ORGANIC LETTERS

2002
Vol. 4, No. 4
565−568

An Efficient Organometallic Approach to New Carbocyclic Nucleoside Analogues†

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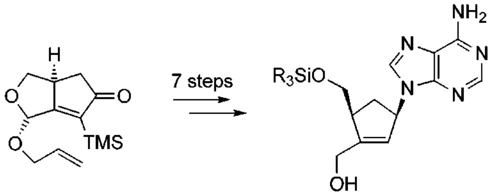
Received December 5, 2001

ABSTRACT



A general synthetic approach to monoprotected carbocyclic nucleoside analogues, having the nucleobase attached to a 3-hydroxymethyl-4-trialkylsilyloxymethyl-cyclopent-2-en-1-yl scaffold, was developed. A (racemic) key intermediate was prepared by a cobalt-mediated Pauson–Khand reaction. In the course of the further synthesis, the introduction of the nucleobase was achieved with complete regio- and diastereoselectivity through a palladium-catalyzed allylic substitution.

As a result of their interesting pharmacological properties, carbocyclic nucleoside analogues have received much attention in recent years.[1] Besides the antibiotic and antitumor active natural products aristeromycin (**1**) and neplanocin A (**2**), especially synthetic antiviral agents such as carbovir (**3**) and abacavir (**4**) have convincingly demonstrated the great potential of this class of compounds (Figure 1). Accordingly, their synthesis has been intensely investigated in several laboratories.[1,2] However, the elaboration of short, efficient, and flexible synthetic routes especially to new types of carbocyclic nucleoside analogues still represents an important challenge.

Recently, we became interested in nucleoside analogues of type **5** (NB = nucleobase) because such compounds may exhibit interesting biological activities and, in addition, would represent promising building blocks for artificial oligonucleotides[3] and other complex molecules (e.g., hybrids with different pharmacophoric units), which are of great biological interest.

We here report an efficient synthetic entry to compounds of type **5** following a novel strategy, which is centrally based on transition metal organic chemistry. The synthesis is further characterized by the fact that it is highly stereoselective and

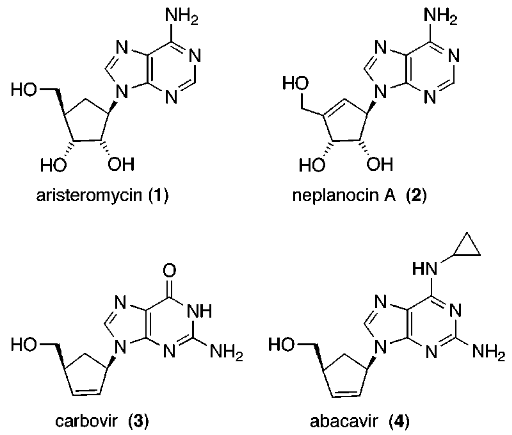


Figure 1. Structures of selected natural (**1** and **2**) and synthetic (**3** and **4**) carbocyclic nucleoside analogues.

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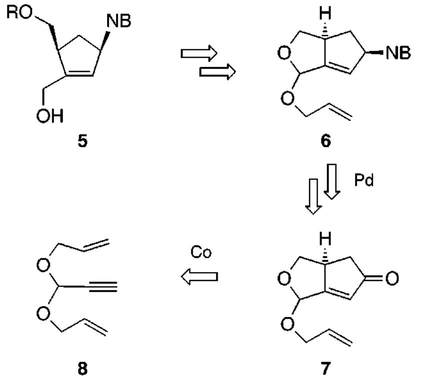
† Dedicated to Prof. Gerhard Quinkert on the occasion of his 75th birthday.

(1) For reviews, see: (a) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. (b) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611. (c) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229. (d) Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319.

10.1021/ol017181+ CCC: $22.00

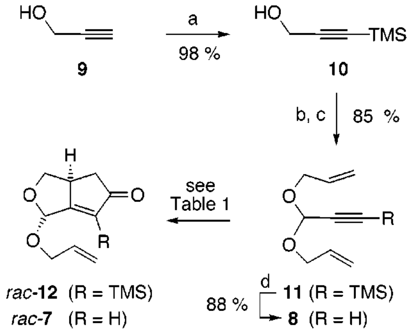
Scheme 1. Retrosynthetic Analysis



generally suited for the preparation of a broad variety of structurally diverse compounds (scaffold approach).

Our retrosynthetic analysis (Scheme 1) is based on the consideration that the target structures (**5**) could be derived from precursors of type **6**, in which the two oxy-functionalized side chains are jointly protected within the acetal function. This also allows their differentiation (selective protection) because cleavage of the acetal would lead to a hydroxy aldehyde. As a suitable precursor of **6** we envisioned using the bicyclic enone **7**, which is formally derived from the symmetric (achiral) dieneyne **8** through an intramolecular Pauson−Khand reaction (PKR).[4] To control the absolute configuration of the target compounds one could either perform the (chirogenic) PKR in an enantioselective fashion[5] or resolve a racemic intermediate at a later stage of the synthesis.

Scheme 2[a]



[a] Reagents and conditions: (a) *n*-BuLi (2.3 equiv), THF, −78 °C to rt, 1 h; then TMSCl (2.3 equiv), −78 °C to rt, 18 h; then 1.3 equiv of H_2SO_4(aq), rt, 1 h; (b) PCC (1.5 equiv), CH_2Cl_2, rt, 3 h; (c) allyl-OH (10 equiv), cat. *p*-TsOH, benzene, reflux (−H_2O), 15 h; (d) TBAF (in THF), allyl-OH/H_2O (2:1), rt, 1 h.

The synthesis (Scheme 2) started with the conversion of propargylic alcohol (**9**) into its C-silylated derivative **10** using slightly modified literature procedures.[6] PCC-oxidation of **10**[7] and subsequent acetalization of the resulting aldehyde with allylic alcohol under azeotropical removal of water afforded the acetal **11**,[8] from which **8** was (optionally) obtained by desilylation with TBAF in a solvent mixture consisting of water and allylic alcohol.

Table 1. Results of the PKRs Employing Substrates **8** (R = H) and **11** (R = TMS) To Give *rac*-**7** and *rac*-**12**, Respectively (Scheme 2)[a]

entry	R	solvent	additive (equiv)	temp (°C)	conditions[a]	yield (%)	dr
1	H	CH_2Cl_2	NMO (6)	rt	A	18	80:20
2	H	CH_2Cl_2	TMANO (6)	0 to 20	A	28	90:10
3	TMS	CH_2Cl_2	NMO (6)	rt	A	28	93:7
4	TMS	CH_2Cl_2	TMANO (6)	0 to 20	A	31	>98:2
5	TMS	pentane	TMANO (6)	0 to 20	A	0	
6	TMS	THF	TMANO (6)	0 to 20	A	50	>98:2
7	TMS	THF	TMANO (6)	0 to 20	B	27	>98:2
8	**TMS**	**CH_2Cl_2**	**TMANO (6)**	**0 to 20**	**B**	**72**	**>98:2**
9	**TMS**	**CH_2Cl_2**	**TMANO (8)**	**0 to 20**	**C**	**76**	**>98:2**

[a] (A) 1.1 equiv of $Co_2(CO)_8$, 2 h, rt, then addition of additive, 15 h at temperature specified in the table. (B) Same as A, except that after addition of the additive, the flask was left opened to the air. (C) Same as B except that 8 wt equiv of molecular sieves (4 Å) were added to the reaction mixture in the beginning.

The results of various experiments concerning the planned PKR (Scheme 2) are summarized in Table 1. At first, standard conditions were applied, which involve the treatment of preformed alkyne−$Co_2(CO)_6$ complexes with amine oxide promoters in dichloromethane (entries 1−4).[9] It was found that trimethylamine *N*-oxide (TMANO) generally gave better

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(2) For recent work on the synthesis of carbocyclic nucleoside analogues, see: (a) Trost, B. M.; Madsen, R.; Guile, S. D.; Brown, B. *J. Am. Chem. Soc.* **2000**, *122*, 5947 and references therein. (b) Gurjar, M.; Maheshwar, K. *J. Org. Chem.* **2001**, *66*, 7552. (c) Bianco, A.; Celletti, L.; Mazzei, R. A.; Umani, F. *Eur. J. Org. Chem.* **2001**, 1331. (d) Choi, W. J.; Park, J. G.; Yoo, S. J.; Kim, H. O.; Moon, H. R.; Chun, M. W.; Jung, Y. H.; Jeong, L. S. *J. Org. Chem.* **2001**, *66*, 6490. (e) Kuang, R.; Ganguly, A. K.; Chan, T.-M.; Pramanik, B. N.; Blythin, D. J.; McPhail, A. T.; Saksena, A. K. *Tetrahedron Lett.* **2000**, *41*, 9575. (f) Brown, B.; Hegedus, L. *J. Org. Chem.* **2000**, *65*, 1865. (g) Crimmins, M. T.; King, B. W.; Zuercher, W. J.; Choy, A. L. *J. Org. Chem.* **2000**, *65*, 8499. (h) Crimmins, M. T.; Zuercher, W. J. *Org. Lett.* **2000**, *2*, 1065. (i) Kitade, Y.; Kozaki, A.; Yatome, C. *Tetrahedron Lett.* **2000**, *42*, 433. (j) Gallos, J. K.; Damianou, K. C.; Dellios, C. C. *Tetrahedron Lett.* **2001**, *42*, 5769. (k) Gallos, J. K.; Dellios, C. C.; Spata, E. E. *Eur. J. Org. Chem.* **2001**, 79. (l) Shireman, B.; Miller, M. J. *Tetrahedron Lett.* **2000**, *41*, 9537. (m) Barrett, S.; O'Brien, P.; Steffens, H. C.; Towers, T. D.; Voith, M. *Tetrahedron* **2000**, *56*, 9633.

(3) Egli, M. *Angew. Chem., Int. Ed Engl.* **1996**, *35*, 1895; *Angew. Chem.* **1996**, *108*, 2021.

(4) (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Chem. Commun.* **1971**, 36. For recent reviews on the PKR, see: (b) Geis, O.; Schmalz, H.-G. *Angew. Chem.* **1998**, *110*, 955; *Angew. Chem., Int. Ed.* **1998**, *37*, 911. (c) Jeong, N. In *Transition Metals in Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. I, p 560. (d) Chung, Y. K. *Coord. Chem. Rev.* **1999**, *188*, 297. (e) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (f) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Chem. Eur. J.* **2001**, *7*, 1589.

(5) (a) Buchwald, S. L.; Hicks, F. A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 491. (b) Jeong, N.; Sung, B. K.; Choi, Y. K. *J. Am. Chem. Soc.* **2000**, *122*, 6771. (c) Shibata, T.; Takagi, K. *J. Am. Chem. Soc.* **2000**, *122*, 9852.

(6) (a) Jones, T. K.; Denmark, S. F. *Org. Synth.* **1986**, *64*, 182. (b) Davison, E. C.; Forbes, I. T.; Holmes, A. B.; Warner, J. A. *Tetrahedron* **1996**, *52*, 11601.

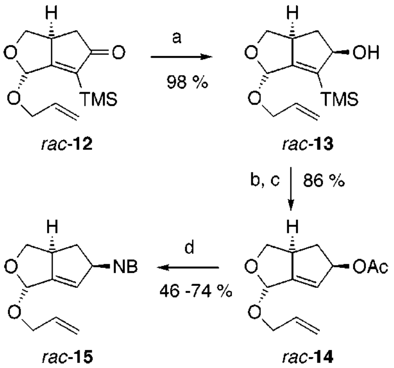
(7) Harris, N. J.; Gajewski, J. J. *J. Am. Chem. Soc.* **1994**, *116*, 6121.

(8) Sleeman, M. J.; Meehan, G. V. *Tetrahedron Lett.* **1989**, *30*, 3345.

results than *N*-methylmorpholine *N*-oxide (NMO), and the silylated compound **11** gave rise to somewhat better yields and higher diastereoselectivities (dr up to >98:2). While variation of the solvent was unsuccessful (entries 4−6), greatly improved yields were obtained in dichloromethane when the reaction mixture was exposed to the air during the reaction course (entry 8).[9a] A further improvement was finally achieved by performing the reaction in the presence of molecular sieves (4 Å).[10] In this way, the product *rac*-**12** could be obtained in 76% yield on a 60 mmol scale.[11,12]

The further course of the synthesis is shown in Scheme 3. Reaction of *rac*-**12** with $NaBH_4$ in the presence of $CeCl_3$[13] afforded alcohol *rac*-**13** with good diastereoselectivity (dr = 95:5). After desilylation (*t*-BuOK in aqueous DMSO),[14] acetylation of the OH functionality, and flash chromatography, the allylic acetate *rac*-**14** was obtained in high yield as a pure diastereomer.

Scheme 3[a]



[a] Reagents and conditions: (a) $NaBH_4$, $CeCl_3$, MeOH, 0 °C to rt, 3 h; (b) *t*-BuOK (1 equiv), DMSO/H_2O (19:1), 80 °C, 2 h; (c) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, rt, 16 h; (d) nucleobase-H, NaH (for pyrimidine bases) or nucleobase-H, Cs_2CO_3 (for adenine), DMSO, 80 °C, 30 min, then → rt, then addition of $Pd(PPh_3)_4$ (5 mol %), PPh_3 (11 mol %) and *rac*-14 in THF, argon atmosphere, 80 °C (50 °C for adenine), 16 h.

The relative configuration of the three stereogenic centers was unambiguously established by X-ray crystal structure analysis (Figure 2) of the acetate (*rac*-**13a**) derived from *rac*-**13**, which in contrast to *rac*-**13** and *rac*-**14** was obtained in crystalline form (mp 42 °C).

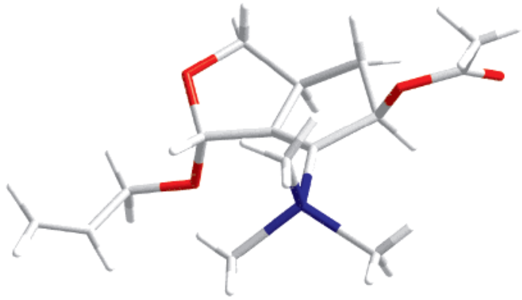


Figure 2. Crystal structure of compound *rac*-**13a**, derived from *rac*-**13** by O-acetylation.

Compound *rac*-**14** proved to be a perfectly suited intermediate for the introduction of various nucleobases by means of a Pd-catalyzed allylic substitution reaction.[2a,15]

Thus, when *rac*-**14** was reacted with preformed salts of nucleobases (sodium salts of pyrimidines or the cesium salt of adenine, respectively)[15a] in the presence of catalytic amounts of $Pd(PPh_3)_4$ at elevated temperatures (50−80 °C) in DMSO/THF, the allylic substitution products *rac*-**15a**−**e** (Scheme 3, Figure 3) were formed in good yield with virtually complete regio- and diastereoselectivity (dr >99:1). The relative configuration of the products was proven by ^{1}H NMR−NOE measurements. This indicates that the Pd-catalyzed transformation had proceeded with clean retention of configuration.[15]

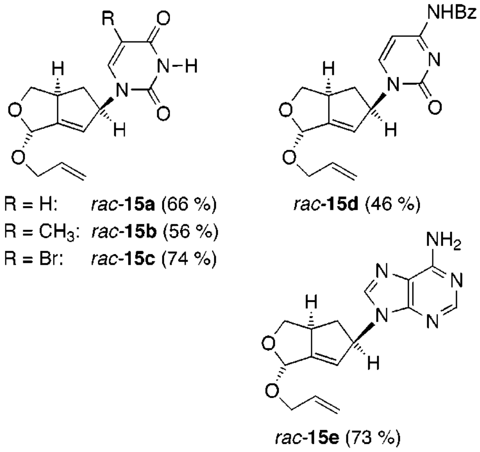


Figure 3. Products (*rac*-**15a**−**e)** of the Pd-catalyzed introduction of nucleobases according to Scheme 3.

To probe the final steps of the projected synthesis (Scheme 4), the pyrimidine derivatives *rac*-**15a**−**c** and the adenine

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[9] (a) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204. (b) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289.

[10] Perez-Serrano, L.; Casarrubios, L.; Dominguez, G.; Perez-Castells, J. *Org. Lett.* **1999**, *1*, 1187.

[11] A variety of other reaction conditions, which had been described in the literature, were also tested. However, the only reasonable result (49% yield) was obtained with *n*-BuSMe as an additive.[4f]

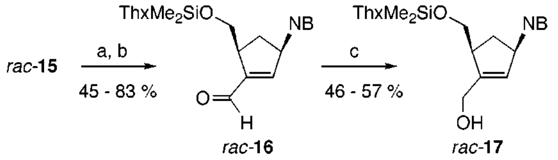
[12] The relative configuration of *rac*-**12** was determined by NMR−NOE measurements. For a related but less practical synthesis of compound *rac*-**12**, see: Jeong, N.; Lee, B. Y.; Lee, S. M.; Chung, Y. K.; Lee, S.-G. *Tetrahedron Lett.* **1993**, *34*, 4023.

[13] Luche, J.-L.; Rodriguez-Hahn, L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601.

[14] Kraft, M. E.; Wright, C. *Tetrahedron Lett.* **1992**, *33*, 151 and references therein.

[15] (a) Gundersen, L.-L.; Benneche, T.; Rise, F.; Gogoll, A.; Undheim, K. *Acta Chem. Scand.* **1992**, *46*, 761. For overviews on Pd-catalyzed allylic substitutions, see also: (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395 and references therein. (c) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Mill Valley, 1999; Chapter 9.

Scheme 4[a]



[a] Reagents and conditions: (a) cat. PPTS (2 equiv in the case of *rac*-**15e**), wet acetone, reflux, 3 h; (b) ThxMe$_2$SiCl (1.5 equiv), pyridine, rt, 18 h; (c) NaBH$_4$, CeCl$_3$; MeOH, rt, 3 h.

derivative *rac*-**15e** were subjected to acetal cleavage using pyridinium *p*-toluenesulfonate (PPTS)[16] in wet acetone. The crude hydroxy aldehydes were directly treated with chlorodimethylthexylsilane (ThxMe$_2$SiCl)[17] to yield the *O*-silylated compounds *rac*-**16a** (80%), *rac*-**16b** (65%), *rac*-**16c** (83%), and *rac*-**16e** (45%) in pure form after flash chromatography. In the case of the adenosine analogue (*rac*-**15e** → *rac*-**16e**) different silylation conditions (3.3 equiv of ThxMe$_2$SiCl, 3.3 equiv of NEt$_3$, 0.3 equiv DMAP, CH$_2$Cl$_2$, rt, 16 h) were used in order to obtain a better (still only moderate) conversion. Employing *rac*-**16c** and *rac*-**16e** it was finally demonstrated that the aldehydes of type *rac*-**16** can be reduced to the envisaged nucleoside analogues of type **5**. Under nonoptimized conditions, the alcohols were isolated in at least acceptable yields (46% for *rac*-**17c** and 57% for *rac*-**17e**).

In conclusion, we have elaborated an efficient and highly diastereoselective synthesis of monoprotected carbocyclic nucleoside analogues of type **5**.[18] Starting from propargylic alcohol, the synthesis requires only 11 steps (ca. 15% overall yield) employing as key steps a Co-mediated Pauson−Khand reaction and a Pd-catalyzed allylic amination.

As a result of the multifunctionality of the central intermediate (*rac*-**14**), the strategy disclosed here should be generally suited for the preparation of a broad variety of nucleoside analogues with potential biological activity. Current investigations in this laboratory are focusing on the exploitation of this potential and on possibilities to render the synthesis enantioselective.

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie. We also thank Dr. Hans Schmickler for NMR and Dr. M. Schäfer for MS measurements. Generous gifts of chemicals from Chemetall AG and Degussa AG are highly appreciated.

Supporting Information Available: Characteristic data for all new compounds and details of the X-ray analysis of compound *rac*-**13a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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