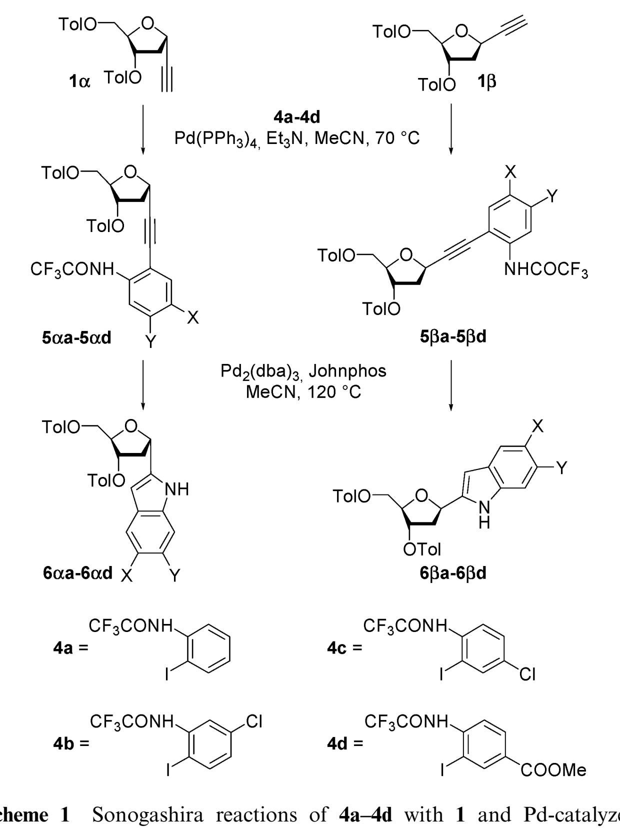
A simple two-step method for the selective preparation of anomerically pure 1α- and 1β-(indol-2-yl)deoxyribose derivatives was developed. The synthesis was based on the Sonogashira reaction of 1α- and 1β-ethynyldeoxyribose and 2-haloanilines followed by a Pd-complex catalyzed cyclization to the corresponding indolyldeoxyribosides.

C-Nucleosides[1] are an important class of compounds with potent biological activities and applications in chemical biology. Development of modular methodologies[2] for their synthesis is of continuing interest in our laboratories. Nitroindoles (in *N*-nucleosides) are used[3] as universal nucleobases that do not discriminate the opposite base in DNA or for studying base-stacking interactions.[4] Several 3-[5] and 2-linked[6,7] indole *C*-ribo and -deoxyribonucleosides have been prepared, usually by addition of highly reactive lithiated protected indoles to sugar lactones or hemiacetals followed by reduction or Mitsunobu cyclization. Indol-3-yl *C*-deoxyribonucleoside has been used[5a] as a base substitution in DNA, whereas unsubstituted indol-2-yl-2′-deoxyribonucleoside has been utilized[7] as an artificial base in extension of the genetic alphabet, taking advantage of the minor-groove interaction of its NH. Difficult syntheses and limited access to series of highly substituted derivatives (especially those bearing reactive functional groups incompatible with organolithium chemistry) by the previously known methods[5–7] prevent wider studies of potential applications of indole *C*-nucleosides in chemical biology.

In the past decade this laboratory and others have shown that 1α- and 1β-alkynyl deoxyribose derivatives could be used as suitable synthetic building blocks for the preparation of various *C*-1-substituted derivatives.[8] As typical examples may serve syntheses of *C*-aryl derivatives by using Rh-[9] or Ru-catalyzed[10] cyclotrimerization, various substituted alkynyl derivatives by using the Sonogashira coupling or other procedures,[11–13] and triazoles by click-chemistry.[14,15] The main advantage of these procedures stemmed from the fact that the corresponding 1α- and 1β-ethynyl derivatives can be prepared in anomerically pure forms.

It has been shown in numerous examples that terminal alkynes could serve as building blocks for the synthesis of variously substituted indoles by coupling them with suitably substituted 2-haloanilines.[16,17] On the other hand it is fair to note that most of the alkyne couplings were carried out with phenylacetylenes and not with alkyl-substituted acetylenes. Nonetheless, we envisioned that the desired indolyldeoxyribosides could be also approached by the same strategy, *i.e.* by coupling of ethynyldeoxyribosides with 2-haloanilines.

The first task was the development of the high yielding Sonogashira reaction of 1-ethynyl-2′-deoxyribose with haloanilines, because undesirable homocoupling to give 1,3-diynes was observed by us[1] as well as by others.[11] The coupling of 1α-ethynyldeoxyribose **1α** with *N*,*N*-dimethyl-2-iodoaniline under various conditions (Scheme 1) was chosen as a model reaction to tune the reaction conditions.



Scheme 1 Sonogashira reactions of **4a–4d** with **1** and Pd-catalyzed cyclizations.

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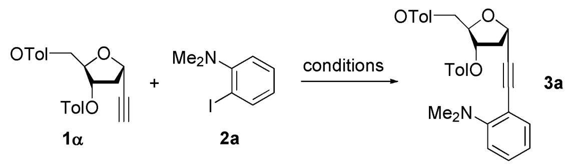
† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of all new compounds and some experimental details. See DOI: 10.1039/c1ob05844d

Table 1 Pd-catalyzed cross-coupling of **1α** with **2a**



Entry	Catalyst (5 mol%)	Cocatalyst	Base	Solvent	Yield (%)[a]
1	$PdCl_2(PPh_3)_2$	CuI	Et_3N	MeCN	25
2	$PdCl_2(PPh_3)_2$	CuI	Et_3N	THF	0
3	$PdCl_2(MeCN)_2$[b]	—	Cs_2CO_3	MeCN	4
4	$PdCl_2(PPh_3)_2$	—	piperidine	—	27
5	$Pd(PPh_3)_4$	—	piperidine	—	26
6	$Pd(PPh_3)_4$	—	piperidine	THF	26
7	$Pd(PPh_3)_4$	—	piperidine	DMF	44
8	$Pd(PPh_3)_4$	—	piperidine	MeCN	52

[a] Isolated yields. [b] Ligand: 2-dicyclohexylphosphino-2,4,6-triisopropylbiphenyl (15 mol.%)

The coupling (Table 1) under classical conditions ($PdCl_2(PPh_3)_2$, CuI, Et_3N) proceeded in MeCN to yield **3α** in only 25% yield (Entry 1). When the reaction was carried out in THF, it did not proceed (Entry 2). An attempt to apply the previously used[13] copper-free conditions in the presence of a sterically hindered phosphine and caesium carbonate[18] gave the title compound only in a marginal yield of 4% (Entry 3). The change of a base to piperidine gave rise to the title compound again in low yield of 27% (Entry 4). The use of $Pd(PPh_3)_4$ either in pure piperidine or in a mixture with THF gave **3α** in 26% yields (Entries 5 and 6). A slight increase in yield (44%) was observed in DMF (Entry 7). Finally, the best yield of the title compound (52%) was achieved in MeCN with piperidine as a base (Entry 8).

With the required product **3α** on hand the intramolecular cyclization under Larock's conditions (I_2, CH_2Cl_2) was attempted.[19] Unfortunately, the cyclization did not proceed and the starting material was recovered intact.

In order to achieve our goal, we decided to change the haloaniline **2** to the protected 2-iodophenyltrifluoroacetamides **4a–4d**, prepared from the corresponding anilines and $(CF_3CO)_2O$, and use them in a similar reaction.[16b] However, the above used conditions proved not to be suitable for Sonogashira couplings of **1α** and **1β** with **4a–4d** and the best yields were obtained with a combination of $Pd(PPh_3)_4$/Et_3N/MeCN/70 °C (Table 2).

The Sonogashira reaction of **1α** and **1β** (Table 1) with a simple acetamide **4a**, two chloro derivatives **4b** and **4c**, carboxyacetamide **4d** furnished the corresponding alkynyldeoxyribose derivatives **5αa–5αd** (Entries 1–4) and **5βa–5βc** (Entries 5–8) in reasonable isolated yields.

Although it was reported that spontaneous addition of the N–H bond to the triple bond in 2-alkynylaniline derivatives followed the Sonogashira coupling forming the indole scaffold, we did not observe such a process in any case. Thus it was necessary to find suitable conditions for the cyclization. After a number of experiments it was found that in the presence of $Pd_2(dba)_3·CHCl_3$ (5 mol%)/(2-biphenyl)di-*t*-butylphosphine (Johnphos, 20 mol%)/120 °C/5 h and then rt (usually 18–20 °C) overnight the cyclization took place.

Ensuing workup of the reaction mixtures proceeded with spontaneous removal of the trifluoroacetyl group yielding the desired indolyl derivatives **6**.

The cyclization of **5αa** to **6αa** proceeded with a very nice yield of 81% (Entry 1). Cyclizations of **5αb–5αd** gave indoles **6αb–6αd** in 57, 48, and 40% isolated yields, respectively (Entries 2–4). Cyclizations of the beta anomeric substrates **5βa–5βc** gave indoles **6βa–6βc** in 51, 42, and 43% isolated yields, respectively (Entries 5–7). Only in the case of **5βd**, was **6βd** obtained in a low yield of 19% (Entry 8)

The last step was the deprotection of the toluoylated indolyldeoxyribosides. Since the removal of the toluoyl protective group under basic conditions is a well established procedure, we decided to use the same method: samples were treated with a solution of NaOMe in MeOH 12 h at rt. The deprotection proceeded uneventfully in all cases with both anomers, **6α** and **6β**, yielding the corresponding free indolyldeoxyriboses **7α** and **7β** (Fig. 1). The isolation had to be carried out by using preparative TLC and the yields were in the range of 42–76%, which was typical for this method.

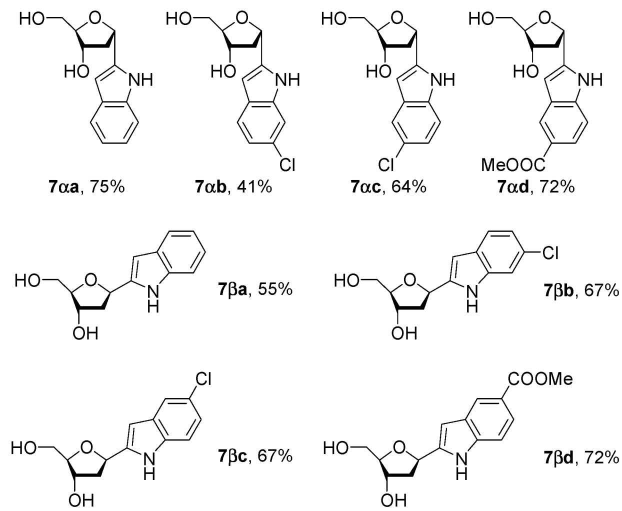


Fig. 1 The prepared free indolyldeoxyriboses **7α** and **7β**.

In summary we have developed a novel methodology suitable for the selective synthesis of α- and β-anomeric indolyldeoxyriboses from easily accessible starting 1α- and 1β-ethynyldeoxyribosides.[20] This method is quite general and modular with respect to the substitution pattern of the aniline leading to diverse types of indolyl-*C*-nucleosides. Moreover, it is expected that this method could be extended to other *C*-ethynylsaccharides leading to analogues of naturally occurring indole glycoside antibiotics[21] and indolyl *C*-mannosides.[22]

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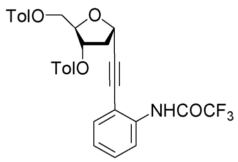
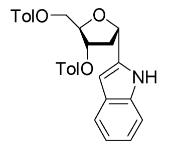
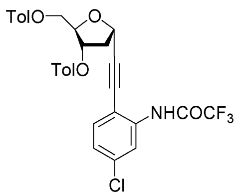
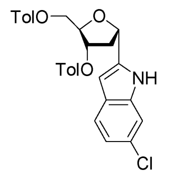
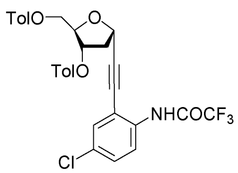
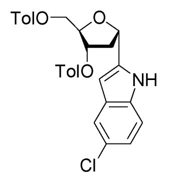
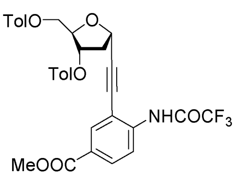
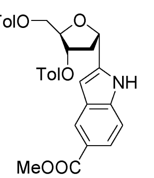
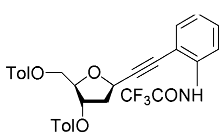
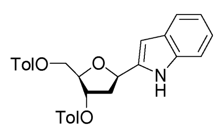
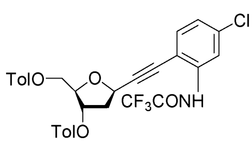
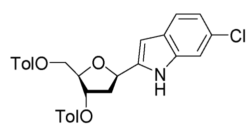
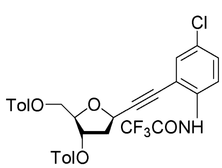
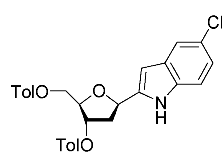
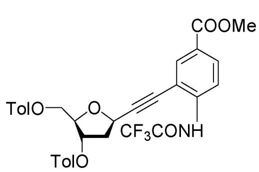
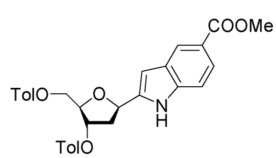
Table 2 Cross-coupling of **1** with **4** to **5** and cyclization to **6**

Entry	Iodoaniline **4**	Product **5**		Yield (%)[a]	Product **6**		Yield (%)[a]
1	**4a**		**5αa**	77		**6αa**	81
2	**4b**		**5αb**	55		**6αb**	57
3	**4c**		**5αc**	47		**6αc**	48
4	**4d**		**5αd**	28		**6αd**	40
5	**4a**		**5βa**	77		**6βa**	51
6	**4b**		**5βb**	62		**6βb**	42
7	**4c**		**5βc**	57		**6βc**	43
8	**4d**		**5βd**	33		**6βd**	19

[a] Isolated yields.

Notes and references

1 Reviews: (*a*) J. Štambaský, M. Hocek and P. Kočovský, *Chem. Rev.*, 2009, **109**, 6729; (*b*) M. F. A. Adamo and R. Pergoli, *Curr. Org. Chem.*, 2008, **12**, 1544; (*c*) Q. P. Wu and C. Simons, *Synthesis*, 2004, 1533.

2 Selected recent examples: (*a*) M. Urban, R. Pohl, B. Klepetářová and M. Hocek, *J. Org. Chem.*, 2006, **71**, 7322; (*b*) N. Joubert, R. Pohl, B. Klepetářová and M. Hocek, *J. Org. Chem.*, 2007, **72**, 6797; (*c*) J. Bárta, R. Pohl, B. Klepetářová, N. P. Ernsting and M. Hocek, *J. Org. Chem.*, 2008, **73**, 3798; (*d*) M. Štefko, L. Slavětínská, B. Klepetářová and M. Hocek, *J. Org. Chem.*, 2010, **75**, 442; (*e*) T. Kubelka, L. Slavětínská, B. Klepetářová and M. Hocek, M., *Eur. J. Org. Chem.*, 2010, 2666.

3 (*a*) D. Loakes, *Nucleic Acids Res.*, 2001, **29**, 2437; (*b*) D. Loakes, *Nucleic Acids Res.*, 1995, **23**, 2362; (*c*) D. Loakes and D. M. Brown, *Nucleic Acids Res.*, 1994, **22**, 4039.

4 (*a*) B. A. Schweitzer and E. C. Kool, *J. Am. Chem. Soc.*, 1995, **117**, 1864; (*b*) K. M. Guckian, B. A. Schweitzer, R. X.-F. Ren, C. J. Shiels, D. C. Tahmessebi and E. C. Kool, *J. Am. Chem. Soc.*, 1996, **118**, 8182; (*c*) K. M. Guckian, B. A. Schweitzer, R. X.-F. Ren, C. J. Shiels, D. C. Tahmessebi and E. C. Kool, *J. Am. Chem. Soc.*, 2000, **122**, 2213.

5 (*a*) J. Barbaric, C. Wanninger-Weiss and H.-A. Wagenknecht, *Eur. J. Org. Chem.*, 2009, 364; (*b*) M. Cornia, G. Casiraghi and L. Zetta, *J. Org. Chem.*, 1991, **56**, 5466.

6 (*a*) W. He, H. Togo and M. Yokoyama, *Tetrahedron Lett.*, 1997, **38**, 5541; (*b*) D. Guianvarc'h, J.-L. Fourrey, M. E. T. H. Dau, V. Guerineau and R. Benhida, *J. Org. Chem.*, 2002, **67**, 3724.

7 S. Matsuda, A. A. Henry, P. G. Schultz and F. E. Romesberg, *J. Am. Chem. Soc.*, 2003, **125**, 6134.

8 (*a*) H. Wamhoff and H. Warnecke, *ARKIVOC*, 2001, 95; (*b*) M. Takase, T. Morikawa, H. Abe and M. Inouye, *Org. Lett.*, 2003, **2**, 625.

9 For synthesis, see: (*a*) P. Novák, R. Pohl, M. Hocek and M. Kotora, *Org. Lett.*, 2006, **8**, 2051; (*b*) P. Novák, S. Číhalová, M. Otmar, M. Hocek and M. Kotora, *Tetrahedron*, 2008, **64**, 5200.

10 (*a*) Y. Yamamoto, T. Saigoku, T. Ohgai, H. Nishiyama and K. Itoh, *Chem. Commun.*, 2004, 2702; (*b*) Y. Yamamoto, T. Saigoku, H. Nishiyama, T. Ohgai and K. Itoh, *Org. Biomol. Chem.*, 2005, **3**, 1768; (*c*) Y. Yamamoto, K. Yamashita, T. Hotta, T. Hashimoto, M. Kikuchi and H. Nishiyama, *Chem.–Asian J.*, 2007, **2**, 1388.

11 M. F. A. Adamo and R. Pergoli, *Org. Lett.*, 2007, **9**, 4443.

12 D. Heinrich, T. Wagner and U. Diederichsen, *Org. Lett.*, 2007, **9**, 5311.

13 T. Bobula, M. Hocek and M. Kotora, *Tetrahedron*, 2010, **66**, 530.

14 Y. Doi, J. Chiba, T. Morikawa and M. Inouye, *J. Am. Chem. Soc.*, 2008, **130**, 8762.

15 M. Nakahar, T. Kuboyama, A. Izawa, Y. Hari, T. Imanishi and S. Obika, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3316.

16 For leading references see: (*a*) G. W. Kabalka, L. Wang and R. M. Pagni, *Tetrahedron*, 2001, **57**, 8017; (*b*) F. S. Cacchi, G. Fabrizi and L. M. Parisi, *Org. Lett.*, 2003, **5**, 3843; (*c*) P. Korakas, S. Chaffee, J. B. Shotwell, P. Duque and J. L. Wood, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 12054; (*d*) B. Z. Lu, W. Zhao, H.-X. Wei, M. Dufour, V. Farina and C. H. Senanayake, *Org. Lett.*, 2006, **8**, 3271; (*e*) H. Sakai, K. Tsutsumi, T. Morimoto and K. Kakiuchi, K., *Adv. Synth. Catal.*, 2008, **350**, 2498; (*f*) P. Li, L. Wang, M. Wang and F. You, *Eur. J. Org. Chem.*, 2008, 5946; (*g*) N. Sakai, K. Annaka, A. Fujita and T. Konakahara, *J. Org. Chem.*, 2008, **73**, 4160; (*h*) K. C. Majumdar, S. Samanta and B. Chattopadhaya, *Tetrahedron Lett.*, 2008, **49**, 7213; (*i*) E. Tyrrell, L. Whiteman and N. Williams, *Synthesis*, 2009, 829; (*j*) K. Okuma, J. Seto, K. Sakaguchi, S. Ozaki, N. Nagahora and K. Shioji, *Tetrahedron Lett.*, 2009, **50**, 2943; (*k*) R. Sanz, V. Guilarte and A. Peréz, *Tetrahedron Lett.*, 2009, **50**, 4423; (*l*) A. Carpita and A. Ribecai, *Tetrahedron Lett.*, 2009, **50**, 6877; (*m*) R. Sanz, V. Guilarte and N. Garcia, *Org. Biomol. Chem.*, 2010, **8**, 3860; (*n*) A. Boyer, N. Isono, S. Lackner and M. Lautens, *Tetrahedron*, 2010, **66**, 6468.

17 For reviews, see: (*a*) G. Battistuzzi, S. Cacchi and G. Fabrizi, *Eur. J. Org. Chem.*, 2002, 2671; (*b*) K. Krüger, A. Tillack and M. Beller, M., *Adv. Synth. Catal.*, 2008, **350**, 2153; (*c*) M. M. Heravi and S. Sadjadi, *Tetrahedron*, 2009, **65**, 7761.

18 D. Gelman and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2003, **42**, 5993.

19 D. W. Yue, T. L. Yao and R. C. Larock, *J. Org. Chem.*, 2006, **71**, 62.

20 A typical procedure: synthesis of **6ba**. To a solution of **5ba** (262 mg, 0.46 mmol) in MeCN (3 mL) was added $Pd_2(dba)_3{\cdot}CHCl_3$ (17.3 mg, 0.016 mmol), (2-biphenyl)di-*t*-butylphosphine(41 mg, 0.14 mmol) and K_2CO_3 (200 mg) and the reaction mixture was heated to 120 °C for 5 h. Then it was stirred at rt (usually 18–20 °C) overnight. Work-up followed by column chromatography on silica gel yielded 111 mg (51%) of the title compound as a yellowish syrup: ^{1}H NMR (600 MHz, C_6D_6) δ 8.57 (s, 1H), 8.08 (dd, J = 30.9, 8.1 Hz, 4H), 7.66 (d, J = 7.6 Hz, 1H), 7.25–7.18 (m, 3H), 6.97 (d, J = 7.9 Hz, 2H), 6.80 (d, J = 8.0 Hz, 2H), 6.33 (bs, 1H), 5.35 (d, J = 5.7 Hz, 1H), 5.30 (dd, J = 10.4, 5.5 Hz, 1H), 4.54 (dd, J = 11.6, 5.7 Hz, 1H), 4.43–4.34 (m, 2H), 2.19 (dd, J = 13.5, 5.1 Hz, 1H), 2.13–2.05 (m, 1H), 2.02 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (151 MHz, C_6D_6) δ 167.27, 166.28, 144.47, 144.27, 138.31, 137.24, 130.50 (2C), 130.45 (2C), 129.84 (2C), 129.82 (2C), 129.40, 128.31, 128.05, 122.63, 121.27, 120.57, 111.88, 100.28, 83.97, 77.58, 76.30, 65.31, 40.44, 21.80, 21.68; IR (KBr) 3352, 2949, 1715, 1610, 1456, 1271, 1178, 1105, 752 cm^{-1}; HRMS calcd for $C_{29}H_{27}NO_5$(M + H) 470.1962, found 470.1964.

21 (*a*) H. Tohyama, S. Miyadoh, M. Ito, T. Shomura, T. Ito, T. Ishikawa and T. Kojima, *J. Antibiot.*, 1984, **37**, 1144; (*b*) J. G. Buchanan, J. Stoddart and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1417.

22 (*a*) A. Loeffler, M.-A. Doucey, A. M. Jansson, D. R. Mueller, T. de Beer, D. Hess, M. Meldal, W. J. Richter, J. F. G. Vliegenthart and J. Hofsteenge, *Biochemistry*, 1996, **35**, 12005; (*b*) T. de Beer, J. F. G. Vliegenthart, A. Loeffler and J. Hofsteenge, *Biochemistry*, 1995, **34**, 12005; (*c*) T. Nishikawa, Y. Koide, A. Kanakubo, H. Yoshimura and M. Isobe, *Org. Biomol. Chem.*, 2006, **4**, 1268–1277.